[0006] Migraine headache is commonly treated acutely, primarily with analgesics and a class of drugs called triptans (Humphrey *et al*. Ann NY Acad Sci., Vol. 600:587-598, 1990; Houston and Vanhoutte, Drugs, Vol. 31:149-163 1986). The triptans, which are selective serotonin 5-HT1B/1D agonists, are effective drugs for acute migraine and are generally well tolerated, but are contraindicated in the presence of cardiovascular disease due to their potential for coronary vasoconstriction. In addition, many migraine patients do not respond favorably to triptans. In a meta-analysis of 53 trials, up to a third of all people with migraine and 40% of all migraine attacks did not respond to triptans (Ferrari *et al*., Lancet, Vol. 358:1668-1675, 2001).

[0007] Migraine prophylaxis is an area of large unmet medical need. Approximately 40% of the migraine patient population would benefit from preventive therapy (Lipton *et al*., Neurology, Vol. 68:343-349, 2007). However, only approximately 12% of patients receive any preventive therapy due in part to limited efficacy and significant tolerability and safety issues with available preventive therapies. Topiramate, an anticonvulsant that blocks voltage-dependent sodium channels and certain glutamate receptors (AMPA-kainate), is the medication most often used for migraine prophylaxis in the United States. Topiramate is the only migraine prophylactic agent with demonstrated efficacy in both episodic and chronic migraine patients through randomized placebo-controlled trials (Diener *et al*., Cephalalgia, Vol. 27:814-823, 2007; Silberstein *et al*., Headache, Vol. 47:170-180, 2007). However, approximately 50% of patients fail to respond to topiramate and it is poorly tolerated. Common adverse events associated with topiramate treatment include paresthesia, anorexia, and cognitive adverse events, including psychomotor slowing, somnolence, language difficulties, and difficulties with memory and concentration (Brandes *et al*., JAMA, Vol. 291:965-973, 2004; Adelman *et al*., Pain Med., Vol. 9:175–185 2008; Silberstein *et al*., Arch Neurol., Vol. 61:490-495, 2004). In an open-label, flexible-dose study, 20% of patients withdrew from topiramate because of adverse effects (Nelles *et al*., Headache, Vol. 49:1454–1465, 2009).

[0008] Thus, migraine sufferers have an urgent medical need for more effective and/or tolerable treatment options.

SUMMARY

[0009] The present disclosure is based, in part, on the identification of a therapeutic regimen for effectively reducing the frequency, severity and/or duration of migraine headache in patients in

need thereof with no or minimal adverse side effects. In one aspect, the present disclosure refers to a pre-filled device for prophylactically treating migraine headache comprising a pharmaceutical composition comprising 70 mg or 140 mg of an anti-calcitonin gene-related peptide (CGRP) receptor monoclonal antibody, wherein the anti-CGRP receptor antibody comprises a CDRH1 having the sequence of SEQ ID NO:14, a CDRH2 having the sequence of SEQ ID NO:23, a CDRH3 having the sequence of SEQ ID NO:34, a CDRL1 having the sequence of SEQ ID NO:44, a CDRL2 having the sequence of SEQ ID NO:55, and a CDRL3 having the sequence of SEQ ID NO:65. Accordingly, in one example, the present disclosure provides a method for preventing or reducing the occurrence of migraine headache in a patient in need thereof comprising administering to the patient an anti-CGRP receptor antibody or antigen-binding fragment thereof at a dose of about 35 mg to about 210 mg per month. In some examples, the present disclosure provides a method for prophylactically treating a patient for migraine comprising administering to the patient an anti-CGRP receptor antibody or antigen-binding fragment thereof at a dose of about 35 mg to about 210 mg per month.

[0010] In some examples of the methods, the anti-CGRP receptor antibody or binding fragment thereof is administered to the patient at a dose sufficient to reduce the number of monthly migraine headache days experienced by the patient as compared to the number of monthly migraine headache days prior to treatment or the number of monthly migraine headache days experienced by a patient not receiving the anti-CGRP receptor antibody or binding fragment thereof. In some examples, the dose of anti-CGRP receptor antibody or binding fragment thereof administered to the patient is sufficient to reduce the number of monthly migraine headache days in the patient by at least 50% as compared to the number prior to treatment or the number experienced by a patient not receiving the anti-CGRP receptor antibody or binding fragment thereof.

[0011] In certain examples of the methods, the anti-CGRP receptor antibody or binding fragment thereof is administered to the patient at a dose sufficient to reduce the number of monthly migraine headache hours experienced by the patient as compared to the number of monthly migraine headache hours prior to treatment or the number of monthly migraine headache hours experienced by a patient not receiving the anti-CGRP receptor antibody or binding fragment thereof. In certain other examples of the methods, the anti-CGRP receptor antibody or binding fragment thereof is administered to the patient at a dose sufficient to reduce the number of

monthly migraine-specific medication use days experienced by the patient as compared to the number of monthly migraine-specific medication use days prior to treatment or the number of monthly migraine-specific medication use days experienced by a patient not receiving the anti-CGRP receptor antibody or binding fragment thereof.

[0012] In some examples of the methods, the anti-CGRP receptor antibody or binding fragment thereof is administered to the patient at a dose sufficient to reduce the number of days of physical impairment due to migraine headaches in the patients as compared to the number prior to treatment or to the number experienced by a patient not receiving the anti-CGRP receptor antibody or binding fragment thereof. In other examples, the anti-CGRP receptor antibody or binding fragment thereof is administered to the patient at a dose sufficient to reduce the impact of migraine headache on everyday activities as compared to the impact prior to treatment or to the impact experienced by a patient not receiving the anti-CGRP receptor antibody or binding fragment thereof. Physical impairment due to migraine headache and the impact of the migraine headache on everyday activities can be assessed using a number of validated questionnaires as described herein.

[0013] In certain examples of the methods, a dose sufficient to reduce the number of monthly migraine headache days, number of monthly migraine headache hours, number of monthly migraine-specific use days, physical impairment due to migraine, and/or impact of migraine on everyday activities in a patient in need thereof is about 35 mg to about 210 mg per month. In some examples, the sufficient dose is about 70 mg to about 140 mg per month. In one particular example, the sufficient dose is about 70 mg per month. In another particular example, the sufficient dose is about 140 mg per month. In these and other examples, the dose of anti-CGRP receptor antibody or binding fragment thereof is administered once a month (QM).

[0014] In some examples of the methods, administration of the anti-CGRP receptor antibody or binding fragment thereof at the dosages described herein does not substantially cause an adverse side effect in the patient. In particular, administration of the anti-CGRP receptor antibody or binding fragment thereof at the dosages described herein does not substantially cause an adverse side effect associated with other migraine prophylactic treatments, including adverse side effects associated with antiepileptics, beta-blockers, and anti-depressants. In certain examples, the number and type of adverse side effects associated with administration of the anti-CGRP

receptor antibody or binding fragment is not statistically different than the number and type of adverse side effects associated with administration of placebo.

[0015] In certain examples of the methods described herein, the anti-CGRP receptor antibody or binding fragment thereof is administered to the patient parenterally. In particular examples, the anti-CGRP receptor antibody or binding fragment thereof is administered to the patient by subcutaneous injection. In one example, the subcutaneous injection is a bolus injection administered to the patient once a month. The subcutaneous injection may be delivered to the patient with a pre-filled syringe or autoinjector containing a monthly dose of the anti-CGRP receptor antibody or binding fragment thereof.

[0016] In some examples, the patients to be administered the anti-CGRP receptor antibody or binding fragment thereof according to the methods of the disclosure have or have been diagnosed with episodic migraine. The episodic migraine may be low-frequency episodic migraine or high-frequency episodic migraine. In other examples, the patients to be administered the anti-CGRP receptor antibody or binding fragment thereof according to the methods of the disclosure have or have been diagnosed with chronic migraine.

[0017] In certain examples of the methods of the disclosure, the patients to be administered the anti-CGRP receptor antibody or binding fragment thereof have not previously received any prophylactic therapy for migraine headache (i.e. the patients are treatment-naïve). In other examples of the methods of the disclosure, the patients to be administered the anti-CGRP receptor antibody or binding fragment thereof have failed or are intolerant to at least one other migraine prophylactic therapy. Thus, the patients to be administered the anti-CGRP receptor antibody or binding fragment thereof have, in some examples, failed or are intolerant to at least one antiepileptic (e.g. topiramate, valproic acid), tricyclic antidepressant (e.g., amitriptyline), beta-blocker (e.g., propranolol, timolol), or botulinum toxin A. In one example, the patient has failed or is intolerant to two prior migraine prophylactic therapies. In another example, the patient has failed or is intolerant to three prior migraine prophylactic therapies.

[0018] In any examples of the methods disclosed herein, the anti-CGRP receptor antibody or antigen-binding fragment thereof specifically binds to an epitope formed from amino acids in both human CRLR and human RAMP1 polypeptide components of the human CGRP receptor and selectively inhibits the human CGRP receptor as compared to the human AM1, AM2, and/or amylin receptors. In some examples, the anti-CGRP receptor antibody or antigen-binding

fragment specifically binds to the human CGRP receptor with a $K_D \leq 100$ nM. In other examples, the anti-CGRP receptor antibody or antigen-binding fragment specifically binds to the human CGRP receptor with a $K_D \leq 10$ nM.

[0019] In one example, the anti-CGRP receptor antibody or antigen-binding fragment thereof administered to the patient according to the methods of the disclosure comprises a CDRH1 having the sequence of SEQ ID NO:14, a CDRH2 having the sequence of SEQ ID NO:23, a CDRH3 having the sequence of SEQ ID NO:34, a CDRL1 having the sequence of SEQ ID NO:44, a CDRL2 having the sequence of SEQ ID NO:55, and a CDRL3 having the sequence of SEQ ID NO:65. In another example, the anti-CGRP receptor antibody or antigen-binding fragment thereof administered to the patient according to the methods of the disclosure comprises a CDRH1 having the sequence of SEQ ID NO:15, a CDRH2 having the sequence of SEQ ID NO:29, a CDRH3 having the sequence of SEQ ID NO:35, a CDRL1 having the sequence of SEQ ID NO:45, a CDRL2 having the sequence of SEQ ID NO:61, and a CDRL3 having the sequence of SEQ ID NO:66.

[0020] The anti-CGRP receptor antibody or binding fragment thereof suitable for use in the methods of the disclosure can comprise a heavy chain variable region comprising the sequence of SEQ ID NO: 92 and a light chain variable region comprising the sequence of SEQ ID NO: 80. In some examples, the anti-CGRP receptor antibody or binding fragment thereof used in the methods of the disclosure comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 98 and a light chain variable region comprising the sequence of SEQ ID NO: 84. In certain examples, the anti-CGRP receptor antibody has a human IgG1 constant region or a human IgG2 constant region. In one example, the anti-CGRP receptor antibody comprises a heavy chain comprising the sequence of SEQ ID NO:105, and a light chain comprising the sequence of SEQ ID NO:123. In another example, the anti-CGRP receptor antibody comprises a heavy chain comprising the sequence of SEQ ID NO:111, and a light chain comprising the sequence of SEQ ID NO:127.

[0021] Any of the specific antibodies described in Table 7 herein or antigen-binding fragments thereof can be used in the methods of the disclosure. In certain examples, the anti-CGRP receptor antibody or binding fragment administered to a patient according to the methods of the disclosure is the 4E4 antibody or binding fragment thereof. In other examples, the anti-CGRP

receptor antibody or binding fragment administered to a patient according to the methods of the disclosure is the 9F5 antibody or binding fragment thereof.

[0022] The present disclosure also provides pharmaceutical compositions of anti-CGRP receptor antibodies or binding fragments thereof for use in the methods described herein. The pharmaceutical compositions can comprise one or more pharmaceutically acceptable diluents, carriers, or excipients, including buffers, surfactants, and stabilizing agents. In certain examples, the pharmaceutical compositions comprise an anti-CGRP receptor antibody or binding fragment thereof, a buffer, a surfactant, and a stabilizing agent. In one example, the pharmaceutical composition comprises an anti-CGRP receptor antibody or binding fragment thereof, an acetate buffer, polysorbate 20 or polysorbate 80, and sucrose. Any of the pharmaceutical compositions described herein can be incorporated into self-administration devices, such as pre-filled syringes or autoinjectors, for administration (e.g. subcutaneous administration) to a patient according to the methods described herein.

[0023] Thus, the present disclosure also includes a pre-filled syringe or autoinjector for use in prophylactically treating migraine headache in a patient in need thereof comprising a pharmaceutical composition comprising an anti-CGRP receptor antibody or binding fragment thereof, an acetate buffer, sucrose, and polysorbate. In some examples, the pre-filled syringe or autoinjector comprises a pharmaceutical composition comprising about 70 mg/ml to about 140 mg/ml of anti-CGRP receptor antibody or binding fragment thereof, about 10 mM to about 15 mM sodium acetate, about 0.008% to about 0.012% w/v polysorbate, and about 8% to about 9% w/v sucrose at a pH of about 4.8 to about 5.5. In certain examples, the injection volume of the pre-filled syringe or autoinjector is about 1 ml or less.

[0024] In some examples, the present disclosure also provides kits comprising a pharmaceutical composition or self-administration device disclosed herein and instructions for using the pharmaceutical composition or self-administration device for delivering a therapeutically effective dose, for example, by subcutaneous injection for prophylactically treating migraine headache in a patient in need thereof. In examples in which the pharmaceutical composition is provided in a lyophilized or dry powder form, the kit may comprise a diluent and instructions for reconstituting the pharmaceutical composition prior to administration.

[0025] The use of anti-CGRP receptor antibodies or binding fragments thereof in any of the methods disclosed herein or for preparation of medicaments for administration according to any

of the methods disclosed herein is specifically contemplated. For instance, the present disclosure includes an anti-CGRP receptor antibody or binding fragment thereof for use in a method for preventing or reducing the occurrence of migraine headache in a patient in need thereof, wherein the method comprises administering to the patient an anti-CGRP receptor antibody or binding fragment thereof at a dose of about 35 mg to about 210 mg per month. The present disclosure also includes an anti-CGRP receptor antibody or binding fragment thereof for use in a method for prophylactically treating a patient for migraine headache, wherein the method comprises administering to the patient an anti-CGRP receptor antibody or binding fragment thereof at a dose of about 35 mg to about 210 mg per month.

[0026] The present disclosure also includes the use of an anti-CGRP receptor antibody or binding fragment thereof in the preparation of a medicament for preventing or reducing the occurrence of migraine headache in a patient in need thereof, wherein the anti-CGRP receptor antibody or binding fragment is at a dose of about 35 mg to about 210 mg per month. The present disclosure further includes the use of an anti-CGRP receptor antibody or binding fragment thereof in the preparation of a medicament for prophylactically treating a patient for migraine headache, wherein the anti-CGRP receptor antibody or binding fragment is at a dose of about 35 mg to about 210 mg per month.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] **Figure 1** depicts the percentage inhibition of capsaicin-induced dermal blood flow (DBF) in healthy human subjects and migraine patients as a function of serum concentration of AMG 334 monoclonal antibody.

[0028] **Figure 2** shows the percentage inhibition of capsaicin-induced dermal blood flow (DBF) and serum concentration of AMG 334 monoclonal antibody over time following single dose and repeated dose (once every four weeks; Q4W) subcutaneous (SC) administration of AMG 334 to healthy human subjects and migraine patients. The duration of maximum DBF inhibition is consistent with the dose concentration-DBF relationship.

[0029] **Figure 3A** depicts the mean serum AMG 334 concentration – time profiles in healthy human subjects (HS) and migraine patients (MP) receiving single, escalating doses of AMG 334 or matching placebo either subcutaneously (SC) or intravenously (IV).

[0030] Figure 3B depicts the mean serum AMG 334 concentration – time profiles in healthy human subjects (HS) and migraine patients (MP) receiving multiple doses on days 1, 29, and 57 of AMG 334 or placebo subcutaneously (SC).

[0031] Figure 4A shows the percentage inhibition of capsaicin-induced dermal blood flow four days after subcutaneous (SC) administration of a single dose of AMG 334 or placebo in healthy subjects and migraine patients in the single, escalating dose study.

CLAIMS

What is claimed:

1. A pre-filled device for prophylactically treating migraine headache comprising a pharmaceutical composition comprising 70 mg or 140 mg of an anti-calcitonin gene-related peptide (CGRP) receptor monoclonal antibody, wherein the anti-CGRP receptor antibody comprises a CDRH1 having the sequence of SEQ ID NO:14, a CDRH2 having the sequence of SEQ ID NO:23, a CDRH3 having the sequence of SEQ ID NO:34, a CDRL1 having the sequence of SEQ ID NO:44, a CDRL2 having the sequence of SEQ ID NO:55, and a CDRL3 having the sequence of SEQ ID NO:65.

2. The pre-filled device of claim 1, wherein the device is a syringe.

3. The pre-filled device of claim 1, wherein the device is an autoinjector.

4. The pre-filled device of any one of claims 1 to 3, wherein the injection volume of the device is 1 ml.

5. The pre-filled device of any one of claims 1 to 4, wherein the pharmaceutical composition further comprises an acetate buffer, sucrose, and polysorbate.

6. The pre-filled device of claim 5, wherein the polysorbate is polysorbate 20 or polysorbate 80.

7. The pre-filled device of any one of claims 1 to 6, wherein the anti-CGRP receptor antibody comprises a heavy chain variable region (VH) comprising the sequence of SEQ ID NO:92, and a light chain variable region (VL) comprising the sequence of SEQ ID NO:80.

8. The pre-filled device of any one of claims 1 to 7, wherein the anti-CGRP receptor antibody comprises a heavy chain comprising the sequence of SEQ ID NO:105, and a light chain comprising the sequence of SEQ ID NO:123.

9. The pre-filled device of any one of claims 1 to 8, wherein the pharmaceutical composition comprises 70 mg of the anti-CGRP receptor monoclonal antibody.

10. The pre-filled device of any one of claims 1 to 8, wherein the pharmaceutical composition comprises 140 mg of the anti-CGRP receptor monoclonal antibody.