

CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 134, and 171, respectively; (d) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 92, 145, and 174, respectively; (e) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 108, and 172, respectively; (f) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 128, and 172, respectively; (g) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 134, and 171, respectively; (h) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 12, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 153, and 171, respectively; (i) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 12, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 154, and 171, respectively; or (j) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 13, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 155, and 171, respectively.

~~[0008b] In another aspect, the present disclosure refers to an isolated antibody or antigen-binding fragment thereof that specifically binds to human PAC1, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein CDRL1 comprises a sequence selected from SEQ ID NOs: 17-25; CDRL2 comprises a sequence selected from SEQ ID NOs: 27-35; CDRL3 comprises a sequence selected from SEQ ID NOs: 39-51; CDRH1 comprises a sequence selected from SEQ ID NOs: 97-105; CDRH2 comprises a sequence selected from SEQ ID NOs: 167-170; and CDRH3 comprises a sequence selected from SEQ ID NOs: 178-190.~~

[0008c] In another aspect, the present disclosure refers to an isolated antibody that specifically binds to human PAC1, wherein the antibody comprises a light chain and a heavy chain, wherein: (a) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises

the sequence of SEQ ID NO: 521; (b) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 522; (c) the light chain comprises the sequence of SEQ ID NO: 504 and the heavy chain comprises the sequence of SEQ ID NO: 523; (d) the light chain comprises the sequence of SEQ ID NO: 504 and the heavy chain comprises the sequence of SEQ ID NO: 524; (e) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 525; (f) the light chain comprises the sequence of SEQ ID NO: 504 and the heavy chain comprises the sequence of SEQ ID NO: 526; (g) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 523; (h) the light chain comprises the sequence of SEQ ID NO: 507 and the heavy chain comprises the sequence of SEQ ID NO: 527; (i) the light chain comprises the sequence of SEQ ID NO: 507 and the heavy chain comprises the sequence of SEQ ID NO: 528; (j) the light chain comprises the sequence of SEQ ID NO: 508 and the heavy chain comprises the sequence of SEQ ID NO: 529; ~~(k) the light chain comprises the sequence of SEQ ID NO: 510 and the heavy chain comprises the sequence of SEQ ID NO: 531; (l) the light chain comprises the sequence of SEQ ID NO: 511 and the heavy chain comprises the sequence of SEQ ID NO: 532; (m) the light chain comprises the sequence of SEQ ID NO: 512 and the heavy chain comprises the sequence of SEQ ID NO: 533; (n) the light chain comprises the sequence of SEQ ID NO: 513 and the heavy chain comprises the sequence of SEQ ID NO: 534; (o) the light chain comprises the sequence of SEQ ID NO: 514 and the heavy chain comprises the sequence of SEQ ID NO: 535; (p) the light chain comprises the sequence of SEQ ID NO: 515 and the heavy chain comprises the sequence of SEQ ID NO: 535; (q) the light chain comprises the sequence of SEQ ID NO: 516 and the heavy chain comprises the sequence of SEQ ID NO: 532; (r) the light chain comprises the sequence of SEQ ID NO: 517 and the heavy chain comprises the sequence of SEQ ID NO: 536; (s) the light chain comprises the sequence of SEQ ID NO: 509 and the heavy chain comprises the sequence of SEQ ID NO: 532; or (t) the light chain comprises the sequence of SEQ ID NO: 518 and the heavy chain comprises the sequence of SEQ ID NO: 530.~~

[0008d] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof as described herein and a pharmaceutically acceptable excipient.

[0008e] In another aspect, the present disclosure refers to an isolated polynucleotide that encodes the isolated antibody or antigen-binding fragment thereof as described herein.

CLAIMS

1. An isolated antibody or antigen-binding fragment thereof that specifically binds to human pituitary adenylate cyclase-activating polypeptide type I receptor (PAC1), wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein:

(a) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 108, and 171, respectively;

(b) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 116, and 171, respectively;

(c) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 134, and 171, respectively;

(d) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 92, 145, and 174, respectively;

(e) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 108, and 172, respectively;

(f) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 128, and 172, respectively;

(g) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 134, and 171, respectively;

(h) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 12, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 153, and 171, respectively;

(i) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 12, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 154, and 171, respectively; or

(j) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 13, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 155, and 171, respectively.

2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the light chain variable region comprises (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 54-66, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 54-66, or (iii) a sequence selected from SEQ ID NOs: 54-66.

3. The isolated antibody or antigen-binding fragment thereof of claim 1 or 2, wherein the heavy chain variable region comprises (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 191-295, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 191-295, or (iii) a sequence selected from SEQ ID NOs: 191-295.

4. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 3, wherein:

(a) the light chain variable region comprises the sequence of SEQ ID NO: 54 and the heavy chain variable region comprises the sequence of SEQ ID NO: 194;

(b) the light chain variable region comprises the sequence of SEQ ID NO: 54 and the heavy chain variable region comprises the sequence of SEQ ID NO: 203;

(c) the light chain variable region comprises the sequence of SEQ ID NO: 55 and the heavy chain variable region comprises the sequence of SEQ ID NO: 228;

(d) the light chain variable region comprises the sequence of SEQ ID NO: 55 and the heavy chain variable region comprises the sequence of SEQ ID NO: 274;

(e) the light chain variable region comprises the sequence of SEQ ID NO: 54 and the heavy chain variable region comprises the sequence of SEQ ID NO: 214;

(f) the light chain variable region comprises the sequence of SEQ ID NO: 55 and the heavy chain variable region comprises the sequence of SEQ ID NO: 240;

(g) the light chain variable region comprises the sequence of SEQ ID NO: 54 and the heavy chain variable region comprises the sequence of SEQ ID NO: 228;

(h) the light chain variable region comprises the sequence of SEQ ID NO: 62 and the heavy chain variable region comprises the sequence of SEQ ID NO: 282;

(i) the light chain variable region comprises the sequence of SEQ ID NO: 62 and the heavy chain variable region comprises the sequence of SEQ ID NO: 283; or

(j) the light chain variable region comprises the sequence of SEQ ID NO: 63 and the heavy chain variable region comprises the sequence of SEQ ID NO: 284.

~~5. An isolated antibody or antigen binding fragment thereof that specifically binds to human PAC1, wherein the antibody or antigen binding fragment thereof comprises a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein CDRL1 comprises a sequence selected from SEQ ID NOs: 17-25; CDRL2 comprises a sequence selected from SEQ ID NOs: 27-35; CDRL3 comprises a sequence selected from SEQ ID NOs: 39-51; CDRH1 comprises a sequence selected from SEQ ID NOs: 97-105; CDRH2 comprises a sequence selected from SEQ ID NOs: 167-170; and CDRH3 comprises a sequence selected from SEQ ID NOs: 178-190.~~

~~6. The isolated antibody or antigen binding fragment thereof of claim 5, wherein:~~

~~(a) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 25, 31, and 42, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 98, 168, and 190, respectively;~~

~~(b) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 20, 30, and 44, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 100, 168, and 182, respectively;~~

~~(c) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 17, 33, and 42, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 99, 168, and 187, respectively;~~

~~(d) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 23, 31, and 50, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 97, 167, and 178, respectively;~~

~~(e) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 17, 31, and 44, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 98, 168, and 189, respectively;~~

~~(f) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 17, 27, and 39, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 100, 168, and 182, respectively;~~

~~(g) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 18, 31, and 46, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 98, 168, and 179, respectively;~~

~~(h) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 17, 28, and 40, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 98, 168, and 179, respectively;~~

~~(i) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 18, 30, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 100, 168, and 182, respectively; or~~

~~(j) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 22, 28, and 49, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 102, 169, and 182, respectively.~~

~~7. The isolated antibody or antigen-binding fragment thereof of claim 5 or 6, wherein the light chain variable region comprises (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 68-87, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 68-87, or (iii) a sequence selected from SEQ ID NOs: 68-87.~~

~~8. The isolated antibody or antigen-binding fragment thereof of any one of claims 5 to 7, wherein the heavy chain variable region comprises (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 296-312, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 296-312, or (iii) a sequence selected from SEQ ID NOs: 296-312.~~

~~9. The isolated antibody or antigen-binding fragment thereof of any one of claims 5 to 8, wherein:~~

~~—— (a) the light chain variable region comprises the sequence of SEQ ID NO: 85 and the heavy chain variable region comprises the sequence of SEQ ID NO: 312;~~

~~—— (b) the light chain variable region comprises the sequence of SEQ ID NO: 72 and the heavy chain variable region comprises the sequence of SEQ ID NO: 300;~~

~~—— (c) the light chain variable region comprises the sequence of SEQ ID NO: 81 and the heavy chain variable region comprises the sequence of SEQ ID NO: 307;~~

~~—— (d) the light chain variable region comprises the sequence of SEQ ID NO: 78 and the heavy chain variable region comprises the sequence of SEQ ID NO: 296;~~

~~—— (e) the light chain variable region comprises the sequence of SEQ ID NO: 83 and the heavy chain variable region comprises the sequence of SEQ ID NO: 310;~~

~~—— (f) the light chain variable region comprises the sequence of SEQ ID NO: 87 and the heavy chain variable region comprises the sequence of SEQ ID NO: 300;~~

~~—— (g) the light chain variable region comprises the sequence of SEQ ID NO: 74 and the heavy chain variable region comprises the sequence of SEQ ID NO: 297;~~

~~—— (h) the light chain variable region comprises the sequence of SEQ ID NO: 68 and the heavy chain variable region comprises the sequence of SEQ ID NO: 297;~~

~~(i) the light chain variable region comprises the sequence of SEQ ID NO: 71 and the heavy chain variable region comprises the sequence of SEQ ID NO: 300; or~~

~~(j) the light chain variable region comprises the sequence of SEQ ID NO: 77 and the heavy chain variable region comprises the sequence of SEQ ID NO: 304.~~

~~105.~~ The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to ~~94~~, wherein the antibody or antigen-binding fragment thereof is a monoclonal antibody or antigen-binding fragment thereof.

~~116.~~ The isolated antibody or antigen-binding fragment thereof of claim ~~105~~, wherein the monoclonal antibody or antigen-binding fragment thereof is a humanized antibody or antigen-binding fragment thereof or a fully human antibody or antigen-binding fragment thereof.

~~127.~~ The isolated antibody or antigen-binding fragment thereof of claim ~~105~~ or ~~116~~, wherein the monoclonal antibody comprises a light chain that comprises a human kappa constant region.

~~138.~~ The isolated antibody or antigen-binding fragment thereof of claim ~~127~~, wherein the human kappa constant region comprises the sequence of SEQ ID NO: 318 or SEQ ID NO: 319.

~~149.~~ The isolated antibody or antigen-binding fragment thereof of claim ~~105~~ or ~~116~~, wherein the monoclonal antibody comprises a light chain that comprises a human lambda constant region.

~~1510.~~ The isolated antibody or antigen-binding fragment thereof of claim ~~149~~, wherein the human lambda constant region comprises the sequence of SEQ ID NO: 315.

~~1611.~~ The isolated antibody or antigen-binding fragment thereof of any one of claims ~~105~~ to ~~1510~~, wherein the monoclonal antibody is a human IgG1, IgG2, IgG3, or IgG4 antibody.

~~17~~12. The isolated antibody or antigen-binding fragment thereof of claim ~~16~~11, wherein the monoclonal antibody is a human IgG1 antibody.

~~18~~13. The isolated antibody or antigen-binding fragment thereof of claim ~~17~~12, wherein the monoclonal antibody is an aglycosylated human IgG1 antibody.

~~19~~14. The isolated antibody or antigen-binding fragment thereof of claim ~~18~~13, wherein the monoclonal antibody comprises a mutation at amino acid position N297 according to EU numbering in its heavy chain.

~~20~~15. The isolated antibody or antigen-binding fragment thereof of claim ~~19~~14, wherein the mutation is N297G.

~~21~~16. The isolated antibody or antigen-binding fragment thereof of claim ~~19-14~~ or ~~20~~15, wherein the monoclonal antibody further comprises R292C and V302C mutations according to EU numbering in its heavy chain.

~~22~~17. The isolated antibody or antigen-binding fragment thereof of claim ~~18~~13, wherein the monoclonal antibody comprises a heavy chain constant region that comprises the sequence of SEQ ID NO: 324 or SEQ ID NO: 325.

~~23~~18. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to ~~22~~17, wherein the antibody or antigen-binding fragment thereof inhibits PACAP-induced activation of rat PAC1 with an IC50 less than 10 nM as measured by a cell-based cAMP assay.

~~24~~19. An isolated antibody that specifically binds to human PAC1, wherein the antibody comprises a light chain and a heavy chain, wherein:

(a) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 521;

(b) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 522;

(c) the light chain comprises the sequence of SEQ ID NO: 504 and the heavy chain comprises the sequence of SEQ ID NO: 523;

(d) the light chain comprises the sequence of SEQ ID NO: 504 and the heavy chain comprises the sequence of SEQ ID NO: 524;

(e) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 525;

(f) the light chain comprises the sequence of SEQ ID NO: 504 and the heavy chain comprises the sequence of SEQ ID NO: 526;

(g) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 523;

(h) the light chain comprises the sequence of SEQ ID NO: 507 and the heavy chain comprises the sequence of SEQ ID NO: 527;

(i) the light chain comprises the sequence of SEQ ID NO: 507 and the heavy chain comprises the sequence of SEQ ID NO: 528; or

(j) the light chain comprises the sequence of SEQ ID NO: 508 and the heavy chain comprises the sequence of SEQ ID NO: 529;

~~(k) the light chain comprises the sequence of SEQ ID NO: 510 and the heavy chain comprises the sequence of SEQ ID NO: 531;~~

~~(l) the light chain comprises the sequence of SEQ ID NO: 511 and the heavy chain comprises the sequence of SEQ ID NO: 532;~~

~~(m) the light chain comprises the sequence of SEQ ID NO: 512 and the heavy chain comprises the sequence of SEQ ID NO: 533;~~

~~(n) the light chain comprises the sequence of SEQ ID NO: 513 and the heavy chain comprises the sequence of SEQ ID NO: 534;~~

~~(o) the light chain comprises the sequence of SEQ ID NO: 514 and the heavy chain comprises the sequence of SEQ ID NO: 535;~~

~~(p) the light chain comprises the sequence of SEQ ID NO: 515 and the heavy chain comprises the sequence of SEQ ID NO: 535;~~

~~(q) the light chain comprises the sequence of SEQ ID NO: 516 and the heavy chain comprises the sequence of SEQ ID NO: 532;~~

~~(r) the light chain comprises the sequence of SEQ ID NO: 517 and the heavy chain comprises the sequence of SEQ ID NO: 536;~~

~~(s) the light chain comprises the sequence of SEQ ID NO: 509 and the heavy chain comprises the sequence of SEQ ID NO: 532; or~~

~~(t) the light chain comprises the sequence of SEQ ID NO: 518 and the heavy chain comprises the sequence of SEQ ID NO: 530.~~

2520. A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 2419 and a pharmaceutically acceptable excipient.

2621. An isolated polynucleotide that encodes the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 2419.

2722. An expression vector comprising the polynucleotide of claim 2621.

2823. A host cell comprising the expression vector of claim 2722.

2924. A method of producing an antibody or antigen-binding fragment thereof that specifically binds to human PAC1 comprising culturing the host cell of claim 2823 under conditions that allow expression of the antibody or antigen-binding fragment thereof; and recovering the antibody or antigen-binding fragment thereof from the culture medium or host cell.

3025. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 2419 for the preparation of a medicament for treating or preventing a headache condition in a patient in need thereof.

~~31~~26. The use of claim ~~30~~25, wherein the headache condition is migraine.

~~32~~27. The use of claim ~~31~~26, wherein the migraine is episodic migraine.

~~33~~28. The use of claim ~~31~~26, wherein the migraine is chronic migraine.

~~34~~29. The use of claim ~~30~~25, wherein the headache condition is cluster headache.

~~35~~30. The use of any one of claims ~~30~~25 to ~~34~~29, wherein the treatment is a prophylactic treatment.

~~36~~31. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to ~~24~~19 for the preparation of a medicament for use in combination therapy for treating or preventing a headache condition in a patient in need thereof, wherein said medicament is to be administered to the patient in combination with a second headache therapeutic agent.

~~37~~32. The use of claim ~~36~~31, wherein the headache condition is as defined in any one of claims ~~31~~26 to ~~34~~29.

~~38~~33. The use of claim ~~36~~31 or ~~37~~32, wherein the second headache therapeutic agent is an acute headache therapeutic agent.

~~39~~34. The use of claim ~~38~~33, wherein the acute headache therapeutic agent is a 5HT1B, 5HT1D and/or 5HT1F serotonin receptor agonist.

~~40~~35. The use of claim ~~39~~34, wherein the serotonin receptor agonist is a triptan or ergotamine.

4136. The use of claim ~~3833~~, wherein the acute headache therapeutic agent is a non-steroidal anti-inflammatory drug or an opioid.

4237. The use of claim ~~3631~~ or ~~3732~~, wherein the second headache therapeutic agent is a prophylactic headache therapeutic agent.

4338. The use of claim 4237, wherein the prophylactic headache therapeutic agent is an antiepileptic, a beta-blocker, an anti-depressant, onabotulinum toxin A, or a CGRP pathway antagonist.

4439. The use of claim 4338, wherein the CGRP pathway antagonist is a human CGRP receptor antagonist.

4540. The use of claim 4439, wherein the human CGRP receptor antagonist is a monoclonal antibody that specifically binds to the human CGRP receptor.

4641. The use of claim 4540, wherein the anti-CGRP receptor monoclonal antibody is erenumab.