US 20050074821, US 20080033157, US 20080182978 and US 20090041717). In animal models of neuropathic pain (*e.g.*, nerve trunk or spinal nerve ligation) systemic injection of neutralizing antibodies to NGF prevents both allodynia and hyperalgesia (Ramer, M.S. and Bisby, M.A. (1999) *Eur. J. Neurosci.* 11:837-846; Ro, L.S. *et al.* (1999) *Pain* 79:265-274). Furthermore, treatment with a neutralizing anti-NGF antibody produces significant pain reduction in a murine cancer pain model (Sevcik, M.A. *et al.* (2005) *Pain* 115:128-141).

Thus, in view of the foregoing, additional NGF antagonists are desirable.

Summary of the ~~Invention~~Disclosure

This ~~invention~~disclosure provides anti-NGF antibodies that exhibit enhanced in *vivo* stability. In particular, the ~~invention~~disclosure provides an anti-NGF antibody comprising a human IgG4 constant region, wherein the human IgG4 constant region comprises a mutation, preferably a hinge region mutation, and wherein the antibody exhibits an unexpectedly long terminal elimination half life, such as a terminal elimination half life in a cynomolgus monkey of at least 15 days and typically in the range of about 15 to about 22 days (or a range of 15 days to 22 days), or in a range of about 15 days to 28 days (or in a range of 15 days to 28 days), or in the range of about 21 days to about 28 days (or in range of 21 days to 28 days). This stabilized anti-NGF antibody (*e.g.*, hinge-stabilized antibody) also exhibits a terminal elimination half life in rats of at least 8 days, typically in the range of about 8 to about 9 days (or in range of 8 to 9 days). In yet other embodiments, the stabilized anti-NGF antibody (*e.g.*, hinge-stabilized antibody) may exhibit a mean terminal elimination half life in humans of at least 10-30 days, or at least 10 days, at least 15 days, at least 20 days, at least 25 days, at least 30 days or in a range of about 10 days to about 40 days or in a range of about 15 days to about 30 days (or in a range of 10 to 40 days or in a range of 15 to 30 days). In yet other embodiments, the stabilized anti-NGF antibody (*e.g.*, hinge-stabilized antibody) may exhibit a mean pharmacologic half life in humans of at least 30 days, or at least 35 days, or at least 40 days, or in a range of at least four to six weeks (or in a range of four to six weeks), or in a range of at least four to seven weeks (or in a range of four to seven weeks) or in a range of at least four to eight weeks (or in a range of four to eight weeks).

Preferably, the mutation in the IgG4 constant region is a hinge region mutation. Even more preferably, the hinge region mutation in the IgG4 constant region comprises mutation of the serine at the amino acid position corresponding to amino acid position 108 of SEQ ID NO: 9 (which shows the wild type amino acid sequence of the human IgG4 constant region). Accordingly, the ~~invention~~disclosure provides an anti-nerve growth factor (NGF) antibody having a human IgG4 constant region, said human IgG4 constant region containing a hinge region mutation comprising the mutation of serine at the amino acid

position corresponding to amino acid position 108 of SEQ ID NO: 9. More preferably, the serine at the amino acid position corresponding to amino acid position 108 of SEQ ID NO: 9 is mutated to proline. In a preferred embodiment, the human IgG4 constant region of the anti-NGF antibody comprises the amino acid sequence of SEQ ID NO: 10. Alternatively, other possible IgG4-stabilizing mutations are described herein.

A preferred anti-NGF antibody of the ~~invention~~disclosure is antibody PG110, the heavy chain amino acid sequence of which is shown in SEQ ID NO: 13 and the light chain amino acid sequence of which is shown in SEQ ID NO: 16. Accordingly, the ~~invention~~disclosure provides an anti-NGF antibody comprising a human IgG4 constant region, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 13 and a light chain comprising the amino acid sequence of SEQ ID NO: 16. In another embodiment, the ~~invention~~disclosure provides anti-NGF antibody comprising a human IgG4 constant region, wherein the antibody comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 11 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 14. In yet another embodiment, the ~~invention~~disclosure provides an anti-NGF antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 13, wherein the antibody has a terminal elimination half-life in a cynomolgus monkey of at least 15 days (and typically in the range of about 15 to about 22 days, or in a range of 15 to 22 days, or in a range of about 15 days to 28 days, or in a range of 15 to 28 days, or in the range of about 21 days to about 28 days or in range of 21 to 28 days), and/or has a terminal elimination half-life in a human of at least 10-30 days (or at least 10 days, or at least 15 days, or at least 20 days, or at least 25 days, or at least 30 days or in a range of about 10 days to about 40 days or in range of about 15 to about 30 days, or in a range of 10 to 40 days or in range of 15 to 30 days). Additionally or alternatively, the antibody may exhibit a mean pharmacologic half life in humans of at least 30 days, or at least 35 days, or at least 40 days, or in a range of at least four to six weeks (or in a range of four to six weeks), or in a range of at least four to seven weeks (or in a range of four to seven weeks) or in a range of at least four to eight weeks (or in a range of four to eight weeks). Preferably, the heavy chain is encoded by the nucleotide sequence of SEQ ID NO: 11. Preferably, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 16. Preferably, the light chain is encoded by the nucleotide sequence of SEQ ID NO: 14.

In another embodiment, the anti-NGF antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 (which shows the heavy chain variable region of PG110). In another embodiment, the anti-NGF antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2 (which shows the light chain variable region of PG110). In yet another embodiment, the anti-NGF antibody comprises a heavy chain variable region comprising

the amino acid sequence of SEQ ID NO: 1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2. In still another embodiment, the anti-NGF antibody competes for binding to NGF with an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2.

In another embodiment, there is provided an anti-nerve growth factor (NGF) antibody comprising:

(i) a heavy chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 3, 4 and 5, respectively,

(ii) a light chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 6, 7 and 8, respectively, and

(iii) a human IgG4 constant region which comprises the amino acid sequence of SEQ ID NO: 10.

In another embodiment, there is provided a pharmaceutical composition comprising the anti-NGF antibody as defined above and a pharmaceutically acceptable carrier.

In another embodiment, there is provided a kit comprising the anti-NGF antibody as defined above.

In another embodiment, there is provided a nucleic acid encoding the heavy chain of the antibody as defined above.

In another embodiment, there is provided an expression vector comprising the nucleic acid as defined above.

In another embodiment, there is provided a host cell comprising the expression vector as defined above.

In another embodiment, there is provided a method of expressing an anti-NGF antibody as defined above comprising culturing the host cell as defined above.

In another embodiment, there is provided an anti-NGF antibody as defined above for use in a method for treating pain.

In another embodiment, there is provided the use of the anti-NGF antibody as defined above for the manufacture of a medicament for treating pain.

In another embodiment, the anti-NGF antibody comprises a heavy chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 3, 4 and 5, respectively (wherein SEQ ID NOs: 3, 4 and 5 show the heavy chain variable region CDRs 1, 2 and 3, respectively, of PG110). In another embodiment, the anti-NGF antibody comprises a light chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 6, 7 and 8, respectively (wherein SEQ ID NOs: 6, 7 and 8 show the light chain variable region CDRs 1, 2 and 3, respectively, of PG110). In still another embodiment, the anti-NGF antibody comprises a heavy chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 3, 4 and 5, respectively, and comprises a light chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 6, 7 and 8, respectively.

Preferably, the anti-NGF antibody has one or more of the following functional properties:

a) binds to human NGF but does not bind to human brain-derived neurotrophic factor (BDNF), human neurotrophin 3 (NT-3) or human neurotrophin 4 (NT-4);

b) binds to human or rat NGF with a K_D of 100 pM or less;

c) inhibits binding of NGF to TrkA or $p75^{NTR}$;

d) inhibits NGF-dependent proliferation of TF-1 cells;

e) inhibits NGF-dependent chick dorsal root ganglion survival;

f) inhibits NGF-dependent PC12 cell neurite outgrowth.

In another embodiment, the anti-NGF antibody of the ~~invention~~disclosure does not exhibit a rebound effect when administered to a subject. For example, a dosage amount and dosing frequency of administration for the antibody can be selected such that the antibody does not exhibit a rebound effect when administered to a subject.

In another embodiment, an anti-NGF antibody of the ~~invention~~disclosure is capable of alleviating pain in a subject for a long duration, for example for a duration of at least about one week, or at least about two weeks, or at least about four weeks, or at least about eight weeks, or at least about twelve weeks, or at least about one week to about twelve weeks, or at least about four weeks to about twelve weeks, or at least about eight weeks to about twelve weeks, or for a duration of at least one week, or at least two weeks, or at least four weeks, or at least eight weeks or at least twelve weeks or at least

one to twelve weeks, or at least four to twelve weeks, or at least eight to twelve weeks after administration of a single dose of the anti-NGF antibody to the subject.

In a particularly preferred embodiment, the ~~invention~~disclosure provides an anti-NGF antibody that has the combined advantageous features of an extended terminal elimination half life and a prolonged duration of pain alleviation. Accordingly, the ~~invention~~disclosure also provides an anti-NGF antibody comprising a human IgG4 constant region, wherein the human IgG4 constant region comprises a mutation (preferably a hinge region mutation), wherein the antibody has a terminal elimination half-life in a human of at least 10-30 days, or at least 10 days, or at least 15 days, or at least 20 days, or at least 25 days, or at least 30 days or in a range of about 10 days to about 40 days or in a range of about 15 days to about 30 days (or in a range of 10-40 days or in a range of 15-30 days), and wherein the antibody alleviates pain for a duration of at least about one week to about twelve weeks, or at least one week to twelve weeks, or at least about four weeks to about twelve weeks, or at least four weeks to twelve weeks, after administration of a single dose the antibody to a human subject (or at least one week, or at least two weeks, or at least four weeks, or at least eight weeks, or at least twelve weeks, or one to twelve weeks, or four to twelve weeks, or eight to twelve weeks, after administration of a single dose of the antibody to a human subject). Preferably, the hinge region mutation comprises mutation of the serine at the amino acid position corresponding to amino acid position 108 of SEQ ID NO: 9, preferably a serine to proline mutation at the amino acid position corresponding to amino acid position 108 of SEQ ID NO: 9. More preferably, the human IgG4 constant region comprises the amino acid sequence of SEQ ID NO: 10. In various embodiments, the antibody may exhibit one or more of the functional properties described herein. In a preferred embodiment, the antibody competes for binding to NGF with an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2.

In yet another embodiment, the ~~invention~~disclosure provides an anti-nerve growth factor (NGF) antibody comprising a human IgG4 constant region, wherein the human IgG4 constant region comprises the amino acid sequence of SEQ ID NO: 10, and wherein the antibody binds to human or rat NGF with a K_D of 100 pM or less, inhibits binding of NGF to TrkA or $p75^{NTR}$ with an IC_{50} of 250 pM or less, and inhibits NGF-dependent proliferation of TF-1 cells with an IC_{50} of 50 ng/ml or less. Preferably, the antibody has mean terminal elimination half-life in humans of at least 10-30 days, or at least 10 days, or at least 15 days, or at least 20 days, or at least 25 days, or at least 30 days or in a range of about 10 days to about 40 days or in a range of about 15 days to about 30 days (or in a range of 10-40 days or in a range of 15-30 days). Additionally or alternatively, the antibody may exhibit a mean pharmacologic half life in humans of at least 30 days,

or at least 35 days, or at least 40 days, or in a range of at least four to six weeks (or in a range of four to six weeks), or in a range of at least four to seven weeks (or in a range of four to seven weeks) or in a range of at least four to eight weeks (or in a range of four to eight weeks). The antibody may further exhibit one or more additional functional properties, such as binding to human NGF but not binding to human brain-derived neurotrophic factor (BDNF), human neurotrophin 3 (NT-3) or human neurotrophin 4 (NT-4); inhibiting NGF-dependent chick dorsal root ganglion survival; and/or inhibiting NGF-dependent PC12 cell neurite outgrowth. Preferably, the antibody alleviates pain for a duration of at least about one week to about twelve weeks, or at least about four weeks to about twelve weeks, or at least about eight weeks to about twelve weeks, or at least one week to twelve weeks, or at least four weeks to twelve weeks or at least eight weeks to twelve weeks (or at least one week, or at least four weeks, or at least eight weeks, or at least twelve weeks, or for one to twelve weeks, or for four to twelve weeks, or for eight to twelve weeks) after administration of a single dose the anti-NGF antibody to a subject. Preferably, the antibody comprises a heavy chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 3, 4 and 5, respectively, or the antibody comprises a light chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 6, 7 and 8, respectively, or the antibody comprises a heavy chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 3, 4 and 5, respectively, and a light chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 6, 7 and 8, respectively. Preferably, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 or the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2, or the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2, or the antibody competes for binding to NGF with an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2.

In various preferred embodiment, the ~~invention~~disclosure provides anti-NGF antibodies having the following features:

An anti-nerve growth factor (NGF) antibody comprising (i) a heavy chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 3, 4 and 5, respectively, (ii) a light chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 6, 7 and 8, respectively, and (iii) a human IgG4 constant region, wherein the human IgG4 constant region comprises the amino acid sequence of SEQ ID NO: 10, wherein the antibody has a mean terminal

human or rat NGF with a K_D of 100 pM or less, inhibits binding of NGF to TrkA or $p75^{NTR}$ with an IC_{50} of 250 pM or less, and inhibits NGF-dependent proliferation of TF-1 cells with an IC_{50} of 50 ng/ml or less.

An anti-nerve growth factor (NGF) antibody comprising a human IgG4 constant region, wherein the human IgG4 constant region comprises a mutation, and wherein the antibody has a mean terminal elimination half-life in humans of at least 10-30 days. Additionally or alternatively, the antibody may exhibit a mean pharmacologic half life in humans of at least 30 days, or at least 35 days, or at least 40 days, or in a range of at least four to six weeks (or in a range of four to six weeks), or in a range of at least four to seven weeks (or in a range of four to seven weeks) or in a range of at least four to eight weeks (or in a range of four to eight weeks).

An anti-nerve growth factor (NGF) antibody comprising a human IgG4 constant region, wherein the human IgG4 constant region comprises a mutation and wherein the antibody has a terminal elimination half-life in a cynomolgus monkey of at least 15 days. Additionally or alternatively, the antibody may exhibit a mean pharmacologic half life in humans of at least 30 days, or at least 35 days, or at least 40 days, or in a range of at least four to six weeks (or in a range of four to six weeks), or in a range of at least four to seven weeks (or in a range of four to seven weeks) or in a range of at least four to eight weeks (or in a range of four to eight weeks).

In various embodiments, the anti-NGF antibody of the ~~invention~~disclosure can be, for example, a chimeric, a humanized or a human antibody, or an antibody in which the potential T cell epitopes have been eliminated.

In another aspect, the ~~invention~~disclosure provides a pharmaceutical composition comprising an anti-NGF antibody of the ~~invention~~disclosure and a pharmaceutically acceptable carrier.

In yet another aspect, the ~~invention~~disclosure provides a method of attenuating or inhibiting an NGF-related disease or condition in a subject, the method comprising administering to the subject an anti-NGF antibody of the ~~invention~~disclosure. Non-limiting examples of NGF-related diseases and conditions include inflammatory pain, post-operative pain, neuropathic pain, fracture pain, gout joint pain, post-herpetic neuralgia, cancer pain, osteoarthritis or rheumatoid arthritis pain, sciatica, pains associated with sickle cell crises, headaches, dysmenorrhea, endometriosis, musculoskeletal pain, chronic low back pain, fibromyalgia, sprains, visceral pain, ovarian cysts, prostatitis, cystitis, interstitial cystitis, incisional pain, migraine, trigeminal neuralgia, pain from burns and/or wounds, pain associated with trauma, pain associated with musculoskeletal diseases, ankylosing spondilitis, periarticular pathologies, pain from bone metastases, pain from HIV, erythromelalgia or pain caused by pancreatitis or kidney stones. Other examples of NGF-related diseases and conditions include malignant melanoma,

Sjogren's syndrome and asthma, such as uncontrolled asthma with severe airway hyper-responsiveness, and intractable cough. Particularly preferred diseases and conditions for treatment according to the methods of the ~~invention~~disclosure include inflammatory pain (particularly osteoarthritis or rheumatoid arthritis pain), musculoskeletal pain (particularly chronic low back pain), neuropathic pain (particularly diabetic neuropathy), cancer pain and pain from bone metastases, interstitial cystitis/ painful bladder syndrome, pain associated with chronic abacterial prostatitis, pain associated with endometriosis and/or uterine fibroids and post-operative pain.

The antibody can be administered, for example, intravenously, subcutaneously (*e.g.*, via an injection pen or subcutaneous implant), intramuscularly or intra-articularly, although other suitable routes of administration are described herein. Preferably, the antibody is administered at a dose in a range of 0.1 mg/kg to 3 mg/kg or at a dose in a range of 0.1 mg/kg to 30 mg/kg. The antibody can be administered, for example, at a dose in a range from about 3 μg/kg to about 3000 μg/kg, with preferred dosages including 100 μg/kg or 300 μg/kg, In other embodiments, the antibody is administered at a dose in a range of 0.1 mg/kg to 30 mg/kg, or in a range of 0.1 mg/kg to 20 mg/kg, or in a range of 0.1 mg/kg to 10 mg/kg, or in a range of 1 mg/kg to 30 mg/kg, or in a range of 1 mg/kg to 20 mg/kg or in a range of 1 mg/kg to 10 mg/kg, although other suitable dosages and dose ranges are described herein. Furthermore, a fixed dose formulation of the antibody can be used.

The antibody can be administered alone or in combination with one or more additional pharmaceutical agents. For example, a second pharmaceutical agent, such as an NSAID, an analgesic (*e.g.*, an opioid analgesic), a local anaesthetic, a nerve block, a phenol block, a therapeutic antibody, an anti-convulsant, an anti-depressant, topical capsaicin, a steroid or an antiviral agent, can be administered in combination with the anti-NGF antibody of the invention. Particularly preferred second pharmaceutical agents for combination treatment with an antibody of the ~~invention~~disclosure include opioid analgesics, such as morphine and the like. Other preferred second pharmaceutical agents for combination treatment include TrkA inhibitors and Protein Kinase C (PKC) inhibitors.

In a preferred embodiment, the ~~invention~~disclosure provides a method of attenuating or inhibiting pain in a subject, the method comprising administering to the subject an anti-nerve growth factor (NGF) antibody comprising a human IgG4 constant region, wherein the human IgG4 constant region comprises the amino acid sequence of SEQ ID NO: 10, and wherein the antibody alleviates pain in the subject for a duration of at least four to twelve weeks (or for at least one to twelve weeks, or for at least eight to twelve weeks, or for four to twelve weeks, or for one to twelve weeks, or for eight to twelve weeks, or for at least one week, or for at least four weeks, or for at least eight weeks, or for at least

twelve weeks) after administration of a single dose of the anti-NGF antibody to a subject. Preferably, the anti-NGF antibody comprises a heavy chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 3, 4 and 5, respectively, and a light chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 6, 7 and 8, respectively. Preferably, the anti-NGF antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2. Preferably, the pain is selected from the group consisting of osteoarthritis pain, chronic low back pain, diabetic neuropathic pain, cancer pain, pain from bone metastases, interstitial cystitis, painful bladder syndrome, pain associated with chronic abacterial prostatitis, pain associated with endometriosis, pain associated with uterine fibroids and post-operative pain. Preferably, the anti-NGF antibody is administered at a dose in a range from 0.1 to 3 mg/kg or at a dose in a range from 0.1 mg/kg to 30 mg/kg. Preferably, the antibody is administered intravenously or subcutaneously. Preferably, the antibody has a terminal elimination half-life in a human of at least 10-30 days (or at least 10 days, or at least 15 days, or at least 20 days, or at least 25 days, or at least 30 days or in a range of about 10 days to about 40 days or in range of about 15 to about 30 days, or in a range of 10 to 40 days or in range of 15 to 30 days).

In another preferred embodiment, the ~~invention~~disclosure provides a method of attenuating or inhibiting a nerve growth factor (NGF)-related disease or condition in a subject such that a rebound effect is avoided in the subject, the method comprising administering to the subject an anti-NGF antibody comprising a human IgG4 constant region, wherein the human IgG4 constant region comprises a hinge region mutation, and wherein the antibody has a terminal elimination half-life in a human of at least 10-30 days (or at least 10 days, or at least 15 days, or at least 20 days, or at least 25 days, or at least 30 days or in a range of about 10 days to about 40 days or in range of about 15 to about 30 days, or in a range of 10 to 40 days or in range of 15 to 30 days), and wherein the antibody is administered at a dosage and at a frequency such that a rebound effect is avoided in the subject. Additionally or alternatively, the antibody may exhibit a mean pharmacologic half life in humans of at least 30 days, or at least 35 days, or at least 40 days, or in a range of at least four to six weeks (or in a range of four to six weeks), or in a range of at least four to seven weeks (or in a range of four to seven weeks) or in a range of at least four to eight weeks (or in a range of four to eight weeks). Preferably, the human IgG4 constant region comprises a mutation at the amino acid position corresponding to amino acid position 108 of SEQ ID NO: 9. Preferably, the serine at the amino acid position corresponding to amino acid position 108 of SEQ ID NO: 9 is mutated to proline. Preferably, the human IgG4 constant region comprises the amino acid sequence of SEQ

ID NO: 10. Preferably, the anti-NGF antibody comprises a heavy chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 3, 4 and 5, respectively, and a light chain variable region comprising CDRs 1, 2 and 3 having the amino acid sequences of SEQ ID NOs: 6, 7 and 8, respectively. Preferably, the anti-NGF antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2. Preferably, the antibody competes for binding to NGF with an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2. Preferably, the NGF-related disease or condition is pain selected from the group consisting of osteoarthritis pain, chronic low back pain, diabetic neuropathic pain, cancer pain, pain from bone metastases, interstitial cystitis, painful bladder syndrome, pain associated with chronic abacterial prostatitis, pain associated with endometriosis, pain associated with uterine fibroids and post-operative pain. Preferably, the anti-NGF antibody is administered at a dose in a range from 0.1 to 3 mg/kg or in a range from 0.1 mg/kg to 30 mg/kg. Preferably, the antibody is administered intravenously or subcutaneously.

In another aspect, the ~~invention~~disclosure provides for the use of the anti-NGF antibody of the ~~invention~~disclosure for the manufacture of a medicament for use to attenuate of inhibit an NGF-related disease or condition in a subject. Non-limiting examples of NGF-related diseases and conditions include those set forth above. A preferred NGF-related disease or condition is pain. Preferably, the pain is selected from the group consisting of osteoarthritis pain, chronic low back pain, diabetic neuropathic pain, cancer pain, pain from bone metastases, interstitial cystitis, painful bladder syndrome, pain associated with chronic abacterial prostatitis, pain associated with endometriosis, pain associated with uterine fibroids and post-operative pain.

In another aspect, the ~~invention~~disclosure provides for the use of the anti-NGF antibody of the ~~invention~~disclosure for the manufacture of a medicament for use to attenuate or inhibit pain in a subject, such that pain is attenuated or inhibited in the subject for a duration of at least about one week to about twelve weeks, or at least about four weeks to about twelve weeks, or at least about eight weeks to about twelve weeks (or for a duration of one to twelve weeks, or four to twelve weeks, or eight to twelve weeks, or at least one week, or at least two weeks, or at least four weeks, or at least eight weeks, or at least twelve weeks) after administration of a single dose of the anti-NGF antibody to a subject.

In another aspect, the ~~invention~~disclosure provides for use of the anti-NGF antibody of the ~~invention~~disclosure for the manufacture of a medicament for use to attenuate or inhibit an NGF-related disease or condition in a subject such that a rebound effect is avoided in the

subject. In particular, the antibody is administered at a dosage and at a frequency such that a rebound effect is avoided in the subject.

In still other aspects, the ~~invention~~disclosure provides nucleic acid molecules encoding the heavy chains and/or light chains of the anti-NGF antibodies of the ~~invention~~disclosure, as well as vectors (*e.g.*, expression vectors) comprising such vectors, host cells comprising such vectors and methods for expressing the anti-NGF antibodies using the host cells of the ~~invention~~disclosure

In another aspect, the ~~invention~~disclosure provides a method of attenuating or inhibiting a nerve growth factor (NGF)-related disease or condition in a subject such that a rebound effect is avoided in the subject. The method comprises administering to the subject an anti-NGF antibody comprising a human IgG4 constant region, wherein the human IgG4 constant region comprises a mutation (preferably a hinge region mutation) and wherein the antibody has a terminal elimination half-life in a cynomolgus monkey of at least 15 days, more preferably of at least 21 days, and wherein the antibody is administered at a dosage and at a frequency such that a rebound effect is avoided in the subject. In another embodiment, the antibody has a terminal elimination half-life in a cynomolgus monkey in a range of about 15 days to about 22 days (or 15-22 days), or a range of about 15 days to about 28 days (or 15-28 days), or in a range of about 21 days to about 28 days (or 21-28 days). In another embodiment, the antibody has a terminal elimination half-life in a rat of at least 8 days. In yet another embodiment, the antibody has a mean terminal elimination half-life in humans of at least 10-30 days (or at least 10 days, or at least 15 days, or at least 20 days, or at least 25 days, or at least 30 days, or in a range of about 10 days to about 40 days, or in a range of about 15 to about 30 days, or in a range of 10-40 days or in a range of 15-30 days). Additionally or alternatively, the antibody may exhibit a mean pharmacologic half life in humans of at least 30 days, or at least 35 days, or at least 40 days, or in a range of at least four to six weeks (or in a range of four to six weeks), or in a range of at least four to seven weeks (or in a range of four to seven weeks) or in a range of at least four to eight weeks (or in a range of four to eight weeks). Preferred mutations include those described above. Preferred antibodies include those having the sequences and/or the additional functional properties as described above. Non-limiting examples of NGF-related diseases and conditions include those set forth above.

The ~~invention~~disclosure also provides for the use of the anti-NGF antibody of the ~~invention~~disclosure for the manufacture of a medicament for use to attenuate or inhibit an NGF-related disease or condition in a subject such that a rebound effect is avoided in the subject.

Kits comprising an anti-NGF antibody of the ~~invention~~disclosure are also provided herein. For example, a kit may comprise anti-NGF antibody and instructions for use of the antibody in treating an NGF-related disease or condition.