

HUMAN ANTIBODIES TO ARTEMIN AND METHODS OF USE THEREOF

FIELD OF THE INVENTION

[001] The present disclosure relates to human antibodies and antigen-binding fragments of human antibodies that specifically bind to artemin, and methods of use thereof.

SEQUENCE LISTING

[002] An official copy of the sequence listing is submitted concurrently with the specification electronically via EFS-Web as an ASCII formatted sequence listing with a file name of 10907WO01_Sequence_Listing_ST25, a creation date of April 19, 2022, and a size of about 69,632 bytes. The sequence listing contained in this ASCII formatted document is part of the specification and is herein incorporated by reference in its entirety.

BACKGROUND

[003] Artemin (ARTN) is a neurotrophic factor that is a member of the glial cell line-derived neurotrophic factor (GDNF) family of ligands. Each GDNF family ligand binds to a glycosylphosphatidylinositol (GPI)-anchored receptor associated with the plasma membrane. This family of receptors is referred to as the GDNF-family receptor alpha (GFR α) family and is composed of four different receptors, GFR α 1–4. ARTN binds preferentially to the receptor GFR α 3 and is the only known ligand for GFR α 3. ARTN and the other GDNF family ligands signal through the RET (“rearranged during transfection”) receptor tyrosine kinase, which was first discovered as a proto-oncogene. RET is activated by GDNF family members only if the ligand is first bound to its GFR α receptor (Airaksinen et al, *Nature Reviews Neuroscience* (2002), 3:383-394).

[004] Both ARTN and GFR α 3 are highly expressed during development and are involved in sympathetic nervous system development. In adult mouse, ARTN is expressed in testis, uterus, thyroid, prostate, and epididymis, as well as in olfactory bulbs and arterioles in the intestine and mesentery (Airaksinen et al, *Nature Reviews Neuroscience* (2002), 3:383-394; Airaksinen et al, *Brain, Behavior and Evolution*, (2006), 68:181-190). GFR α 3 expression in adults is largely restricted to the sensory neurons of the dorsal root ganglia (DRG) (Orozco et al, *European J. Neuroscience*, (2001), 13:2177-2182). Mice lacking ARTN or GFR α 3 exhibit abnormalities in the migration and axonal projection pattern of the sympathetic nervous system, resulting in abnormal innervation of target tissues (Honma et al., *Neuron*, (2002), 35:267-282).

[005] A potential role for ARTN and GFR α 3 in pain and thermal perception has been shown in several studies. For example, it has been demonstrated that an injection of the artemin protein into the hindpaw of a rodent caused thermal hyperalgesia and this nociception was enhanced when artemin was co-injected with NGF (Malin et al, *J. Neuroscience*, (2006), 26(33): 8588-8599). Other studies showed that artemin mRNA expression was upregulated in a murine inflammatory model, and that artemin transgenic mice have elevated expression of TRPV1 and TRPA1 and increased behavioral sensitivity to heat and cold (Elitt et al, *J. Neuroscience*, (2006), 26(33): 8578-8587). Additionally, artemin and GFR α 3 expression are increased in a rat model of migraine (Shang et al., *J Headache Pain*, (2016), 17(1):81) and in dogs treated with radiotherapy (Nolan et al, *Radiat Res*, (2020), 193(3):241-248). Artemin expression is also increased in tongue mucosa of patients with burning mouth syndrome and in a mouse model of burning mouth syndrome (Shinoda et al., *PAIN*, (2015), 156(12):2528-2537).

SUMMARY

[006] In one aspect, the present disclosure provides an isolated monoclonal antibody or an antigen-binding fragment thereof that specifically binds to human artemin, wherein the antibody or antigen-binding fragment thereof comprises: (a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; or (b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 32, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 34, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 36; or (c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 44, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 46, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 48, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 52, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 56; or (d) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 64, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 66, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 68, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 72, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 74, and an LCDR3 comprising the amino acid sequence of

SEQ ID NO: 76.

[0006a] In another aspect, the present disclosure provides a pharmaceutical composition comprising the monoclonal antibody or antigen-binding fragment thereof as described herein and a pharmaceutically acceptable carrier. In another aspect, the present disclosure provides a nucleic acid molecule comprising a nucleotide sequence encoding the monoclonal antibody or antigen-binding fragment thereof as described herein. In another aspect, the present disclosure provides an expression vector comprising the nucleic acid molecule as described herein. In another aspect, the present disclosure provides a host cell comprising the expression vector as described herein. In one example, isolated antibodies or antigen-binding fragment thereof that specifically bind to artemin are provided. In some examples, the antibody is a monoclonal antibody or an antigen-binding fragment thereof that binds to human artemin. In some examples, the antibody or antigen-binding fragment thereof binds to human artemin with a K_D of less than 5 nM as measured by surface plasmon resonance at 25°C.

[007] In some examples, the antibody or antigen-binding fragment thereof:

- (a) blocks at least 65% of human artemin binding to a solid support coated with human GFR α 3 as measured by ELISA;
- (b) inhibits or reduces artemin-activated signaling through GFR α 3 and RET receptor tyrosine kinase; and/or
- (c) inhibits or reduces artemin-induced thermal hyperalgesia *in vivo*.

[008] In some examples, the antibody or antigen-binding fragment thereof cross-reacts with artemin from at least one non-human species. In some examples, the antibody or antigen-binding fragment thereof cross-reacts with monkey artemin. In some examples, the antibody or antigen-binding fragment thereof cross-reacts with mouse artemin.

[009] In some examples, the antibody or antigen-binding fragment thereof comprises:

- (a) a heavy chain complementarity determining region 1 (HCDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:4, 24, 44, and 64;
- (b) a heavy chain complementarity determining region 2 (HCDR2) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:6, 26, 46, and 66;

- (c) a heavy chain complementarity determining region 3 (HCDR3) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:8, 28, 48, and 68;
- (d) a light chain complementarity determining region 1 (LCDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:12, 32, 52, and 72;
- (e) a light chain complementarity determining region 2 (LCDR2) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:14, 34, 54, and 74; and
- (f) a light chain complementarity determining region 3 (LCDR3) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:16, 36, 56, and 76.

[010] In some examples, the antibody or antigen-binding fragment thereof comprises:

- (a) an HCDR1 comprising the amino acid sequence of SEQ ID NO:4, an HCDR2 comprising the amino acid sequence of SEQ ID NO:6, an HCDR3 comprising the amino acid sequence of SEQ ID NO:8, an LCDR1 comprising the amino acid sequence of SEQ ID NO:12, an LCDR2 comprising the amino acid sequence of SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:16; or
- (b) an HCDR1 comprising the amino acid sequence of SEQ ID NO:24, an HCDR2 comprising the amino acid sequence of SEQ ID NO:26, an HCDR3 comprising the amino acid sequence of SEQ ID NO:28, an LCDR1 comprising the amino acid sequence of SEQ ID NO:32, an LCDR2 comprising the amino acid sequence of SEQ ID NO:34, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:36; or
- (c) an HCDR1 comprising the amino acid sequence of SEQ ID NO:44, an HCDR2 comprising the amino acid sequence of SEQ ID NO:46, an HCDR3 comprising the amino acid sequence of SEQ ID NO:48, an LCDR1 comprising the amino acid sequence of SEQ ID NO:52, an LCDR2 comprising the amino acid sequence of SEQ ID NO:54, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:56; or
- (d) an HCDR1 comprising the amino acid sequence of SEQ ID NO:64, an HCDR2 comprising the amino acid sequence of SEQ ID NO:66, an HCDR3 comprising the amino acid sequence of SEQ ID NO:68, an LCDR1 comprising the amino acid sequence of SEQ ID NO:72, an LCDR2 comprising the amino acid sequence of SEQ ID NO:74, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:76.

[011] In some examples, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) comprising an amino acid sequence that has at least 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs:2, 22, 42, and 62.

[012] In some examples, the antibody or antigen-binding fragment thereof comprises a light chain variable region (LCVR) comprising an amino acid sequence that has at least

85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs:10, 30, 50, and 70.

[013] In some examples, the antibody or antigen-binding fragment thereof comprises:

- (a) an HCVR comprising the amino acid sequence of SEQ ID NO:2 and an LCVR comprising the amino acid sequence of SEQ ID NO:10; or
- (b) an HCVR comprising the amino acid sequence of SEQ ID NO:22 and an LCVR comprising the amino acid sequence of SEQ ID NO:30; or
- (c) an HCVR comprising the amino acid sequence of SEQ ID NO:42 and an LCVR comprising the amino acid sequence of SEQ ID NO:50; or
- (d) an HCVR comprising the amino acid sequence of SEQ ID NO:62 and an LCVR comprising the amino acid sequence of SEQ ID NO:70.

[014] In some examples, the antibody or antigen-binding fragment thereof comprises:

- (a) a heavy chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:18 and a light chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:20; or
- (b) a heavy chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:38 and a light chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:40; or
- (c) a heavy chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:58 and a light chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:60; or
- (d) a heavy chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:78 and a light chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:80.

[015] In some examples, the antibody or antigen-binding fragment thereof comprises heavy chain comprising the amino acid sequence of SEQ ID NO:18 and a light chain comprising the amino acid sequence of SEQ ID NO:20. In some examples, the antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:38 and a light chain comprising the amino acid sequence of SEQ ID NO:40. In some examples, the antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:58 and a light chain comprising the amino acid sequence of SEQ ID NO:60. In some examples, the antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino

acid sequence of SEQ ID NO:78 and a light chain comprising the amino acid sequence of SEQ ID NO:80.

[016] In some examples, the antibody or antigen-binding fragment thereof is fully human.

[017] In another example, pharmaceutical compositions comprising the antibody or antigen-binding fragment thereof and a pharmaceutically acceptable carrier are provided.

[018] In another example, nucleic acid molecules comprising a nucleotide sequence encoding the antibody or antigen-binding fragment thereof are provided. In some examples, the nucleic acid molecule comprises one or more nucleotide sequences set forth in Table 9.

[019] In yet another example, expression vectors and host cells comprising a nucleic acid molecule as disclosed herein are provided, as are methods of producing anti-artemin antibodies using the nucleic acid molecules, expression vectors, and host cells disclosed herein. In yet another aspect, the present disclosure provides a method of producing an anti-human artemin antibody or antigen-binding fragment thereof, the method comprising introducing the expression vector as described herein into a host cell, growing the host cell under conditions permitting production of the antibody or antigen-binding fragment thereof, and recovering the antibody or antigen-binding fragment that is produced.

[020] In yet another aspect, the present disclosure provides an *in vitro* or *ex vivo* method of inhibiting artemin-activated signaling in a cell, the method comprising contacting the cell with the monoclonal antibody or antigen-binding fragment thereof as described herein, thereby inhibiting artemin-activated signaling in the cell. In another example, methods of inhibiting artemin-activated signaling in a cell are provided. In some examples, the method comprises contacting the cell with an antibody or antigen-binding fragment or pharmaceutical composition as disclosed herein, thereby inhibiting artemin-activated signaling in the cell. In some examples, the cell is within a subject. In some examples, the cell is *in vitro* or *ex vivo*.

[021] In yet another aspect, the present disclosure provides a use of the monoclonal antibody or antigen-binding fragment thereof as described herein in the manufacture of a medicament for treating a pain-related disease, disorder, or condition associated with increased artemin expression or activity, comprising administering the medicament to a subject in need thereof. In another example, methods of treating a disease, disorder, or condition associated with artemin expression or activity are provided. In some examples, the method comprises administering an antibody or antigen-binding fragment thereof or pharmaceutical composition as disclosed herein to a subject in need thereof (e.g., a subject having the disease, disorder, or condition associated with artemin expression or activity). In some examples, the antibody or antigen-binding fragment thereof or pharmaceutical composition is administered to the subject in combination with a second therapeutic agent.

[022] In another example, an anti-artemin antibody or antigen-binding fragment thereof, or a pharmaceutical composition comprising an anti-artemin antibody or antigen-binding fragment thereof, is provided for use in a method of treating a disease, disorder, or condition associated with artemin expression or activity. In some examples, the method comprises administering an antibody or antigen-binding fragment thereof or pharmaceutical composition as disclosed herein to a subject in need thereof (e.g., a subject having the disease, disorder, or condition associated with artemin expression or activity). In some examples, the antibody or antigen-binding fragment thereof or pharmaceutical composition is therapeutically combined with a second therapeutic agent. In some examples, the antibody or antigen-binding fragment thereof or pharmaceutical composition is combined with a second therapeutic agent.

[023] In another example, the use of an anti-artemin antibody or antigen-binding fragment thereof, or a pharmaceutical composition comprising an anti-artemin antibody or antigen-binding fragment thereof, in the manufacture of a medicament for use in a method of treating a disease, disorder, or condition associated with artemin expression or activity is provided. In some examples, the method comprises administering an antibody or antigen-binding fragment thereof or pharmaceutical composition as disclosed herein to a subject in need thereof (e.g., a subject having the disease, disorder, or condition associated with artemin expression or activity). In some examples, the antibody or antigen-binding fragment thereof or pharmaceutical composition is therapeutically combined with a second therapeutic agent. In some examples, the antibody or antigen-binding fragment thereof or pharmaceutical composition is combined with a second therapeutic agent.

[024] In some examples, the disease, disorder, or condition is acute pain, chronic pain, neuropathic pain, inflammatory pain, trigeminal neuralgia, postherpetic neuralgia, general neuralgia, visceral pain, osteoarthritis pain, gout, radicular pain, sciatica, back pain, head or neck pain, breakthrough pain, post-surgical pain, chemotherapy induced neuropathic pain, radiotherapy-induced neuropathic pain, radiation-associated pain, or cancer pain. In some examples, the disease, disorder, or condition is migraine, cluster headache, chronic headache, or tension headache.

[025] Other examples will be apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[026] FIG. 1. Binding of different concentrations of hArtemin-MMH (human Artemin) to Artemin mAb-captured Octet biosensor surface.

[027] FIG. 2. Binding of different concentrations of MfArtemin-MMH (cyno Artemin) to Artemin mAb-captured Octet biosensor surface.

[028] FIG. 3. Binding of different concentrations of mArtemin-MMH (mouse Artemin) to Artemin mAb-captured Octet biosensor surface.

[029] FIG. 4. Inhibition of artemin-induced plantar thermal hyperalgesia in animals administered an anti-artemin antibody (H4H33331P, H4H33335P, H4H33336P, or H4H33349P) or isotype control antibody (negative control) at 10 mg/kg.

DETAILED DESCRIPTION

Definitions

[030] Before the present invention is described, it is to be understood that the invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[031] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[032] As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (e.g., 99.1, 99.2, 99.3, 99.4, etc.).

[033] The term "artemin" or "ARTN," as used herein, refers to a glial cell line-derived neurotrophic factor (GDNF) family ligand. See, Baloh et al., *Neuron*, (1998), 21(6):1291-1302. As used herein, the term "artemin" may refer to a precursor form or a mature (i.e., processed form) such as the full-length processed form or a fragment thereof. In some embodiments, the term "artemin" refers to a human artemin protein or fragment thereof. In some embodiments, the artemin protein comprises the amino acid sequence of human artemin set forth in NCBI Accession No. NP_476432.2, or a fragment thereof (e.g., a proteolytically processed portion). In some embodiments, the artemin protein comprises the amino acid sequence of human artemin set forth in Uniprot Accession No. Q5T4W7, or a fragment thereof (e.g., a proteolytically processed portion), or an isoform thereof. In some embodiments, the artemin protein comprises the amino acid sequence of an artemin protein or fragment set forth in US Patent No. 6,284,540.

[034] The term "an antibody that binds artemin" or an "anti-artemin antibody" includes antibodies and antigen-binding fragments thereof that specifically recognize a monomeric artemin, as well as antibodies and antigen-binding fragments thereof that specifically recognize a dimeric artemin.

[035] The term "antibody," as used herein, refers to an antigen-binding molecule or molecular complex comprising a set of complementarity determining regions (CDRs) that specifically bind to or interact with a particular antigen (e.g., ARTN). The term "antibody," as used herein, includes immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (e.g., IgM). In a typical antibody, each heavy chain comprises a heavy

chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region comprises three domains, C_{H1} , C_{H2} and C_{H3} . Each light chain comprises a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region comprises one domain (C_{L1}). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In some embodiments, the FRs of the antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[036] The term "antibody," as used herein, also includes antigen-binding fragments of full antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, "antigen-binding domain," and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, e.g., from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, e.g., commercial sources, DNA libraries (including, e.g., phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[037] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) $F(ab')_2$ fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (e.g., monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.

[038] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H - V_H , V_H - V_L or V_L - V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[039] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody include: (i) V_H - C_H1 ; (ii) V_H - C_H2 ; (iii) V_H - C_H3 ; (iv) V_H - C_H1 - C_H2 ; (v) V_H - C_H1 - C_H2 - C_H3 ; (vi) V_H - C_H2 - C_H3 ; (vii) V_H - C_L ; (viii) V_L - C_H1 ; (ix) V_L - C_H2 ; (x) V_L - C_H3 ; (xi) V_L - C_H1 - C_H2 ; (xii) V_L - C_H1 - C_H2 - C_H3 ; (xiii) V_L - C_H2 - C_H3 ; and (xiv) V_L - C_L . In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (e.g., by disulfide bond(s)).

[040] The term "antibody," as used herein, also includes multispecific (e.g., bispecific) antibodies. A multispecific antibody or antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multispecific antibody format may be adapted for use in the context of an antibody or antigen-binding fragment of an antibody of the present disclosure using routine techniques available in the art. For example, the present disclosure includes methods comprising the use of bispecific antibodies wherein one arm of an immunoglobulin is specific for ARTN or a fragment thereof, and the other arm of the immunoglobulin is specific for a second therapeutic target or is conjugated to a therapeutic moiety. Exemplary bispecific formats that can be used in the context of the present disclosure include, without limitation, e.g., scFv-based or diabody bispecific formats, IgG-scFv fusions, dual variable domain (DVD)-Ig, Quadroma, knobs-into-holes, common light chain (e.g., common light chain with knobs-into-holes, etc.), CrossMab, CrossFab, (SEED) body, leucine zipper, Duobody, IgG1/IgG2, dual

acting Fab (DAF)-IgG, and Mab² bispecific formats (*see, e.g., Klein et al.* 2012, mAbs 4:6, 1-11, and references cited therein, for a review of the foregoing formats). Bispecific antibodies can also be constructed using peptide/nucleic acid conjugation, *e.g.,* wherein unnatural amino acids with orthogonal chemical reactivity are used to generate site-specific antibody-oligonucleotide conjugates which then self-assemble into multimeric complexes with defined composition, valency and geometry. (*See, e.g., Kazane et al., J. Am. Chem. Soc.* [Epub: Dec. 4, 2012]).

[041] The term “human antibody,” as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the disclosure may nonetheless include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.,* mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term “human antibody,” as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[042] The term “recombinant antibody,” as used herein, is intended to include all antibodies that are prepared, expressed, created or isolated by recombinant means. The term includes, but is not limited to, antibodies expressed using a recombinant expression vector transfected into a host cell (*e.g.,* Chinese hamster ovary (CHO) cell, NS0 cell, BHK cell, or HEK293 cell) or cellular expression system, antibodies isolated from a recombinant, combinatorial human antibody library, and antibodies isolated from a non-human animal (*e.g.,* a mouse, such as a mouse that is transgenic for human immunoglobulin genes (*see e.g., Taylor et al. (1992) Nucl. Acids Res.* 20:6287-6295)). In some embodiments, the recombinant antibody is a recombinant human antibody. In some embodiments, recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[043] An “isolated antibody” refers to an antibody that has been identified and separated and/or recovered from at least one component of its natural environment. For example, an antibody that has been separated or removed from at least one component of an organism, or from a tissue or cell in which the antibody naturally exists or is naturally produced, is an “isolated antibody.” An isolated antibody also includes an antibody *in situ* within a

recombinant cell. Isolated antibodies are antibodies that have been subjected to at least one purification or isolation step. According to certain embodiments, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[044] The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by an equilibrium dissociation constant of at least about 1×10^{-6} M or less, e.g., 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, or 10^{-12} M (a smaller K_D denotes a tighter binding). Methods for determining whether an antibody specifically binds to an antigen are known in the art and include, for example, equilibrium dialysis, surface plasmon resonance (e.g., BIACORE™), bio-layer interferometry assay (e.g., Octet® HTX biosensor), solution-affinity ELISA, and the like. In some embodiments, specific binding is measured in a surface plasmon resonance assay, e.g., at 25°C or 37°C. An antibody or antigen-binding fragment that specifically binds an antigen from one species may or may not have cross-reactivity to other antigens, such as an orthologous antigen from another species.

[045] The term " K_D ," as used herein, refers to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[046] The term "surface plasmon resonance," as used herein, refers to an optical phenomenon that allows for the analysis of real-time biomolecular interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system (Cytiva, Marlborough, MA).

[047] The term "bio-layer interferometry" or "BLI," as used herein, refers to an optical technique for measuring real-time biomolecular interactions by analyzing interference patterns caused by the binding of one biomolecule dispensed in the sample plate to a second biomolecule immobilized on a biosensor plate, for example using the Octet® system (Sartorius AG, Göttingen, Germany).

[048] The term "epitope," as used herein, refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. The term "epitope" also refers to a site on an antigen to which B and/or T cells respond. It also refers to a region of an antigen that is bound by an antibody. Epitopes may be either linear or discontinuous (e.g., conformational). A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or

sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics. Epitopes may also be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. An epitope typically includes at least 3, and more usually, at least 5 or at least 8-10 amino acids in a unique spatial conformation.

[049] Methods for determining the epitope of an antigen-binding protein, e.g., an antibody or antigen-binding fragment, include alanine scanning mutational analysis, peptide blot analysis (Reineke, *Methods Mol Biol* 2004, 248:443-463), peptide cleavage analysis, crystallographic studies, and NMR analysis. In addition, methods such as epitope exclusion, epitope extraction, and chemical modification of antigens can be employed (Tomer, *Prot Sci* 2000, 9:487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antigen-binding protein (e.g., an antibody or antigen-binding fragment) interacts is hydrogen/deuterium exchange detected by mass spectrometry (HDX). See, e.g., Ehrling, *Analytical Biochemistry* 1999, 267:252-259; Engen and Smith, *Anal Chem* 2001, 73:256A-265A.

[050] The terms "substantial identity" and "substantially identical," as used with reference to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 85%, e.g., at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%, of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or GAP, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

[051] As applied to polypeptides, the terms "substantial identity" and "substantially identical" mean that two peptide sequences, when optimally aligned, share at least about 85% sequence identity, e.g., at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity. In some embodiments, residue positions that are not identical differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein.

[052] Sequence similarity for polypeptides is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative

amino acid substitutions. For instance, GCG software contains programs such as GAP and BESTFIT which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA with default or recommended parameters; a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, 2000 *supra*). Another preferred algorithm when comparing a sequence of the disclosure to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. (See, e.g., Altschul et al., 1990, *J. Mol. Biol.* 215: 403-410 and 1997 *Nucleic Acids Res.* 25:3389-3402).

[053] A "variant" of a polypeptide, such an immunoglobulin, VH, VL, heavy chain, light chain, or CDR comprising an amino acid sequence specifically set forth herein, refers to a polypeptide comprising an amino acid sequence that is at least about 70%-99.9% (e.g., at least 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, or 99.9%) identical to the reference polypeptide sequence (e.g., as set forth in the sequence listing below), when the comparison is performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences. In some embodiments, a variant of a polypeptide includes a polypeptide having the amino acid sequence of a reference polypeptide sequence (e.g., as set forth in the sequence listing below) but for one or more (e.g., 1 to 10, or less than 20, or less than 10) missense mutations (e.g., conservative substitutions), nonsense mutations, deletions, or insertions.

[054] The term "therapeutically effective amount" refers to an amount that produces the desired effect for which it is administered. The exact amount will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) *The Art, Science and Technology of Pharmaceutical Compounding*).

Anti-Artemin Antibodies and Antigen-Binding Fragments Thereof

[055] In one aspect, the present disclosure relates to antibodies and antigen-binding fragments thereof that bind to artemin. Artemin can exist in a precursor form (e.g., a pre-protein) or in a proteolytically processed form, for example as described in US Patent No. 6,284,540, incorporated by reference herein. In some embodiments, the antibody or antigen-binding fragment thereof binds a precursor form of artemin or a fragment thereof. In some

embodiments, the antibody or antigen-binding fragment thereof binds a proteolytically processed form of artemin or a fragment thereof.

[056] In some embodiments, the antibody or antigen-binding fragment thereof specifically binds to human artemin (e.g., a human proprotein or a proteolytically processed form). In some embodiments, the antibody or antigen-binding fragment thereof specifically binds to human artemin and cross-reacts with artemin from one or more other non-human species, such as but not limited to mouse, rat, guinea pig, hamster, gerbil, pig, cat, dog, rabbit, goat, sheep, cow, horse, camel, cynomolgus, marmoset, rhesus or chimpanzee artemin. In some embodiments, the antibody or antigen-binding fragment thereof specifically binds to human artemin and cross-reacts with at least some (e.g., some but not all) non-human forms of artemin (e.g., mouse, rat, guinea pig, hamster, gerbil, pig, cat, dog, rabbit, goat, sheep, cow, horse, camel, cynomolgus, marmoset, rhesus or chimpanzee artemin). In some embodiments, the antibody or antigen-binding fragment thereof does not cross-react with artemin from a non-human species.

[057] In some embodiments, the anti-artemin antibody or antigen-binding fragment thereof comprises:

- (a) a heavy chain complementarity determining region 1 (HCDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:4, 24, 44, and 64;
- (b) a heavy chain complementarity determining region 2 (HCDR2) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:6, 26, 46, and 66;
- (c) a heavy chain complementarity determining region 3 (HCDR3) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:8, 28, 48, and 68;
- (d) a light chain complementarity determining region 1 (LCDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:12, 32, 52, and 72;
- (e) a light chain complementarity determining region 2 (LCDR2) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:14, 34, 54, and 74; and
- (f) a light chain complementarity determining region 3 (LCDR3) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:16, 36, 56, and 76.

[058] In some embodiments, the anti-artemin antibody comprises a heavy chain variable region (HCVR) comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs:2, 22, 42, and 62. In some embodiments, the anti-artemin antibody comprises an HCVR comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 22, 42, and 62.

[059] In some embodiments, the anti-artemin antibody comprises a light chain variable region (LCVR) comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs:10, 30, 50, and 70. In some embodiments, the anti-artemin antibody comprises an LCVR comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:10, 30, 50, and 70.

[060] In some embodiments, the anti-artemin antibody or antigen-binding fragment thereof comprises:

(a) an HCDR1 comprising the amino acid sequence of SEQ ID NO:4, an HCDR2 comprising the amino acid sequence of SEQ ID NO:6, and an HCDR3 comprising the amino acid sequence of SEQ ID NO:8; or

(b) an HCDR1 comprising the amino acid sequence of SEQ ID NO:24, an HCDR2 comprising the amino acid sequence of SEQ ID NO:26, and an HCDR3 comprising the amino acid sequence of SEQ ID NO:28; or

(c) an HCDR1 comprising the amino acid sequence of SEQ ID NO:44, an HCDR2 comprising the amino acid sequence of SEQ ID NO:46, and an HCDR3 comprising the amino acid sequence of SEQ ID NO:48; or

(d) an HCDR1 comprising the amino acid sequence of SEQ ID NO:64, an HCDR2 comprising the amino acid sequence of SEQ ID NO:66, and an HCDR3 comprising the amino acid sequence of SEQ ID NO:68.

[061] In some embodiments, the anti-artemin antibody comprises an HCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:2. In some embodiments, the anti-artemin antibody comprises an HCVR comprising the amino acid sequence of SEQ ID NO:2. In some embodiments, the anti-artemin antibody comprises an HCVR comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO:4, an HCDR2 comprising the amino acid sequence of SEQ ID NO:6, and an HCDR3 comprising the amino acid sequence of SEQ ID NO:8, wherein the HCVR has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:2. In some embodiments, the anti-artemin antibody comprises a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:18. In some embodiments, the anti-artemin antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:18.

[062] In some embodiments, the anti-artemin antibody comprises an HCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:22. In some embodiments, the anti-artemin antibody comprises an HCVR comprising the amino acid sequence of SEQ ID NO:22. In some embodiments, the anti-artemin antibody comprises an HCVR comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO:24, an HCDR2 comprising the amino acid sequence of SEQ ID NO:26, and an HCDR3 comprising the amino acid sequence of SEQ ID NO:28, wherein the HCVR has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:22. In some embodiments, the anti-artemin antibody comprises a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:38. In some embodiments, the anti-artemin antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:38.

[063] In some embodiments, the anti-artemin antibody comprises an HCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:42. In some embodiments, the anti-artemin antibody comprises an HCVR comprising the amino acid sequence of SEQ ID NO:42. In some embodiments, the anti-artemin antibody comprises an HCVR comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO:44, an HCDR2 comprising the amino acid sequence of SEQ ID NO:46, and an HCDR3 comprising the amino acid sequence of SEQ ID NO:48, wherein the HCVR has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:42. In some embodiments, the anti-artemin antibody comprises a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:58. In some embodiments, the anti-artemin antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:58.

[064] In some embodiments, the anti-artemin antibody comprises an HCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:62. In some embodiments, the anti-artemin antibody comprises an HCVR comprising the amino acid sequence of SEQ ID NO:62. In some

embodiments, the anti-artemin antibody comprises an HCVR comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO:64, an HCDR2 comprising the amino acid sequence of SEQ ID NO:66, and an HCDR3 comprising the amino acid sequence of SEQ ID NO:68, wherein the HCVR has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:62. In some embodiments, the anti-artemin antibody comprises a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:78. In some embodiments, the anti-artemin antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:78.

[065] In some embodiments, the anti-artemin antibody or antigen-binding fragment thereof comprises:

(a) an LCDR1 comprising the amino acid sequence of SEQ ID NO:12, an LCDR2 comprising the amino acid sequence of SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:16; or

(b) an LCDR1 comprising the amino acid sequence of SEQ ID NO:32, an LCDR2 comprising the amino acid sequence of SEQ ID NO:34, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:36; or

(c) an LCDR1 comprising the amino acid sequence of SEQ ID NO:52, an LCDR2 comprising the amino acid sequence of SEQ ID NO:54, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:56; or

(d) an LCDR1 comprising the amino acid sequence of SEQ ID NO:72, an LCDR2 comprising the amino acid sequence of SEQ ID NO:74, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:76.

[066] In some embodiments, the anti-artemin antibody comprises an LCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:10. In some embodiments, the anti-artemin antibody comprises an LCVR comprising the amino acid sequence of SEQ ID NO:10. In some embodiments, the anti-artemin antibody comprises an LCVR comprising an LCDR1 comprising the amino acid sequence of SEQ ID NO:12, an LCDR2 comprising the amino acid sequence of SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:16, wherein the LCVR has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:10. In some embodiments, the anti-artemin antibody comprises a light chain comprising an amino acid sequence that has at least 85%,

at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:20. In some embodiments, the anti-artemin antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:20.

[067] In some embodiments, the anti-artemin antibody comprises an LCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:30. In some embodiments, the anti-artemin antibody comprises an LCVR comprising the amino acid sequence of SEQ ID NO:30. In some embodiments, the anti-artemin antibody comprises an LCVR comprising an LCDR1 comprising the amino acid sequence of SEQ ID NO:32, an LCDR2 comprising the amino acid sequence of SEQ ID NO:34, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:36, wherein the LCVR has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:30. In some embodiments, the anti-artemin antibody comprises a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:40. In some embodiments, the anti-artemin antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:40.

[068] In some embodiments, the anti-artemin antibody comprises an LCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:50. In some embodiments, the anti-artemin antibody comprises an LCVR comprising the amino acid sequence of SEQ ID NO:50. In some embodiments, the anti-artemin antibody comprises an LCVR comprising an LCDR1 comprising the amino acid sequence of SEQ ID NO:52, an LCDR2 comprising the amino acid sequence of SEQ ID NO:54, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:56, wherein the LCVR has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:50. In some embodiments, the anti-artemin antibody comprises a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:60. In some embodiments, the anti-artemin antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:60.

[069] In some embodiments, the anti-artemin antibody comprises an LCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:70. In some embodiments, the anti-artemin antibody comprises an LCVR comprising the amino acid sequence of SEQ ID NO:70. In some embodiments, the anti-artemin antibody comprises an LCVR comprising an LCDR1 comprising the amino acid sequence of SEQ ID NO:72, an LCDR2 comprising the amino acid sequence of SEQ ID NO:74, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:76, wherein the LCVR has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:70. In some embodiments, the anti-artemin antibody comprises a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:80. In some embodiments, the anti-artemin antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:80.

[070] In some embodiments, the anti-artemin antibody comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO:4, an HCDR2 comprising the amino acid sequence of SEQ ID NO:6, an HCDR3 comprising the amino acid sequence of SEQ ID NO:8, an LCDR1 comprising the amino acid sequence of SEQ ID NO:12, an LCDR2 comprising the amino acid sequence of SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:16. In some embodiments, the anti-artemin antibody comprises an HCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:2 and an LCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:10. In some embodiments, the anti-artemin antibody comprises an HCVR comprising the amino acid sequence of SEQ ID NO:2 and an LCVR comprising the amino acid sequence of SEQ ID NO:10. In some embodiments, the anti-artemin antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:18 and a light chain comprising the amino acid sequence of SEQ ID NO:20.

[071] In some embodiments, the anti-artemin antibody comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO:24, an HCDR2 comprising the amino acid sequence of SEQ ID NO:26, an HCDR3 comprising the amino acid sequence of SEQ ID NO:28, an LCDR1 comprising the amino acid sequence of SEQ ID NO:32, an LCDR2 comprising the amino acid sequence of SEQ ID NO:34, and an LCDR3 comprising the amino acid

sequence of SEQ ID NO:36. In some embodiments, the anti-artemin antibody comprises an HCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:22 and an LCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:30. In some embodiments, the anti-artemin antibody comprises an HCVR comprising the amino acid sequence of SEQ ID NO:22 and an LCVR comprising the amino acid sequence of SEQ ID NO:30. In some embodiments, the anti-artemin antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:38 and a light chain comprising the amino acid sequence of SEQ ID NO:40.

[072] In some embodiments, the anti-artemin antibody comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO:44, an HCDR2 comprising the amino acid sequence of SEQ ID NO:46, an HCDR3 comprising the amino acid sequence of SEQ ID NO:48, an LCDR1 comprising the amino acid sequence of SEQ ID NO:52, an LCDR2 comprising the amino acid sequence of SEQ ID NO:54, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:56. In some embodiments, the anti-artemin antibody comprises an HCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:42 and an LCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:50. In some embodiments, the anti-artemin antibody comprises an HCVR comprising the amino acid sequence of SEQ ID NO:42 and an LCVR comprising the amino acid sequence of SEQ ID NO:50. In some embodiments, the anti-artemin antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:58 and a light chain comprising the amino acid sequence of SEQ ID NO:60.

[073] In some embodiments, the anti-artemin antibody comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO:64, an HCDR2 comprising the amino acid sequence of SEQ ID NO:66, an HCDR3 comprising the amino acid sequence of SEQ ID NO:68, an LCDR1 comprising the amino acid sequence of SEQ ID NO:72, an LCDR2 comprising the amino acid sequence of SEQ ID NO:74, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:76. In some embodiments, the anti-artemin antibody comprises an HCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:62 and an LCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least

93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:70. In some embodiments, the anti-artemin antibody comprises an HCVR comprising the amino acid sequence of SEQ ID NO:62 and an LCVR comprising the amino acid sequence of SEQ ID NO:70. In some embodiments, the anti-artemin antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:78 and a light chain comprising the amino acid sequence of SEQ ID NO:80.

[074] In some embodiments, the antibody or antigen-binding fragment thereof binds to a monomeric form of artemin. In some embodiments, the antibody or antigen-binding fragment thereof binds to a dimeric form of artemin. In some embodiments, the antibody or antigen-binding fragment thereof binds to a mature form of the artemin protein (e.g., amino acids 108-220 of SEQ ID NO:81).

[075] In some embodiments, the anti-artemin antibodies or antigen-binding fragments of the present disclosure can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment to produce a bispecific or a multispecific antibody with a second binding specificity.

Sequence Variants

[076] The antibodies or antigen-binding fragments of the present disclosure may comprise one or more amino acid substitutions, insertions, and/or deletions in the framework and/or CDR regions of the heavy and/or light chain variable domains as compared to the corresponding germline sequences from which the individual antibodies were derived. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germ line sequences available from, for example, public antibody sequence databases. The antibodies of the present disclosure may comprise antigen binding fragments which are derived from any of the exemplary amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as "germline mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the V_H and/or V_L domains are mutated back to the residues found in the original

germline sequence from which the antibody was originally derived. In other embodiments, only certain residues are mutated back to the original germline sequence, e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (i.e., a germline sequence that is different from the germ line sequence from which the antibody was originally derived). Furthermore, the antibodies or antigen-binding fragments may contain any combination of two or more germline mutations within the framework and/or CDR regions, e.g., wherein certain individual residues are mutated to the corresponding residue of a particular germ line sequence while certain other residues that differ from the original germ line sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antibodies or antigen-binding fragments that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties, reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present disclosure.

[077] The present disclosure also includes antibodies or antigen-binding fragments that comprise variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present disclosure includes antibodies or antigen-binding fragments comprising HCVR, LCVR, and/or CDR amino acid sequences with, e.g., 10 or fewer, 9 or fewer, 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, 2 or fewer, or 1 conservative amino acid substitution(s) relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. Examples of groups of amino acids that have side chains with similar chemical properties include (1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; (2) aliphatic-hydroxyl side chains: serine and threonine; (3) amide-containing side chains: asparagine and glutamine; (4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; (5) basic side chains: lysine, arginine, and histidine; (6) acidic side chains: aspartate and glutamate, and (7) sulfur-containing side chains are cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in

Gonnet et al. (1992) Science 256: 1443-1445. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[078] The present disclosure also includes antibodies or antigen-binding fragments comprising an HCVR, LCVR, and/or CDR amino acid sequence that is substantially identical to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein. In some embodiments, an antigen-binding molecule comprises HCVR, LCVR, and/or CDR amino acid sequence having at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to a sequence disclosed in Table 1, Table 2, or Table 9. In some embodiments, an antigen-binding molecule comprises HCVR, LCVR, and/or CDR amino acid sequence having at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to a sequence disclosed in Table 1, Table 2, or Table 9, wherein the differences in the amino acid residue(s) relative to the sequence disclosed in Table 1, Table 2, or Table 9 are conservative substitutions or moderately conservative substitutions.

[079] In some embodiments, the antibody or antigen-binding fragment thereof is chimeric, humanized, or fully human. In some embodiments, the antibody or antigen-binding fragment thereof is humanized. In some embodiments, the antibody or antigen-binding fragment thereof is fully human.

Antibodies Comprising Fc Variants

[080] In some embodiments, anti-artemin antibodies or antigen-binding fragments thereof are provided which comprise an Fc domain comprising one or more mutations that enhance or diminish antibody binding to the FcRn receptor, e.g., at acidic pH as compared to neutral pH. For example, the present disclosure includes antibodies or antigen-binding fragments comprising one or more mutations in the CH2 and/or CH3 region of the Fc domain, wherein the mutation(s) increases the affinity of the Fc domain to FcRn in an acidic environment (e.g., in an endosome where pH ranges from about 5.5 to about 6.0). Such mutations may result in an increase in serum half-life of the antibody when administered to an animal. Non-limiting examples of such Fc modifications include, e.g., a modification at position 250 (e.g., E or Q); 250 and 428 (e.g., L or F); 252 (e.g., L/Y/F/W or T), 254 (e.g., S or T), and 256 (e.g., S/R/Q/E/D or T); or a modification at position 428 and/or 433 (e.g., H/L/R/S/P/Q or K) and/or 434 (e.g., H/F or Y); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (e.g., 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (e.g., M428L) and 434S (e.g., N434S) modification; a 428L, 259I (e.g., V259I), and 308F (e.g., V308F) modification; a 433K (e.g., H433K) and a 434 (e.g., 434Y) modification; a

252, 254, and 256 (e.g., 252Y, 254T, and 256E) modification; a 250Q and 428L modification (e.g., T250Q and M428L); and a 307 and/or 308 modification (e.g., 308F or 308P).

[081] As a non-limiting example, the present disclosure includes anti-artemin antibodies comprising an Fc domain comprising one or more pairs or groups of mutations selected from the group consisting of: 250Q and 248L (e.g., T250Q and M248L); 252Y, 254T and 256E (e.g., M252Y, S254T and T256E); 428L and 434S (e.g., M428L and N434S); and 433K and 434F (e.g., H433K and N434F). All possible combinations of the foregoing Fc domain mutations, and other mutations within the antibody variable domains disclosed herein, are contemplated within the scope of the present disclosure.

Polynucleotides, Vectors, and Host Cells

[082] In another aspect, the present disclosure provides nucleic acid molecules comprising one or more polynucleotide sequences encoding the antibodies or antigen-binding fragments disclosed herein, as well as vectors (e.g., expression vectors) encoding such polynucleotide sequences and host cells into which such vectors have been introduced.

[083] In some embodiments, the nucleic acid molecule comprises one or more polynucleotide sequences encoding an antibody or antigen-binding fragment disclosed in Table 1 or Table 9. In some embodiments, the nucleic acid molecule comprises one or more polynucleotide sequences set forth in Table 2 or Table 9.

[084] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an HCVR comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs:4, 6, and 8, respectively. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an HCVR comprising the sequence of SEQ ID NO:2. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequences of SEQ ID NOs:3, 5, and 7. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:1 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:1. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:17 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:17.

[085] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an HCVR comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs:24, 26, and 28, respectively. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an HCVR comprising the sequence of

SEQ ID NO:22. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequences of SEQ ID NOs:23, 25, and 27. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:21 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:21. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:37 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:37.

[086] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an HCVR comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs:44, 46, and 48, respectively. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an HCVR comprising the sequence of SEQ ID NO:42. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequences of SEQ ID NOs:43, 45, and 47. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:41 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:41. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:57 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:57.

[087] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an HCVR comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs:64, 66, and 68, respectively. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an HCVR comprising the sequence of SEQ ID NO:62. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequences of SEQ ID NOs:63, 65, and 67. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:61 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:61. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:77 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:77.

[088] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an LCVR comprising the LCDR1, LCDR2, and LCDR3 of SEQ ID

NOs:12, 14, and 16, respectively. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an LCVR comprising the sequence of SEQ ID NO:10. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequences of SEQ ID NOs:11, 13, and 15. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:9 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:9. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:19 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:19.

[089] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an LCVR comprising the LCDR1, LCDR2, and LCDR3 of SEQ ID NOs:32, 34, and 36, respectively. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an LCVR comprising the sequence of SEQ ID NO:30. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequences of SEQ ID NOs:31, 33, and 35. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:29 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:29. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:39 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:39.

[090] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an LCVR comprising the LCDR1, LCDR2, and LCDR3 of SEQ ID NOs:52, 54, and 56, respectively. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an LCVR comprising the sequence of SEQ ID NO:50. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequences of SEQ ID NOs:51, 53, and 55. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:49 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:49. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:59 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:59.

[091] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an LCVR comprising the LCDR1, LCDR2, and LCDR3 of SEQ ID NOs:72, 74, and 76, respectively. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an LCVR comprising the sequence of SEQ ID NO:70. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequences of SEQ ID NOs:71, 73, and 75. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:69 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:69. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO:79 or has at least 90% sequence identity (e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity) to SEQ ID NO:79.

[092] In some embodiments, compositions are provided comprising one or more nucleic acid molecules as disclosed herein (e.g., a first nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR of an anti-artemin antibody, and a second nucleic acid molecule comprising a polynucleotide sequence encoding an LCVR of an anti-artemin antibody).

[093] The present disclosure also provides recombinant expression vectors carrying one or more nucleic acid molecules as disclosed herein, as well as host cells into which such vectors have been introduced. In some embodiments, two or more expression vectors are provided (e.g., a first expression vector comprising a first nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR of an anti-artemin antibody, and a second expression vector comprising a second nucleic acid molecule comprising a polynucleotide sequence encoding an LCVR of an anti-artemin antibody). In some embodiments, an expression vector comprises two or more nucleic acid molecules (e.g., an expression vector comprising (i) a first nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR of an anti-artemin antibody and (ii) a second nucleic acid molecule comprising a polynucleotide sequence encoding an LCVR of an anti-artemin antibody). Also provided herein are methods of producing anti-artemin antibodies or antigen-binding fragments using the nucleic acid sequences and/or vectors as described herein. In some embodiments, the method of producing the antibody or antigen-binding fragment thereof comprises culturing a host cell comprising one or more nucleic acid sequences and/or expression vectors as described herein under conditions permitting production of the antibodies or antigen-binding fragments, and recovering the antibodies or antigen-binding fragments so produced.

[094] In some embodiments, a host cell comprising one or more nucleic acid sequences and/or vectors as described herein is a prokaryotic cell (e.g., *E. coli*). In some embodiments,

the host cell is a eukaryotic cell, such as a non-human mammalian cell (e.g., a Chinese Hamster Ovary (CHO) cell, NS0 cell, BHK cell, or HEK293 cell). Also provided herein are methods of producing anti-artemin antibodies or antigen-binding fragments by culturing the host cells under conditions permitting production of the antibodies or antigen-binding fragments, and recovering the antibodies or antigen-binding fragments so produced.

Characterization of Anti-Artemin Antibodies

[095] The present disclosure includes antibodies and antigen-binding fragments thereof that bind to human artemin with high affinity. In some embodiments, the present disclosure includes antibodies and antigen-binding fragments thereof that bind human ARTN (e.g., at 25°C) with a K_D of less than about 5 nM as measured by surface plasmon resonance or bio-layer interferometry, e.g., using an assay format as defined in Example 2 herein. In some embodiments, the human ARTN is a mature form of ARTN, e.g., amino acids 108-220 of the human ARTN protein sequence set forth in SEQ ID NO:81. In certain embodiments, the antibodies or antigen-binding fragments of the present disclosure bind human ARTN with a K_D of less than about 5 nM, less than about 1 nM, less than about 500 pM, less than about 400 pM, less than about 300 pM, less than about 200 pM, less than about 100 pM, less than about 90 pM, less than about 80 pM, less than about 70 pM, less than about 60 pM, less than about 50 pM, less than about 40 pM, less than about 30 pM, less than about 20 pM, less than about 10 pM, less than about 5 pM, less than about 4 pM, less than about 2 pM, less than about 1 pM, less than about 0.5 pM, less than about 0.2 pM, less than about 0.1 pM, or less than about 0.05 pM, as measured by surface plasmon resonance e.g., using an assay format as defined in Example 2 herein, or a substantially similar assay.

[096] In some embodiments, the present disclosure includes antibodies and antigen-binding fragments thereof that bind human ARTN with a dissociative half-life ($t_{1/2}$) of greater than about 30 minutes as measured by surface plasmon resonance or bio-layer interferometry at 25°C, e.g., using an assay format as defined in Example 2 herein, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments of the present disclosure bind human ARTN with a $t_{1/2}$ of greater than about 30 minutes, greater than about 40 minutes, greater than about 50 minutes, greater than about 60 minutes, greater than about 70 minutes, greater than about 80 minutes, greater than about 90 minutes, greater than about 100 minutes, greater than about 150 minutes, greater than about 200 minutes, greater than about 250 minutes, or greater than about 300 minutes, as measured by surface plasmon resonance at 25°C, e.g., using an assay format as defined in Example 2 herein, or a substantially similar assay.

[097] In some embodiments, the present disclosure includes antibodies and antigen-binding fragments thereof that block ARTN protein from binding to GFR α 3. In some

embodiments, the present disclosure includes antibodies and antigen-binding fragments thereof that block monomeric ARTN (e.g., human, cynomolgus monkey, and/or mouse ARTN) protein binding to human GFR α 3, as measured by a blocking ELISA assay, e.g., using an assay format as defined in Example 2 herein, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments of the present disclosure block at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90% of human ARTN binding to human GFR α 3 as measured by blocking ELISA, e.g., using an assay format as defined in Example 3 herein, or a substantially similar assay.

[098] In some embodiments, the present disclosure includes antibodies and antigen-binding fragments thereof that inhibit artemin-mediated cell signaling. In some embodiments, the present disclosure includes antibodies and antigen-binding fragments thereof that inhibit artemin-mediated cell signaling as measured using a bioassay in a cell line expressing human GFR α 3 and human RET, e.g., as set forth in Example 4 or a substantially similar assay.

Epitope Mapping and Related Technologies

[099] In some embodiments, the epitope on ARTN to which the antibodies of the present disclosure bind may consist of a single contiguous sequence of 3 or more (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) amino acids of a ARTN protein. Alternatively, the epitope may consist of a plurality of non-contiguous amino acids (or amino acid sequences) of ARTN. In some embodiments, the antibodies of the disclosure may interact with amino acids contained within an ARTN monomer, or may interact with amino acids on two different chains of an ARTN dimer. The term "epitope," as used herein, refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstance, an epitope may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

[0100] Various techniques known to persons of ordinary skill in the art can be used to determine whether an antibody "interacts with one or more amino acids" within a polypeptide or protein. Exemplary techniques that can be used to determine an epitope or binding domain of a particular antibody include, e.g., routine crossblocking assay such as that described in *Antibodies*, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harbor, NY), point mutagenesis (e.g., alanine scanning mutagenesis, arginine scanning

mutagenesis, etc.), peptide blots analysis (Reineke, 2004, *Methods Mol Biol* 248:443-463), protease protection, and peptide cleavage analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer, 2000, *Protein Science* 9:487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antibody to the deuterium-labeled protein. Next, the protein/antibody complex is transferred to water to allow hydrogen-deuterium exchange to occur at all residues except for the residues protected by the antibody (which remain deuterium-labeled). After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues which correspond to the specific amino acids with which the antibody interacts. See, e.g., Ehring (1999) *Analytical Biochemistry* 267(2):252-259; Engen and Smith (2001) *Anal. Chem.* 73:256A-265A. X-ray crystal structure analysis can also be used to identify the amino acids within a polypeptide with which an antibody interacts.

[0101] In some embodiments, the present disclosure provides anti-artemin antibodies that bind to the same epitope as any of the specific exemplary antibodies described herein (e.g., antibodies comprising any of the amino acid sequences set forth in Table 1 or Table 9 below).

[0102] In some embodiments, the present disclosure provides anti-artemin antibodies that compete for binding to ARTN with any of the specific exemplary anti-artemin antibodies described herein.

[0103] One skilled in the art can determine whether a particular antibody thereof binds to the same epitope as, or competes for binding with, a reference antibody of the present disclosure by using routine methods known in the art. For example, to determine if a test antibody binds to the same epitope on ARTN as a reference antibody of the present disclosure, the reference antibody is first allowed to bind to an ARTN protein. Next, the ability of a test antibody to bind to the ARTN protein is assessed. If the test antibody is able to bind to ARTN following saturation binding with the reference antibody, it can be concluded that the test antibody binds to a different epitope of ARTN than the reference antibody. On the other hand, if the test antibody is not able to bind to ARTN following saturation binding with the reference antibody, then the test antibody may bind to the same epitope of ARTN as the epitope bound by the reference antibody of the disclosure. Additional routine experimentation (e.g., peptide mutation and binding analyses) can then be carried out to confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference antibody or if steric blocking (or another phenomenon) is responsible for the lack of observed binding. Experiments of this sort can be performed

using ELISA, RIA, Biacore, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art. In accordance with certain embodiments of the present disclosure, two antibodies bind to the same (or overlapping) epitope if, e.g., a 1-, 2-, 5-, 10-, 20- or 100-fold excess of one antibody inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans et al., *Cancer Res.* 1990:50:1495-1502). Alternatively, two antibodies are deemed to bind to the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies are deemed to have "overlapping epitopes" if only a subset of the amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0104] To determine if a test antibody or antigen-binding fragment thereof competes for binding with a reference antibody, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antibody is allowed to bind to an ARTN protein under saturating conditions followed by assessment of binding of the test antibody to the ARTN protein. In a second orientation, the test antibody is allowed to bind to an ARTN protein under saturating conditions followed by assessment of binding of the reference antibody to the ARTN protein. If, in both orientations, only the first (saturating) antibody is capable of binding to ARTN, then it is concluded that the test antibody and the reference antibody compete for binding to ARTN. As will be appreciated by a person of ordinary skill in the art, an antibody that competes for binding with a reference antibody may not necessarily bind to the same epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

Preparation of Antibodies

[0105] Antibodies as disclosed herein can be prepared by any antibody generating technology known in the art. In certain embodiments, one or more of the individual components (e.g., heavy and light chains) of the antibodies are derived from chimeric, humanized or fully human antibodies. Methods for making such antibodies are well known in the art. For example, one or more of the heavy and/or light chains of the antibodies of the present disclosure can be prepared using VELOCIMMUNE™ technology. Using VELOCIMMUNE™ technology (or any other human antibody generating technology), high affinity chimeric antibodies to a particular antigen (e.g., ARTN) are initially isolated having a human variable region and a mouse constant region. The antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions are replaced with a desired human constant region to generate fully human heavy and/or light chains that can be incorporated into the antibodies.

[0106] In some embodiments, antibodies can be generated by administering to a mouse an immunogen (e.g., a peptide as shown in SEQ ID NO:82, optionally conjugated to a carrier), optionally in combination with an adjuvant. Following immunization, splenocytes are harvested and fused with mouse myeloma cells to preserve their viability and form hybridoma cell lines. The hybridoma cell lines are screened and selected to identify cell lines that produce artemin-specific antibodies. Alternatively, DNA encoding antigen-specific chimeric antibodies or the variable domains of the light and heavy chains can be isolated directly from antigen-positive B cells without fusion to myeloma cells, as described in U.S. 2007/0280945 or WO2016077666, each of which is incorporated by reference in its entirety.

[0107] In some embodiments, genetically engineered animals may be used to make human antibodies. Non-limiting exemplary genetically modified mice, and methods of generating antibodies from genetically modified mice, are described in US 8,697,940, US 10,130,081, US 10,561,124, and US 10,640,800, the entire contents of each of which are incorporated by reference herein. As used herein, "fully human" refers to an antigen-binding molecule, e.g., an antibody, or antigen-binding fragment or immunoglobulin domain thereof, comprising an amino acid sequence encoded by a DNA derived from a human sequence over the entire length of each polypeptide of the antigen-binding molecule, antibody, antigen-binding fragment, or immunoglobulin domain thereof. In some instances, the fully human sequence is derived from a protein endogenous to a human. In other instances, the fully human protein or protein sequence comprises a chimeric sequence wherein each component sequence is derived from human sequence. While not being bound by any one theory, chimeric proteins or chimeric sequences are generally designed to minimize the creation of immunogenic epitopes in the junctions of component sequences, e.g., compared to any wild-type human immunoglobulin regions or domains.

Bioequivalents

[0108] The present disclosure encompasses antibodies having amino acid sequences that vary from those of the described antibodies but that retain the ability to bind ARTN. Such variant molecules comprise one or more additions, deletions, or substitutions of amino acids when compared to a parent sequence, but exhibit biological activity that is essentially equivalent to that of the described antibodies. Likewise, the nucleic acid sequences encoding the antibodies of the present disclosure encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an antibody that is essentially bioequivalent to the antibodies disclosed herein.

[0109] The present disclosure includes antibodies that are bioequivalent to any of the exemplary antibodies set forth herein. Two antibodies are considered bioequivalent if, for

example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single dose or multiple dose. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, e.g., chronic use, and are considered medically insignificant for the particular drug product studied.

[0110] In one embodiment, two antibodies are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[0111] In one embodiment, two antibodies are bioequivalent if a patient can be switched one or more times between the first antibody (e.g., reference product) and the second antibody (e.g., biological product) without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

[0112] In one embodiment, two antibodies are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

[0113] Bioequivalence may be demonstrated by *in vivo* and *in vitro* methods. Non-limiting examples of bioequivalence measures include, e.g., (a) an *in vivo* test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an *in vitro* test that has been correlated with and is reasonably predictive of human *in vivo* bioavailability data; (c) an *in vivo* test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody.

[0114] Bioequivalent variants of the exemplary antibodies set forth herein may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other embodiments, bioequivalent antibodies may include the exemplary antibodies set forth herein comprising amino acid changes which modify the glycosylation characteristics of the antibodies, e.g., mutations which eliminate or remove glycosylation.

Pharmaceutical Compositions

[0115] In another aspect, the present disclosure provides pharmaceutical compositions comprising the anti-artemisin antibodies and antigen-binding fragments disclosed herein. The pharmaceutical compositions are formulated with one or more pharmaceutically acceptable vehicle, carriers, and/or excipients. Various pharmaceutically acceptable carriers and excipients are well-known in the art. See, e.g., Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. In some embodiments, the carrier is suitable for intravenous, intramuscular, oral, intraperitoneal, intrathecal, transdermal, topical, or subcutaneous administration.

[0116] In some embodiments, the pharmaceutical composition comprises an injectable preparation, such as a dosage form for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by known methods. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared can be filled in an appropriate ampoule.

[0117] The dose of antibody administered to a patient according to the present disclosure may vary depending upon the age and the size of the patient, symptoms, conditions, route of administration, and the like. The dose is typically calculated according to body weight or body surface area. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. Effective dosages and schedules for administering pharmaceutical compositions as disclosed herein may be determined empirically; for example, patient progress can be monitored by periodic assessment, and the dose adjusted accordingly. Moreover, interspecies scaling of dosages can be performed using well-known methods in the art (e.g., Mordenti *et al.*, 1991, *Pharmaceut. Res.* 8:1351).

[0118] Various delivery systems are known and can be used to administer the pharmaceutical composition, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu *et al.*, 1987, *J. Biol. Chem.* 262:4429-4432). Methods of

administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. In some embodiments, a pharmaceutical composition as disclosed herein is administered intravenously. In some embodiments, a pharmaceutical composition as disclosed herein is administered subcutaneously.

[0119] In some embodiments, an antibody or a pharmaceutical composition comprising an antibody as disclosed herein is contained within a container. Thus, in another aspect, containers comprising an antibody or pharmaceutical composition as disclosed herein are provided. For example, in some embodiments, an antibody or pharmaceutical composition is contained within a container selected from the group consisting of a glass vial, a syringe, a pen delivery device, and an autoinjector.

[0120] In some embodiments, an antibody or pharmaceutical composition of the present disclosure is delivered, *e.g.*, subcutaneously or intravenously, with a standard needle and syringe. In some embodiments, the syringe is a pre-filled syringe. In some embodiments, a pen delivery device or autoinjector is used to deliver an antibody or pharmaceutical composition of the present disclosure (*e.g.*, for subcutaneous delivery). A pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0121] Examples of suitable pen and autoinjector delivery devices include, but are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Bergdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany). Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but

are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand Oaks, CA), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.), and the HUMIRA™ Pen (Abbott Labs, Abbott Park IL).

[0122] In some embodiments, the antibody or pharmaceutical composition is delivered using a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201). In another embodiment, polymeric materials can be used; see, *Medical Applications of Controlled Release*, Langer and Wise (eds.), 1974, CRC Pres., Boca Raton, Florida. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, 1984, in *Medical Applications of Controlled Release*, supra, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, *Science* 249:1527-1533.

[0123] In some embodiments, pharmaceutical compositions for use as described herein are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. In some embodiments, the amount of the antigen-binding molecule contained in the dosage form is about 5 to about 500 mg, e.g., from about 5 to about 100 mg or from about 10 to about 250 mg.

Therapeutic Uses

[0124] In another aspect, the present disclosure provides for methods of using the anti-artemin antibodies and antigen-binding fragments disclosed herein. In some embodiments, the anti-artemin antibodies and antigen-binding fragments disclosed herein are useful for the treatment, prevention and/or amelioration of any disease, disorder, or condition associated with artemin expression (e.g., overexpression) or activity. In some embodiments, the disease, disorder, or condition is pain, e.g., acute pain, chronic pain, neuropathic pain, inflammatory pain, neuralgia (e.g., trigeminal neuralgia, postherpetic neuralgia, or general neuralgia), visceral pain, osteoarthritis pain, gout, radicular pain, sciatica, back pain, head or neck pain, breakthrough pain, post-surgical pain, chemotherapy induced neuropathic pain, radiotherapy-induced neuropathic pain, radiation-associated pain, or cancer pain (e.g., pain associated with bone cancer or pancreatic cancer).

[0125] In some embodiments, anti-artemin antibodies and antigen-binding fragments disclosed herein are useful for the treatment, prevention and/or amelioration of headache or pain associated with headache (e.g., for migraine, cluster headache, chronic headache, or tension headache).

[0126] In some embodiments, the antibodies or antigen-binding fragments thereof disclosed herein may also be used to treat any of the following conditions: non-malignant acute, chronic, or fracture bone pain; pain associated with arthritis (e.g., osteoarthritis or rheumatoid arthritis); spinal stenosis; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; visceral pain; chronic headache pain; tension headache, including cluster headaches; migraine; diabetic neuropathy; HIV-associated neuropathy; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome (CRPS); phantom pain; intractable pain; musculoskeletal pain; joint pain; acute gout pain; pruritus; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; abdominal pain; chest pain, including cardiac pain; pelvic pain; renal colic pain; acute obstetric pain, including labor pain; cesarean section pain; burn and trauma pain; endometriosis; herpes zoster pain; breakthrough pain; orofacial pain including sinusitis pain or dental pain; multiple sclerosis pain; leprosy pain; Guillain-Barre pain; and Burning Mouth Syndrome.

Dosage and Administration Regimens

[0127] In some embodiments, an amount of an anti-artemin antibody or antigen-binding fragment that is administered to a subject according to the methods disclosed herein is a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" means an amount that produces the desired effect for which it is administered.

[0128] In some embodiments, the antibody is administered to a subject as a weight-based dose. A "weight-based dose" (e.g., a dose in mg/kg) is a dose of the antibody that will change depending on the subject's weight.

[0129] In other embodiments, the antibody is administered as a fixed dose. A "fixed dose" (e.g., a dose in mg) means that one dose of the antibody is used for all subjects regardless of any specific subject-related factors, such as weight. In one particular embodiment, a fixed dose of an antibody is based on a predetermined weight or age.

[0130] Typically, a suitable dose of the antibody can be in the range of about 0.001 to about 200.0 milligram per kilogram body weight of the recipient, generally in the range of about 1 to 50 mg per kilogram body weight. For example, the antibody can be administered at about 0.1 mg/kg, about 0.2 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 3 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 40 mg/kg, or about 50 mg/kg per single dose.

Values and ranges intermediate to the recited values are also intended to be part of this disclosure.

[0131] In some embodiments, the antibody is administered as a fixed dose of between about 5 mg to about 2500 mg. In some embodiments, the antibody is administered as a fixed dose of about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1500 mg, about 2000 mg, or about 2500 mg. Values and ranges intermediate to the recited values are also intended to be part of this disclosure.

[0132] In some embodiments, the antibody is administered to a subject at a dosing frequency of about four times a week, twice a week, once a week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every eight weeks, once every twelve weeks, or less frequently so long as a therapeutic response is achieved.

[0133] In some embodiments, multiple doses of an antibody as disclosed herein are administered to a subject over a defined time course. In some embodiments, the methods of the present disclosure comprise sequentially administering to a subject multiple doses of the antibody. As used herein, "sequentially administering" means that each dose of the antibody is administered to the subject at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks or months). In some embodiments, the methods of the disclosure comprise sequentially administering to the patient a single initial dose of the antibody, followed by one or more secondary doses of the antibody, and optionally followed by one or more tertiary doses of the antibody.

[0134] The terms "initial dose," "secondary dose(s)," and "tertiary dose(s)" refer to the temporal sequence of administration of the antibody. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "loading dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. In some embodiments, the initial, secondary, and tertiary doses may all contain the same amount of the antibody, but may differ from one another in terms of frequency of administration. In some embodiments, the amount of the antibody contained in the initial, secondary and/or tertiary doses varies from one another (e.g., adjusted up or down as

appropriate) during the course of treatment. In certain embodiments, one or more (e.g., 1, 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (e.g., "maintenance doses"). In some embodiments, the initial dose and the one or more secondary doses each contain the same amount of the antibody. In other embodiments, the initial dose comprises a first amount of the antibody, and the one or more secondary doses each comprise a second amount of the antibody. For example, the first amount of the antibody can be 1.5x, 2x, 2.5x, 3x, 3.5x, 4x or 5x or more than the second amount of the antibody.

[0135] In some embodiments, each secondary and/or tertiary dose is administered 1 to 14 (e.g., 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of the antibody that is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0136] The methods of the disclosure may comprise administering to a patient any number of secondary and/or tertiary doses of an antibody. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[0137] In some embodiments involving multiple secondary doses, each secondary dose is administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1, 2, 3, or 4 weeks after the immediately preceding dose. Similarly, in some embodiments involving multiple tertiary doses, each tertiary dose is administered at the same frequency as the other tertiary doses. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

Combination Therapies

[0138] In some embodiments, an antibody or antigen-binding fragment of the disclosure can be used in combination with one more other therapeutic agents. In some embodiments, the additional therapeutic agent(s) is an antibody, small molecule, inhibitory nucleic acid (e.g., RNAi), antibody drug conjugate, bispecific antibody, or a combination thereof.

[0139] In some embodiments, an anti-artemin antibody of the disclosure can be administered in combination with another artemin inhibitor, an inhibitor of GFR α 3 (e.g., an antibody disclosed in WO 2014/031712, incorporated by reference herein), an inhibitor of another GDNF family ligand or receptor, e.g. an inhibitor of GDNF, neurturin (NRTN), persephin (PSPN), GFR α 1, GFR α 2, or GFR α 4, or a RET inhibitor.

[0140] In some embodiments, the anti-artemin antibody is administered in combination with an additional therapeutic agent that reduces, relieves, or ameliorates pain. Exemplary additional therapeutic agents include, but are not limited to: a COX-2 inhibitor; a local anesthetic; an NMDA modulator; a cannabinoid receptor agonist; a P2X family modulator; a VR1 antagonist; a substance P antagonist; an inhibitor of a voltage-gated sodium channel (Nav), for example, a Nav1.7 antagonist, Nav1.8 antagonist, or Nav1.9 antagonist (e.g., an antibody, small molecule inhibitor, or inhibitory nucleic acid against Nav1.7, Nav1.8, or Nav1.9); a calcium channel inhibitor; a potassium channel inhibitor; a cytokine inhibitor or cytokine receptor antagonist (e.g., an interleukin-1 (IL-1) inhibitor (such as rilonacept ("IL-1 trap"; Regeneron) or an interleukin-1 receptor (IL-1R) inhibitor, an IL-18 inhibitor, an IL-6 or IL-6R inhibitor, an IL-17 inhibitor, a tumor necrosis factor (TNF) or TNF receptor inhibitor (e.g., adalimumab), or an inhibitor of TWEAK (TNF-related WEAK inducer of apoptosis)); a growth factor inhibitor (e.g., nerve growth factor (NGF) inhibitor such as a small molecule NGF antagonist or an anti-NGF antibody); a neurotrophic factor inhibitor (e.g., an inhibitor of BDNF, TrkA, TrkB or p75, or another inhibitor of a GDNF family ligand or receptor); an antiepileptic/anti-convulsant drug (e.g., gabapentin, pregabalin); an opioid; morphine; low dose colchicine; aspirin or another NSAID; steroids (e.g., prednisone, methotrexate, etc.); low dose cyclosporine A; a selective serotonin reuptake inhibitor (SSRI); a serotonin norepinephrine reuptake inhibitor (SNRI); a tricyclic; an inhibitor of an acid sensing ion channel (e.g. ASIC1 or ASIC3); uric acid synthesis inhibitors (e.g., allopurinol); uric acid excretion promoters (e.g., probenecid, sulfapyrazone, benzbromarone, etc.); and/or corticosteroids.

[0141] The additional therapeutically active component(s) may be administered just prior to, concurrent with, or shortly after the administration of an antibody of the present disclosure. For the purposes of the present disclosure, such administration regimens are considered the administration of an antibody "in combination with" an additional therapeutically active component.

[0142] The present disclosure includes pharmaceutical compositions in which an antibody of the present disclosure is co-formulated with one or more of the additional therapeutically active component(s) as described elsewhere herein.

EXAMPLES

[0143] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the disclosure, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1: Generation of Human Antibodies to Human Artemin

[0144] Antibodies against human artemin were obtained by immunizing a VELOCIMMUNE® mouse (i.e., an engineered mouse comprising DNA encoding human Immunoglobulin heavy and kappa chain variable regions) with a human artemin antigen (hARTN(A108-G220) with a C-terminal mmH tag; SEQ ID NO:82), followed by a booster with the same immunogen.

[0145] Following immunization, antibodies were isolated directly from antigen-positive mouse B cells, e.g., as described in U.S. Pat. No. 7,582,298, incorporated by reference herein. Using this method, fully human anti-hARTN antibodies (i.e., antibodies possessing human variable domains and human constant domains) were obtained. Anti-ARTN antibodies generated using this method were designated H4H33331P, H4H33335P, H4H33336P, and H4H33349P. Certain biological properties of the exemplary anti-ARTN antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Table 1: Amino Acid Sequence Identifiers

Antibody Designation	SEQ ID NOs:									
	HCVR	HCDR1	HCDR2	HCDR3	HC	LCVR	LCDR1	LCDR2	LCDR3	LC
H4H33331P	2	4	6	8	18	10	12	14	16	20
H4H33335P	22	24	26	28	38	30	32	34	36	40
H4H33336P	42	44	46	48	58	50	52	54	56	60
H4H33349P	62	64	66	68	78	70	72	74	76	80

Table 2: Nucleic Acid Sequence Identifiers

Antibody Designation	SEQ ID NOs:									
	HCVR	HCDR1	HCDR2	HCDR3	HC	LCVR	LCDR1	LCDR2	LCDR3	LC
H4H33331P	1	3	5	7	17	9	11	13	15	19

H4H33335P	21	23	25	27	37	29	31	33	35	39
H4H33336P	41	43	45	47	57	49	51	53	55	59
H4H33349P	61	63	65	67	77	69	71	73	75	79

Example 2: Binding Characterization for Artemin Antibodies

Octet Binding of Artemin Monoclonal Antibodies

[0146] The binding of Artemin to each of Artemin monoclonal antibodies (mAbs) H4H33331P, H4H33335P, H4H33336P, and H4H33349P was determined using a real time, label-free bio-layer interferometry (BLI) assay on the Octet HTX biosensor platform (Pall ForteBio Corp.). Tagged Artemin proteins were generated comprising the mature region of the human (hArtemin, Uniprot Q5T4W7-1, amino acids A108-G220), cynomolgous monkey (Macaca fascicularis, MfArtemin, XP_015292608.1, amino acids A108-G220; X110G, X111P, X112G, X113S, X114R, X115P, X116R; X denotes human sequences at those specific positions) or mouse (mArtemin, Uniprot Q9Z0L2-1, amino acids A112-G224) protein fused to an epitope tag, myc-myc-6xHis, at the c-terminus). The sequence of tagged human Artemin, referred to as "hArtemin-MMH", is set forth at SEQ ID NO:82; the sequence of tagged monkey Artemin, referred to as "MfArtemin-MMH", is set forth at SEQ ID NO:83; and the sequence of tagged mouse Artemin, referred to as "mArtemin-MMH" or "msArtemin-MMH", is set forth at SEQ ID NO:84.

[0147] The entire experiment was performed at 25°C in 10 mM HEPES, 150 mM NaCl, 3 mM EDTA, 0.02% NaN₃ and 0.05% v/v Surfactant Tween-20, 1 mg/mL BSA, pH7.4 (HBS-EBT) buffer with the plate shaking at a speed of 1000 rpm. Different Artemin mAbs were first captured onto anti-human antibody (AHC) coated Octet biosensor tips (ForteBio Inc, # 18-5064) by submerging the biosensor tips for 40 seconds in wells containing 2 µg/mL of Artemin mAb. The Artemin mAb-captured biosensor tips were later dipped in wells containing different concentrations (30–3.75 nM, 2-fold serial dilution) of tagged human, monkey, or mouse Artemin protein for 3 minutes and their dissociation in HBS-EBT buffer was monitored for 20 minutes. All the Artemin and Artemin mAb samples were prepared in HBS-EBT buffer. The real-time binding response was monitored during the entire course of the experiment and the binding response at the end of every step was recorded.

[0148] The binding of various Artemin reagents to the different Artemin mAbs are reported in Table 3 and the concentration dependent binding data are also provided in Figures 1 to 3.

[0149] As shown in Table 3 and Figure 1, all four Artemin mAbs bound to hArtemin-MMH at 25°C.

[0150] As shown in Table 3 and Figure 2, all four Artemin mAbs bound to MfArtemin-MMH at 25°C.

[0151] As shown in Table 3 and Figure 3, all four Artemin mAbs bound to mArtemin-MMH at 25°C.

Table 3: Binding of Various Artemin Reagents to Different Artemin mAbs

mAb Captured	Artemin Binding Tested	mAb Capture Level (nm)	Artemin Binding Response (nm)			
			3.75nM	7.5nM	15nM	30nM
H4H33331P	hArtemin-MMH	0.34 ± 0.01	0.02	0.07	0.11	0.11
	MfArtemin-MMH	0.35 ± 0.01	0.00	0.01	0.03	0.09
	mArtemin-MMH	0.35 ± 0.01	0.03	0.07	0.08	0.10
H4H33335P	hArtemin-MMH	0.32 ± 0.01	0.02	0.07	0.11	0.11
	MfArtemin-MMH	0.33 ± 0.01	0.00	0.00	0.04	0.09
	mArtemin-MMH	0.33 ± 0.01	0.02	0.05	0.07	0.08
H4H33336P	hArtemin-MMH	0.37 ± 0.01	0.03	0.05	0.09	0.12
	MfArtemin-MMH	0.38 ± 0.01	0.01	0.01	0.03	0.06
	mArtemin-MMH	0.37 ± 0.01	0.01	0.00	0.01	0.03
H4H33349P	hArtemin-MMH	0.36 ± 0.01	0.07	0.11	0.11	0.11
	MfArtemin-MMH	0.38 ± 0.01	0.02	0.04	0.09	0.12
	mArtemin-MMH	0.36 ± 0.01	0.07	0.11	0.11	0.11
Isotype mAb	hArtemin-MMH	0.34	NT [§]	NT	NT	0.00
	MfArtemin-MMH	0.35	NT	NT	NT	0.00
	mArtemin-MMH	0.35	NT	NT	NT	0.00

[§] indicates that the binding of Artemin to isotype mAb-captured surface was not tested at the indicated concentrations.

Biacore Binding Kinetics of Artemin Monoclonal Antibodies

[0152] The equilibrium dissociation constant (K_D) for Artemin binding to each of Artemin monoclonal antibodies (mAbs) H4H33331P, H4H33335P, H4H33336P, and H4H33349P was determined using a real-time surface plasmon resonance Biacore T200 biosensor. All binding studies were performed in 10 mM HEPES, 150 mM NaCl, 3 mM EDTA, and 0.05% v/v Surfactant Tween-20, pH 7.4 (HBS-ET) running buffer at 25°C. The Biacore CM4 sensor chip surface was first derivatized by amine coupling with anti-myc mAb to capture hArtemin-

MMH, MfArtemin-MMH, or mArtemin-MMH. Different concentrations of Artemin mAbs (60–2.2 nM, 3-fold serial dilution) prepared in HBS-EP running buffer were injected over the Artemin-captured surfaces for 3 min at a flow rate of 50 μ L/min and their dissociation in HBS-ET running buffer was monitored for 5 minutes. At the end of each cycle, the Artemin-captured surfaces were regenerated using a 6 sec injection of 20 mM phosphoric acid.

[0153] The association rate (k_a) and dissociation rate (k_d) were determined by fitting the real-time binding sensorgrams to a 1:1 binding model with mass transport limitation using Scrubber 2.0c curve-fitting software. Binding dissociation equilibrium constant (K_D) and dissociative half-life ($t_{1/2}$) were calculated from the kinetic rates as: K_D (M) = k_d / k_a , and $t_{1/2}$ (min) = $[\ln 2 / (60 * k_d)]$.

[0154] Binding kinetics parameters for Artemin binding to different Artemin mAbs of the invention at 25°C are shown in Tables 4-6.

[0155] As shown in Table 4, all four Artemin mAbs bound to hArtemin-MMH at 25°C with K_D values ranging from 119 pM to 2.91 nM.

[0156] As shown in Table 5, three out of four Artemin mAbs (H4H33331P, H4H33335P, and H4H33349P) bound to MfArtemin-MMH at 25°C with K_D values ranging from 111 pM to 1.51 nM. Specific binding was also observed for the mAb H4H33335P, but binding kinetic parameters could not be determined under the current experimental conditions.

[0157] As shown in Table 6, two out of four Artemin mAbs (H4H33331P and H4H33349P) bound to mArtemin-MMH at 25°C with K_D values of 113 pM and 346 pM, respectively. Specific binding was also observed for the mAbs H4H33335P and H4H33336P, but binding kinetic parameters could not be determined under the current experimental conditions.

Table 4: Binding Kinetics Parameters of Different Artemin Monoclonal Antibodies Binding to hArtemin-MMH at 25°C

mAb Tested	hArtemin-MMH Capture Level (RU)	60nM Artemin mAb Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
H4H33331P	3.5 $\pm$ 0.1	7	1.26E+05	3.66E-04	2.91E-09	32
H4H33335P	3.5 $\pm$ 0.1	4	8.53E+04	1.90E-04	2.22E-09	61
H4H33336P	3.6 $\pm$ 0.1	15	2.49E+05	3.75E-05	1.50E-10	308
H4H33349P	3.6 $\pm$ 0.1	18	4.97E+05	5.90E-05	1.19E-10	196
Isotype Control mAb	3.6 $\pm$ 0.1	0	NB*	NB*	NB*	NB*

* indicates that no binding (NB) was observed under the current experimental conditions.

**Table 5: Binding Kinetics Parameters of Different Artemin Monoclonal Antibodies Binding to
MfArtemin-MMH at 25°C**

mAb Tested	MfArtemin-MMH Capture Level (RU)	60nM Artemin mAb Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
H4H33331P	4.8 ± 0.1	5	1.31E+05	1.99E-04	1.51E-09	58
H4H33335P	4.8 ± 0.1	3	NA [#]	NA [#]	NA [#]	NA [#]
H4H33336P	4.6 ± 0.1	11	2.07E+05	2.30E-05	1.11E-10	502
H4H33349P	4.7 ± 0.1	14	4.57E+05	9.60E-05	2.10E-10	120
Isotype Control mAb	4.8 ± 0.1	0	NB*	NB*	NB*	NB*

* indicates that no binding (NB) was observed under the current experimental conditions.

indicates that specific binding was observed, but binding kinetic parameters could not be determined under the current experimental conditions and therefore not available (NA).

**Table 6: Binding Kinetics Parameters of Different Artemin Monoclonal Antibodies Binding to
mArtemin-MMH at 25°C**

mAb Tested	mArtemin-MMH Capture Level (RU)	60nM Artemin mAb Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
H4H33331P	2.6 ± 0.1	7	1.56E+05	5.40E-05	3.46E-10	214
H4H33335P	2.7 ± 0.1	3	NA [#]	NA [#]	NA [#]	NA [#]
H4H33336P	2.8 ± 0.1	3	NA [#]	NA [#]	NA [#]	NA [#]
H4H33349P	2.9 ± 0.1	20	5.21E+05	5.91E-05	1.13E-10	195
Isotype Control mAb	3.0 ± 0.1	0	NB*	NB*	NB*	NB*

* indicates that no binding (NB) was observed under the current experimental conditions.

indicates that specific binding was observed, but binding kinetic parameters could not be determined under the current experimental conditions and therefore not available (NA).

Example 3: Anti-ARTN Antibody Blocking of ARTN Binding to GFRα3

[0158] Multiple artemin blocking assays were developed using an ELISA-based format to determine the ability of anti-artemin (ARTN) antibodies to block monomeric human, monkey (Macaca fascicularis) and mouse ARTN proteins binding to human GFRα3 (glial cell line derived neurotrophic factor (GDNF) family receptor alpha 3).

[0159] The artemin proteins used in the experiments were hArtemin-MMH, MfArtemin-MMH, or mArtemin-MMH, disclosed in Example 2 above. The human GFR α 3 used in the experiments was comprised of UniProtKB Accession No. O60609, amino acids D32-W382, with the Fc portion of the human IgG1 at the c-terminus, and is referred to as "hGFR α 3.hFc" (SEQ ID NO:85).

[0160] Experiments were carried out using the following procedures. Plates were coated with hGFR α 3.hFc at 2 μ g/ml in PBS on a 96-well microtiter plate at 4°C overnight for all three assays. After overnight coating, nonspecific binding sites were subsequently blocked using a 0.5% (w/v) BSA in PBS for one hour at room temperature. In other microtiter plates, a constant amount of either 75 pM hARTN.mmh, 400 pM mfARTN.mmh, or 150 pM msARTN.mmh were separately bound with anti-ARTN antibodies and an irrelevant IgG4 antibody control at a serial dilution series from 0.0017 nM to 100 nM in PBS +0.5% BSA. After a one-hour incubation, the mixture solutions were transferred to microtiter plates coated with hGFR α 3.hFc. After one hour of incubation at RT, the wells were washed with PBST, and plate-bound ARTN was detected with an anti-penta-His antibody conjugated with horseradish peroxidase (HRP) (Qiagen). The plates were then developed using TMB substrate solution (BD Biosciences, #555214) according to manufacturer's recommendation and absorbance at 450 nm was measured on a Victor X5 plate reader.

[0161] Binding data were analyzed using a sigmoidal dose-response model within Prism™ software (GraphPad). The calculated IC50 value, defined as the concentration of antibody required to block 50% of ARTN.mmh binding to plate-coated hGFR α 3.hFc, was used as an indicator of blocking potency. The lower limit of the assay (LLOA) for the IC50 of hARTN.mmh, mfARTN.mmh, and mARTN.mmh were 18.8 pM, 100 pM, and 37.5 pM respectively, based on the binding stoichiometry of two artemin to one antibody. If the calculated IC50 value was below the LLOA, less than LLOA was reported. Percent blocking at 100 nM antibody was calculated based on the background-corrected binding signal observed at the highest antibody concentration tested using the formula listed below and reported for all tested antibodies:

$$\% \text{ Blocking} = 100 - \frac{[\text{Experimental Signal}_{(\text{highest Ab conc})} - \text{Background Signal}_{(\text{buffer})}]}{[\text{Maximum Signal}_{(\text{ARTN.mmh alone})} - \text{Background Signal}_{(\text{buffer})}]} \times 100$$

Results

[0162] The ability of anti-ARTN antibodies to block human, monkey and mouse artemin binding to human GFR α 3 was assessed using multiple blocking ELISA formats. In these assays 75 pM hARTN.mmh, 400 pM mfARTN.mmh or 150 pM msARTN.mmh were titrated with a wide range of concentrations of anti-ARTN antibodies and the binding of the three

species of artemin to hGFR α 3.hFc in the presence of antibodies were evaluated. The plate bound ARTN.mmh was detected with an HRP conjugated anti-penta-His antibody.

[0163] The four test antibodies potently blocked human, monkey, and mouse artemin binding to plate-bound human GFR α 3, with IC50s below 1 nM and greater than 50% blocking at the highest concentration of antibody tested. The blocking IC50s and percent blocking at the highest tested concentrations of the anti-ARTN antibodies are summarized in Table 7. The irrelevant isotype control antibody showed no blocking activity.

Table 7: Potency of Antibodies Blocking Human, Monkey, and Mouse Artemin Binding to Human GFR α 3

Ab	Human ARTN		Monkey ARTN		Mouse ARTN	
	IC50 (M)	% Blocking with 100 nM Ab	IC50 (M)	% Blocking with 100 nM Ab	IC50 (M)	% Blocking with 100 nM Ab
H4H33331P	3.80E-10	88	1.05E-10	90	1.36E-11*	83
H4H33335P	5.05E-10	65	2.33E-10	71	8.76E-11	63
H4H33336P	1.61E-10	93	7.50E-11*	86	4.10E-10	81
H4H33349P	1.28E-10	95	3.02E-11*	88	7.65E-12*	88
hlgG4 isotype control	--	-3	--	-28	--	-31
LLOA	1.88E-11		1.00E-10		3.75E-11	

* below lower limit of assay

Example 4: Inhibition of Artemin-Mediated Cell Signaling by Artemin Monoclonal Antibodies

[0164] To assess anti-Artemin antibody inhibition of Artemin-mediated cell signaling, a bioassay was established in HEK293 cells (human embryonic kidney, ATCC, #CRL-1573). HEK293 cells were transduced with a serum response element luciferase reporter (SRE-Luc, SA Biosciences) and engineered to stably express full-length human GFR α 3 (amino acids M1 to W400 of Genbank Accession No. NP_001487.2) and full-length human RET isoform c (amino acids M1 to F1073 of Genbank Accession No. NP_065681.1 with two amino acid substitutions at G691S and R982C). An optimal cell clone was isolated and the resulting cell line was named HEK293/SRELuc/hRET/hGFR α 3 cl.A3. Artemin proteins hArtemin-MMH, MfArtemin-MMH, or mArtemin-MMH are disclosed in Example 2 above.

[0165] For the bioassay, cells were seeded into 96-well plates at 2.5×10^4 cells/well using assay buffer (0.1% FBS in Opti-MEM medium) and cultured overnight (37°C, 5% CO₂). The following day, antibodies of the invention or an isotype control antibody were serially diluted (1:3) in assay media to final concentrations ranging from 100 nM to 1.7 pM (with an additional well for assay media alone without test molecule) and added to cells with a fixed

concentration of Artemin (500 pM hArtemin, 3 nM of mfArtemin, or 1 nM of mArtemin) at 37°C in 5% CO₂. To assess the extent of signaling activation, Artemin (h, mf, or m) was serially diluted (1:3) to final concentrations of 100 nM to 1.7 pM (with an additional well for assay media alone) and added to cells. After a 5-hour incubation, luciferase activity was evaluated by the addition of OneGlo™ luciferase assay system reagent (Promega E6130) and Relative Luminescence Units (RLU) were measured using an Envision multilabel plate reader (Perkin Elmer). Results were analyzed using a nonlinear regression (4-parameter logistic) in Prism® 8 to obtain EC50 and IC50 values. The percentage of inhibition was calculated using the following equation:

$$\% \text{ Inhibition} = 100 \times [(\text{RLU}_{\text{Artemin}} - \text{RLU}_{\text{inhibition}}) / (\text{RLU}_{\text{Artemin}} - \text{RLU}_{\text{Baseline}})]$$

[0166] In this equation “RLU_{Artemin}” refers to the RLU value from cells treated with constant Artemin without antibodies. “RLU_{inhibition}” refers to the RLU value measured at the maximum concentration of the antibody with constant Artemin. “RLU_{Baseline}” refers to RLU value of the cells measured in the absence of ligand or antibodies.

[0167] As shown in Table 8, anti-Artemin antibodies H4H33331P, H4H33335P, H4H33336P, and H4H33349P were tested on HEK293/SRELuc/hRET/hGFRα3 cl.A3 cells with 500 pM hArtemin, 3 nM of mfArtemin, or 1 nM of mArtemin. Human, cyno monkey and mouse Artemin activated signaling through human GFRα3 and Ret receptors with EC50 values of 813 pM, 2.26 nM and 620 pM, respectively.

Table 8: Inhibition of Human, Cyno Monkey, and Mouse Artemin by Anti-Artemin Antibodies in HEK293/SRELuc/hRET/hGFRα3 cl.A3 Cells

Antibody	500 pM hArtemin		3 nM mfArtemin		1 nM mArtemin	
	IC50	Max inhibition (%)	IC50	Max inhibition (%)	IC50	Max inhibition (%)
H4H33331P	7.06E-11	100	3.06E-10	100	1.72E-10	100
H4H33335P	1.13E-10	100	3.86E-10	100	1.42E-09	95
H4H33336P	4.96E-11	100	2.33E-10	100	8.35E-10	100
H4H33349P	2.60E-11	100	1.45E-10	100	9.65E-11	100
Isotype Control	No Inhibition	9	No Inhibition	10	No Inhibition	1

Example 5: Inhibition of Intra-Plantar Artemin-Induced Thermal Hyperalgesia by Artemin Monoclonal Antibodies

Animal Subjects

[0168] 10-16 week old adult C57BL/6 male mice (Jackson Laboratories) were used for the experiment. Animals were housed in groups of up to five in a temperature-controlled environment on a 12-hour light/dark cycle with water and standard laboratory chow available ad libitum. All experimental procedures were approved by Regeneron's Animal Care and Use Committee and were performed by an experimenter blind to the group assignments of the animals.

Acclimation and Baseline

[0169] In the week prior to intra-plantar injection, mice were handled and placed in the Hargreaves behavioral testing apparatus for at least two hours per day to acclimate them to the room and equipment. Animals were additionally acclimated for at least one hour before every testing session. Baseline nociceptive responses were taken at the end of the week.

Induction of Growth Factor-Induced Plantar Thermal Hyperalgesia

[0170] Baseline thermal hyperalgesia was evaluated using the Hargreaves Test (described below) before subcutaneous (s.c.) injections of artemin antibodies at 10 mg/kg were administered. PBS (one group) or recombinant mouse artemin from R&D Systems in 20 µl saline (five groups) was injected into the hindpaw three days later by placing mice into a clear plastic restrainer with their hind limbs exposed. The left hind limb was extended to inject 0.5 µg of artemin into the plantar surface of the paw. Thermal hyperalgesia was re-evaluated 4 days later. Using pilot results from artemin injections at a power level of .80 and alpha of .05, it was calculated that an n of 7-8 animals was needed to detect a return to baseline latencies to withdraw with antibody treatment. A sample size of 7 animals was chosen for the experiments because full blockade of the growth factor response was expected, and thus animal use could be minimized by selecting the smallest recommended sample size from the power analysis.

[0171] *Thermal hyperalgesia:* Animals were tested for heat sensitivity using the Hargreaves Test (Hargreaves et al, *Pain*, 1988, 32:77-88). Mice were placed on a 30°C-heated glass (IITC model 390G with model 400 heated base) in individual chambers and acclimated before the reading session. The apparatus was set at a laser intensity of 15% and testing was performed using repeated measures (three measures per foot) on the plantar surface of the ipsilateral hind paw. Mean latency to withdraw was recorded, with a maximum beam exposure of 20 sec allowed to avoid tissue damage. Latency to withdraw was statistically analyzed using a one way independent groups ANOVA to compare treatment groups, with α set at 0.05. The significant main effect of treatment was probed using Tukey post hoc tests.

Results

[0172] The four selected human anti-artemin antibodies (H4H33331P, H4H33335P, H4H33336P, and H4H33349P) were evaluated in the intraplantar growth factor-induced

hyperalgesia model. As shown in Figure 4, all four were shown to completely block thermal hyperalgesia induced by artemin in the Hargreaves Test at 10mg/kg s.c. such that withdrawal latencies were similar to the group treated with intra-plantar PBS. The withdrawal thresholds of the animals receiving the anti-artemin antibodies were significantly different than those of the animals receiving the isotype control antibody, suggesting that all four artemin antibodies were effective at inhibiting artemin-induced hyperalgesia.

Table 9: Informal Sequence Listing		
SEQ ID NO	Sequence	Description
1	GAGGTGCAGCTGGTGGAGAGCGGCGGCGACCTGGTGCAGCCGGCGGCAGCC TGAAGCTGAGCTGCGCCGAGCGGCTTACCTTCAGCGGCAGCGCCATGCACT GGGTGAGGCAGGCCAGCGGCAAGGGCCTGGAGTGGGTGGGCAGGATCAGGA ACAAGGTGCACAGGTACGCCACCGAGTACGGCGCCAGCGTGAAGGGCAGGTT CACCATCAGCAGGGACGACAGCAAGAACACCGCCTACCTGCAGATGAACAGCC TGAAGATCGAGGACACCGCCGTGTACTACTGCGTGGTGGTGGTGGCCGGCAGC ATCGAGGCCTTCGACATCTGGGGCCAGGGCACCATGGTGACCGTGAGCAGC	H4H33331P HCVR nucleotide sequence
2	EVQLVESGGDLVQPGGSLKLSCAASGFTFSGSAMHWVRQASGKLEWVGRIRNK VHRYATEYGASVKGRFTISRDDSKNTAYLQMNSLKIEDTAVYYCVVVVPGSIEAFDI WGQGTMTVSS	H4H33331P HCVR amino acid sequence
3	GGCTTCACCTTCAGCGGCAGCGCC	H4H33331P HCDR1 nucleotide sequence
4	GFTFSGSA	H4H33331P HCDR1 amino acid sequence
5	ATCAGGAACAAGGTGCACAGGTACGCCACC	H4H33331P HCDR2 nucleotide sequence
6	IRNKVHRYAT	H4H33331P HCDR2 amino acid sequence
7	GTGGTGGTGGTGCCCGGCAGCATCGAGGCCTTCGACATC	H4H33331P HCDR3 nucleotide sequence
8	VVVVPGSIEAFDI	H4H33331P HCDR3 amino acid sequence
9	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAG GGTGACCATCACCTGCAGGGCCAGCCAGAGCATCAGCACCTACCTGAACTGGT ACCAGCAGAAGCCCGCAAGGCCCAACCTGCTGATCTACGCCGCCAGCACCC TGGAGAGCGGCGTGGCCAGCAGGTTACGCGGCAGCGGCAGCGGCACCGACTT CACCCTGACCATCAGCAGCCTGCAGCCGAGGACTTCGAGATCTACTACTGCCA GCAGAGCTACAACATCCCCTGGACCTTCGGCCAGGGCACCAAGGTGGAGATCA AG	H4H33331P LCVR nucleotide sequence
10	DIQMTQSPSSLSASVGDRTITCRASQSISTYLNWYQKPGKAPNLLIYAASLTESGV PSRFGSGSGTDFTLTISLQPEDFEIYYCQQSYNIPWTFGQGTKEIK	H4H33331P LCVR amino acid sequence
11	CAGAGCATCAGCACCTAC	H4H33331P LCDR1 nucleotide sequence
12	QSISTY	H4H33331P LCDR1 amino acid sequence
13	GCCGCCAGC	H4H33331P LCDR2 nucleotide sequence
14	AAS	H4H33331P LCDR2 amino acid sequence
15	CAGCAGAGCTACAACATCCCCTGGACC	H4H33331P LCDR3 nucleotide sequence
16	QQSYNIPWT	H4H33331P LCDR3 amino acid sequence

17	GAGGTGCAGCTGGTGGAGAGCGGCGGCGACCTGGTGCAGCCCGGCGGCAGCC TGAAGCTGAGCTGCGCCGCCAGCGGCTTACCTTCAGCGGCAGCGCCATGCACT GGGTGAGGCAGGCCAGCGGCAAGGGCCTGGAGTGGGTGGGCAGGATCAGGA ACAAGGTGCACAGGTACGCCACCGAGTACGGCGCCAGCGTGAAGGGCAGGTT CACCATCAGCAGGGACGACAGCAAGAACACCGCCTACCTGCAGATGAACAGCC TGAAGATCGAGGACACCGCCGTGTACTACTGCGTGGTGGTGGTGGCCGCGAGC ATCGAGGCCTTCGACATCTGGGGCCAGGGCACCATGGTGACCGTGAGCAGCGC CAGCACCAAGGGCCCCAGCGTGTCCCCCTGGCCCCCTGCAGCAGGAGCACCA GCGAGAGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCC GTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGACACCTTCCC CGCCGTGCTGCAGAGCAGCGGCTGTACAGCCTGAGCAGCGTGGTGACCGTGC CCAGCAGCAGCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGCCC AGCAACACCAAGGTGGACAAGAGGGTGGAGAGCAAGTACGGCCCCCTGCCC CCCCGCCCCGCCCGAGTTCTGGGCGGCCCCAGCGTGTCTCTGTTCCCCCCC AAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGT GGTGGACGTGAGCCAGGAGGACCCCGAGGTGCAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCACAACGCCAAGACCAAGCCAGGGAGGAGCAGTTCAACA GCACCTACAGGGTGGTGAAGCGTGTGACCGTGTGCACCAGGACTGGCTGAAC GGCAAGGAGTACAAGTGAAGGTGAGCAACAAGGCGCTGCCAGCAGCATCG AGAAGACCATCAGCAAGGCCAAGGGCCAGCCAGGGAGCCCCAGGTGTACACC CTGCCCCCAGCCAGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCT GGTGAAGGGCTTCTACCCAGCGACATCGCGTGGAGTGGGAGAGCAACGGCC AGCCCCGAGAACAACTACAAGACCAACCCCCCGTGTGGACAGCGACGCGAGC TTCTTCTGTACAGCAGGCTGACCGTGGACAAGAGCAGGTGGCAGGAGGGCAA CGTGTTCACTGTCAGCGTGTGACGAGGCGCTGCACAACCTACACCCAGAA GAGCCTGAGCCTGAGCTGGGCAAG	H4H33331P heavy chain nucleotide sequence
18	EVQLVESGGDLVQPGGSLKLSAASGFTFSGSAMHWVRQASGKLEWVGRIRNK VHRYATEYGASVKGRFTISRDDSKNTAYLQMNSLKIEDTAVYYCVVVVPGSIEAFDI WGQGTMTVTSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTITCNVDHKPSNTKVDKRVESKYG PPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYV DGEVFNHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNYTQKSLSLSLGK	H4H33331P heavy chain amino acid sequence
19	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAG GGTGACCATCACCTGCAGGGCCAGCCAGAGCATCAGCACCTACCTGAAGTGGT ACCAGCAGAAGCCCGGCAAGGCCCAACCTGCTGATCTACGCCGCCAGCACCC TGGAGAGCGGCGTGGCCAGCAGGTTACGCGGCAGCGGCAGCGGCACCGACTT CACCCGTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGAGATCTACTACTGCCA GCAGAGCTACAACATCCCTGGACCTTCGGCCAGGGCACCAAGGTGGAGATCA AGAGGACCGTGGCCGCCCGCAGCGTTCATCTTCCCCCAGCGACGAGCAGC TGAAGAGCGGCCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCAGG GAGGCCAAGGTGCAGTGGAAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCC AGGAGAGCGTGACCGAGCAGGACGCAAGGACAGCACCTACAGCCTGAGCAG CACCCGTGACCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCG AGGTGACCCACCAAGGCGCTGAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGC GAGTGC	H4H33331P light chain nucleotide sequence
20	DIQMTQSPSSLSASVGRVTITCRASQSISTYLNWYQKPKAPNLLIYAASLESV PSRFSGSGSGTDFTLTISLQPEDFEIYYCQQSYNIPWTFGQGTKEIKRTVAAPSVFI FPPSDEQLKSGTASVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKST YLSLTSLTSLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	H4H33331P light chain amino acid sequence

21	GAGGTGCAGCTGGTGGAGAGCGGCGGCGCCTGGTGCAGCCGGCGGCAGCC TGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACGACATGCACT GGGTGAGGCAGGCCACCGGCAAGGGCCTGGAGTGGGTGAGCACCATCGACAC CGCCGGCGACACCTACTACCCCGGCAGCGTGAAGGGCAGGTTACCATCAGCA GGGAGAACGCCAAGAAGCAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCGG CGACACCGCCGTGTACTACTGCGCCAGGGACGGCGAGCTGGAGCTGCAGGGCT ACTTCGACCTGTGGGGCAGGGGCACCCTGGTGACCGTGAGCAGC	H4H33335P HCVR nucleotide sequence
22	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYDMHWVRQATGKGLEWVSTIDTAG DTYYPGSVKGRFTISRENAKNSLYLQMNSLRAGDTAVYYCARDGELELQGYFDLWG RGTLLTVSS	H4H33335P HCVR amino acid sequence
23	GGCTTCACCTTCAGCAGCTACGAC	H4H33335P HCDR1 nucleotide sequence
24	GFTFSSYD	H4H33335P HCDR1 amino acid sequence
25	ATCGACACCGCCGGCGACACC	H4H33335P HCDR2 nucleotide sequence
26	IDTAGDT	H4H33335P HCDR2 amino acid sequence
27	GCCAGGGACGGCGAGCTGGAGCTGCAGGGCTACTTCGACCTG	H4H33335P HCDR3 nucleotide sequence
28	ARDGELELQGYFDL	H4H33335P HCDR3 amino acid sequence
29	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAG GGTGACCATCACCTGCAGGGCCAGCCAGATCATCAGCATCTACCTGAACTGGTA CCAGCAGAAGCCCGGCAAGGCCCAAGCTGCTGATCTACGCCGCCAGCAGCC TGCAGAGCGGCGTGCCAGCAGGTTACGCGGCAGCGGCAGCGGCACCGACTTC ACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAG CAGAGCTACACCACCCCTGACCTTCGGCGGCGGCACCAAGGTGGAGATCAA G	H4H33335P LCVR nucleotide sequence
30	DIQMTQSPSSLSASVGDRTVITCRASQIISYLNWYQQKPGKAPKLLIYAASSLQSGV PSRFGSGSGTDFLTITSLQPEDFATYYCQSYTTPLTFGGGKVEIK	H4H33335P LCVR amino acid sequence
31	CAGATCATCAGCATCTAC	H4H33335P LCDR1 nucleotide sequence
32	QIISY	H4H33335P LCDR1 amino acid sequence
33	GCCGCCAGC	H4H33335P LCDR2 nucleotide sequence
34	AAS	H4H33335P LCDR2 amino acid sequence
35	CAGCAGAGCTACACCACCCCTGACC	H4H33335P LCDR3 nucleotide sequence
36	QQSYTTPLT	H4H33335P LCDR3 amino acid sequence

37	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCTGGTGCAGCCCGGCGGCAGCC TGAGGCTGAGCTGCGCCGCCAGCGGCTTACCTTCAGCAGCTACGACATGCACT GGGTGAGGCAGGCCACCGGCAAGGGCCTGGAGTGGGTGAGCACCATCGACAC CGCCGGCGACACCTACTACCCCGGCAGCGTGAAGGGCAGGTTACCATCAGCA GGGAGAACGCCAAGAAGCAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCGG CGACACCGCCGTGTACTACTGCGCCAGGGACGGCGAGCTGGAGCTGCAGGGCT ACTTCGACCTGTGGGGCAGGGGCACCTGGTGACCGTGAGCAGCGCCAGCACC AAGGGCCCCAGCGTGTCCCCCTGGCCCCCTGCAGCAGGAGCACCAGCGAGAG CACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCGAGCCCGTGACCGT GAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCGGTGC TGCAGAGCAGCGGCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCAGCAGC AGCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGCCCAGCAACAC CAAGGTGACAAGAGGGTGGAGAGCAAGTACGGCCCCCTGCCGCCCTGCC CCGCCCCGAGTTCTGGGCGGCCCCAGCGTGTTCCTGTTCCCCCAGGCCA AGGACACCTGATGATCAGCAGGACCCCGAGGTGACCTGCGTGGTGGTGAG GTGAGCCAGGAGGACCCGAGGTGCAGTTCAACTGGTACGTGGACGCGGTGG AGGTGACAACGCCAAGACCAAGGCCAGGAGGAGCAGTTCAACAGCACCTAC AGGGTGGTGAAGCTGCTGACCGTGTGCACCAAGGACTGGTGAACGGCAAGG AGTACAAGTGAAGGTGAGCAACAAGGGCCTGCCAGCAGCATCGAGAAGACC ATCAGCAAGGCCAAGGGCCAGCCAGGGAGGCCCAGGTGTACACCTGCCCCC CAGCCAGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAG GGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCGA GAACAACCTACAAGACACCCCCCGTGTGGACAGCGACGGCAGCTTCTTCTC GTACAGCAGGCTGACCGTGGACAAGAGCAGGTGGCAGGAGGGCAACGTGTT AGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCT GAGCCTGAGCCTGGGCAAG	H4H33335P heavy chain nucleotide sequence
38	EVQLVESGGGLVQPGGSLRLSCAASGFTSSYDMHWVRQATGKGLEWVSTIDTAG DTYYPGSVKGRFTISRANKNSLYLQMNSLRAGDTAVYYCARDGELELQGYFDLWG RGTLTVTSSASTKGPSVFPLAPCSRSTSESTAALGLVKDYFPEPVTWSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGPPCP PCPAPEFLGGPSVFLFPPKPKDTLMISRTEPTEVTCVVVDVSDQEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTSKAK GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSLGK	H4H33335P heavy chain amino acid sequence
39	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAG GGTGACCATCACCTGCAGGGCCAGCCAGATCATCAGCATCTACCTGAACTGGTA CCAGCAGAAGCCCGGCAAGGCCCAAGCTGCTGATCTACGCCGCCAGCAGCC TGCAGAGCGGCGTGCCAGCAGGTTACGCGGCAGCGGCAGCGCACCAGCTTC ACCCTGACCATCAGCAGCCTGCAGCCCCAGGACTTCGCCACCTACTACTGCCAG CAGAGCTACACCACCCCCCTGACCTTCGGCGGCGGCACCAAGGTGGAGATCAA GAGGACCGTGGCCGCCCCAGCGTGTTATCTTCCCCCAGCGACGAGCAGCT GAAGAGCGGCACCGCCAGCGTGGTGTGCTGCTGAACAATTCTACCCAGGG AGGCCAAGGTGAGTGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCA GGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGC ACCCTGACCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGA GGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCG AGTGC	H4H33335P light chain nucleotide sequence
40	DIQMTQSPSSLSASVGRVTITCRASQISIYLNWYQQKPKAPKLLIYAASLSQSGV PSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYTPTLTFGGGTKEIKRTVAAPSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	H4H33335P light chain amino acid sequence

41	CAGGTGCAGCTGGTGGAGAGCGGCGGCGGCTGGTGCAGCCGGCAGGAGCC TGAGGCTGAGCTGCGTGGCCAGCGGCTTCATCCTGAGCCACTACGGCATGCACT GGGTGAGGCAGGCCCCGGCAAGGGCCTGGAGTGGTGGCCGTGATCTGGTT CGACGGCACCAACAAGTACTACGCCGACAGCGTGAAGGGCAGGTTACCGTGA GCAGGGACAACAGCAAGAACACCTGTACATGCAGATGAACAGCCTGAGGGCC GAGGACACCGCGTGTACTACTGCGCCAGGGACCCCCCCCCGCCAGGAGGGG CAACTACAACGGCATGGACGTGTGGGGCCAGGGCACCACCTGACCGTGAGCA GC	H4H33336P HCVR nucleotide sequence
42	QVQLVESGGGVVQPRSLRLSCVASGFILSHYGMHWVRQAPGKGLEWVAVIWF GTNKKYADSVKGRFTVSRDNSKNTLYMQMNSLRAEDAVYYCARDPPPARRGNY NGMDVWVGQGTITVTSS	H4H33336P HCVR amino acid sequence
43	GGCTTCATCCTGAGCCACTACGGC	H4H33336P HCDR1 nucleotide sequence
44	GFILSHYG	H4H33336P HCDR1 amino acid sequence
45	ATCTGGTTCGACGGCACCAACAAG	H4H33336P HCDR2 nucleotide sequence
46	IWFDGNTK	H4H33336P HCDR2 amino acid sequence
47	GCCAGGGACCCCCCCCCGCCAGGAGGGGCAACTACAACGGCATGGACGTG	H4H33336P HCDR3 nucleotide sequence
48	ARDPPPARRGNYNMGMDV	H4H33336P HCDR3 amino acid sequence
49	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAG GGTGACCATCACCTGCAGGGCCAGCCAGGACATCAGGAACGACCTGGGCTGGT ACCAGCAGAAGCCCGGCAAGGCCCAAGAGGCTGATCTTCGGCGCCAGCAGC CTGCAGAGCGGCGTGCCCTGAGGTTAGCGGCAGCGGCAGCGGCACCGAGTT CACCTGACCATCAACAACCTGCAGCCGAGGACTTCGCCACCTTCTACTGCCTG CAGGACAACAGCTACCCCTGGACCTTCGGCCAGGGCACCAGGTGGAGATCAA G	H4H33336P LCVR nucleotide sequence
50	DIQMTQSPSSLSASVGRVTITCRASQDIRNDLGWYQQKPKAPKRLIFGASSLQS GVPLRFSGSGSGTEFTLTINNLPEDFATFYCLQDNSYPWTFGQGKVEIK	H4H33336P LCVR amino acid sequence
51	CAGGACATCAGGAACGAC	H4H33336P LCDR1 nucleotide sequence
52	QDIRND	H4H33336P LCDR1 amino acid sequence
53	GGCGCCAGC	H4H33336P LCDR2 nucleotide sequence
54	GAS	H4H33336P LCDR2 amino acid sequence
55	CTGCAGGACAACAGCTACCCCTGGACC	H4H33336P LCDR3 nucleotide sequence
56	LQDNSYPWT	H4H33336P LCDR3 amino acid sequence

57	CAGGTGCAGCTGGTGGAGAGCGGCGGCGCTGGTGCAGCCCGCAGGAGCC TGAGGCTGAGCTGCGTGGCCAGCGGCTTCATCCTGAGCCACTACGGCATGCACT GGGTGAGGCAGGCCCCGGCAAGGGCCTGGAGTGGGTGGCCGTGATCTGGTT CGACGGCACCACAAAGTACTACGCCGACAGCGTGAAGGGCAGGTTACCCGTGA GCAGGGACAACAGCAAGAACACCCTGTACATGCAGATGAACAGCCTGAGGGCC GAGGACACCGCCGTGTACTACTGCGCCAGGGACCCCCCCCCGCCAGGAGGGG CAACTACAACGGCATGGACGTGTGGGGCCAGGGCACCACCGTGACCGTGAGCA GCGCCAGCACCAGGGCCCCAGCGTGTCCCCCTGGCCCCCTGCAGCAGGAGC ACCAGCGAGAGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGA GCCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGACACCT TCCCCGCGGTGCTGCAGAGCAGCGGCTGTACAGCCTGAGCAGCGTGGTGACC GTGCCAGCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAA GCCCAGCAACCAAGGTGGACAAGAGGGTGGAGAGCAAGTACGGCCCCCCT GCCCCCCTGCCCGCCCCGAGTTCCTGGGCGGCCCCAGCGTGTCTCTGTTCCC CCCCAAGCCCAAGGACACCTGATGATCAGCAGGACCCCCGAGGTGACCTGCG TGGTGGTGGACGTGAGCCAGGAGGACCCGAGGTGCAAGTCAACTGGTACGTG GACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCAGGGAGGAGCAGTTCA ACAGCACCTACAGGGTGGTGAAGCGTGTGACCGTGTGACCAAGGACTGGCTG AACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGGCCTGCCAGCAGCA TCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCAGGGAGCCCCAGGTGTAC ACCCTGCCCCAGCAGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTG CCTGGTGAAGGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAACG GCCAGCCCGAGAACAACTACAAGACCAACCCCCCGTGTGACAGCAGCAGGC AGCTTCTTCTGTACAGCAGGCTGACCGTGGACAAGAGCAGGTGGCAGGAGGG CAACGTGTTAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCA GAAGAGCCTGAGCCTGAGCCTGGGCAAG	H4H33336P heavy chain nucleotide sequence
58	QVQLVESGGGVVQPGRLSLRSCVASGFILSHYGMHWVRQAPGKGLEWVAVIWF GTNKKYADSVKGRFTVSRDNSKNTLYMQMNSLRAEDTAVYYCARDPPPPARRGNY NGMDVWGQGTITVSSASTKGPSVFPLAPCSRSTSESTAALGLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKR VESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCVSMHEALHNHYTQKS LSLSLGK	H4H33336P heavy chain amino acid sequence
59	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAG GGTGACCATCACCTGCAGGGCCAGCCAGGACATCAGGAACGACCTGGGCTGGT ACCAGCAGAAGCCCGCAAGGCCCAAGAGGCTGATCTTCGGCGCCAGCAGC CTGCAGAGCGGCGTGCCCTGAGGTTACGCGGCAGCGGCAGCGGCACCGAGTT CACCTGACCATCAACAACCTGCAGCCCGAGGACTTCGCCACCTTCTACTGCCTG CAGGACAACAGCTACCCCTGGACCTTCGGCCAGGGCACCAAGGTGGAGATCAA GAGGACCGTGGCCGCCCGCCAGCGTGTTCATCTTCCCCCAGCGACGAGCAGCT GAAGAGCGGCACCGCCAGCGTGGTGTGCTGCTGAACAACCTTACCCAGGG AGGCCAAGGTGCAGTGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCA GGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGC ACCCTGACCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGA GGTGACCCACCAAGGCCCTGAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCG AGTGC	H4H33336P light chain nucleotide sequence
60	DIQMTQSPSSLSASVGDRTITCRASQDIRNDLGWYQQKPGKAPKRLIFGASSLQS GVPLRFSGSGSGTEFTLTINNLPEDFATFYCLQDNSYPWTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC	H4H33336P light chain amino acid sequence

61	CAGGTGCAGCTGGTGGAGAGCGGCGGCGGCTGGTGCAGCCGGCAGGAGCC TGAGGCTGAGCTGCGAGGCCAGCGGCTTCACCTTCAGCGACTACGACCTGCACT GGGTGAGGCAGGCCCCGGCAAGGGCCTGGAGTGGGTGGCCTTCATCAGCAA CGACGGCAGCAACGAGTACTACCCCAAGAGCGTGAAGGGCAGGTTTCAGCATCA GCAGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAGGGCC GAGGACACCGCCGTGTACCTGCACCAAGGAGAGGGACTACTACTACGACAG CAGCGGCAGCCTGGACTACTGGGGCCAGGGCACCTGGTGACCGTGAGCAGC	H4H33349P HCVR nucleotide sequence
62	QVQLVESGGGVVQPGRLRLSCEASGFTFSDYDLHWVRQAPGKGLEWVAFISNDG SNEYYPKSVKGRFSISRDNKNTLYLQMNSLRAEDTAVYHCTKERDYYYDSSGSLDY WGQGTLLTVSS	H4H33349P HCVR amino acid sequence
63	GGCTTCACCTTCAGCGACTACGAC	H4H33349P HCDR1 nucleotide sequence
64	GFTFSDYD	H4H33349P HCDR1 amino acid sequence
65	ATCAGCAACGACGGCAGCAACGAG	H4H33349P HCDR2 nucleotide sequence
66	ISNDGSNE	H4H33349P HCDR2 amino acid sequence
67	ACCAAGGAGAGGGACTACTACTACGACAGCAGCGGCAGCCTGGACTAC	H4H33349P HCDR3 nucleotide sequence
68	TKERDYYYDSSGSLDY	H4H33349P HCDR3 amino acid sequence
69	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAG GGTGACCATCACCTGCAGGGCCAGCCAGACCATCAACAACCTACCTGAACTGGTA CCAGCAGAAGCCCGGCAAGGCCCAAGCTGCTGATCTACACCACGCGGCC TGCAGAGCGGCGTGCCAGCAGGTTACGCGGCAGGGGCAGCGGCACCGACTT CACCTGGCCATCAGCAGCCTGCAGCCGAGGACTTCGCCACCTACTACTGCCA GCAGAGTACCACAGCCCCTTACCTTCGGCCCCGGCACCAAGGTGGACATCAA G	H4H33349P LCVR nucleotide sequence
70	DIQMTQSPSSLSASVGDRTITCRASQTINNYLNWYQQKPGKAPKLLIYTTSGLSG VPSRFSGRSGTDFTLAISSLQPEDFATYYCQQSYHSPFTFGPGTKVDIK	H4H33349P LCVR amino acid sequence
71	CAGACCATCAACAACCTAC	H4H33349P LCDR1 nucleotide sequence
72	QTINNY	H4H33349P LCDR1 amino acid sequence
73	ACCACCAGC	H4H33349P LCDR2 nucleotide sequence
74	TTS	H4H33349P LCDR2 amino acid sequence
75	CAGCAGAGCTACCACAGCCCCTTACC	H4H33349P LCDR3 nucleotide sequence
76	QQSYHSPFT	H4H33349P LCDR3 amino acid sequence

77	CAGGTGCAGCTGGTGGAGAGCGGCGGCGGCTGGTGCAGCCCGCAGGAGCC TGAGGCTGAGCTGCGAGGCCAGCGGCTTACCTTCAGCGACTACGACCTGCACT GGGTGAGGCAGGCCCCGGCAAGGGCCTGGAGTGGGTGGCTTCATCAGCAA CGACGGCAGCAACGAGTACTACCCCAAGAGCGTGAAGGGCAGGTTGAGCATCA GCAGGGACAACAGCAAGAACACCTGTACCTGCAGATGAACAGCCTGAGGGCC GAGGACACCGCCGTGTACCTGCACCAAGGAGAGGGACTACTACTACGACAG CAGCGGCAGCCTGGACTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGC GCCAGACCAAGGGCCCCAGCGTGTCCCCCTGGCCCCCTGCAGCAGGAGCAC CAGCGAGAGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGC CCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGACACCTTC CCCGCGTGTGCAGAGCAGCGGCTGTACAGCCTGAGCAGCGTGGTGACCGT GCCCCAGCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGC CCAGCAACACCAAGGTGGACAAGAGGGTGGAGAGCAAGTACGGCCCCCTGC CCCCCTGCCCGCCCCGAGTTCTGGGCGGCCCCAGCGTGTCTCTGTTCCCCC CCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTG GTGGTGACGTGAGCCAGGAGGACCCCGAGGTGCAAGTCAACTGGTACGTGG ACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCAGGGAGGAGCAGTTCAA CAGCACCTACAGGTGGTGAGCGTGTGACCGTGTGCACCAGGACTGGCTGA ACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGGCCTGCCAGCAGCAT CGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCAGGGAGCCCCAGGTGTAC ACCCTGCCCGCCAGCAGGAGAGATGACCAAGAACCAGGTGAGCCTGACCTG CCTGGTGAAGGGCTTCTACCCAGCGACATCGCGTGGAGTGGGAGAGCAACG GCCAGCCCCGAGAACAACACTACAAGACCAACCCCCCGTGTGGACAGCGACGGC AGCTTCTTCTGTACAGCAGGCTGACCGTGGACAAGAGCAGGTGGCAGGAGGG CAACGTGTTAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCA GAAGAGCCTGAGCCTGAGCCTGGGCAAG	H4H33349P heavy chain nucleotide sequence
78	QVQLVESGGGVVQPGRLRLSCEASGFTFSDYDLHWVRQAPGKGLEWVAFISNDG SNEYYPKSVKGRFSISRDNSTNTLYLQMNLSRAEDTAVYHCTKERDYYYDSSGLDY WGQGTLTIVSSASTKGPSVFPLAPCSRSTSESTAALGLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGP PCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRITVDKSRWQEGNVFSCSMHEALHNHYTQKSLSLSLGK	H4H33349P heavy chain amino acid sequence
79	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGCAG GGTGACCATCACCTGCAGGGCCAGCCAGACCATCAACAACCTGAACTGGTA CCAGCAGAAGCCCGGCAAGGCCCAAGCTGCTGATCTACACCACAGCGGCC TGCAGAGCGGCGTGCCAGCAGGTTACGCGGCAGGGGCAGCGGCACCGACTT CACCTTGCCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCA GCAGAGCTACCACAGCCCCTTACCTTCGGCCCCGGCACCAGGTGGACATCAA GAGGACCGTGGCCGCCCCAGCGTGTTCATCTCCCCCAGCGACGAGCAGCT GAAGAGCGGCACCGCCAGCGTGGTGTGCTGCTGAACAACCTTACCCCAAGG AGGCCAAGGTGCAGTGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCA GGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGC ACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTGCGA GGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCG AGTGC	H4H33349P light chain nucleotide sequence
80	DIQMTQSPSSLSASVGRVTITCRASQTINNYLNWYQKPGKAPKLLIYTSGLQSG VPSRFSGRSGTDFTLAISSLQPEDFATYYCQQSYHSPFTFGPGTKVDIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	H4H33349P light chain amino acid sequence
81	MELGLGLSTLSHCPWPRQPALWPTLAALALLSSVAEASLGAPRSPAPREGPPP VLASPAGHLPGGRTARWCSGRARRPPPPQPSRPAPPPAPPSPALPRGGRAARAGGP GSRARAAGARGCRLRSQVLPVRALGLGHRSDLVRFRCGSGCRRARSPHDLASL LGAGALRPPPGSRPVSQPCCRPTRYEAVSFMVDVNSTWRTVDRLSATACGCLG	Human ARTN protein (UniProtKB Accession No. Q5T4W7.1)

82	AGGPGSRARAAGARGCRLRSQVLPVRLGLGHRSDLVRFRCGSGCRRARSPHDL SLASLLGAGALRPPPGSRPVSPCCRPTRYEAVSFMDVNSTWRTVDRLSATAACGCL <u>GEQKLISEEDLGGEQKLISEEDLHHHHHH</u>	hARTN (A108-G220).mmh (mmh tag is underlined)
83	AGGPGSRPRAAGARGCRLRSQVLPVRLGLGHRSDLVRFRCGSGCRRARSPHDL SLASLLGAGALRPPPGSRPVSPCCRPTRYEAVSFMDVNSTWRTVDRLSATAACGCL <u>GEQKLISEEDLGGEQKLISEEDLHHHHHH</u>	mfARTN (A108-G22).mmh (mmh tag is underlined)
84	AGTRSSRARTTDARGCRLRSQVLPVSALGLGHSSDELIRFRFCGSGCRRARSQHDL ASLLGAGALRPPPGSRPVSPCCRPTRYEAVSFMDVNSTWRTVDHLSATAACGCLGE <u>QKLISEEDLGGEQKLISEEDLHHHHHH</u>	mARTN (A112-G224).mmh (mmh tag is underlined)
85	DPLPTESRLMNSCLQARRKQADPTCSAAYHHLDSTSSISTPLPSEEPSVPADCLEA AQQLRNSSLIGCMCHRRMKNQVACLDIYWTVHRARSLGNYELDVSPYEDTVTSKP WKMNLSKLNMLKPDSDLCLKFAMLCITLNDKCDRLRKAYGEACSGPHCQRHVCLR QLLTFFEKAAEPHAQGLLLCPCAPNDRGCGERRRNTIAPNCALPPVAPNCLELRRLC FSDPLCRSRLVDFQTHCHPMDILGTCAEQSRCLRAYLGLIGTAMTPNFVSNVNTS VALSCTCRGSGNLQEECEMLEGFFSHNPCLTEAIAAKMRHFSQLFSQDWPHTFA VMAHQENENPAVRPQPWDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK	hGFra3.hFc

[0173] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims. The disclosures of all patents and non-patent literature cited herein are expressly incorporated in their entirety by reference.

What is claimed is:

1. An isolated monoclonal antibody or an antigen-binding fragment thereof that specifically binds to human artemin, wherein the antibody or antigen-binding fragment thereof comprises:

(a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; or

(b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 32, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 34, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 36; or

(c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 44, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 46, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 48, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 52, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 56; or

(d) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 64, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 66, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 68, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 72, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 74, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 76.

2. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

an HCDR1 comprising the amino acid sequence of SEQ ID NO: 64, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 66, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 68, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 72, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 74, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 76.

3. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

4. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 32, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 34, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 36.

5. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

an HCDR1 comprising the amino acid sequence of SEQ ID NO: 44, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 46, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 48, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 52, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 56.

6. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) comprising an amino acid sequence that has at least 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID Nos: 2, 22, 42, and 62.

7. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region (LCVR) comprising an amino acid sequence that has at least 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 30, 50, and 70.

8. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 62 and an LCVR comprising the amino acid sequence of SEQ ID NO: 70.

9. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

10. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22 and an LCVR comprising the amino acid sequence of SEQ ID NO: 30.

11. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 42 and an LCVR comprising the amino acid sequence of SEQ ID NO: 50.

12. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 18 and a light chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 20; or

(b) a heavy chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 38 and a light chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 40; or

(c) a heavy chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 58 and a light chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 60; or

(d) a heavy chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 78 and a light chain comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 80.

13. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 6, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 78 and a light chain comprising the amino acid sequence of SEQ ID NO: 80.

14. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 18 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.

15. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain comprising the amino acid sequence of SEQ ID NO: 40.

16. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 58 and a light chain comprising the amino acid sequence of SEQ ID NO: 60.

17. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof is fully human.

18. A pharmaceutical composition comprising the monoclonal antibody or antigen-binding fragment thereof of claim 1 and a pharmaceutically acceptable carrier.

19. A nucleic acid molecule comprising a nucleotide sequence encoding the monoclonal antibody or antigen-binding fragment thereof of claim 1.

20. An expression vector comprising the nucleic acid molecule of claim 19.

21. A host cell comprising the expression vector of claim 20.

22. A method of producing an anti-human artemin antibody or antigen-binding fragment thereof, the method comprising introducing the expression vector of claim 20 into a host cell, growing the host cell under conditions permitting production of the antibody or antigen-binding fragment thereof, and recovering the antibody or antigen-binding fragment that is produced.

23. An *in vitro* or *ex vivo* method of inhibiting artemin-activated signaling in a cell, the method comprising contacting the cell with the monoclonal antibody or antigen-binding fragment thereof of claim 1, thereby inhibiting artemin-activated signaling in the cell.

24. Use of the monoclonal antibody or antigen-binding fragment thereof of claim 1 in the manufacture of a medicament for treating a pain-related disease, disorder, or condition associated with increased artemin expression or activity, comprising administering the medicament to a subject in need thereof.

25. The use of claim 24, wherein the pain-related disease, disorder, or condition is acute pain, chronic pain, neuropathic pain, inflammatory pain, trigeminal neuralgia, postherpetic neuralgia, general neuralgia, visceral pain, osteoarthritis pain, gout, radicular pain, sciatica, back pain, head or neck pain, breakthrough pain, post-surgical pain, chemotherapy induced neuropathic pain, radiotherapy-induced neuropathic pain, radiation-associated pain, or cancer pain.

26. The use of claim 24, wherein the pain-related disease, disorder, or condition is migraine, cluster headache, chronic headache, or tension headache.