TREATMENT OF MOST BOTHERSOME SYMPTOM (MBS) ASSOCIATED WITH MIGRAINE USING ANTI-CGRP ANTIBODIES

SEQUENCE LISTING DISCLOSURE

[0001] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on April 7, 2020, is named "1250-US-PSP_ST25.txt" and is 357,579 bytes in size.

BACKGROUND OF THE INVENTION

[0002] Field of the invention

[0003] This invention pertains to methods of treatment of most bothersome symptom associated with migraine, using antibodies and fragments thereof (including Fab fragments) that specifically bind to human Calcitonin Gene Related Peptide (hereinafter "CGRP").

[0004] Description of Related Art

[0005] 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).

[0006] Migraines are neurovascular disorder affecting approximately 10% of the adult population in the U.S., and are typically accompanied by intense headaches. CGRP is believed to play a prominent role in the development of migraines. In fact, several companies, *i.e.*, Amgen, Eli Lilly, Teva and Alder Biopharmaceuticals (recently acquired by Lundbeck A/S) have developed anti-CGRP and anti-CGRP-R antibodies for use in treating or preventing migraine headaches. The present assignee has previously filed patent applications related to anti-CGRP antibodies and uses thereof including published PCT Application

WO/2012/162243 filed May 21, 2012 entitled "ANTI-CGRP COMPOSITIONS AND USE THEREOF", published PCT Application WO/2012/162257 filed May 21, 2012, entitled “USE OF ANTI-CGRP ANTIBODIES AND ANTIBODY FRAGMENTS TO PREVENT OR INHIBIT PHOTOPHOBIA OR LIGHT AVERSION IN SUBJECTS IN NEED THEREOF, ESPECIALLY MIGRAINE SUFFERERS” published PCT Application WO/2012/162253, filed May 21, 2012, entitled “USE OF ANTI-CGRP OR ANTI-CGRP-R ANTIBODIES OR ANTIBODY FRAGMENTS TO TREAT OR PREVENT CHRONIC AND ACUTE FORMS OF DIARRHEA” and published PCT Application WO/2015/003122, filed July 3, 2014, entitled “REGULATION OF GLUCOSE METABOLISM USING ANTI-CGRP ANTIBODIES” all of which applications are incorporated by reference in their entirety.

BRIEF SUMMARY

[0007] The present disclosure provides methods of treatment of most bothersome symptom (MBS) associated with migraine in patient suffering from chronic migraine, comprising administering to a patient in need an effective amount of at least one anti-CGRP antibody or antibody fragment thereof or an anti-CGRP-R antibody or antibody fragment thereof or one or more formulations comprising said antibody or antibody fragment as disclosed herein. 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 or antibody fragment is denoted Ab6. Ab6 is an anti-CGRP antibody or antibody fragment thereof having the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208; or having the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively. Said anti-CGRP antibody may comprise the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202. Said anti-CGRP antibody may comprise the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212. Said anti-CGRP antibody may comprise the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566. Said anti-CGRP antibody may comprise the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567. Said anti-CGRP antibody may comprise the antibody expression product isolated from

recombinant cells which express nucleic acid sequences encoding the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, *e.g.*, human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, *e.g.*, *Pichia pastoris* or CHO cells. Said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, *e.g.*, *Pichia pastoris* or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions. Any of the aforementioned anti-CGRP antibodies or antibody fragments, preferably Ab6, may be optionally comprised in a formulation as disclosed herein, *e.g.*, comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8. The administered dosage of said antibody may be between about 100 mg and about 300 mg, such as about 100 mg, about 300 mg, 100 mg, or 300 mg. The dosage may be administered by different means, *e.g.*, intravenously, *e.g.*, in a saline solution such as 0.9% sodium chloride in a suitable volume, such as 100 mL.

[0008] Said patient may exhibit less than 25 headache days per month, less than 20 headache days per month, less than 15 headache days per month, or less than 10 headache days per month. For example, said patient may exhibit less than 14 headache days, less than 13 headache days, less than 12 headache days, less than headache 11 days, less than 10 headache days, less than 9 headache days, less than 8 headache days, less than 7 headache days, or less than 6 headache days per month. Said patient may exhibit between 2-15 headache days, *e.g.*, 3-14 headache days, 4-13 headache days, 5-12 headache days, 6-11 headache days, or 7-10 headache days/month.

[0009] Said patient may exhibit less than 10 migraines per month, such as between 1-9 migraines per month, such as between 2-8 migraines per month, between 3-7 migraine per month, between 4-6 migraine per month, or about 5 migraines per month. Said patient may exhibit fewer than 1 migraine per month on average, *e.g.*, on average one migraine every 2 months, one every 3 months, one every 4 or 6 months, or intermediate values such as 2 every 3 months, etc. Said migraine may be diagnosed in accord with the ICHD-3 guidelines.

[0010] In addition to headache and associated symptoms as described in the diagnostic criteria of the International Classification of Headache Disorders (ICHD-3) for migraine with or without aura, migraine

patients experience a variety of autonomic, cognitive, sensory and motor symptoms during migraine, these symptoms are experienced uniquely by individual patients. In the present invention, the patients were allowed to self-identify a specific symptom associated with chronic migraine that they considered to be most bothersome. In the present application these symptoms will be referred to at the most bothersome symptom (MBS) associated with migraine. In the present invention the patient could identify their MBS without limitation, which provides a unique patient-centered approach for identifying and measuring the efficacy of antibodies of the invention as treatment of these most bothersome migraine-associated symptoms and hence is expected to have a meaningful impact on the patients ability to function during migraine. Although nausea, vomiting, photophobia, and phonophobia are migraine-associated symptoms included in ICDH-3 diagnostic criteria, many other symptoms may be observed to occur prior to, after, and even between days with diagnosable migraine. Over the duration of a migraine attack, these can include cognitive symptoms (e.g. memory, executive function, attention deficit), affective symptoms (e.g. mood changes, depression, anxiety, irritability), other sensory symptoms (e.g. osmophobia, taste abnormalities), as well as blurry vision, nasal congestion, rhinorrhea, lacrimation, sweating, ptosis, yawning, polyuria, abdominal cramps, diarrhea, dizziness, and neck pain. The MBS associated with migraine reported by the patients enrolled in the clinical trial described in Example 2 is summarized in **Table 1**. Although nausea/vomiting, photophobia, and phonophobia were common in the patient population in Example 2, less than half of these patients named one of these 3 symptoms included in ICDH-3 diagnostic criteria as their patient-identified MBS.

[0011] Migraine is a complex disorder of the brain associated with multifaceted symptomatology yet expressed in a personalized unique manner. Often persisting over multiple days, the peri-ictal period of migraine can be classified into four distinct phases—prodrome/premonitory, preictal/aura, ictal/headache, postdrome/postictal—with overlapping symptoms occurring during each phase of migraine. The various types and timing of MBS across the course of the migraine is illustrated in **FIG. 15.** It is highly relevant to assess MBS in migraine patients during clinical trials, since it is recognized that headache pain alone is not considered sufficient to adequately eliminate the impact of migraine on the patients daily living and health status. The reduction in mean monthly migraine days (MMDs) or a similar endpoints in clinical trials do not fully capture the burden of migraine and the associated symptoms that are affected by therapeutic intervention. The inventors of the present invention found that in addition to reducing MMDs Ab6, an anti-CGRP antibody, was also effective in improving MBS in migraine patients. Improvements in these symptoms associated with treatment were correlated with improved patients' perception of disease status and indirectly with satisfaction with treatment response. It is known that migraine patients often continue to seek treatment

for their migraine because of the burden of their MBS, thus supporting the clinical value of treating both the primary migraine pathology and the MBS associated with said migraine.

[0012] The present invention provides anti-CGRP antibodies or antibody fragments thereof, which are able to improve the MBS associated with migraine in patients suffering from migraine, such as chronic or episodic migraine. The MBS parameter rates the patient's assessment of change (improvement or worsening since the start of the study) in this symptom.

[0013] The present invention provides anti-CGRP antibodies or antibody fragments thereof, which are able to improve the patient global impression of change (PGIC) associated with migraine treatment in patients impacted by migraine, such as chronic or episodic migraine. The patient global impression of change (PGIC) associated with migraine parameter comprises a single question concerning the patient's impression of the overall change (improvement or worsening since the start of the study) in their disease status evaluated on a 7 point Likert scale anchored by very much improved and very much worse.

[0014] The present invention provides anti-CGRP antibodies or antibody fragments thereof, which are able to reduce MMDs as well as improve the patient's most bothersome symptom (MBS) associated with migraine in a manner that is highly corelated with positive change I the patient's global impression of change (PGIC) of migraine treatment. This dual action constitutes an improved treatment option for patient suffering from migraine, which goes beyond treating the migraine headache, and provides treatment for the collective migraine burden experienced by the patient comprising both migraine headache as well as MBS associated with migraine.

[0015] The present invention provides methods of improving most bothersome symptom (MBS) associated with migraine, comprising intravenously administering to a patient in need thereof between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody preferably comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566.

[0016] The present invention provides methods of improving patient global impression of change (PGIC), comprising intravenously administering to a patient in need thereof between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody preferably comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566.

[0017] In another aspect, the invention provides methods of improving most bothersome symptom (MBS) associated with migraine and simultaneously reduce the MMDs, comprising intravenously administering to a patient in need thereof between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody preferably comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566.

[0018] In another aspect, the invention provides methods of improving patient global impression of change (PGIC) associated with migraine and simultaneously reduce the MMDs, comprising intravenously administering to a patient in need thereof between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody preferably comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566.

[0019] In another aspect, the invention provides methods of improving most bothersome symptom (MBS) associated with migraine and patient global impression of change (PGIC) associated with migraine, comprising intravenously administering to a patient in need thereof between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody preferably comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566

[0020] In another aspect, the invention provides methods of improving most bothersome symptom (MBS) associated with migraine and/or patient global impression of change (PGIC) associated with migraine and simultaneously reduce the MMDs, comprising intravenously administering to a patient in need thereof between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody preferably comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566.

[0021] In some exemplary embodiments the dosage of said anti-CGRP antibody may be 100 mg.

[0022] In other exemplary embodiments the dosage of said anti-CGRP antibody may be 300 mg.

[0023] The method may further comprise intravenously administering 100 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

[0024] The method may further comprise intravenously administering 300 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

[0025] The antibody may be provided or administered in a formulation as disclosed herein, *e.g.*, comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8.

[0026] Prior to first dosage, the patient may exhibit between about 10 and about 22 migraine days per month, such as between about 13 and about 19 migraine days per month, such as about 16 migraine days per month.

[0027] Prior to first dosage, the patient may exhibit between about 14 and about 27 headache days per month, such as between about 17 and about 24 headache days per month, such as about 20 or about 21 headache days per month.

[0028] Said patient may have been diagnosed with migraine at least 10 years prior to said first dosage, such as at least 15 years prior to said first dosage, such as at least 18 or at least 19 years prior to said first dosage.

[0029] Said patient may have been diagnosed with chronic migraine at least 5 years prior to said first dosage, such as at least 8 years prior to said first dosage, such as at least 11 or at least 12 years prior to said first dosage.

[0030] The patient may have a headache when administered the anti-CGRP antibody or fragments thereof of the invention.

[0031] The patient may have a migraine, such as a migraine with aura, when administered anti-CGRP antibody or fragments thereof of the invention.

[0032] Said patient may have a reduction in the number of migraine days by at least 50% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

[0033] Said patient may have a reduction in the number of migraine days by at least 75% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

[0034] Said patient may have a reduction in the number of migraine days by 100% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

[0035] Said patient may have a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

[0036] Said patient may have a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

[0037] Said patient may have a reduction in the number of migraine days by 100% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

[0038] Said patient may experience an improvement in their MBS associated with migraine in the one month period after being administered said first dose measured as the change from the baseline MBS.

[0039] Said patient may experience an improvement in their MBS associated with migraine in the 3 month period after being administered said first dose measured as the change from the baseline MBS.

[0040] Said patient may experience an improvement in their MBS associated with migraine in the 6 month period after being administered said first dose measured as the change from the baseline MBS.

[0041] Said patient may experience an improvement in their PGIC associated with migraine in the one month period after being administered said first dose measured as the change from the baseline.

[0042] Said patient may experience an improvement in their PGIC associated with migraine in the 3 month period after being administered said first dose measured as the change from the baseline.

[0043] Said patient may experience an improvement in their PGIC associated with migraine in the 6 month period after being administered said first dose measured as the change from the baseline.

[0044] The method may further comprise administering, *e.g.*, intravenously, a second dose of an anti-CGRP antibody of the invention to said patient within about 10-14 weeks, preferably 11-13 weeks, more preferably about 12 weeks or about 3 months, after said first dose.

[0045] Said first dose may comprise about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

[0046] Prior to said administration, the patient may exhibit between about 15 and about 30 migraine days per month, such as between about 16 and about 28 migraine days per month, such as between about 17 and about 26 migraine days per month, such as about 16 migraine days per month.

[0047] Prior to said administration, the patient may exhibit between about 15 and about 27 headache days per month, such as between about 17 and about 24 headache days per month, such as about 20 or about 21 headache days per month.

[0048] Said patient may have been diagnosed with migraine at least 10 years prior to said administration, such as at least 15 years prior to said administration, such as at least 18 or at least 19 years prior to said administration.

[0049] Said patient may have been diagnosed with chronic migraine at least 5 years prior to said administration, such as at least 8 years prior to said administration, such as at least 11 or at least 12 years prior to said administration.

[0050] Said patient may have a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0051] Said patient may have a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0052] Said patient may have a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0053] Said patient may have a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0054] Said patient may have a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0055] Said patient may have a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0056] The method may further comprise administering, *e.g.*, intravenously, a second dose of said anti-CGRP antibody to said patient within about 10-14 weeks, preferably 11-13 weeks, more preferably about 12 weeks or about 3 months, after said administration.

[0057] Said administration may comprise about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

[0058] Said anti-CGRP antibody may be aglycosylated or if glycosylated only may contain only mannose residues.

[0059] Said anti-CGRP antibody may consist of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566. Said anti-CGRP antibody may consist of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0060] In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the variable light chain of SEQ ID NO: 222 and/or the variable heavy chain of SEQ ID NO: 202. In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the variable light chain encoded by SEQ ID NO: 232 and/or the variable heavy chain encoded by SEQ ID NO: 212.

[0061] In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the light chain of SEQ ID NO: 221 and/or the heavy chain of SEQ ID NO: 201 or SEQ ID NO: 566. In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the light chain encoded by SEQ ID NO: 231 and/or the heavy chain encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0062] In some embodiments, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the VL polypeptide of SEQ ID NO: 222 and the VH polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, *e.g.*, human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, *e.g.*, *Pichia pastoris* or CHO cells.

[0063] In some embodiments, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, *e.g.*, *Pichia pastoris* or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions.

[0064] Inn some embodiments any of the aforementioned anti-CGRP antibodies or antibody fragments may be comprised in a formulation as disclosed herein, *e.g.*, comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8. The antibody or fragment may be administered by different means, *e.g.*, intravenously, *e.g.*, in a saline solution such as 0.9% sodium chloride in a suitable volume, such as 100 mL.

[0065] In some embodiments, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody or antibody fragment is administered, *e.g.*, intravenously.

[0066] In other embodiments, about 100 mg of said anti-CGRP antibody or antibody fragment is administered.

[0067] In other embodiments, about 300 mg of said anti-CGRP antibody or antibody fragment is administered, *e.g.*, intravenously.

[0068] In exemplary embodiments, the anti-human CGRP antibody or antibody fragment is administered, *e.g.*, intravenously at a frequency which is at most every 10-14 weeks, preferably every 11-13 weeks, more preferably every 3 months or every 12 weeks, wherein the antibody dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 10-14 weeks, preferably every 11-13 weeks, more preferably every 3 months or every 12 weeks. The phrase “the antibody dosage is administered in a single formulation or divided into different formulations” refers to the administration of the recited amount of antibody within a relatively short period of

time, *e.g.*, within a period of several hours, *e.g.*, 1 to 8 hours, about one day, within about two days, or within about one week, which may be by the same or different routes (*e.g.*, i.v., i.m., and/or s.c.), sites of administration. The term "different formulations" in this context refers to antibody dosages that are administered at different times and/or at different sites and/or different routes, irrespective of whether the dosages are the same or different with respect to the chemical composition of the pharmaceutical formulation in with each dosage is administered; for example, the concentration, excipients, carriers, pH, and the like may be the same or different between the different administered dosages.

[0069] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 8 weeks or every 2 months.

[0070] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks or every 3 months.

[0071] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 16 weeks or every 4 months.

[0072] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 20 weeks or every 5 months.

[0073] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 24 weeks or every 6 months.

[0074] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 28 weeks or every 7 months.

[0075] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 32 weeks or every 8 months.

[0076] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 36 weeks or every 9 months.

[0077] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 40 weeks or every 8 months.

[0078] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 44 weeks or every 9 months.

[0079] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 48 weeks or every 10 months.

[0080] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 52 weeks or every 11 months.

[0081] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 56 weeks or every 12 months.

[0082] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 15-18 months.

[0083] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 18-21 months.

[0084] In other exemplary embodiments, the anti-human CGRP antibody dosage or antibody fragment used in the afore-mentioned methods is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 2 years.

[0085] In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods is administered systemically.

[0086] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment used in the afore-mentioned methods is administered by a mode of administration is selected from intravenous, intramuscular, intravenous, intrathecal, intracranial, topical, intranasal, and oral. In a preferred embodiment, the anti-human CGRP antibody or antibody fragment used in the afore-mentioned methods is administered intravenously.

[0087] In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods has an *in vivo* half-life of at least 10 days.

[0088] In other exemplary embodiments, the anti-human CGRP antibody has an *in vivo* half-life of at least 15 days.

[0089] In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods has an *in vivo* half-life of at least 20 days.

[0090] In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods has an *in vivo* half-life of at least 20-30 days.

[0091] In other exemplary embodiments, the anti-human CGRP antibody is administered at a dosage of between about 100 mg and about 300 mg has an *in vivo* half-life of ± 20% of at least about (284 ± 44 hours).

[0092] In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods binds to human α- and β-CGRP.

[0093] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 30 days after antibody administration.

[0094] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 60 days after antibody administration.

[0095] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in inhibition of vasodilation induced by topically applied capsaicin at least 90 days after antibody administration.

[0096] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 120 days after antibody administration.

[0097] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 150 days after antibody administration.

[0098] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 180 days after antibody administration.

[0099] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin more than 180 days after antibody administration.

[0100] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in sustained pharmacodynamic (PK) activity, within 5% of the maximal response (Imax) (as compared to lower antibody doses).

[0101] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in sustained pharmacodynamic (PK) activity which is maintained for at least 2-3 months after antibody administration, wherein PK analysis of the anti-human CGRP antibody is derived from plasma concentrations.

[0102] In other exemplary embodiments, the administered anti-human CGRP antibody dosage is between about 100 mg and about 300 mg or more which is administered no more frequently than every 2 months.

[0103] The present invention is additionally directed to the use of specific antibodies and fragments thereof having binding specificity for CGRP, in particular antibodies having desired epitopic specificity, high affinity or avidity and/or functional properties. A preferred embodiment of the invention is directed to usage of chimeric or humanized antibodies and fragments thereof (including Fab fragments) capable of binding to CGRP and/or inhibiting the biological activities mediated by the binding of CGRP to the CGRP receptor ("CGRP-R") *e.g.*, wherein such antibodies optionally are derived from recombinant cells engineered to express same, optionally yeast or mammalian cells, further optionally *Pichia pastoris* and CHO cells.

[0104] In another preferred embodiment of the invention, full length antibodies and Fab fragments thereof are contemplated that inhibit the CGRP-alpha-, CGRP-beta-, and rat CGRP-driven production of cAMP. In a further preferred embodiment of the invention, full length and Fab fragments thereof are contemplated that reduce vasodilation in a recipient following administration.

[0105] The invention also contemplates usage of conjugates of anti-CGRP antibodies and binding fragments thereof conjugated to one or more functional or detectable moieties. The invention also contemplates usage of chimeric or humanized anti-CGRP or anti-CGRP/CGRP-R complex antibodies and binding fragments thereof. In one embodiment, binding fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, Fv, scFv fragments, SMIPs (small molecule immunopharmaceuticals), camelbodies, nanobodies, and IgNAR.

BRIEF DESCRIPTION OF THE DRAWINGS

[0106] **FIG. 1** provide the polypeptide sequences of the full-length heavy chain for antibody Ab6 with framework regions (FR), complementarity determining regions (CDRs), and constant region sequences delimited.

[0107] **FIG. 2** provide the polypeptide sequences of the full-length light chain for antibody Ab6 with framework regions (FR), complementarity determining regions (CDRs), and constant region sequences delimited.

[0108] **FIG. 3** provide exemplary polynucleotide sequences encoding the full-length heavy chain for antibody Ab6 with framework regions (FR), complementarity determining regions (CDRs), and variable region coding sequences delimited.

[0109] **FIG. 4** provide exemplary polynucleotide sequences encoding the full-length light chain for antibody Ab6 with their framework regions (FR), complementarity determining regions (CDRs), and variable region coding sequences delimited.

[0110] **FIG. 5** provides the polypeptide sequence coordinates within the full-length heavy chain polypeptide sequences of antibodies Ab6 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

[0111] **FIG. 6** provides the polypeptide sequence coordinates within the full-length heavy chain polypeptide sequences of antibody Ab6 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

[0112] **FIG. 7** provides the polypeptide sequence coordinates within the full-length light chain polypeptide sequences of antibody Ab6 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

[0113] **FIG. 8** provides the polypeptide sequence coordinates within the full-length light chain polypeptide sequences of antibody Ab6 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

[0114] **FIG. 9** provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length heavy chain polypeptide sequences of antibody Ab6 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

[0115] **FIG. 10** provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length heavy chain polypeptide sequences of antibody Ab6 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

[0116] **FIG. 11** provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length light chain polypeptide sequences of antibody Ab6 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

[0117] **FIG. 12** provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length light chain polypeptide sequences of antibody Ab6 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

[0118] **FIG. 13** Study design of the clinical trial protocol as summarized in Example 2.

[0119] **FIG. 14** displays the efficacy of Ab6 on Mean Monthly Migraine Days (MMDs) in the clinical trial described in Example 2.

[0120] **FIG. 15** Illustrates the types and timing of Most Bothersome Symptoms (MBS) across the course of the migraine

[0121] **FIG. 16** Illustrates the MBS change from baseline during the 28 day screening period of the clinical trial described in Example 2– *i.e.* before the first infusion of Ab6.

[0122] **FIG. 17** Illustrates the MBS change from baseline 1 month after the first infusion of Ab6 in the clinical trial described in Example 2.

[0123] **FIG. 18** Illustrates the PGIC from baseline 1 month after the first infusion of Ab6 in the clinical trial described in Example 2.

[0124] **FIG. 19** Illustrates the MBS change from baseline 3 month after the first infusion of Ab6 in the clinical trial described in Example 2.

[0125] **FIG. 20** Illustrates the PGIC from baseline 3 month after the first infusion of Ab6 in the clinical trial described in Example 2.

[0126] **FIG. 21** Illustrates the MBS change from baseline 6 month after the first infusion of Ab6 in the clinical trial described in Example 2.

[0127] **FIG. 22** Illustrates the PGIC from baseline 6 month after the first infusion of Ab6 in the clinical trial described in Example 2.

DETAILED DESCRIPTION

[0128] Use of anti-CGRP antibodies for treatment of MBS and/or PGIC associated with migraine, such as chronic migraine or episodic migraine is described herein. Additionally, anti-CGRP antibodies are demonstrated herein to be effective for treatment of MMDs. The treatment efficacy on both MBS and PGIC

are shown to be effective in providing relief of MBS and PGIC at 1 month, 3 months and 6 months following the first infusion of an anti-CGRP antibody or fragments thereof of the invention.

[0129] Definitions

[0130] 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.

[0131] As used herein, the term "most bothersome symptom associated with migraine" refers to symptoms which is identified by an individual patient to be the most bothersome symptom they associate with their migraine. In the present invention the "most bothersome symptom associated with migraine" is specified in **Table 1**. The "most bothersome symptom associated with migraine" of the present invention described by the patient to the study investigator who assists in medical interpretation of the patients symptom. The investigator in the clinical study was able to with the patient consultation selected from the group of known migraine symptoms consisting of: Sensitivity to light (photophobia), Nausea/vomiting, Headache, Sensitivity to sound (phonophobia), Aura, Pain with activity, Pain, Throbbing/pulsation, Cognitive disruption, Fatigue, Mood changes, Sensitivity to smell (osmophobia or olfactophobia), Visual impact, Pressure/tightness, Pain (anatomical), Eye pain, Neck pain, Dizziness, Allodynia, Inactivity, Sensory disturbance, Sleep disturbance and Speech difficulty. A patient's "most bothersome symptom associated with migraine" as used in the present invention refers to the self-identified "most bothersome symptom associated with migraine", which may be one or more of the symptoms described herein above or may be classified as "other"

[0132] As used herein, the term "improvement of" or "improving" most bothersome symptom associated with migraine refers the change in the patient's assessment of the MBS compared to baseline (i.e the MBS prior to the first dosing with anti-CGRP antibodies or fragments thereof of the invention). An improvement is characterized as ≥1 categorical change in the patients assesment of the MBS compared to baseline on the 7 point Likert scale described in Example 2.

[0133] As used herein, the term “improvement of” or “improving” patient global impression of change associated with migraine refers the change in the patient’s assessment of their disease status compared to baseline (i.e the disease status prior to the first dosing with anti-CGRP antibodies or fragments thereof of the invention). An improvement is characterized as ≥1 categorical change in the patients assesment of the PGIC compared to baseline on the 7-step scale described in Example 2.

[0134] 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.

[0135] 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.

[0136] 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, such as 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).

[0137] 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.

[0138] 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.

[0139] 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.

[0140] *Calcitonin Gene Related Peptide* (*CGRP*): As used herein, CGRP encompasses not only the following *Homo sapiens* CGRP-alpha and *Homo sapiens* CGRP-beta amino acid sequences available from American Peptides (Sunnyvale CA) and Bachem (Torrance, CA):

[0141] *CGRP-alpha*: ACDTATCVTHRLAGLLSRSGGVVKNNFVPTNVGSKAF-NH_2 (SEQ ID NO: 561), wherein the terminal phenylalanine is amidated;

[0142] *CGRP-beta*: ACNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF-NH_2 (SEQ ID NO: 562), 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.

[0143] *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 such as *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.

[0144] 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.

[0145] 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.

[0146] 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^{R} Technology; Invitrogen, Carlsbad California). If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

[0147] 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.

[0148] 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.

[0149] 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 such as 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.

[0150] 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 such as, 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.

[0151] The polypeptides of interest 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).

[0152] 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.

[0153] 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.

[0154] 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.

[0155] 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.

[0156] *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.

[0157] *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.

[0158] 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.

[0159] 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.

[0160] The terms "*desired protein*" or "*desired antibody*" are used interchangeably and refer generally to a parent antibody specific to a target, *i.e.*, CGRP 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 IgGetc., from all sources, *e.g.* human, rodent, rabbit, cow, sheep, pig, dog, other mammals, chicken, other avians, etc., are considered to be “antibodies.” A preferred source for producing antibodies useful as starting material according to the invention is rabbits. 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.

[0161] 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.

[0162] 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.

[0163] 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.

[0164] 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.

[0165] 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.

[0166] 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*.

[0167] 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.

[0168] 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.

[0169] 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.

[0170] 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.

[0171] "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.

[0172] 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.

[0173] 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.

[0174] 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.

[0175] 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.

[0176] 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.

[0177] "Cmax" 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 Cmax 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.

[0178] "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.

[0179] "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.

Anti-CGRP Antibodies and Binding Fragments Thereof Having Binding Specificity for CGRP

[0180] The invention specifically includes the use of Ab6, which is a specific anti-CGRP antibody or antibody fragment, which comprises or consists of the CDR, VL, VH, CL, CH polypeptides sequences identified in **FIGs. 1-12**. The polypeptides comprised in the anti-CGRP antibody, Ab6 is further described below.

[0181] Antibody Ab6

[0182] In a preferred exemplary embodiment, the invention includes humanized antibodies having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below:

QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTLASGVPSRFSGSG
SGTDFTLTISSLQPEDVATYYCLGSYDCTNGDCFVFGGGTKVEIKR (SEQ ID NO: 222).

[0183] The invention also includes humanized antibodies having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below:

QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTLASGVPSRFSGSG
SGTDFTLTISSLQPEDVATYYCLGSYDCTNGDCFVFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS
VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC (SEQ ID NO: 221).

[0184] The invention further includes humanized antibodies having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGINGATYYASWAKG
RFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVTVSS (SEQ ID NO: 202).

[0185] The invention also includes humanized antibodies having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGINGATYYASWAKG
RFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGT
AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP
SNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 201).

[0186] Alternatively, the heavy chain of Ab6 may lack the C-terminal lysine of SEQ ID NO: 201, *i.e.*, a heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGINGATYYASWAKG
RFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGT
AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP
SNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA

KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 566).

[0187] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221, and/or one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[0188] The invention also contemplates fragments of the antibody having binding specificity to CGRP. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 222 or SEQ ID NO: 221. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 202 or SEQ ID NO: 201 or SEQ ID NO: 566.

[0189] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221.

[0190] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566.

[0191] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 222; the variable heavy chain

region of SEQ ID NO: 202; the complementarity-determining regions (SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228) of the variable light chain region of SEQ ID NO: 222; and the complementarity-determining regions (SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208) of the variable heavy chain region of SEQ ID NO: 202.

[0192] In a particularly preferred embodiment of the invention, the humanized anti- CGRP antibody is Ab6, comprising, or alternatively consisting of, SEQ ID NO: 221 and SEQ ID NO: 201 or SEQ ID NO: 566, and having at least one of the biological activities set forth herein.

[0193] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab6, the Fab fragment includes the variable light chain sequence of SEQ ID NO: 222 and the variable heavy chain sequence of SEQ ID NO: 202. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 222 and/or SEQ ID NO: 202 in said Fab while retaining binding specificity for CGRP.

[0194] In another particularly preferred embodiment of the invention, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, *e.g.*, human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, *e.g.*, *Pichia pastoris* or CHO cells.

[0195] In another particularly preferred embodiment of the invention, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, *e.g.*, *Pichia pastoris* or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions.

[0196] In another particularly preferred embodiment of the invention, any of the aforementioned anti-CGRP antibodies or antibody fragments may be optionally comprised in a formulation as disclosed herein, *e.g.*, comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8.

[0197] 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, anti-CGRP antibodies such as 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*.

[0198] In another embodiment, antibody fragments may be present in one or more of the following non-limiting forms: Fab, Fab', $F(ab')_2$, Fv and single chain Fv antibody forms. In a preferred embodiment, the anti-CGRP antibodies described herein further comprises the kappa constant light chain sequence comprising the sequence set forth below:

[0199] TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 563).

[0200] In another preferred embodiment, the anti-CGRP antibodies described herein further comprises the gamma-1 constant heavy chain polypeptide sequence comprising the sequence set forth below or the same sequence lacking the carboxy terminal lysine residue (SEQ ID NO: 564 and SEQ ID NO: 565, respectively):

[0201] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK (SEQ ID NO: 564).

[0202] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO: 565).

[0203] For clarity, any antibody disclosed herein is intended to include any variant of the disclosed constant region variant sequences, *e.g.*, Ab6 may comprise the constant region of SEQ ID NO: 564 containing the C-terminal lysine or may comprise the constant region of SEQ ID NO: 565 lacking the C-terminal lysine. Thus, every disclosure herein of the heavy chain of SEQ ID NO: 201 also includes a variant lacking the C-terminal lysine residue thereof, *i.e.*, having the heavy chain variable region sequence of Ab6

(SEQ ID NO: 202) and the constant region sequence of SEQ ID NO: 565. For example, the sequence encoding an antibody comprising a C-terminal lysine in the heavy chain may, when expressed in cell lines such as CHO cells, produce an antibody lacking said C-terminal lysine due to proteolysis, or a mixture of heavy chains containing or lacking said C-terminal lysine.

[0204] In one embodiment of the invention, the antibodies or V_H or V_L polypeptides originate or are selected from one or more rabbit B cell populations prior to initiation of the humanization process referenced herein.

[0205] In another embodiment of the invention, the anti-CGRP antibodies and fragments thereof do not have binding specificity for CGRP-R. In a further embodiment of the invention, the anti-CGRP antibodies and fragments thereof inhibit the association of CGRP with CGRP-R. In another embodiment of the invention, the anti-CGRP antibodies and fragments thereof inhibit the association of CGRP with CGRP-R and/or additional proteins and/or multimers thereof, and/or antagonizes the biological effects thereof.

[0206] 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.

[0207] 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.

[0208] 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.

[0209] 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.

[0210] 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).

[0211] 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.

[0212] 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 (^{125}I), Carbon 14 (^{14}C), Sulfur 35 (^{35}S), Tritium (^{3}H) and Phosphorus 32 (^{32}P).

[0213] 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, cyclothosphamide, 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 antimytotic 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, tenoposide, colchicin, dihydroxy anthracin dione, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, procarbazine, hydroxyurea, asparaginase, corticosteroids, mytotane (O,P'-(DDD)), interferons, and mixtures of these cytotoxic agents.

[0214] 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)).

[0215] 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 (^{32}P), Scandium-47 (^{47}Sc), Copper-67 (^{67}Cu), Gallium-67 (^{67}Ga), Yttrium-88 (^{88}Y), Yttrium-90 (^{90}Y), Iodine-125 (^{125}I), Iodine-131 (^{131}I), Samarium-153 (^{153}Sm), Lutetium-177 (^{177}Lu), Rhenium-186 (^{186}Re) or Rhenium-188 (^{188}Re), and alpha-emitters such as Astatine-211 (^{211}At), Lead-212 (^{212}Pb), Bismuth-212 (^{212}Bi) or -213 (^{213}Bi) or Actinium-225 (^{225}Ac).

[0216] 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).

[0217] 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.

[0218] 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.

[0219] In another embodiment, the invention further contemplates the above-recited polypeptide homologs of the antibody fragments, variable regions and CDRs set forth herein further having anti-CGRP activity. Non-limiting examples of anti-CGRP activity are set forth herein.

[0220] The invention further contemplates treatment methods wherein the one or more anti-human CGRP antibodies discussed above are aglycosylated or if glycosylated are only mannosylated; that contain an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation; are

human, humanized, single chain or chimeric; and are a humanized antibody derived from a rabbit (parent) anti-human CGRP antibody. An exemplary mutation which impairs glycosylation comprises the mutation of the Asn residue at position 297 of an IgG heavy chain constant region such as IgG1 to another amino acid, such as Ala as described in U.S. Pat. No. 5,624,821, which is incorporated by reference in its entirety.

[0221] The invention further contemplates one or more anti-human CGRP antibodies wherein the framework regions (FRs) in the variable light region and the variable heavy regions of said antibody respectively are human FRs which are unmodified or which have been modified by the substitution of one or more human FR residues in the variable light or heavy chain region with the corresponding FR residues of the parent rabbit antibody, and wherein said human FRs have been derived from human variable heavy and light chain antibody sequences which have been selected from a library of human germline antibody sequences based on their high level of homology to the corresponding rabbit variable heavy or light chain regions relative to other human germline antibody sequences contained in the library.

[0222] The invention also contemplates that the treatment method may involve the administration of two or more anti-CGRP antibodies or fragments thereof and disclosed herein. If more than one antibody is administered to the patient, the multiple antibodies may be administered simultaneously or concurrently, or may be staggered in their administration. The anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, may also be described by their strength of binding or their affinity for CGRP. In one embodiment of the invention, the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to CGRP with a dissociation constant (K_D) of less than or equal to $5x10^{-7}$ M, 10^{-7} M, $5x10^{-8}$ M, 10^{-8} M, $5x10^{-9}$ M, 10^{-9} M, $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, 10^{-12} M, $5x10^{-13}$ M, or 10^{-13} M. Preferably, the anti-CGRP antibodies and fragments thereof bind CGRP with a dissociation constant of less than or equal to 10^{-11} M, $5x10^{-12}$ M, or 10^{-12} M. In a specific embodiment of the invention the anti-CGRP antibody is Ab6 having a dissociation constant of less than or equal to 10 pM, such as 2-8 pM, such as 3-6 pM, such as less than or equal to about 5 pM when measured using surface plasmon resonance (Misura, K et al, July 2019, Poster P220LB, AHS 61st annual scientific meeting). In another embodiment of the invention, the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to a linear or conformational CGRP epitope.

[0223] In another embodiment of the invention, the anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to CGRP with an off-rate of less than or equal to 10^{-4} S^{-1}, $5x10^{-5}$ S^{-1}, 10^{-5} S^{-1}, $5x10^{-6}$ $S^{-}1$, 10^{-6} S^{-1}, 5x10-7 S-1, or 10^{-7} S^{-1}. In a specific embodiment of the invention the anti-CGRP antibody is Ab6 having an off-rate of less than or equal

to $5x10^{-6}$ S^{-1}, such as less than or equal to $4x10^{-6}$ S^{-1}, such as less than or equal to $3x10^{-6}$ S^{-1}, such as less than or equal to $2x10^{-6}$ S^{-1} , such as less than or equal to $1x10^{-6}$ S^{-1} when measured using surface plasmon resonance.

Polynucleotides Encoding Anti-CGRP Antibody Polypeptides

[0224] As aforementioned the invention specifically includes the use of specific anti-CGRP antibody or antibody fragment referred to herein as Ab6, which comprises or consists of the CDR, VL, VH, CL, and CH polypeptides having the sequences identified in **FIGs. 1-12**. The nucleic acid sequences encoding the foregoing VL, VH, CL, and CH polypeptides comprised in Ab6 are also comprised in **FIGs. 1-12**. The nucleic acid sequences which encode the CDR, VL, VH, CL, and CH polypeptides of an especially preferred anti-CGRP antibody, Ab6, are further described below.

[0225] Polynucleotides Encoding Antibody Ab6

[0226] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 222:

[0227] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCAGGCCAGTCAG AGTGTTTATCATAACACCTACCTGGCCtggtatcagcagaaaccagggaaagttcctaagCAActgatctatGATGCATCC ACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctgggacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaac ttattactgtCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 232).

[0228] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 221:

[0229] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCAGGCCAGTCAG AGTGTTTATCATAACACCTACCTGGCCtggtatcagcagaaaccagggaaagttcctaagCAActgatctatGATGCATCC ACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctgggacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaac ttattactgtCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgt ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGC CTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGAT AACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACC TACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCC TGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTT AG (SEQ ID NO: 231).

[0230] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 202:

[0231] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCtctggaATCGACC TCagtGGCTACTACATGAACtgggtccgtcaggctccagggaaggggctggagtgggtcGGAGTCATTGGTATTAATGG TGCCACATACTACGCGAGCTGGGCGAAAGGCcgattcaccatctccagagacaattccaagACCACGGTGtatcttcaaa tgaacagcctgagagctgaggacactgctgtgtatTTCtgtGCTAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAG C (SEQ ID NO: 212).

[0232] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 201:

[0233] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCtctggaATCGACC TCagtGGCTACTACATGAACtgggtccgtcaggctccagggaaggggctggagtgggtcGGAGTCATTGGTATTAATGG TGCCACATACTACGCGAGCTGGGCGAAAGGCcgattcaccatctccagagacaattccaagACCACGGTGtatcttcaaa tgaacagcctgagagctgaggacactgctgtgtatTTCtgtGCTAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAG CGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCAcCCTCCTCCaAGAGCACCTCTGGGGGCA CAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTC AGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCC TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAA TCACAAGCCCAGCAACACCAAGGTGGACGCGAGAGTTGAGCCCAAATCTTGTGACAAAACTCA CACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAA AACCCAAGGACACCCTCATGaTCTCCCgGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGC CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAG ACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGC ACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCC CCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGC CCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTA TCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCAC GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGC AGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 211).

[0234] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 566:

gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCtctggaATCGACCTCagtGGC
TACTACATGAACtgggtccgtcaggctccagggaaggggctggagtgggtcGGAGTCATTGGTATTAATGGTGCCACA
TACTACGCGAGCTGGGCGAAAGGCcgattcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctg
agagctgaggacactgctgtgtatTTCtgtGCTAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGCGCCTCC
ACCAAGGGCCCATCGGTCTTCCCCCTGGCAcCCTCCTCCaAGAGCACCTCTGGGGGCACAGCGGC
CCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAG
CCCAGCAACACCAAGGTGGACGCGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGC
CCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCA
AGGACACCCTCATGaTCTCCCgGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA
AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCG
AGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCAT
CCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAG
CGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCC
CGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGG
CAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGA
AGAGCCTCTCCCTGTCTCCGGGTTGA (SEQ ID NO: 567).

[0235] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221.

[0236] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218 which correspond to polynucleotides

encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566.

[0237] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 232 encoding the light chain variable sequence of SEQ ID NO: 222; the polynucleotide SEQ ID NO: 231 encoding the light chain sequence of SEQ ID NO: 221; the polynucleotide SEQ ID NO: 212 encoding the heavy chain variable sequence of SEQ ID NO: 202; the polynucleotide SEQ ID NO: 211 encoding the heavy chain sequence of SEQ ID NO: 201; the polynucleotide SEQ ID NO: 567 encoding the heavy chain sequence of SEQ ID NO: 566; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238) of the light chain variable sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218) of the heavy chain variable sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566.

[0238] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab6, the polynucleotides encoding the full length Ab6 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 231 encoding the light chain sequence of SEQ ID NO: 221 and the polynucleotide SEQ ID NO: 211 encoding the heavy chain sequence of SEQ ID NO: 201 or the polynucleotide SEQ ID NO: 567 encoding the heavy chain sequence of SEQ ID NO: 566.

[0239] 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*.

[0240] Host cells and vectors comprising said polynucleotides are also contemplated.

[0241] 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.*

[0242] Methods of Producing Antibodies and Fragments thereof

[0243] 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 polyploidal, 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.

[0244] 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).

[0245] 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); Verhoeyen, M, et al, *Science*, 239:1534-36 (1988), the disclosures of each of which are herein incorporated by reference in their entireties).

[0246] The present invention further includes the use of any of the pharmaceutical formulations disclosed herein in the manufacture of a medicament for the treatment, prevention and/or amelioration of most bothersome symptom associated with migraine.

[0247] Administration

[0248] In one embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject at a concentration of between about 0.1 and 100.0 mg/kg of body weight of recipient subject. In a preferred embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject at a concentration of about 0.4 mg/kg of body weight of recipient subject and/or at a dosage of 100 or 300 mg. In a preferred embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a recipient subject with a frequency of once every twenty-six weeks or six months or less, such as once every sixteen weeks or four months or less, once every eight weeks or two months or less, once every four weeks or monthly or less, once every two weeks or bimonthly or less, once every week or less, or once daily or less. In general the administration of sequential doses may vary by plus or minus a few days from the aforementioned schedule, *e.g.*, administration every 3 months or every 12 weeks includes administration of a dose varying from the schedule day by plus or minus 1, 2, 3, 4, 5, 5, or 7 days.

[0249] Fab fragments may be administered every two weeks or less, every week or less, once daily or less, multiple times per day, and/or every few hours. In one embodiment of the invention, a patient receives Fab fragments of 0.1 mg/kg to 40 mg/kg per day given in divided doses of 1 to 6 times a day, or in a sustained release form, effective to obtain desired results.

[0250] It is to be understood that the concentration of the antibody or Fab administered to a given patient may be greater or lower than the exemplary administration concentrations set forth above.

[0251] A person of skill in the art would be able to determine an effective dosage and frequency of administration through routine experimentation, for example guided by the disclosure herein and the teachings in Goodman, L. S., Gilman, A., Brunton, L. L., Lazo, J. S., & Parker, K. L. (2006). Goodman & Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill; Howland, R. D., Mycek, M. J., Harvey, R. A., Champe, P. C., & Mycek, M. J. (2006). Pharmacology. Lippincott's illustrated reviews. Philadelphia: Lippincott Williams & Wilkins; and Golan, D. E. (2008). Principles of pharmacology: the pathophysiologic basis of drug therapy. Philadelphia, Pa., [etc.]: Lippincott Williams & Wilkins.

[0252] In another embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject in a pharmaceutical formulation.

[0253] 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 buccal, epicutaneous, epidural, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal**,** intravenous, oral, parenteral, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal, preferably intravenous. In addition, administration can occur by means of injection, powder, liquid, gel, drops, or other means of administration.

[0254] 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.

[0255] 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.

[0256] 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.

[0257] 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.

[0258] An exemplary composition comprises, consists essentially of Ab6, an excipient such as histidine, an isotonic agent such as sorbitol, and a surfactant such as polysorbate 80 in an aqueous solution. For example, the composition may comprise, consist essentially of, or consist of histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg Ab6, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8, or approximately that constitution, *e.g.*, within 10% of those values, within 5% of those values, within 1% of those values, within 0.5% of those values, or within 0.1% of those values, and water. For example, the pH value may be within 10% of 5.8, *i.e.*, between 5.22 and 6.38. The Ab6 antibody may comprise or consist of the variable light and heavy chain polypeptides of SEQ ID NO: 222 and SEQ ID NO: 202 respectively, or the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 201 respectively, or the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 566 respectively. The composition may be in the form of an aqueous solution, or a concentrate (*e.g.*, lyophilized) which when reconstituted, *e.g.*, by addition of water, yields the aforementioned constitution. An exemplary composition consists of, per mL, 100 mg of the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 201 respectively, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, and water Q.S, or approximately that constitution, *e.g.*, within 10% of those quantities, within 5% of those quantities, within 1% of those quantities, within 0.5% of those quantities, or within 0.1% of those quantities. Another exemplary composition consists of, per mL, 100 mg of the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 566 respectively, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, and water Q.S, or approximately that constitution, *e.g.*, within 10% of those quantities, within 5% of those quantities, within 1% of those quantities, within 0.5% of those quantities, or within 0.1% of those quantities. The composition may be suitable for intravenous or subcutaneous administration, preferably intravenous administration. For example, the composition may be suitable for mixing with an intravenous solution (such as 0.9% sodium chloride) at an amount of between about 100 mg and about 300 mg antibody added to 100 mL of intravenous solution. Preferably the composition may be shelf-stable for at least 1, 3, 6,

12, 18, or 24 months, *e.g.*, showing formation of aggregates of no more than 5% or no more than 10% of the antibody or fragment after storage at room temperature or when refrigerated at 4°C for the specified duration, or in an accelerated aging test that simulates storage for that duration.

[0259] For each of the recited embodiments, the compounds can be administered by a variety of dosage forms. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, powders, granules, particles, microparticles, dispersible granules, cachets, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, injectables (including subcutaneous, intramuscular, intravenous, and intradermal, preferably intravenous), infusions, and combinations thereof.

[0260] 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.

[0261] 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.

[0262] 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.

[0263] Certain CGRP antibody polynucleotides and polypeptides are disclosed in the sequence listing accompanying this patent application filing, and the disclosure of said sequence listing is herein incorporated by reference in its entirety.

[0264] 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.

[0265] 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.

[0266] ADDITIONAL EXEMPLARY EMBODIMENTS

[0267] Additional exemplary embodiments of the invention are provided as follows:

[0268] S1. Use of an anti-CGRP antibody for the manufacturing of a medicament for treating most bothersome symptom (MBS) associated with migraine, comprising administering to a migraine patient an anti-CGRP antibody.

[0269] S2. Use of an anti-CGRP antibody for the manufacturing of a medicament for treating most bothersome symptom (MBS) associated with migraine, comprising administering to a migraine patient an anti-CGRP antibody, wherein said migraine patient suffers from chronic migraine.

[0270] S3. Use of an anti-CGRP antibody for the manufacturing of a medicament for treating most bothersome symptom (MBS) associated with migraine, comprising administering to a migraine patient an anti-CGRP antibody, wherein said patient suffers from episodic migraine.

[0271] S4. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved at 1-12 hours post-completion of administration or infusion, such as 1-5 hours post-completion of administration or infusion, 1-2 hours post-completion of administration or infusion, or about 2 hours post-completion of administration or infusion.

[0272] S5. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 1 month from the first dosing with said anti-CGRP antibody.

[0273] S6. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 3 month from the first dosing with said anti-CGRP antibody.

[0274] S7. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 6 month from the first dosing with said anti-CGRP antibody.

[0275] S8. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the improvement is sustained for at least 3 months from the first dosing with said anti-CGRP antibody.

[0276] S9. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the improvement is sustained for at least 6 months from the first dosing with said anti-CGRP antibody.

[0277] S10. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the MBS is selected from the group consisting of: Sensitivity to light (photophobia), Nausea/vomiting, Headache, Sensitivity to sound (phonophobia), Aura, Pain with activity, Pain, Throbbing/pulsation, Cognitive disruption, Fatigue, Mood changes, Sensitivity to smell (osmophobia or olfactophobia), Visual impact, Pressure/tightness, Pain (anatomical), Eye pain, Neck pain, Dizziness, Allodynia, Inactivity, Sensory disturbance, Sleep disturbance and Speech difficulty.

[0278] S11. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the MBS is selected from the group consisting of: Sensitivity to light (photophobia), Nausea/vomiting, Headache, Sensitivity to sound (phonophobia), Pain with activity, Pain, Throbbing/pulsation, Cognitive disruption, Fatigue, Mood changes and Sensitivity to smell (osmophobia or olfactophobia).

[0279] S12. Use of an anti-CGRP antibody for the manufacturing of a medicament for improving patient global impression of change (PGIC) associated with migraine, comprising administering to a migraine patient an anti-CGRP antibody.

[0280] S13. Use of an anti-CGRP antibody for the manufacturing of a medicament for improving patient global impression of change (PGIC) associated with migraine, comprising administering to a migraine patient an anti-CGRP antibody, wherein said migraine patient suffers from chronic migraine.

[0281] S14. Use of an anti-CGRP antibody for the manufacturing of a medicament for improving patient global impression of change (PGIC) associated with migraine, comprising administering to a migraine patient an anti-CGRP antibody, wherein said patient suffers from episodic migraine.

[0282] S15. Use of the anti-CGRP antibody of any one of embodiments S12-S14, wherein the administration of said medicament improves patient global impression of change (PGIC) associated with migraine within 1 month from the first dosing with said anti-CGRP antibody.

[0283] S16. Use of the anti-CGRP antibody of any one of embodiments S12-S14, wherein the administration of said medicament improves patient global impression of change (PGIC) associated with migraine within 3 month from the first dosing with said anti-CGRP antibody.

[0284] S17. Use of the anti-CGRP antibody of any one of embodiments S12-S14, wherein the administration of said medicament improves patient global impression of change (PGIC) associated with migraine within 6 month from the first dosing with said anti-CGRP antibody.

[0285] S18. Use of the anti-CGRP antibody of any one of embodiments S12-S17, wherein the administration of said medicament improves patient global impression of change (PGIC) associated with

migraine, and wherein the improvement is sustained for at least 3 months from the first dosing with said anti-CGRP antibody.

[0286] S19. Use of the anti-CGRP antibody of any one of embodiments S12-S18, wherein the administration of said medicament improves patient global impression of change (PGIC) associated with migraine, and wherein the improvement is sustained for at least 6 months from the first dosing with said anti-CGRP antibody.

[0287] S20. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is for intravenous or subcutaneous infusion.

[0288] S21. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is for intravenous infusion.

[0289] S22. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient is headache free 2 hours post-completion of administration or infusion.

[0290] S23. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises Ab6.

[0291] S24. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively.

[0292] S25. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively.

[0293] S26. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0294] S27. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0295] S28. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0296] S29. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0297] S30. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

[0298] S31. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

[0299] S32. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

[0300] S33. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0301] S34. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

[0302] S35. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0303] S36. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

[0304] S37. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

[0305] S38. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0306] S39. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0307] S40. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0308] S41. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0309] S42. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is between about 100 mg and about 300 mg, or is about 100 mg, or is about 300 mg.

[0310] S43. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is 100 mg.

[0311] S44. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is for intravenous administration in a dosage of 100 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

[0312] S45. Use of the anti-CGRP antibody of any one of embodiments S1-S42, wherein said medicament is for intravenous administration in a dosage of 300 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

[0313] S46. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits between 1-10 migraine attacks per month in the month or in the 3 months prior to administration.

[0314] S47. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits between 2-8 migraine attacks per month in the month or in the 3 months prior to administration.

[0315] S48. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits between 3-7 migraine attacks per month in the month or in the 3 months prior to administration.

[0316] S49. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits less than 25 headache days per month in the month or in the 3 months prior to administration.

[0317] S50. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits less than 20 headache days per month in the month or in the 3 months prior to administration.

[0318] S51. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits less than 15 headache days per month in the month or in the 3 months prior to administration.

[0319] S52. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits less than 10 headache days per month in the month or in the 3 months prior to administration.

[0320] S53. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 10 years prior to administration of said medicament.

[0321] S54. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 15 years prior to administration of said medicament.

[0322] S55. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to administration of said medicament.

[0323] S56. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient further has a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

[0324] S57. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient further has a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

[0325] S58. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient further has a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

[0326] S59. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient further has a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

[0327] S60. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient further has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

[0328] S61. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient further has a reduction in the number of migraine days by 100% in the 12 week period after being

administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

[0329] S62. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is further for administration in a second dose of said anti-CGRP antibody about 10-14 weeks, preferably 11-13 weeks, more preferably about 12 weeks or about 3 months after administration of said medicament.

[0330] S63. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament comprises about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

[0331] S64. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody is aglycosylated or if glycosylated only contains only mannose residues.

[0332] S65. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0333] S66. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0334]

[0335] S67. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said headache or said migraine is diagnosed according to the third edition of the International Classification of Headache Disorders.

[0336] S68. Use of the anti-CGRP antibody of any of any one of the foregoing embodiments, wherein said anti-CGRP antibody is expressed in or obtained by expression in Pichia pastoris.

[0337] S69. Use of the anti-CGRP antibody of any of any one of embodiments S1-S67, wherein said anti-CGRP antibody is expressed in or obtained by expression in CHO cells.

[0338] S70. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

[0339] S71. Use of the anti-CGRP antibody of embodiment S70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 10% of said values, and having a pH of 5.8 or within +/- 10% of said value.

[0340] S72. Use of the anti-CGRP antibody of embodiment S70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 5% of said values, and/or having a pH of 5.8 or within +/- 5% of said value.

[0341] S73. Use of the anti-CGRP antibody of embodiment S70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 1% of said values, and/or having a pH of 5.8 or within +/- 1% of said value.

[0342] S74. Use of the anti-CGRP antibody of embodiment S70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.5% of said values, and/or having a pH of 5.8 or within +/- 0.5% of said value.

[0343] S75. Use of the anti-CGRP antibody of embodiment S70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.1% of said values, and/or having a pH of 5.8 or within +/- 0.1% of said value.

[0344] S76. Use of the anti-CGRP antibody of any of any one of the foregoing embodiments, wherein the anti-CGRP antibody has a dissociation constant of less than or equal to 10 pM, such as 2-8 pM, such as 3-6 pM, such as less than or equal to about 5 pM.

[0345] FURTHER EXEMPLARY EMBODIMENTS

[0346] Further exemplary embodiments of the invention are provided as follows:

[0347] E1. An anti-CGRP antibody for use in treating most bothersome symptom (MBS) associated with migraine in a patient suffering from migraine.

[0348] E2. The anti-CGRP antibody for use of embodiment E1, wherein the patient suffers from chronic migraine.

[0349] E3. The anti-CGRP antibody for use of embodiment E1, wherein the patient suffers from episodic migraine.

[0350] E4. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved at 1-12 hours post-completion of administration or infusion, such as 1-5 hours post-completion of administration or infusion, 1-2 hours post-completion of administration or infusion, or about 2 hours post-completion of administration or infusion.

[0351] E5. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 1 month from the first dosing with said anti-CGRP antibody.

[0352] E6. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 3 month from the first dosing with said anti-CGRP antibody.

[0353] E7. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 6 month from the first dosing with said anti-CGRP antibody.

[0354] E8. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the improvement is sustained for at least 3 months from the first dosing with said anti-CGRP antibody.

[0355] E9. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the improvement is sustained for at least 6 months from the first dosing with said anti-CGRP antibody.

[0356] E10. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the MBS is selected from the group consisting of: Sensitivity to light (photophobia), Nausea/vomiting, Headache, Sensitivity to sound (phonophobia), Aura, Pain with activity, Pain, Throbbing/pulsation, Cognitive disruption, Fatigue, Mood changes, Sensitivity to smell (osmophobia or olfactophobia), Visual impact, Pressure/tightness, Pain (anatomical), Eye pain, Neck pain, Dizziness, Allodynia, Inactivity, Sensory disturbance, Sleep disturbance and Speech difficulty.

[0357] E11. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the MBS is selected from the group consisting of: Sensitivity to light (photophobia), Nausea/vomiting, Headache, Sensitivity to sound (phonophobia), Aura, Pain with activity, Pain, Throbbing/pulsation, Cognitive disruption, Fatigue, Mood changes and Sensitivity to smell (osmophobia or olfactophobia).

[0358] E12. An anti-CGRP antibody for use in improving patient global impression of change (PGIC) associated with migraine in a patient suffering from migraine.

[0359] E13. The anti-CGRP antibody for use of embodiment E12, wherein the patient suffers from chronic migraine.

[0360] E14. The anti-CGRP antibody for use of embodiment E12, wherein the patient suffers from episodic migraine.

[0361] E15. The anti-CGRP antibody for use according to any of embodiments E12-E14, wherein the improvement of patient global impression of change (PGIC) associated with migraine is observed within 1 month from the first dosing with said anti-CGRP antibody.

[0362] E16. The anti-CGRP antibody for use according to any of embodiments E12-E14, wherein the improvement of patient global impression of change (PGIC) associated with migraine is observed within 3 month from the first dosing with said anti-CGRP antibody.

[0363] E17. The anti-CGRP antibody for use according to any of embodiments E12-E14, wherein the improvement of patient global impression of change (PGIC) associated with migraine is observed within 6 month from the first dosing with said anti-CGRP antibody.

[0364] E18. The anti-CGRP antibody for use according to any of embodiments E12-E17, wherein the improvement of patient global impression of change (PGIC) associated with migraine is sustained for 3 months from the first dosing with said anti-CGRP antibody.

[0365] E19. The anti-CGRP antibody for use according to any of embodiments E12-E18, wherein the improvement of patient global impression of change (PGIC) associated with migraine is sustained for 6 months from the first dosing with said anti-CGRP antibody.

[0366] E20. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody is for intravenous or subcutaneous infusion.

[0367] E21. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody is for intravenous infusion.

[0368] E22. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient is headache free **2 hours** post-completion of administration or infusion.

[0369] E23. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises Ab6.

[0370] E24. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively.

[0371] E25. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively.

[0372] E26. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0373] E27. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0374] E28. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0375] E29. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0376] E30. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

[0377] E31. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

[0378] E32. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

[0379] E33. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0380] E34. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

[0381] E35. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0382] E36. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

[0383] E37. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

[0384] E38. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0385] E39. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0386] E40. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0387] E41. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0388] E42. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is between about 100 mg and about 300 mg, or is about 100 mg, or is about 300 mg.

[0389] E43. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is 100 mg.

[0390] E44. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody is for intravenous administration in a dosage of 100 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

[0391] E45. The anti-CGRP antibody for use of any one of embodiments E1-E42, wherein said anti-CGRP antibody is for intravenous administration in a dosage of administering 300 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

[0392] E46. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits between 1-10 migraine attacks per month in the month or in the 3 months prior to administration.

[0393] E47. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits between 2-8 migraine attacks per month in the month or in the 3 months prior to administration.

[0394] E48. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits between 3-7 migraine attacks per month in the month or in the 3 months prior to administration.

[0395] E49. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits less than 25 headache days per month in the month or in the 3 months prior to administration.

[0396] E50. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits less than 20 headache days per month in the month or in the 3 months prior to administration.

[0397] E51. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits less than 15 headache days per month in the month or in the 3 months prior to administration.

[0398] E52. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits less than 10 headache days per month in the month or in the 3 months prior to administration.

[0399] E53. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 10 years prior to the administration of said anti-CGRP antibody.

[0400] E54. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 15 years prior to the administration of said anti-CGRP antibody.

[0401] E55. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to the administration of said anti-CGRP antibody.

[0402] E56. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

[0403] E57. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

[0404] E58. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

[0405] E59. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 50% in the 12 week period after being

administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

[0406] E60. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

[0407] E61. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

[0408] E62. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said use comprises administering a second dose of said anti-CGRP antibody to said patient about 10-14 weeks, preferably 11-13 weeks, more preferably about 12 weeks or about 3 months after the administration of said anti-CGRP antibody.

[0409] E63. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said use comprises administering about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

[0410] E64. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody is aglycosylated or if glycosylated only contains only mannose residues.

[0411] E65. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0412] E66. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0413] E67. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said headache or said migraine is diagnosed according to the third edition of the International Classification of Headache Disorders.

[0414] E68. The anti-CGRP antibody for use of any of any one of the foregoing embodiments, wherein said anti-CGRP antibody is expressed in or obtained by expression in *Pichia pastoris*.

[0415] E69. The anti-CGRP antibody for use of any of any one of embodiments E1-E67, wherein said anti-CGRP antibody is expressed in or obtained by expression in CHO cells.

[0416] E70. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

[0417] E71. The anti-CGRP antibody for use of embodiment E70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 10% of said values, and having a pH of 5.8 or within +/- 10% of said value.

[0418] E72. The anti-CGRP antibody for use of embodiment E70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 5% of said values, and/or having a pH of 5.8 or within +/- 5% of said value.

[0419] E73. The anti-CGRP antibody for use of embodiment E70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 1% of said values, and/or having a pH of 5.8 or within +/- 1% of said value.

[0420] E74. The anti-CGRP antibody for use of embodiment E70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.5% of said values, and/or having a pH of 5.8 or within +/- 0.5% of said value.

[0421] E75. The anti-CGRP antibody for use of embodiment E70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.1% of said values, and/or having a pH of 5.8 or within +/- 0.1% of said value.

[0422] E76. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein the anti-CGRP antibody has a dissociation constant of less than or equal to 10 pM, such as 2-8 pM, such as 3-6 pM, such as less than or equal to about 5 pM.

EXAMPLES

[0423] 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.

[0424] EXAMPLE 1

[0425] Preparation of Antibodies that Bind CGRP

[0426] The preparation of exemplary anti-CGRP antibody Ab6 having the sequences in **FIGs. 1-12** is disclosed in commonly owned PCT Application WO/2012/162243, published on November 29, 2012, the contents of which are incorporated by reference herein. This application exemplifies synthesis of these antibodies in *Pichia pastoris* cells. The present Applicant further contemplates synthesis of anti-CGRP antibody Ab6 particularly in CHO cells.

[0427] EXAMPLE 2

[0428] Human Clinical Study Evaluating the Safety and Efficacy of an Anti-CGRP Antibody in Chronic Migraine Patients

[0429] This example describes a randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of Ab6 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. The study design is depicted in **FIG. 13**. 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. The primary endpoint of the present study was the change from baseline in mean monthly migraine days (MMDs) over weeks 1-12 following the first infusion of Ab6. The change from baseline in mean monthly migraine days (MMDs) following the second infusion at week 12 was also assessed and the results are shown in **FIG. 14.**

[0430] Study endpoints further included patient-identified MBS as part of the predefined key secondary endpoints. At screening, patients verbally identified the MBS associated with their migraine, which was pooled across treatment arms for this analysis. The change from baseline of these symptoms were than rated by the patient every month of the study beginning from Day 0.

[0431] In the present study, patients verbally identified the most bothersome symptom (MBS) associated with their migraine at screening. The MBS associated with their migraine was then categorized by the investigator into a predefined list of 8 symptoms or an “other” option. The predefined list included the terms nausea, vomiting, sensitivity to light, sensitivity to sound, mental cloudiness, fatigue, pain with activity, and mood changes. The “other” option provided investigators the opportunity to identify any migraine-associated symptom without limitation described by the patient as most bothersome but did not easily fit into the check list of symptoms included in the work study checklist. For those patients who selected the “other” category for their MBS, their “write-in” responses were re-coded post hoc and re-classified to the predefined list or to new symptom classes. At subsequent visits, patients were asked to rate the change from the screening visit in their self-reported MBS on a 7-point scale, which is shown below:

Very Much Improved	Much Improved	Minimally Improved	No Change	Minimally Worse	Much Worse	Very Much Worse

[0432] In addition to MBS, the patients were also requested to evaluate the efficacy of the treatment on patient global impression of change (PGIC), which is a parameter comprising a single question assessing the patient's own impression of the overall change in their disease status since the start of the study. This parameter was also rated by the patients at a 7-point scale identical to the one used to assess change in MBS as displayed above and at the same time points in the study. In **FIGs. 16-22** the "worse" category includes "minimally worse, "much worse", and "very much worse".

[0433] At the screening visit in, patients indicated a wide range of symptoms as their MBS, with the "other" category being the most frequent response (40%–42% across the 3 treatment groups). The patients who selected the "other" category generally provided more details and/or had more than 1 symptom as their MBS, allowing for these symptoms to be recoded. The overall list of MBS is summarized in **Table 1** below.

Table 1: Summary of patient-identified MBS in the present study as described in Example 2

Symptom, n (%)	Eptinezumab 100 mg (n=356)	Eptinezumab 300 mg (n=350)	Placebo (n=366)	Total (N=1072)
ICHD-3 Symptoms				
Sensitivity to light	67 (18.8)	64 (18.3)	69 (18.9)	200 (18.7)
Nausea/vomiting	55 (15.4)	46 (13.1	61 (16.7)	162 (15.1)
Headache	45 (12.6)	43 (12.3)	32 (8.7)	120 (11.2)
Sensitivity to sound	22 (6.2)	28 (8.0)	28 (7.7)	78 (7.3)
Aura	4 (1.1)	1 (<1)	2 (<1)	7 (0.7)
Additional Symptoms				
Pain with activity	53 (14.9)	45 (12.9)	49 (13.4)	147 (13.7)
Pain	35 (9.8)	45 (12.9)	53 (14.5)	133 (12.4)
Throbbing/pulsation	18 (5.1)	17 (4.9)	15 (4.1)	50 (4.7)
Cognitive disruption	17 (4.8)	14 (4.0)	13 (3.6)	44 (4.1)
Fatigue	7 (2.0)	11 (3.1)	8 (2.2)	26 (2.4)
Mood changes	8 (2.2)	4 (1.1)	4 (1.1)	16 (1.5)
Sensitivity to smell	1 (<1)	1 (<1)	8 (2.2)	10 (0.9)
Visual impact	2 (<1)	3 (<1)	3 (<1)	8 (0.7)
Pressure/tightness	2 (<1)	2 (<1)	3 (<1)	7 (0.7)
Pain, anatomical	3 (<1)	3 (<1)	0	6 (0.6)
Eye pain	4 (1.1)	1 (<1)	1 (<1)	6 (0.6)
Neck pain	1 (<1)	1 (<1)	3 (<1)	5 (0.5)
Dizziness	2 (<1)	2 (<1)	1 (<1)	5 (0.5)
Allodynia	1 (<1)	1 (<1)	1 (<1)	3 (0.3)
Inactivity	0	1 (<1)	1 (<1)	2 (0.2)
Sensory disturbance	1 (<1)	0	0	1 (0.1)
Sleep disturbance	0	0	1 (<1)	1 (0.1)
Speech difficulty	0	0	1 (<1)	1 (0.1)
Multiple*	7 (2.0)	12 (3.4)	8 (2.2)	27 (2.5)
Other	1 (<1)	5 (1.4)	1 (<1)	7 (0.7)

*Patient's most bothersome symptom included more than 1 symptom type.
ICHD-3 = International Classification of Headache Disorders 3rd edition.

[0434] The most commonly reported symptoms were light sensitivity, nausea/vomiting, pain with activity, pain, headache, sound sensitivity, throbbing/pulsation, cognitive disruption, fatigue, mood changes, and sensitivity to smell, with each category having at least 10 patients reporting these events as their MBS. At

the end of the 28-day screening period (i.e, before dosing at the baseline visit), patients were asked to rate the change in their identified MBS from very much worse to very much improved, with >90% reporting no change in their MBS, which is illustrated in **FIG 16**. This suggests that the bothersomeness of patient-identified MBS was quite stable among this cohort with chronic migraine during the screening period.

[0435] Infusion of Ab6 in doses of 100 mg and 300 mg provided significantly reduction in mean MMDs across months 1–3 of the study, with further reduction after an additional infusion at week 12 of the study. This effect is shown in **FIG. 14**.

[0436] The efficacy of Ab6 on the MBS was demonstrated at 1 month (**FIG. 17**), 3 months (**FIG. 19**), and 6 months (**FIG. 21**), following the first infusion of Ab6 in doses of 100 mg and 300 mg. The efficacy of Ab6 on the PGIC was demonstrated at 1 month (**FIG. 18**), 3 months (**FIG. 20**), and 6 months (**FIG. 22**), following the first infusion of Ab6 in doses of 100 mg and 300 mg. The efficacy on these parameters were sustained or increased through 2 doses of Ab6 over 6 months; at Month 1, 75-82% of Ab6-treated patients indicated some level of improvement compared to 56-59% for the placebo-treated patients; at Month 3 ratings of improvement were similar to those of month 1; at Month 6, ~80% of Ab6-treated patients indicated ≥1 categorical level of improvement in MBS and PGIC. The distribution of ratings for MBS improvement and PGIC were similar across time points, suggesting that the 2 identically rated measures in patients with chronic migraine move in parallel. These data suggest that improvements in patient-identified most bothersome migraine-associated symptoms are highly correlated with the patient's perception of an improved disease status in patients with chronic migraine.

[0437] The administered antibody, Ab6, is an anti-CGRP antibody consisting of the light chain polypeptide of SEQ ID NO: 221 and heavy chain polypeptide of SEQ ID NO: 201.

[0438] Patient characteristics are summarized in **Table 2** below, 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. In addition, patients with a dual diagnosis of chronic migraine and medications overuse excluding opioid and butalbital over were included in this study. 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.

Table 2: Summarizes the characteristics of patients in each treatment group in the clinical trial described in Example 2.

	Eptinezumab 100 mg n=356	Eptinezumab 300 mg n=350	Placebo n=366
Age (years), mean (SD)	41.0 (11.72)	41.0 (10.36)	39.6 (11.28)
Sex, n (%)			
Male	49 (13.8%)	36 (10.3%)	41 (11.2%)
Female	307 (86.2%)	314 (89.7%)	325 (88.8%)
Race, n (%)			
White	332 (93.3%)	322 (92.0%)	321 (87.7%)
Black or African American	21 (5.9%)	23 (6.6%)	38 (10.4%)
Other*	3 (0.8%)	5 (1.4%)	7 (1.9%)
BMI (kg/m^2), mean (SD)	26.4 (4.98)	26.3 (7.14)	27.0 (5.56)
Age at migraine diagnosis (years), mean (SD)	22.8 (10.64)	22.0 (9.30)	22.6 (9.98)
Duration of migraine diagnosis (years), mean (SD)	18.3 (12.22)	19.0 (11.50)	17.0 (11.63)
Duration of chronic migraines (years), mean (SD)	11.6 (11.72)	12.3 (11.15)	11.6 (10.90)
Number of migraine days, mean (SD)†	16.1 (4.61)	16.1 (4.77)	16.2 (4.55)
Medication-overuse headache diagnosis, n (%)§	139 (39.0%)	147 (42.0%)	145 (39.6%)

BMI, body mass index; SD, standard deviation. *Other includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiple races, and other. †As reported by the eDiary in the 28-day screening period. §Based on 3rd edition of the International Classification of Headache Disorders (beta).

CLAIMS

What is claimed is:

1. A method for improving most bothersome symptom (MBS) associated with migraine, comprising administering to a patient in need an effective amount of an anti-CGRP antibody.

2. The method of claim 1, wherein the patient suffers from chronic migraine.

3. The method of claim 1, wherein the patient suffers from episodic migraine.

4. The method of any of the foregoing claims, wherein the patients most bothersome symptom (MBS) associated with migraine is improved at 1-12 hours post-completion of administration or infusion, such as 1-5 hours post-completion of administration or infusion, 1-2 hours post-completion of administration or infusion, or about 2 hours post-completion of administration or infusion.

5. The method of any of the foregoing claims, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 1 month from the first dosing with said anti-CGRP antibody.

6. The method of any of the foregoing claims, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 3 months from the first dosing with said anti-CGRP antibody.

7. The method of any of the foregoing claims, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 6 months from the first dosing with said anti-CGRP antibody.

8. The method of any of the foregoing claims, wherein the improvement is sustained for at least 3 months from the first dosing with said anti-CGRP antibody.

9. The method of any of the foregoing claims, wherein the improvement is sustained for at least 6 months from the first dosing with said anti-CGRP antibody.

10. The method of any of the foregoing claims, wherein the MBS is selected from the group consisting of: Sensitivity to light (photophobia), Nausea/vomiting, Headache, Sensitivity to sound (phonophobia), Aura, Pain with activity, Pain, Throbbing/pulsation, Cognitive disruption, Fatigue, Mood changes, Sensitivity to smell (osmophobia or olfactophobia), Visual impact, Pressure/tightness, Pain

(anatomical), Eye pain, Neck pain, Dizziness, Allodynia, Inactivity, Sensory disturbance, Sleep disturbance and Speech difficulty.

11. The method of any of the foregoing claims, wherein the MBS is selected from the group consisting of: Sensitivity to light (photophobia), Nausea/vomiting, Headache, Sensitivity to sound (phonophobia), Aura, Pain with activity, Pain, Throbbing/pulsation, Cognitive disruption, Fatigue, Mood changes and Sensitivity to smell (osmophobia or olfactophobia).

12. A method of improving patient global impression of change (PGIC) associated with migraine, comprising administering to a patient in need an effective amount of an anti-CGRP antibody.

13. The method of claim 12, wherein the patient suffers from chronic migraine.

14. The method of claim 13, wherein the patient suffers from episodic migraine.

15. The method of any of claims 12-14, wherein the improvement of patient global impression of change (PGIC) associated with migraine is observed within 1 month from the first dosing with said anti-CGRP antibody.

16. The method of any of claims 12-14, wherein the improvement of patient global impression of change (PGIC) associated with migraine is observed within 3 months from the first dosing with said anti-CGRP antibody.

17. The method of any of claims 12-14, wherein the improvement of patient global impression of change (PGIC) associated with migraine is observed within 6 months from the first dosing with said anti-CGRP antibody.

18. The method of any of claims 12-17, wherein the improvement is sustained for at least 3 months from the first dosing with said anti-CGRP antibody.

19. The method of any of claims 12-18, wherein the improvement is sustained for at least 6 months from the first dosing with said anti-CGRP antibody.

20. The method of any one of the foregoing claims, wherein said administration is done by infusion, such as intravenous or subcutaneous infusion.

21. The method of any one of the foregoing claims, wherein said administration is done by intravenous infusion.

22. The method of any one of the foregoing claims, wherein said patient is headache free **2 hours** post-completion of administration or infusion.

23. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises Ab6.

24. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively.

25. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively.

26. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

27. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

28. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

29. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

30. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

31. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

32. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

33. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

34. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

35. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

36. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

37. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

38. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

39. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

40. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

41. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

42. The method of any one of the foregoing claims, wherein the administered amount of said anti-CGRP antibody is between about 100 mg and about 300 mg, or is about 100 mg, or is about 300 mg.

43. The method of any one of the foregoing claims, wherein the administered amount of said anti-CGRP antibody is 100 mg.

44. The method of any one of the foregoing claims, further comprising intravenously administering 100 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

45. The method of any one claims 1-42, wherein the administered amount of said anti-CGRP antibody is 100 mg.

46. The method of any one of claims 1-42 or 45, further comprising intravenously administering 300 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

47. The method of any of the foregoing claims wherein, prior to said administration, the patient exhibits between 1-10 migraine attacks per month in the month or in the 3 months prior to administration.

48. The method of any of the foregoing claims wherein, prior to said administration, the patient exhibits between 2-8 migraine attacks per month in the month or in the 3 months prior to administration.

49. The method of any of the foregoing claims wherein, prior to said administration, the patient exhibits between 3-7 migraine attacks per month in the month or in the 3 months prior to administration.

50. The method of any of the foregoing claims wherein, prior to said administration, the patient exhibits less than 25 headache days per month in the month or in the 3 months prior to administration.

51. The method of any of the foregoing claims wherein, prior to said administration, the patient exhibits less than 20 headache days per month in the month or in the 3 months prior to administration.

52. The method of any of the foregoing claims wherein, prior to said administration, the patient exhibits less than 15 headache days per month in the month or in the 3 months prior to administration.

53. The method of any of the foregoing claims wherein, prior to said administration, the patient exhibits less than 10 headache days per month in the month or in the 3 months prior to administration.

54. The method of any of the foregoing claims wherein said patient was diagnosed with migraine at least 10 years prior to said administration.

55. The method of any of the foregoing claims wherein said patient was diagnosed with migraine at least 15 years prior to said administration.

56. The method of any of the foregoing claims wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to said administration.

57. The method of any of the foregoing claims, wherein said patient has a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

58. The method of any of the foregoing claims, wherein said patient has a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

59. The method of any of the foregoing claims, wherein said patient has a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

60. The method of any of the foregoing claims, wherein said patient has a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

61. The method of any of the foregoing claims, wherein said patient has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

62. The method of any of the foregoing claims, wherein said patient has a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

63. The method of any one of the foregoing claims, further comprising administering a second dose of said anti-CGRP antibody to said patient about 10-14 weeks, preferably 11-13 weeks, more preferably about 12 weeks or about 3 months after said administration.

64. The method of any one of the foregoing claims, wherein said administration comprises administering about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

65. The method of any one of the foregoing claims, wherein said anti-CGRP antibody is aglycosylated or if glycosylated only contains only mannose residues.

66. The method of any one of the foregoing claims, wherein said anti-CGRP antibody consists of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

67. The method of any one of the foregoing claims, wherein said anti-CGRP antibody consists of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

68. The method of any one of the foregoing claims, wherein said headache or said migraine is diagnosed according to the third edition of the International Classification of Headache Disorders.

69. The method of any of any one of the foregoing claims, wherein said anti-CGRP antibody is expressed in or obtained by expression in *Pichia pastoris*.

70. The method of any of any one of claims 1-68, wherein said anti-CGRP antibody is expressed in or obtained by expression in CHO cells.

71. The method of any one of the foregoing claims, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

72. The method of claim 71, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 10% of said values, and having a pH of 5.8 or within +/- 10% of said value.

73. The method of claim 71, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 5% of said values, and/or having a pH of 5.8 or within +/- 5% of said value.

74. The method of claim 71, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 1% of said values, and/or having a pH of 5.8 or within +/- 1% of said value.

75. The method of claim 71, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.5% of said values, and/or having a pH of 5.8 or within +/- 0.5% of said value.

76. The method of claim 71, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.1% of said values, and/or having a pH of 5.8 or within +/- 0.1% of said value.

77. The method of any one of the foregoing claims, wherein said anti-CGRP antibody has a dissociation constant of less than or equal to 10 pM, such as 2-8 pM, such as 3-6 pM, such as less than or equal to about 5 pM, optionally when measured by surface plasmon resonance, which is optionally carried out at 25° C or 37° C.

78. The method of any one of the foregoing claims, which improves both MBS and PGIC in said patient.