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.

## 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 example of the present disclosure the patient suffers from chronic migraine. In the present disclosure, 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.

[0007a] In one aspect, the present disclosure refers to use of an effective amount of an anti-Calcitonin Gene Related Peptide (CGRP) IgG antibody in the manufacture of a medicament for improving a most bothersome symptom (MBS) associated with migraine in a migraine patient who has nausea or vomiting associated with migraine, wherein the CGRP IgG antibody comprises: (a) a heavy chain variable domain (VH) comprising the heavy chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively; and (b) a light chain variable domain (VL) comprising 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.

[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 disclosure, 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 disclosure 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 disclosure 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 disclosure 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 disclosure 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 disclosure 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 disclosure 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 disclosure 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 disclosure 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 example, the disclosure 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 example, the disclosure 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 example, the disclosure 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 example, the disclosure 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 examples the dosage of said anti-CGRP antibody may be 100 mg.

[0022] In other examples 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 disclosure.

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

[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 disclosure 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples 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 examples, 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 examples, about 100 mg of said anti-CGRP antibody or antibody fragment is administered.

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

[0068] In examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the anti-human CGRP antibody used in the afore-mentioned methods is administered systemically.

[0086] In other examples, 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 example, the anti-human CGRP antibody or antibody fragment used in the afore-mentioned methods is administered intravenously.

[0087] In other examples, 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 examples, the anti-human CGRP antibody has an *in vivo* half-life of at least 15 days.

[0089] In other examples, 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 examples, 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 examples, 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 examples, the anti-human CGRP antibody used in the afore-mentioned methods binds to human α- and β-CGRP.

[0093] In other examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 disclosure 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 example of the disclosure 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 example of the disclosure, 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 example of the disclosure, full length and Fab fragments thereof are contemplated that reduce vasodilation in a recipient following administration.

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

## CLAIMS

*What is claimed is*:

1. Use of an effective amount of an anti-Calcitonin Gene Related Peptide (CGRP) IgG antibody in the manufacture of a medicament for improving a most bothersome symptom (MBS) associated with migraine in a migraine patient who has nausea or vomiting associated with migraine, wherein the CGRP IgG antibody comprises:

(a) a heavy chain variable domain (VH) comprising the heavy chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively; and

(b) a light chain variable domain (VL) comprising 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.

2. The use of claim 1, wherein the anti-CGRP antibody is to be administered intravenously.

3. The use of claim 1, wherein the amount of said anti-CGRP antibody to be administered is between about 100 mg and about 300 mg, optionally 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.

4. The use of claim 1, wherein the anti-CGRP antibody is to be administered intravenously, further wherein the amount of said anti-CGRP antibody to be administered is between about 100 mg and about 300 mg, optionally 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.

5. The use of claim 1, wherein the VH comprises the polypeptide sequence of SEQ ID NO: 202 and/or the VL comprises the polypeptide sequence of SEQ ID NO: 222.

6. The use of claim 1, wherein the anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or 566 and the light chain polypeptide of SEQ ID NO: 221.

7. The use of claim 6, wherein the anti-CGRP antibody consists of the heavy and light chain polypeptides.

8. The use of claim 1, wherein the patients' nausea is improved within 3 months, optionally within 1 month, from administration of said anti-CGRP antibody.

9. The use of claim 1, wherein a second dose of the anti-CGRP antibody is to be administered to the patient about 10-14 weeks, optionally about 11-13 weeks, further optionally about 12 weeks or about 3 months, after administration of said anti-CGRP antibody.

10. The use of claim 1, wherein the anti-CGRP antibody is to be administered to the patient every 10-14 weeks, optionally every 11-13 weeks, further optionally every 12 weeks or every 3 months.