Current standard of care for OA pain consists of non-steroidal anti-inflammatory drugs (NSAIDs) and selective Cox-2 inhibitors. Over time, many patients will become insensitive to these treatments or are not able to tolerate the high doses needed for effective pain relief. Follow-up treatments consist of intra-articular injections (hyaluronan) or opiates. The final treatment is surgical total joint replacement. Many of these treatments have negative side effects, ranging from gastro-intestinal (NSAIDs) to cardiovascular (Cox-2 inhibitors), are cumbersome and/or not very efficacious (intra-articular injections), carry the risk for abuse (opiates), or are restricted to only 1 joint (intra-articular injections, surgery).

Although CGRP antibodies for treating migraines and for treating inflammation pain have been disclosed (migraines-WO 2007/076336 and WO 2007/054809; OA-see, Antibody G1 of WO2009/109908A1), there is still a need for alternatives. Preferably, the treatment alternative is safe and efficacious. More preferably, the alternative treatment for OAwill provide long-lasting pain relief across multiple joints that is tolerable to patients without the risk for dependence and/or abuse.

The present ~~invention~~disclosure provides a human engineered CGRP antibody comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR comprises LCDR1, LCDR2, and LCDR3 amino acid sequences and HCVR comprises HCDR1, HCDR2, and HCDR3 amino acid sequences which are selected from the group consisting of:

a) LCDR1 is RASQDIDNYLN (SEQ ID NO: 3), LCDR2 is YTSEYHS (SEQ ID NO: 4), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGDTRYIQKFAG (SEQ ID NO: 13), and HCDR3 is LSDYVSGFSY (SEQ ID NO: 14);

b) LCDR1 is RASQDIDNYLN (SEQ ID NO: 3), LCDR2 is YTSEYHS (SEQ ID NO: 4), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGKTVYIQKFAG (SEQ ID NO: 15), and HCDR3 is LSDYVSGFSY (SEQ ID NO: 14);

c) LCDR1 is RASKDISKYLN (SEQ ID NO: 6), LCDR2 is YTSGYHS (SEQ ID NO: 7), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGKTVYIQKFAD (SEQ ID NO: 16), and HCDR3 is LSDYVSGFGY (SEQ ID NO: 39);

d) LCDR1 is RASRPIDKYLN (SEQ ID NO: 8), LCDR2 is YTSEYHS (SEQ ID NO: 4), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGKTVYIQKFAG (SEQ ID NO: 15), and HCDR3 is LSDYVSGFGY (SEQ ID NO: 39); and

e) LCDR1 is RASQDIDKYLN (SEQ ID NO: 9), LCDR2 is YTSGYHS (SEQ ID NO: 7), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGKTVYIQKFAG (SEQ ID NO: 15), and HCDR3 is LSDYVSGFGY (SEQ ID NO: 39),

wherein the human engineered CGRP antibody binds to human CGRP.

In one aspect, there is provided a human engineered CGRP antibody comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR comprises LCDR1, LCDR2, LCDR3 amino acid sequences and HCVR comprises HCDR1, HCDR2, HCDR3 amino acid sequences, wherein LCDR1 is SEQ ID NO: 10, LCDR2 is SEQ ID NO: 11, LCDR3 is SEQ ID NO: 5 HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 37and HCDR3 is SEQ ID NO: 38, wherein the human CGRP antibody binds to human CGRP.

The present ~~invention~~disclosure provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 3, LCDR2 is SEQ ID NO: 4, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 13, and HCDR3 is SEQ ID NO: 14, wherein the human engineered CGRP antibody binds to human CGRP. The present ~~invention~~disclosure provides a human engineered CGRP antibody or antigen-binding fragment thereof comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 3, LCDR2 is SEQ ID NO: 4, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 15, and HCDR3 is SEQ ID NO: 14,

wherein the human engineered CGRP antibody binds to human CGRP. The present ~~invention~~disclosure provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 6, LCDR2 is SEQ ID NO: 7, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 16, and HCDR3 is SEQ ID NO: 39, wherein the human engineered CGRP antibody binds to human CGRP. The present ~~invention~~disclosure provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 8, LCDR2 is SEQ ID NO: 4, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 15, and HCDR3 is SEQ ID NO: 39,

wherein the human engineered CGRP antibody binds to human CGRP. The present ~~invention~~disclosure provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 9, LCDR2 is SEQ ID NO: 7, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 15, and HCDR3 is SEQ ID NO: 39, wherein the human engineered CGRP antibody binds to human CGRP.

The present ~~invention~~disclosure provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is $RASX_1X_2IX_3X_4YLN$ (SEQ ID NO: 10), LCDR2 is $YTSX_5YHS$ (SEQ ID NO: 11), LCDR3 is QQGDALPPT(SEQ ID NO: 5) and HCDR1 is GYTFGNYWMQ (SEQ ID NO:12), HCDR2 is $AIYEGTGX_6TX_7YIQKFAX_8$ (SEQ ID NO: 37), and HCDR3 is $LSDYVSGFX_9Y$ (SEQ ID NO: 38), wherein X_1 is Q, R, or K; X_2 is D or P, X_3 is D or S, X_4 is N or K, X_5 is G or E, X_6 is K or D, X_7 is V or R, X_8 is D or G, and X_9 is G or S, wherein the antibody binds to human CGRP.

In another embodiment, the present ~~invention~~disclosure provides a human engineered CGRP antibody comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises

$DIQMTQSPSSLSASVGDRVTITCRASX_1X_2IX_3X_4YLNWYQQKPGKAPKLLIYYTSX_5$ $YHSGVPSRFSGSGSGTDFTX_6TISSLQPEDX_7ATYYCQQGDALPPTFGX_8GTKX_9EIK$ wherein X_1 is Q, K, or R; X_2 is D or P; X_3 is D or S; X_4 is K or N; X_5 is E or G; X_6 is F or L; X_7 is I or F; X_8 is Q or G; and X_9 is L or V. (SEQ ID NO: 42)

and the HCVR comprises

$QVQLVQSGAEVKKPGX_1SVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI$ $YEGTGX_2TX_3YIQKFAX_4RVTX_5TX_6DX_7STSTX_8YMELSSLRSEDTAVYYCARLSDY$ $VSGFX_9YWGQGTX_{10}VTVSS$, wherein X_1= A or S; X_2= K or D; X_3=V or R; X_4= G or D; X_5= M or I; X_6=R or A; X_7=T or K; X_8=V or A; X_9=G or S; and X_{10}=L or T. (SEQ ID NO: 43), wherein the antibody binds to human CGRP.

In another embodiment, the present ~~invention~~disclosure provides a human engineered CGRP antibody comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR and HCVR are amino acid sequences selected from the group consisting of:

a. LCVR is SEQ ID NO: 17 and HCVR is SEQ ID NO: 22;
b. LCVR is SEQ ID NO: 18 and HCVR is SEQ ID NO: 23;
c. LCVR is SEQ ID NO: 19 and HCVR is SEQ ID NO: 24;
d. LCVR is SEQ ID NO: 20 and HCVR is SEQ ID NO: 25; and
e. LCVR is SEQ ID NO: 21 and HCVR is SEQ ID NO: 26.

The present ~~invention~~disclosure provides a human engineered CGRP antibody comprising a LCVR of SEQ ID NO: 17 and an HCVR of SEQ ID NO: 22. In a preferred embodiment, the present ~~invention~~disclosure provides a human engineered CGRP antibody comprising a LCVR of SEQ ID NO: 18 and an HCVR of SEQ ID NO: 23. The present ~~invention~~disclosure provides a human engineered CGRP antibody comprising a LCVR of SEQ ID NO: 19 and an HCVR of SEQ ID NO: 24. The present ~~invention~~disclosure provides a human engineered CGRP antibody comprising a LCVR of SEQ ID NO: 20 and an HCVR of SEQ ID NO: 25. The present ~~invention~~disclosure provides a human engineered CGRP antibody comprising a LCVR of SEQ ID NO: 21 and an HCVR of SEQ ID NO: 26.

The present ~~invention~~disclosure also provides a human engineered CGRP antibody comprising a light chain (LC) and a heavy chain (HC), wherein the LC and HC amino acid sequences are selected from the group consisting of:

a) LC is SEQ ID NO: 27 and HC is SEQ ID NO: 32;
b) LC is SEQ ID NO: 28 and HC is SEQ ID NO: 33;
c) LC is SEQ ID NO: 29 and HC is SEQ ID NO: 34;
d) LC is SEQ ID NO: 30 and HC is SEQ ID NO: 35; and
e) LC is SEQ OD NO: 31 and HC is SEQ ID NO: 36.

In an embodiment, the human engineered CGRP antibody comprises an LC of SEQ ID NO: 27 and a HC of SEQ ID NO: 32. In another embodiment, the human engineered CGRP antibody comprises an LC of SEQ ID NO: 28 and an HC of SEQ ID NO: 33. In another embodiment, the human engineered CGRP antibody comprises an LC of SEQ ID NO: 29 and an HC of SEQ ID NO: 34. In another embodiment, the human engineered CGRP antibody comprises an LC of SEQ ID NO: 30 and an HC of SEQ ID NO: 35. In another embodiment, the human engineered CGRP antibody comprises an LC

of SEQ ID NO: 31 and an HC of SEQ ID NO: 36. In an embodiment, the human engineered CGRP antibody comprises two light chains and two heavy chains wherein each LC amino acid sequence is SEQ ID NO: 27 and each HC amino acid sequence is SEQ ID NO: 32. In an embodiment, the human engineered CGRP antibody comprises two light chains and two heavy chains wherein each LC amino acid sequence is SEQ ID NO: 28 and each HC amino acid sequence is SEQ ID NO: 33. In an embodiment, the human engineered CGRP antibody comprises two light chains and two heavy chains wherein each LC amino acid sequence is SEQ ID NO: 29 and each HC amino acid sequence is SEQ ID NO: 34. In a embodiment, the human engineered CGRP antibody comprises two light chains and two heavy chains wherein each LC amino acid sequence is SEQ ID NO: 30 and each HC amino acid sequence is SEQ ID NO: 35. In an embodiment, the human engineered CGRP antibody comprises two light chains and two heavy chains wherein each LC amino acid sequence is SEQ ID NO: 31 and each HC amino acid sequence is SEQ ID NO: 36. The present ~~invention~~disclosure also provides antigen-binding fragment of the antibodies described herein.

The present ~~invention~~disclosure also provides human engineered CGRP antibodies which have an IC50 < 1.0 nM in an assay essentially as described in Example 4. In an embodiment, the present ~~invention~~disclosure provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 6, LCDR2 is SEQ ID NO: 7, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 16, and HCDR3 is SEQ ID NO: 39, and wherein the human engineered CGRP antibody binds to human CGRP and also has an IC50 < 1.0 nM in an assay essentially as described in Example 4. In an embodiment, the present ~~invention~~disclosure provides a human engineered CGRP antibody comprising a LCVR amino acid sequence of SEQ ID NO: 19 and an HCVR amino acid sequence of SEQ ID NO: 24, wherein the human engineered CGRP antibody has an IC50 < 1.0 nM in an assay essentially as described Example 4. In an embodiment, the present ~~invention~~disclosure provides a human engineered CGRP antibody comprising a LC amino acid sequence of SEQ ID NO: 29 and a HC amino acid sequence of SEQ ID NO: 34, wherein the human engineered CGRP antibody has an IC50 < 1.0 nM in an assay essentially as described in Example 4.

The present ~~invention~~disclosure also provides human engineered CGRP antibodies which have an IC50 < 0.5 nM in an assay essentially as described in Example 4. In an embodiment, the present ~~invention~~disclosure provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 6, LCDR2 is SEQ ID NO: 7, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 16, and HCDR3 is SEQ ID NO: 39, and wherein the human engineered CGRP antibody binds to human CGRP and also has an IC50 < 0.5 nM nM in an assay essentially as described in Example 4. In an embodiment, the present ~~invention~~disclosure provides a human engineered CGRP antibody comprising a LCVR amino acid sequence of SEQ ID NO: 19 and an HCVR amino acid sequence of SEQ ID NO: 24, wherein the human engineered CGRP antibody has an IC50 < 0.5 nM nM in an assay essentially as described Example 4. In an embodiment, the present ~~invention~~disclosure provides a human engineered CGRP antibody comprising a LC amino acid sequence of SEQ ID NO: 29 and a HC amino acid sequence of SEQ ID NO: 34, wherein the human engineered CGRP antibody has an IC50 < 0.5 nM nM in an assay essentially as described in Example 4.

The present ~~invention~~disclosure also provides a pharmaceutical composition comprising a human engineered CGRP antibody or antigen-binding fragment thereof of the present ~~invention~~disclosure and a pharmaceutically acceptable carrier, diluent or excipient. The present ~~invention~~disclosure further provides a pharmaceutical composition comprising a CGRP antibody of the present ~~invention~~disclosure together with a pharmaceutically acceptable carrier and optionally, other therapeutic ingredients.

In another aspect, there is provided a pharmaceutical composition, comprising the human engineered CGRP antibody as defined above and a pharmaceutically acceptable carrier, diluent, or excipient.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of treating osteoarthritis pain comprising administering to a patient in need thereof a human engineered CGRP antibody or antigen-binding fragment thereof of the present ~~invention~~disclosure. In another ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of treating migraines comprising administering to a patient in need thereof a human engineered CGRP antibody or antigen-binding fragment thereof of the present ~~invention~~disclosure.

The present ~~invention~~disclosure also provides a human engineered CGRP antibody or antigen-binding fragment thereof of the present ~~invention~~disclosure for use in therapy. In another

~~aspect~~embodiment, the present ~~invention~~disclosure provides a human engineered CGRP antibody or antigen-binding fragment thereof of the present ~~invention~~disclosure for the treatment of osteoarthritis pain. In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a human engineered CGRP antibody or antigen-binding fragment thereof of the present ~~invention~~disclosure for the treatment of migraines.

In another aspect, there is provided a human engineered CGRP antibody thereof as defined above for use in therapy.

In another aspect, there is provided a human engineered CGRP antibody thereof as defined above for use in the treatment of osteoarthritis pain.

In another aspect, there is provided the use of a human engineered CGRP antibody as defined above for use in the manufacture of a medicament for the treatment of osteoarthritis pain.

In another aspect, there is provided a human engineered CGRP antibody as defined above for use in the treatment of migraines.

In another aspect, there is provided the use of a human engineered CGRP antibody as defined above for use in the manufacture of a medicament for the treatment of migraines.

The present ~~invention~~disclosure also provides the use of a human engineered CGRP antibody or antigen-binding fragment thereof of the present ~~invention~~disclosure for use in the treatment of osteoarthritis pain. In another ~~aspect~~embodiment, the present ~~invention~~disclosure also provides the use of a human engineered CGRP antibody or antigen-binding fragment thereof of the present ~~invention~~disclosure for use in the treatment of migraines. The present ~~invention~~disclosure also provides the use of a human engineered CGRP antibody or antigen binding fragment thereof in the manufacture of a medicament for the treatment of osteoarthritis. The present ~~invention~~disclosure also provides the use of a human engineered CGRP antibody or antigen binding fragment thereof in the manufacture of a medicament for the treatment of migraines.

A full-length antibody as it exists naturally is an immunoglobulin molecule comprising 2 heavy (H) chains and 2 light (L) chains interconnected by disulfide bonds. The amino terminal portion of each chain includes a variable region of about 100-110 amino acids primarily responsible for antigen recognition via the complementarity determining regions (CDRs) contained therein. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function.

The CDRs are interspersed with regions that are more conserved, termed framework regions (FR). Each light chain variable region (LCVR) and heavy chain variable region (HCVR) is composed of 3 CDRs and 4 FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The 3 CDRs of the light chain are referred to as "LCDR1, LCDR2, and LCDR3" and the 3 CDRs of the heavy chain are referred to as "HCDR1, HCDR2, and HCDR3." The CDRs contain most of the residues which form specific interactions with the antigen. The numbering and positioning of CDR amino acid residues within the