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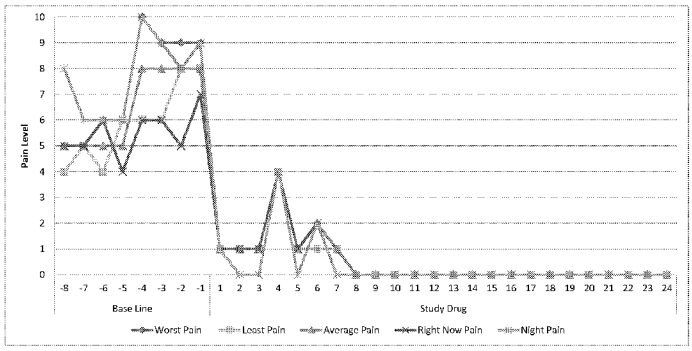

Figure 1

(57) Abstract: This disclosure relates to the use of a composition comprising opioid/Toll-like receptor 4 (TLR4) antagonists (opioid antagonists that treats pain by blocking Toll-like receptor 4 (TLR4)) and dextro enantiomers thereof for the treatment of pain. Examples of opioid antagonist and their dextro enantiomers include naltrexone, naloxone and nalmefene, and pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof and their use in the treatment of pain, particularly neuropathic pain. Also disclosed are compositions for treatment of pain comprising opioid/Toll-like receptor 4 (TLR4) antagonists, dextro enantiomers thereof or pharmaceutically acceptable salt thereof, and at least one of an alpha-2 adrenergic receptor agonist, acetyl-para-aminophenol (APAP), a cyclooxygenase (COX) inhibitor, and an alpha-2-delta ligand that enhances the pain treatment effect of the first compound.

WO 2014/160077 A1

COMPOSITIONS TO REDUCE PAIN COMPRISING AN OPIOID/TOLL-LIKE RECEPTOR 4 ANTAGONIST, DEXTRO ENANTIOMERS THEREOF, AND METHODS OF USE THEREFOR

RELATED APPLICATIONS

[0001] This application claims priority from U.S. Patent Application No. 13/799,287, filed on March 13, 2013; U.S. Patent Application No. 13/837,099, filed on March 15, 2013; U.S. Patent Application No. 13/841,100, filed on March 15, 2013; U.S. Patent Application No.13/851,773, filed on March 27, 2013 and U.S. Patent Application No. 13/851,267, filed on March 27, 2013, each of which is incorporated by reference, herein, in their entireties.

FIELD

[0002] This disclosure relates to compositions comprising an opioid/TLR4 antagonist and dextro enantiomers thereof, compositions comprising combinations of an opioid/TLR4 antagonist and dextro enantiomers thereof with an alpha-2 adrenergic receptor agonist, acetyl-para-aminophenol (APAP), a cyclooxygenase (COX) inhibitor, and/or an alpha-2-delta ligand, particularly those that exhibit a synergistic effect for the treatment, prevention and reversal of pain. This disclosure further relates to methods of treatment, prevention, and reversal of pain comprising administration of the compositions defined above.

BACKGROUND

[0003] It is well established in medical literature that treatments currently available for pain have limitations. Opioid drugs cause tolerance, dependence and side effects sufficiently serious to prompt recent action by the FDA to further restrict the drugs. NSAIDs, taken for prolonged periods of time, are known to cause gastro-intestinal bleeding as well as toxicity to the liver, kidneys, and other organs. Newly approved treatments, like the calcium channel alpha-2-delta ligands gabapentin and pregabalin and the serotonin and norepinephrine reuptake inhibitors milnacipran and duloxetine, require high doses to show nominal effectiveness, have a high dropout rate and carry many side effects.

[0004] This disclosure is a novel approach for the treatment of pain. It is directed to the treatment of neuropathic and nociceptive pain with an allodynic component. The

components of the combination are directed to reducing neuropathic pain and the allodynic component associated with nociceptive pain. Specific combinations of drugs and the dosage needed to create that effect is the subject of the disclosure.

[0005] In essence the opioid receptor antagonists exert their action in a site other than the opioid receptors. That site is the immune system receptor TLR4 located on glia cells.

SUMMARY

[0006] The disclosure provides a composition comprising a compound that is an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or a pharmaceutically acceptable salt thereof and its use for the treatment, prevention, and reversal of pain. The disclosure also provides synergistic compositions comprising an opioid/TLR4 antagonist, dextro enantiomeric mixtures thereof, or pharmaceutically acceptable salts thereof and an alpha-2 adrenergic receptor agonist, acetyl-para-aminophenol (APAP), a cyclooxygenase (COX) inhibitor, and/or an alpha-2-delta ligand. The disclosure further provides a method of use of these synergistic compositions for the treatment, prevention, and reversal of pain, particularly neuropathic pain.

[0007] In one embodiment, the disclosure provides a composition for treatment of pain in a mammal comprising a synergistic ratio of (a) an opioid/TLR4 antagonist, or pharmaceutically acceptable salts or solvates thereof and (b) a direct-acting alpha-2 adrenergic agonist, or pharmaceutically acceptable salts or solvates thereof. In a further embodiment, the opioid/TLR4 antagonist is selected from a group consisting of naltrexone, norbinaltorphimine, nalmefene, naloxone, nalorphine, methylnaltrexone, samidorphan, cyprodime, naltrindole, amentoflavone, naltriben, norbinaltorphimine, 6-ß-naltrexol, metabolites and pro drugs thereof, including all enantiomeric and epimeric forms as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof. In another embodiment, the opioid/TLR4 antagonist is naltrexone as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

[0008] In a further embodiment, the opioid/TLR4 antagonist is naltrexone in a sustained release formulation, as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof. In another embodiment, the opioid/TLR4 antagonist is (+)–naltrexone (dextro-naltrexone), as well as appropriate mixtures thereof, as well as pro drugs thereof, or

pharmaceutically acceptable salts or solvates thereof. Dextro-naltrexone ((+)-naltrexone) blocks only the TLR-4 while not blocking the morphine receptors. Therefore, the side effects arising from blocking of the morphine receptors by the racemic naltrexone (a mix of (-)-naltrexone and (+)-naltrexone), which are caused by (-)-naltrexone, are eliminated by use of (+)-naltrexone.

[0009] In another embodiment, the direct-acting alpha 2 adrenergic agonist is selected from a group consisting of apraclonidine, brimonidine, clonidine, detomidine, dexmedetomidine, guanabenz, guanfacine, lofexidine, medetomidine, romifidine, tizanidine, tolonidine, xylazine and fadolmidine, or pharmaceutically acceptable salts or solvates of any thereof.

[0010] In another embodiment, the direct-acting alpha-2 adrenergic agonist is clonidine, or pharmaceutically acceptable salts or solvates thereof. In another embodiment, the direct-acting alpha-2 adrenergic agonist is clonidine in a sustained release formulation, or pharmaceutically acceptable salts or solvates thereof.

[0011] In another embodiment, the opioid/TLR4 antagonist is naltrexone, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount and the direct-acting alpha-2 adrenergic agonist is clonidine, or pharmaceutically acceptable salts or solvates thereof, in therapeutically effective amount. In a further embodiment, naltrexone and clonidine, or pharmaceutically acceptable salts or solvates of any thereof, are in a weight to weight combination range which corresponds to a synergistic combination range of the order of 90:1 to 22.5:1 parts by weight. In another embodiment, the dose range of naltrexone, or pharmaceutically acceptable salts or solvates thereof, is about 0.004 mg/kg-0.71 mg/kg per day. And wherein, the dose range of clonidine, or pharmaceutically acceptable salts or solvates thereof, is about 0.00018 mg/kg - 0.0086mg/kg per day. In another embodiment, the human dose range of naltrexone is 0.25 mg - 50 mg per day and the dose range of clonidine is 0.0125 mg - 0.6 mg, wherein said composition is formulated into a single fixed combination dosage form. In another embodiment, the human dose range of naltrexone is 0.25 mg - 15 mg per day and the dose range of clonidine is 0.0125 mg - 0.3 mg, wherein said composition is formulated into a single fixed combination dosage form. In a further embodiment, the composition is administered once, twice, three or four times through the day.

[0012] In another embodiment, the therapeutically effective dose of the pharmaceutical composition is administered systemically, including but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical or sublingual routes.

[0013] In some embodiments, the combination is in a single dosage form, and said single dosage form is in the form of tablets, lozenges, troches, hard candies, liquid, powders, sprays, creams, salves and suppositories.

[0014] In some embodiments the composition is for treating, preventing and reversing pain. In a further embodiment, the pain is back pain. In another embodiment, the pain is neuropathic pain. In another embodiment, the pain is migraine. In another embodiment, the pain is trigeminal neuralgia. In another embodiment, the pain is vulvodynia. In another embodiment, the pain is irritable bowel syndrome. In another embodiment, the pain is post herpetic neuralgia. In another embodiment, the pain is diabetic neuropathy. In another embodiment, the pain is nociceptive pain with an allodynic component.

[0015] In one embodiment, the disclosure provides a composition for treatment of pain in a mammal comprising a synergistic ratio of (a) an opioid/TLR4 antagonist, or pharmaceutically acceptable salts or solvates thereof and (b) a acetyl-para-aminophenol, or pharmaceutically acceptable salts or solvates thereof. In another embodiment, the opioid/TLR4 antagonist is selected from a group consisting of naltrexone, norbinaltorphimine, nalmefene, naloxone, nalorphine, methylnaltrexone, samidorphan, cyprodime, naltrindole, amentoflavone, naltriben, norbinaltorphimine, 6-ß-naltrexol, metabolites and pro drugs thereof, including all enantiomeric and epimeric forms as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof. In another embodiment, the opioid/TLR4 antagonist is naltrexone as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

[0016] In a further embodiment, the opioid/TLR4 antagonist is naltrexone in a sustained release formulation, as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

[0017] In an embodiment, the opioid/TLR4 antagonist can be (+)–naltrexone (dextro-naltrexone), as well as appropriate mixtures thereof, as well as pro drugs thereof, or pharmaceutically acceptable salts or solvates thereof. In another embodiment, the acetyl-para-aminophenol or pharmaceutically acceptable salts or solvates thereof, is the second compound. In another embodiment, the opioid/TLR4 antagonist is naltrexone, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount and the acetyl-para-aminophenol is in therapeutically effective amount.

[0018] In another embodiment, the naltrexone and acetyl-para-aminophenol, or pharmaceutically acceptable salts or solvates of any thereof, are in a weight to weight combination range which corresponds to a synergistic combination of 3:200 parts by weight. In a further embodiment, the dose range of naltrexone, or pharmaceutically acceptable salts or solvates thereof, is about 0.004 mg/kg-0.71 mg/kg and the dose range of acetyl-para-aminophenol, or pharmaceutically acceptable salts or solvates thereof, is about 5 mg/kg - 57mg/kg per day. In another embodiment, the human dose range of naltrexone is 0.25 mg - 50 mg per day and the dose range of acetyl-para-aminophenol is 325 mg - 4000 mg, wherein said composition is formulated into a single fixed combination dosage form. In another embodiment, the human dose range of naltrexone is 0.25 mg - 15 mg per day and the human the dose range of acetyl-para-aminophenol is 325 mg - 4000 mg, wherein said composition is formulated into a single fixed combination dosage form.

[0019] In one embodiment, the composition is administered once, twice, three or four times through the day. In another embodiment, the therapeutically effective dose of the pharmaceutical composition is administered systemically, including but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical or sublingual routes.

[0020] In another embodiment, the combination is in a single dosage form, and said single dosage form is in the form of tablets, lozenges, troches, hard candies, liquid, powders, sprays, creams, salves and suppositories.

[0021] In another embodiment, the description provides a composition for treating, preventing and reversing pain.

[0022] In another embodiment, the description provides a method of treating neuropathic pain, nociceptive pain, nociceptive pain with an allodynic component, migraine, inflammation, osteoarthritis, rheumatoid arthritis, psoriatic arthritis, trigeminal neuralgia, vulvodynia, irritable bowel syndrome, post herpetic neuralgia, or diabetic neuropathy in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a composition.

[0023] In one embodiment, the description provides a composition for treatment of pain in a mammal comprising a synergistic ratio of an opioid/TLR4 antagonist, or pharmaceutically acceptable salts or solvates thereof and a cyclooxygenase (COX) inhibitor, or pharmaceutically acceptable salts or solvates thereof.

[0024] In another embodiment, the opioid/TLR4 antagonist is selected from a group consisting of naltrexone, norbinaltorphimine, nalmefene, naloxone, nalorphine,

methylnaltrexone, samidorphan, cyprodime, naltrindole, amentoflavone, naltriben, norbinaltorphimine, 6-ß-naltrexol, metabolites and pro drugs thereof, including all enantiomeric and epimeric forms as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof. In another embodiment, A composition comprising the formulation of claim 43, wherein, the opioid/TLR4 antagonist is naltrexone as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

[0025] In one embodiment the opioid/TLR4 antagonist is naltrexone in a sustained release formulation, as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof. In another embodiment, the opioid/TLR4 antagonist is (+)–naltrexone (dextro-naltrexone), as well as appropriate mixtures thereof, as well as pro drugs thereof, or pharmaceutically acceptable salts or solvates thereof.

[0026] In one embodiment, the cyclooxygenase (COX) inhibitor is selected from a group consisting of aspirin diflunisal, salsalate. ibuprofen, dexibuprofen, naproxen, fenoprofen, ketoprofen, dexketoprofen, flurbiprofen, oxaprozin, loxoprofen. indomethacin, tolmetin, ,sulindac, etodolac, ketorolac, iclofenac, nabumetone. piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam. mefenamic acid,meclofenamic acid, flufenamic acid, tolfenamic acid. celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricoxib, firocoxib, sulphonanilides, nimesulide, licofelone, lysine, clonixinate, hyperforin, figwort, calcitriol or pharmaceutically acceptable salts or solvates of any thereof. In another embodiment, the cyclooxygenase (COX) inhibitor is ibuprofen, or pharmaceutically acceptable salts or solvates thereof.

[0027] In a particular embodiment, the opioid/TLR4 antagonist is naltrexone, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount and the cyclooxygenase (COX) inhibitor is ibuprofen, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount. In a further embodiment, the naltrexone and ibuprofen, or pharmaceutically acceptable salts or solvates of any thereof, are in a weight to weight combination range which corresponds to a synergistic combination of 1:90 parts by weight. In one embodiment, the dose range of naltrexone, or pharmaceutically acceptable salts or solvates thereof, is about 0.004 mg/kg-0.71 mg/kg and the dose range of ibuprofen, or pharmaceutically acceptable salts or solvates thereof, is about 3 mg/kg -

35mg/kg per day. In another embodiment the human dose range of naltrexone is 0.25 mg - 50 mg per day and the dose range of ibuprofen is 200 mg - 2400 mg, wherein said composition is formulated into a single fixed combination dosage form.

[0028] In a particular embodiment, the human dose range of naltrexone is 0.25 mg - 15 mg per day and the human the dose range of ibuprofen is 200 mg - 2400 mg, wherein said composition is formulated into a single fixed combination dosage form. In another embodiment, the composition is administered once, twice, three or four times through the day. In another embodiment, the therapeutically effective dose of the pharmaceutical composition is administered systemically, including but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical or sublingual routes.

[0029] In another embodiment, the combination is in a single dosage form, and wherein, said single dosage form is in the form of tablets, lozenges, troches, hard candies, liquid, powders, sprays, creams, salves and suppositories.

[0030] In one embodiment, the disclosure provides a composition for treating, preventing and reversing pain.

[0031] In another embodiment is provided a method of treating neuropathic pain, nociceptive pain, nociceptive pain with an allodynic component, migraine, trigeminal neuralgia, vulvodynia, irritable bowel syndrome, post herpetic neuralgia, or diabetic neuropathy in a mammal in need thereof, comprising administering to the mammal in a therapeutically effective amount of a combination.

[0032] In one embodiment, the disclosure provides a composition for treatment of pain in a mammal comprising a synergistic ratio of (a) an opioid/TLR4 antagonist, or pharmaceutically acceptable salts or solvates thereof and (b) an alpha-2-delta ligand, or pharmaceutically acceptable salts or solvates thereof. In a further embodiment, the opioid/TLR4 antagonist is selected from a group consisting of naltrexone, norbinaltorphimine, nalmefene, naloxone, nalorphine, methylnaltrexone, samidorphan, cyprodime, naltrindole, amentoflavone, naltriben, norbinaltorphimine, 6-alpha-naltrexol, 6-beta-naltrexol metabolites and pro drugs thereof, including all enantiomeric and epimeric forms as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof. In another embodiment, the opioid/TLR4 antagonist is naltrexone as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

[0033] In one embodiment, the opioid/TLR4 antagonist is naltrexone in a sustained release formulation, as well as metabolites and pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof. In another embodiment, the opioid/TLR4 antagonist is (+)–naltrexone (dextro-naltrexone), as well as appropriate mixtures thereof, as well as metabolites or pro drugs thereof, or pharmaceutically acceptable salts or solvates thereof. In an embodiment, the alpha-2-delta ligand is selected from Gabapentin or Pregabalin or pharmaceutically acceptable salts or solvates of any thereof.

[0034] In one embodiment, the alpha-2-delta ligand inhibitor is Gabapentin, or pharmaceutically acceptable salts or solvates thereof. In another embodiment, the alpha-2-delta ligand inhibitor is pregabalin, or pharmaceutically acceptable salts or solvates thereof.

[0035] In one embodiment, the opioid/TLR4 antagonist is naltrexone, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount and the alpha-2-delta inhibitor is Gabapentin or Pregabalin, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount. In another embodiment, the opioid/TLR4 antagonist is dextro naltrexone, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount and the alpha-2-delta inhibitor is Gabapentin or Pregabalin, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount. In an embodiment, the naltrexone and alpha-2-delta ligand, or pharmaceutically acceptable salts or solvates of any thereof, are in a weight to weight combination range which corresponds to a synergistic combination of 1:30-1:125 parts by weight.

[0036] In one embodiment, the dose range of naltrexone, or pharmaceutically acceptable salts or solvates thereof, is about 0.004 mg/kg-0.71 mg/kg. In another embodiment, the human dose range of naltrexone is 0.25 mg - 50 mg per day. In another embodiment, the human dose range of naltrexone is 0.25 mg - 25 mg per day. In another embodiment, the human dose range of naltrexone is 0.25 mg - 15 mg per day.

[0037] In one embodiment, the composition is formulated into a single fixed combination dosage form and wherein, the composition is administered once, twice, three or four times through the day. In another embodiment, the therapeutically effective dose of the pharmaceutical composition is administered systemically, including but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical or sublingual routes. In yet another embodiment, the combination is in a single dosage form, and wherein, said single dosage

form is in the form of tablets, lozenges, troches, hard candies, liquid, powders, sprays, creams, salves and suppositories.

[0038] In one embodiment, the disclosure provides a composition for treating, preventing and reversing pain. In another embodiment, the disclosure provides a method of treating neuropathic pain, nociceptive pain with an allodynic component, migraine, trigeminal neuralgia, vulvodynia, irritable bowel syndrome, post herpetic neuralgia, or diabetic neuropathy in a mammal in need thereof, comprising administering to the mammal in a therapeutically effective amount of a combination.

[0039] In one embodiment, the disclosure provides a method for the treatment of pain in a mammal comprising administration to said mammal a therapeutically effective amount of a composition comprising an opioid/TLR4 antagonist, or a dextro enantiomer of the opioid/TLR4 antagonist or a racemic mixture thereof, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment is provided a method for the treatment of pain in a mammal comprising administration to said mammal a therapeutically effective amount of a composition predominantly comprising a dextro enantiomer of an opioid/TLR4 antagonist or a pharmaceutically acceptable salt or solvate thereof.

[0040] In another embodiment is provided a method for the treatment of pain in a mammal comprising administration of a composition comprising a therapeutically effective amount of an opioid/TLR4 antagonist. The opioid/TLR4 antagonist is selected from a group consisting of naltrexone, norbinaltorphimine, nalmefene, naloxone, nalorphine, methylnaltrexone, samidorphan, cyprodime, naltrindole, amentoflavone, naltriben, norbinaltorphimine, 6-beta-naltrexol, and 6-alpha-naltrexol, including all enantiomeric and epimeric forms as well as the appropriate mixtures thereof, as well as pro drugs or metabolites thereof or pharmaceutically acceptable salts or solvates of any thereof. In another embodiment the method of treatment of pain in a mammal comprises administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of naltrexone, naloxone or nalmefene, or a predominantly dextro enantiomeric mixture of naltrexone, naloxone or nalmefene, or a pharmaceutically acceptable salt or solvate of any thereof. In an embodiment the method for treatment of pain in a mammal comprises administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of naltrexone or a pharmaceutically acceptable salt or solvate thereof.

[0041] In another embodiment, the method for treatment of pain in a mammal comprises administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt or solvate thereof.
[0042] In another embodiment the method for treatment of pain in a mammal comprises administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of nalmefene or a pharmaceutically acceptable salt or solvate thereof.
[0043] In another embodiment the method comprises administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of predominantly dextro naltrexone mixture or a pharmaceutically acceptable salt or solvate thereof. In one embodiment the method comprises administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of predominantly dextro naloxone mixture or a pharmaceutically acceptable salt or solvate thereof.
[0044] In another embodiment the method comprises administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of predominantly dextro nalmefene mixture or a pharmaceutically acceptable salt or solvate thereof. In another embodiment the amount of the opioid/TLR4 antagonist varies from about 0.004mg/kg to about 4.3mg/kg, preferably from about 0.004mg/kg to about 0.71mg/kg, and most preferably from about 0.004mg/kg to about 0.21 mg/kg.
[0045] In one embodiment the amount of naltrexone varies from about 0.004mg/kg to about 4.3mg/kg, preferably from about 0.004mg/kg to about 0.71mg/kg, and most preferably from about 0.004mg/kg to about 0.21 mg/kg. In another embodiment, the amount of dextro naltrexone varies from about 0.004mg/kg to about 4.3mg/kg, preferably from about 0.004mg/kg to about 0.71mg/kg, and most preferably from about 0.004mg/kg to about 0.21 mg/kg.
[0046] In one embodiment the disclosure provides a method for treatment of pain wherein the human dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, varies from about 0.25mg - 50mg per day, preferably from about 0.25mg - 25mg per day, most preferably from about 0.25 mg – 15 mg per day wherein said dose is formulated into a single dosage form. In another embodiment, the composition comprises greater than 50% to 60% dextro enantiomer. In yet another embodiment the composition comprises greater than 60% dextro enantiomer. In one embodiment, the composition comprises greater than 70% dextro enantiomer. In another embodiment, the composition comprises greater than 80%

dextro enantiomer. In yet another embodiment, the composition comprises greater than 90% dextro enantiomer.

[0047] In one embodiment, the disclosure provides a method for treatment of pain wherein the single fixed dosage form is administered once, twice, three or four times through the day. In another embodiment, a therapeutically effective dose is administered systemically, via routes of mucosal, nasal, oral, parenteral, gastrointestinal, tropical or sublingual. In yet another embodiment, the composition is in a single dosage form, and said single dosage form is in the form of tablets, lozenges, troches, hard candies, liquid, powders, sprays, creams, salves and suppositories.

[0048] In one embodiment, the disclosure provides a method for treatment of pain wherein the pharmaceutical composition is used for the treatment, prevention and reversal of neuropathic pain, back pain, chronic pain, diabetic neuropathic pain, trigeminal neuralgia pain, phantom limb pain, complex regional pain syndrome pain, post herpetic pain, causalgia pain, idiopathic pain, inflammatory pain, cancer pain,postoperative pain, fibromyalgia pain, headache pain, migraine pain, allodynia pain, vulvodynia pain, interstitial cystitis pain, irritable bowel syndrome (IBS), arthritic joint pain and tendinitis. In another embodiment, the disclosure provides a method in which the pharmaceutical composition is used for the treatment, prevention and reversal of nociceptive pain with an allodynic component.

Brief Description of the Figures

[0049] Figure 1 is a graph of the various pain intensity scores over time in a patient suffering from lower back pain.

[0050] Figure 2 is a graph of the percent relief over time reported by the above patient suffering from lower back pain. .

[0051] Figure 3 is a graph of the various pain intensity scores over time in a patient suffering from pain associated with vulvodynia.

[0052] Figure 4 is a graph of the percent relief over time reported by the above patient suffering from pain associated with vulvodynia over time.

[0053] Figure 5 is a graph of the various pain intensity scores over time in a patient suffering from pain associated with trigeminal neuralgia.

[0054] Figure 6 is a graph of the percent relief reported by the above patient suffering from pain associated with trigeminal neuralgia over time.

[0055] Figure 7 is a graph of various IBS symptom intensity scores over time in a patient suffering from IBS.

[0056] Figure 8 is a graph of various headache parameter intensity scores over time in a patient suffering from migraine.

[0057] Figure 9 is a graph of the worst pain intensity by day of the ATNC05 group (N=44) versus the placebo group (N=34) in the Double-Blind phase. Missing data were imputed by Baseline Observation Carried Forward (BOCF).

[0058] Figure 10 is a graph of the least pain intensity by day of the ATNC05 group (N=44) versus the placebo group (N=34) in the Double-Blind phase.. Missing data were imputed by BOCF.

[0059] Figure 11 is a graph of the average pain intensity by day of the ATNC05 group (N=44) versus the placebo group (N=34) in the Double-Blind phase. Missing data were imputed by BOCF.

[0060] Figure 12 is a graph of the "right now" pain intensity by day of the ATNC05 group (N=44) versus the placebo group (N=34) in the Double-Blind phase. Missing data were imputed by BOCF.

[0061] Figure 13 is a graph of the night pain intensity by day of the ATNC05 group (N=44) versus the placebo group (N=34) in the Double-Blind phase. Missing data were imputed by BOCF.

[0062] Figure 14 is a graph depicting the Open Phase Relief by Day compared with a baseline measurement.

[0063] Figure 15 is a graph demonstrating in the Oswestry Disability Index score of cervical pain over time comparing the ATNC05 group, Placebo Group, and Open-Label Phase group.

[0064] Figure 16 is a graph demonstrating the Oswestry Disability Index score of lumbar pain over time in the ATNC05 group, Placebo group, and Open-Label Phase group.

[0065] Figure 17 is a graph demonstrating the Pittsburgh Insomnia Rating Scale score over time comparing ATNC05, Placebo, and Open-Label Phase. Figure 18 is a graph depicting the Roland-Morris Low Back Pain Disability Questionnaire (RMQ) scores over time comparing ATNC05, Placebo, and Open-Label Phase.

[0066] Figure 19 is a graph depicting change in pulse from baseline over time comparing ATNC05, Placebo, and Open-Label Phase.

[0067] Figure 20 is a graph depicting change in the systolic blood pressure (BP) from baseline over time comparing ATNC05, Placebo, and Open-Label Phase.

[0068] Figure 21 is a graph depicting change in the diastolic blood pressure (BP) from baseline over time comparing ATNC05, Placebo, and Open-Label Phase.

[0069] Figure 22 is a graph depicting the level of cervical pain and anxiety/irritability over time in a patient with cervical pain treated with naltrexone 2 mg twice daily.

[0070] Figure 23 is a graph depicting the level of pain and enjoyment of life over time for a patient with cervical pain treated with on naltrexone 12.5 mg per day.

[0071] Figure 24 is a graph depicting Right Now Pain Severity score after the initial dose(on average two hours) compared to the baseline period mean comparing ATNC05 (N=44) and Placebo (N=34) in the Double-Blind phase.

[0072] Figure 25 is a graph depicting the response rates as measured by PGI-I during Week 3 during both the double-blind and open-label phases.

[0073] Figure 26 is a graph depicting the daily mean Average Pain Scores by day with standard error bars comparing ATNC05 and placebo groups. The Baseline Period Mean is shown on the chart as Day 0. Missing data were imputed by BOCF.

[0074] Figure 27 is a graph depicting the summary of pain severity scores by week for placebo in the Double-Blind phase. It shows the five pain severity measures. Missing data were imputed by BOCF.

[0075] Figure 28 is a graph depicting the summary of pain severity scores by week for ATNC05 in the Double-Blind phase. It shows the five pain severity measures . Missing data were imputed by BOCF.

[0076] Figure 29 is a graph depicting the summary of pain interference scores by week for placebo in the Double-Blind phase. It shows the nine interference measures. Missing data were imputed by BOCF.

[0077] Figure 30 is a graph depicting the summary of pain interference scores by week for ATNC05 in the Double-Blind phase. It shows the nine interference measures. Missing data were imputed by BOCF.

[0078] Figure 31 is a graph depicting the ODI score by week for each treatment group. For each subject, the score was taken for their primary area of back pain (cervical or lumbar, one per subject). Missing data in the double-blind period were imputed by BOCF.

[0079] Figure 32 is a graph depicting the average Roland-Morris score by week for each treatment group. Missing data in the double-blind period were imputed by BOCF

[0080] Figure 33 is a graph depicting the average PIRS-20 score by week for each treatment group. Missing data in the double-blind period were imputed by BOCF.

[0081] Figure 34 is a graph depicting the average length of time subjects were able to stand on one leg, in seconds.

[0082] Figure 35 is a graph depicting the weekly mean BPI-Severity for subjects during the open-label extension phase.

[0083] Figure 36 is a graph depicting the weekly mean BPI-Interference scores for subjects during the open-label extension phase.

[0084] Figure 37 is a graph depicting the mean number of doses of other pain medications taken per week per subject.

[0085] Figure 38 is a graph depicting the number of migraine days per week. The number of migraine days in the treatment period was converted to weekly frequency by dividing by 3. The difference in the changes from baseline in the Treatment Period is significant with p=0.049.

[0086] Figure 39 is a graph depicting the subjects' reported change in energy level during the treatment period.

[0087] Figure 40 is a graph depicting the subjects' reported change in activity level during the treatment period.

[0088] Figure 41 is a graph depicting the mean joint pain (for subjects who reported concomitant joint pain) during the back pain study.

[0089] Figure 42 is a graph depicting the long-term pain relief of participants surveyed after the back pain study as percentage of subjects with post-treatment follow-up and as a percentage of all subjects who received ATNC05.

DETAILED DESCRIPTION

[0090] The composition and methods of use disclosed herein will now be described more fully, with reference to the accompanying drawings, in which embodiments are disclosed. However, the compositions and methods of use therefor described should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of this work to those skilled in the art.

Opioid/TLR4 Antagonists

[0091] Various μ-opioid receptor ligands have been tested and were found to also possess action as agonists or antagonists of Toll-like receptor 4 (TLR4). Toll-like receptors, found in the glia, are a class of receptors that play a key role in the innate immune system. They recognize pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) that are expressed on infectious agents, and mediate the production of cytokines necessary for the development of effective immunity. Opioid agonists such as morphine act as TLR4 agonists, while opioid antagonists such as naloxone and naltrexone were found to be TLR4 antagonists. The disclosure provides combination therapies including opioid/TLR4 antagonists and any of the substances described in the sections below. In this section, dosage regimens for combinations of opioid/TLR4 antagonists and the substances described below are provided.

[0092] Activation of TLR4 by opioid agonists such as morphine leads to downstream release of inflammatory modulators including TNF-α and interleukin-1. Constant low-level release of these modulators is thought to reduce the efficacy of opioid drug treatment with time and to be involved in both the development of tolerance to opioid analgesic drugs and in the emergence of side effects such as hyperalgesia and allodynia which can become problems following extended use of opioid drugs.

[0093] Accordingly, the disclosure relates to μ-opioid receptor ligand as ligands of TLR4 as well and contemplates that allodynia is caused by activation of TLR4. Blockage of TLR4 accordingly will eliminate allodynia.

[0094] Several opioid antagonist drugs were found to act as antagonists for TLR4, including naloxone, naltrexone and nalmefene. However it was found that not only the "normal" (-) enantiomers, but also the "unnatural" (+) enantiomers of these drugs acted as TLR4 antagonists. The unnatural enantiomers of the opioid antagonists, (+)-naltrexone and (+)-naloxone, dextro-naltrexone and dextro-naloxone, have been discovered to act as selective antagonists of TLR4. Since (+)-naloxone and (+)-naltrexone lack affinity for opioid receptors, they do not block the effects of opioid analgesic drugs, and so can be used to counteract the TLR4-mediated side effects of opioid agonists without affecting analgesia. (+)-Naloxone was also found to be neuroprotective, and both (+)-naloxone and (+)-naltrexone are effective in their own right at treating symptoms of neuropathic pain in animal models.

[0095] The best known opioid receptor antagonists are naltrexone, naloxone and nalmefene. Naltrexone is an opioid receptor antagonist used primarily in the management of alcohol

dependence and opioid dependence. A dose of 50-300 mg once daily is recommended for most patients. Naloxone is an opioid inverse agonist: it is a drug used to counter the effects of opiate overdose.

[0096] Low dose naltrexone describes the off label use of naltrexone at doses less than 15 mg per day for indications other than chemical dependency or intoxication.

[0097] It has been suggested in the literature that low dose naltrexone exerts the opposite effect of naltrexone in full dose. While the full dose naltrexone blocks the opiate system, the low dose naltrexone promotes the production of endorphins by the mechanism of up regulation caused by partial opiate receptor blockage. The beneficial effect of naltrexone was attributed to the increase in endorphins. The beneficial effect of low dose naltrexone can be further explained by its antagonism of TLR4.

[0098] Other opioid receptor antagonists used in clinical or scientific practice which also can be used for the treatment of pain include but are not limited to the following: naloxone, nalmefene, norbinaltorphimine, nalorphine, methylnaltrexone, samidorphan, cyprodime, naltrindole, amentoflavone, naltriben, norbinaltorphimine, and the naltrexone metabolite 6-ß-naltrexol.

[0099] Our understanding of pathological pain has primarily revolved around neuronal mechanisms. However, neighboring glia, were TLL4 reside, including astrocytes and microglia; have recently been recognized as powerful modulators of pain. Studies show that TLRs can be activated not only by well-known “non-self” molecular signals but also by endogenous signals (IL-1β, TNFα, IL-6 and NO) produced during chronic neuropathic pain states. Fibronectin, an endogenous TLR4 ligand that is produced in response to tissue injury, leads to an up regulation of the purinoceptor P2X4, which is expressed exclusively on microglia.

[00100] The cause of neuropathic pain can be traced to the nervous system going awry. Blocking TLR4s with an opioid receptor antagonist solves the perplexing problem of neuropathic pain. The disclosure includes findings from studies including a double-blind placebo-controlled clinical trial of 78 subjects treated with the opioid receptor naltrexone which proved the efficacy of this treatment for pain.

[00101] The package insert for full dose naltrexone reports single-digit incidence of nervousness, insomnia, and anxiety. In contrast, a study by Ploesser evaluating side effects of low dose naltrexone showed double digit incidence of nervousness, insomnia, and anxiety. This disclosure contemplates the use of an alpha-2 adrenergic agonist in order to abate the

adverse effects caused by the low dose opioid/TLR4 antagonist. The direct-acting alpha-2 adrenergic agonist is selected from a group consisting of apraclonidine, brimonidine, clonidine, detomidine, dexmedetomidine, guanabenz, guanfacine, lofexidine, medetomidine, romifidine, tizanidine, tolonidine, xylazine and fadolmidine, or pharmaceutically acceptable salts or solvates of any thereof.

[00102] This disclosure provides an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvates thereof. The opioid/TLR4 antagonist may be selected from a group consisting of (but not limited to) naltrexone, norbinaltorphimine, nalmefene, naloxone, nalorphine, methylnaltrexone, samidorphan, cyprodime, naltrindole, amentoflavone, naltriben, norbinaltorphimine, 6-ß-naltrexol and metabolites thereof, including all enantiomeric and epimeric forms as well as the appropriate mixtures thereof, as well as pro drugs or metabolites thereof or pharmaceutically acceptable salts or solvates of any thereof. In a particular embodiment of a method and a pharmaceutical composition, the opioid/ TLR4 antagonist is (+)–naltrexone (dextro-naltrexone), as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

[00103] In a particular embodiment of a method and a pharmaceutical composition, the dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof , or of any opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof when combined with any of the substances described below, is about 0.001 to about 1.0 mg/kg, e.g. is about 0.004 mg/kg- about 0.71 mg/kg (e.g. is about 0.004 mg/kg, 0.005mg/kg, 0.006 mg/kg, 0.007 mg/kg, 0.008 mg/kg, 0.009 mg/kg, 0.010 mg/kg, 0.011 mg/kg, 0.012 mg/kg, 0.013 mg/kg, 0.014 mg/kg, 0.015 mg/kg, 0.016 mg/kg, 0.017 mg/kg, 0.018 mg/kg, 0.019 mg/kg, 0.02 mg/kg, 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, 0.06 mg/kg, 0.07 mg/kg, 0.08 mg/kg, 0.09 mg/kg, 0.10 mg/kg, 0.11 mg/kg, 0.12 mg/kg, 0.13 mg/kg, 0.14 mg/kg, 0.15 mg/kg, 0.16 mg/kg, 0.17 mg/kg, 0.18 mg/kg, 0.19 mg/kg, 0.20 mg/kg, 0.21 mg/kg, 0.22 mg/kg, 0.23 mg/kg, 0.24 mg/kg, 0.25 mg/kg, 0.26 mg/kg, 0.27 mg/kg, 0.28 mg/kg, 0.29 mg/kg, 0.30 mg/kg, 0.31 mg/kg, 0.32 mg/kg, 0.33 mg/kg, 0.34 mg/kg, 0.35 mg/kg, 0.36 mg/kg, 0.37 mg/kg, 0.38 mg/kg, 0.39 mg/kg, 0.40 mg/kg, 0.41 mg/kg, 0.42 mg/kg, 0.43 mg/kg, 0.44 mg/kg, 0.45 mg/kg, 0.46 mg/kg, 0.47 mg/kg, 0.48 mg/kg, 0.49 mg/kg, 0.50 mg/kg, 0.51 mg/kg, 0.52 mg/kg, 0.53 mg/kg, 0.54 mg/kg, 0.55 mg/kg, 0.56 mg/kg, 0.57 mg/kg, 0.58 mg/kg, 0.59 mg/kg, 0.60 mg/kg, 0.61 mg/kg, 0.62 mg/kg, 0.63 mg/kg, 0.64

mg/kg, 0.65 mg/kg, 0.66 mg/kg, 0.67 mg/kg, 0.68 mg/kg, 0.69 mg/kg, 0.70 mg/kg, or 0.71 mg/kg.

[00104] In a particular embodiment of a method and a pharmaceutical composition, the dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof , or of any opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof when combined with any of the substances described below, is administered in a range of about 0.001 to about 1.0 mg/kg, e.g. a range of about 0.004 mg/kg to about 0.71 mg/kg (e.g. the range is about 0.004 to about 0.35 mg/kg, about 0.35 to about 0.71 mg/kg, about 0.004 to about 0.24 mg/kg, about 0.24 to about 0.47 mg/kg, about 0.47 to about 0.71 mg/kg, about 0.004 to about 0.18 mg/kg, about 0.18 to about 0.35 mg/kg, about 0.35 to about 0.53 mg/kg, about 0.53 to about 0.71 mg/kg, about 0.004 to about 0.07 mg/kg, 0.07 to about 0.14 mg/kg, about 0.14 to about 0.21 mg/kg, about 0.21 to about 0.28 mg/kg, 0.28 to about 0.35 mg/kg, about 0.35 to about 0.42 mg/kg, about 0.42 to about 0.49 mg/kg, about 0.49 to about 0.56 mg/kg, about 0.56 to about 0.63 mg/kg, about 0.63 to about 0.71 mg/kg, 0.004 to about 0.047 mg/kg, 0.024 to about 0.71 mg/kg, about 0.18 to about 0.53 mg/kg, or about 0.18 to about 0.71 mg/kg).

[00105] In a particular embodiment of a method and a pharmaceutical composition, the human dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof , or of any opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.1 mg to about 100 mg per day, e.g. is about 0.25 mg to about 15 mg per day, about 0.25 mg to about 25 mg per day, or about 0.25 mg to about 50 mg per day (e.g. about 0.25 mg, 0.26 mg, 0.27 mg, 0.28 mg, 0.29 mg, 0.30 mg, 0.31 mg, 0.32 mg, 0.33 mg, 0.34 mg, 0.35 mg, 0.36 mg, 0.37 mg, 0.38 mg, 0.39 mg, 0.40 mg, 0.41 mg, 0.42 mg, 0.43 mg, 0.44 mg, 0.45 mg, 0.46 mg, 0.47 mg, 0.48 mg, 0.49 mg, 0.50 mg, 0.51 mg, 0.52 mg, 0.53 mg, 0.54 mg, 0.55 mg, 0.56 mg, 0.57 mg, 0.58 mg, 0.59 mg, 0.60 mg, 0.61 mg, 0.62 mg, 0.63 mg, 0.64 mg, 0.65 mg, 0.66 mg, 0.67 mg, 0.68 mg, 0.69 mg, 0.70 mg, 0.71 mg, 0.72 mg, 0.73 mg, 0.74 mg, 0.75 mg, 0.76 mg, 0.77 mg, 0.78 mg, 0.79 mg, 0.80 mg, 0.81 mg, 0.82 mg, 0.83 mg, 0.84 mg, 0.85 mg, 0.86 mg, 0.87 mg, 0.88 mg, 0.89 mg, 0.90 mg, 0.91 mg, 0.92 mg, 0.93 mg, 0.94 mg, 0.95 mg, 0.96 mg, 0.97 mg, 0.98 mg, 0.99 mg, 1 mg, 2 mg, 3 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, or 50 mg).

In a particular embodiment of a method and a pharmaceutical composition, the dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof , or of any opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof when combined with any of the substances described below, is administered in a range of about 0.001 to about 1.0 mg per day, e.g. a range of about 0.25 mg to about 15 mg per day (e.g. the range is about 0.25 to about 7.6 mg, about 7.6 to about 15 mg, about 0.25 to about 5.1 mg, about 5.1 to about 10.8 mg, about 10.8 to about 15 mg, about 0.25 to about 3.93 mg, about 3.93 to about 7.6 mg, about 7.6 to about 11.3 mg, about 11.3 to about 15 mg, about 0.25 to about 10 mg, 5.1 to about 15 mg, about 3.9 to about 11.3 mg, or about 3.9 to about 15 mg per day), about 0.25 to about 25 mg per day (e.g. the range is about 0.25 to about 12.6 mg, about 12.6 to about 25 mg, about 0.25 to about 8.5 mg, about 8.5 to about 16.7 mg, about 16.7 to about 25 mg, about 0.25 to about 6.43 mg, about 6.43 to about 12.6 mg, about 12.6 to about 18.7 mg, about 18.7 to about 25 mg, about 0.25 to about 16.7 mg, 8.5 to about 25 mg, about 6.4 to about 18.8 mg, or about 6.4 to about 25 mg per day), or about 0.25 to about 50 mg per day (e.g. the range is about 0.25 to about 25 mg, about 25 to about 50 mg, about 0.25 to about 16.8 mg, about 16.8 to about 33.4 mg, about 33.4 to about 50 mg, about 0.25 to about 12.6 mg, about 12.6 to about 25.1 mg, about 25.1 to about 37.5 mg, about 37.5 to about 50 mg, about 0.25 to about 33.4 mg, 16.8 to about 50 mg, about 12.6 to about 37.5 mg, or about 12.6 to about 50 mg per day).

Combinations of Opioid/TLR4 Antagonists with Alpha-2-adrenergic agonists

[00106] This disclosure also provides a combination, comprising an opioid/TLR4 antagonist, and pharmaceutically acceptable salts or solvates of any thereof, and alpha-2 adrenergic agonist, and pharmaceutically acceptable salts or solvates of any thereof. The alpha-2 adrenergic agonist can be selected from a group consisting of apraclonidine, brimonidine, clonidine, detomidine, dexmedetomidine, guanabenz, guanfacine, lofexidine, medetomidine, romifidine, tizanidine, tolonidine, xylazine and fadolmidine, or pharmaceutically acceptable salts or solvates of any thereof.

[00107] In certain embodiments, the alpha-2 adrenergic agonist is clonidine. Clonidine is a sympatholytic medication, classified as a direct-acting α-2 adrenergic agonist. It is an imidazoline derivative. An alternative hypothesis that has been proposed is that clonidine acts centrally as an imidazoline-2 receptor agonist. The imidazoline-2 receptor is an allosteric binding site of monoamine oxidase and is involved in pain modulation and neuroprotection. Clonidine is used to treat medical conditions such as high blood pressure, ADHD,

anxiety/panic disorder, and certain pain conditions. The therapeutic doses most commonly employed have ranged from about 0.1 to about 1.0 mg, e.g. from about 0.2 mg to about 0.6 mg (e.g. about 0.20 mg, 0.21 mg, 0.22 mg, 0.23 mg, 0.24 mg, 0.25 mg, 0.26 mg, 0.27 mg, 0.28 mg, 0.29 mg, 0.30 mg, 0.31 mg, 0.32 mg, 0.33 mg, 0.34 mg, 0.35 mg, 0.36 mg, 0.37 mg, 0.38 mg, 0.39 mg, 0.40 mg, 0.41 mg, 0.42 mg, 0.43 mg, 0.44 mg, 0.45 mg, 0.46 mg, 0.47 mg, 0.48 mg, 0.49 mg, 0.50 mg, 0.51 mg, 0.52 mg, 0.53 mg, 0.54 mg, 0.55 mg, 0.56 mg, 0.57 mg, 0.58 mg, 0.59 mg or 0.60 mg) per day given in divided doses.

[00108] Clonidine enhances the pain treatment effect of naltrexone by agonism of the imidazoline-2 receptor, while its sympatholytic properties are the cause of the abatement of naltrexone's adverse reactions.

[00109] In a particular embodiment of a method and a pharmaceutical composition, the alpha-2 adrenergic agonist is a pharmaceutically acceptable salt or solvate thereof. In a particular embodiment of a method and a pharmaceutical composition, the direct-acting alpha-2 adrenergic agonist is in a sustained release formulation, or a pharmaceutically acceptable salt or solvate thereof. In a particular embodiment of a method and a pharmaceutical composition, the opioid/TLR4 antagonist is naltrexone or a pharmaceutically acceptable salt or solvate thereof, in a therapeutically effective amount and is combined with a direct-acting alpha-2 adrenergic agonist, or a pharmaceutically acceptable salt or solvate thereof, in a therapeutically effective amount.

[00110] In a particular embodiment of a method and a pharmaceutical composition, the opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, and the alpha-2 adrenergic agonist, or a pharmaceutically acceptable salt or solvate thereof, are in a weight to weight combination range which corresponds to a synergistic combination range of the order of about 100:1 to about 1:1 parts by weight, e.g. about 90:1 to about 22.5:1 parts by weight (e.g. about 22.5:1, 23:1, 24:1, 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1, 36:1, 37:1, 38:1, 39:1, 40:1, 41:1, 42:1, 43:1, 44:1, 45:1, 46:1, 47:1, 48:1, 49:1, 50:1, 41:1, 42:1, 43:1, 44:1, 45:1, 46:1, 47:1, 48:1, 49:1, 50:1, 51:1, 52:1,53:1, 54:1, 55:1, 56:1, 57:1, 58:1, 59:1, 60:1, 61:1, 62:1, 63:1, 64:1, 65:1, 66:1, 67:1, 68:1, 69:1, 70:1, 71:1, 72:1, 73:1, 74:1, 75:1, 76:1, 77:1, 78:1, 79:1, 80:1, 81:1, 82:1, 83:1, 84:1, 85:1, 86:1, 87:1, 88:1, 89:1, 90:1).

[00111] In certain embodiments, the weight to weight combination range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, and the alpha-2 adrenergic agonist, or a pharmaceutically acceptable salt or solvate thereof, are of the order of

about 100:1 to about 1:1 parts by weight, e.g. is about 90:1 to about 22.5:1 parts by weight (e.g. may range from about (e.g. may range from about 22.5:1 to about 56:1, about 56:1 to about 90:1, about 22.5:1 to about 45:1, about 46:1 to about 67.5:1, about 67.6:1 to about 90:1, about 22.5:1 to about 39:1, about 40:1 to about 56:1, about 57:1 to about 73:1, about 74:1 about 90:1, about 22.5:1 to about 73:1, 39:1 to about 90:1, about 39:1 to about 73:1, or about 39:1 to about 90:1 parts by weight).

[00112] In a particular embodiment of a method and a pharmaceutical composition, the dose range of the opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.001 mg/kg to about 1 mg/kg, e.g. is about 0.004 mg/kg to about 0.71 mg/kg, as described herein.

[00113] In a particular embodiment of a method and a pharmaceutical composition, the dose range of the alpha-2 adrenergic agonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.0001 mg/kg to about 0.01 mg/kg per day, e.g. is about 0.00018 mg/kg - 0.0086mg/kg per day (e.g. is about 0.00018 mg/kg, 0.00019 mg/kg, 0.002 mg/kg, 0.0021 mg/kg, 0.0022 mg/kg, 0.0023 mg/kg, 0.0024 mg/kg, 0.0025 mg/kg, 0.0026 mg/kg, 0.0027 mg/kg, 0.0028 mg/kg, 0.0029 mg/kg, 0.003 mg/kg, 0.0031 mg/kg, 0.0032 mg/kg, 0.0033 mg/kg, 0.0034 mg/kg, 0.0035 mg/kg, 0.0036 mg/kg, 0.0037 mg/kg, 0.0038 mg/kg, 0.0039 mg/kg, 0.004 mg/kg, 0.0041 mg/kg, 0.0042 mg/kg, 0.0043 mg/kg, 0.0044 mg/kg, 0.0045 mg/kg, 0.0046 mg/kg, 0.0047 mg/kg, 0.0048 mg/kg, 0.0049 mg/kg, 0.005 mg/kg, 0.0051 mg/kg, 0.0052 mg/kg, 0.0053 mg/kg, 0.0054 mg/kg, 0.0055 mg/kg, 0.0056 mg/kg, 0.0057 mg/kg, 0.0058 mg/kg, 0.0059 mg/kg, 0.006 mg/kg, 0.0061 mg/kg, 0.0062 mg/kg, 0.0063 mg/kg, 0.0064 mg/kg, 0.0065 mg/kg, 0.0066 mg/kg, 0.0067 mg/kg, 0.0068 mg/kg, 0.0069 mg/kg, 0.007 mg/kg, 0.0071 mg/kg, 0.0072 mg/kg, 0.0073 mg/kg, 0.0074 mg/kg, 0.0075 mg/kg, 0.0076 mg/kg, 0.0077 mg/kg, 0.0078 mg/kg, 0.0079 mg/kg, 0.008 mg/kg, 0.0081 mg/kg, 0.0082 mg/kg, 0.0083 mg/kg, 0.0084 mg/kg, 0.0085 mg/kg, or 0.0086 mg/kg).

[00114] In certain embodiments, the dose range of the alpha-2 adrenergic agonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.0001 mg/kg to about 0.01 mg/kg per day, e.g. may range from about 0.00018 mg/kg to 0.0086 mg/kg per day (e.g. may range from about 0.00018 to about 0.0044 mg/kg, about 0.0044 to about 0.0086 mg/kg, about 0.00018 to about 0.003 mg/kg, about 0.003 to about 0.006 mg/kg, about 0.006 to about 0.0086 mg/kg, about 0.00018 to about 0.003 mg/kg, about 0.003 to about 0.004 mg/kg, about 0.004 to about 0.006 mg/kg, about 0.006 to about 0.0086 mg/kg, about 0.00018 to about

0.0006 mg/kg, 0.003 to about 0.0086 mg/kg, about 0.003 to about 0.006 mg/kg, or about 0.003 to about 0.0086 mg/kg per day).

[00115] In a particular embodiment of a method and a pharmaceutical composition, the human dose range of the opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.1 mg to about 100 mg per day, e.g. is about 0.25 mg to about 50 mg per day, is about 0.25 mg to about 25 mg per day, or is about 0.25 mg - about 15 mg per day , as described above.

[00116] In a particular embodiment of a method and a pharmaceutical composition, the human the dose range of the alpha-2 adrenergic agonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.01 to about 1 mg per day, e.g. is about 0.0125 mg – about 0.6 mg (e.g. about 0.0125 mg, 0.0126 mg, 0.0127 mg, 0.0128 mg, 0.0129 mg, 0.0130 mg, 0.0131 mg, 0.0132 mg, 0.0133 mg, 0.0134 mg, 0.0135 mg, 0.0136 mg, 0.0137 mg, 0.0138 mg, 0.0139 mg, 0.0140 mg, 0.0141 mg, 0.0142 mg, 0.0143 mg, 0.0144 mg, 0.0145 mg, 0.0146 mg, 0.0147 mg, 0.0148 mg, 0.0149 mg, 0.0150 mg, 0.0160 mg, 0.00170 mg, 0.018 mg, 0.019 mg, 0.02 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.07 mg, 0.08 mg, 0.09 mg, 0.10 mg, 0.11 mg, 0.12 mg, 0.13 mg, 0.14 mg, 0.15 mg, 0.16 mg, 0.17 mg, 0.18 mg, 0.19 mg, 0.20 mg, 0.21 mg, 0.22 mg, 0.23 mg, 0.24 mg, 0.25 mg, 0.26 mg, 0.27 mg, 0.28 mg, 0.29 mg, 0.30 mg, 0.31 mg, 0.32 mg, 0.33 mg, 0.34 mg, 0.35 mg, 0.36 mg, 0.37 mg, 0.38 mg, 0.39 mg, 0.40 mg, 0.41 mg, 0.42 mg, 0.43 mg, 0.44 mg, 0.45 mg, 0.46 mg, 0.47 mg, 0.48 mg, 0.49 mg, 0.50 mg, 0.51 mg, 0.52 mg, 0.53 mg, 0.54 mg, 0.55 mg, 0.56 mg, 0.57 mg, 0.58 mg, 0.59 mg or 0.60 mg).

[00117] In certain embodiments, the dose range of the alpha-2 adrenergic agonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.0001 mg/kg to about 0.01 mg/kg per day, e.g. may range from about 0.0125 mg to about 0.6 mg per day (e.g. may range from about 0.0125 mg to about 0.31 mg, about 0.31 to about 0.6 mg, about 0.0125 mg to about 0.21 mg, about 0.21 to about 0.40 mg, about 0.40 to about 0.6 mg, about 0.0125 to about 0.16 mg, about 0.16 to about 0.31 mg, about 0.31 to about 0.45 mg, or about 0.45 to about 0.6 mg, about 0.0125 to about 0.45 mg, 0.16 to about 0.6 mg, about 0.16 to about 0.45 mg, or about 0.16 to about 0.6 mg per day).

[00118] In a particular embodiment of a method and a pharmaceutical composition, the human the dose range of the alpha-2 adrenergic agonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.01 to about 1.0 mg , e.g. is about 0.0125 mg to about 0.3 mg (e.g. about 0.0125 mg, 0.0126 mg, 0.0127 mg, 0.0128 mg, 0.0129 mg, 0.0130 mg, 0.0131 mg, 0.0132 mg, 0.0133 mg, 0.0134 mg, 0.0135 mg, 0.0136 mg, 0.0137 mg, 0.0138 mg,

0.0139 mg, 0.0140 mg, 0.0141 mg, 0.0142 mg, 0.0143 mg, 0.0144 mg, 0.0145 mg, 0.0146 mg, 0.0147 mg, 0.0148 mg, 0.0149 mg, 0.0150 mg, 0.0160 mg, 0.00170 mg, 0.018 mg, 0.019 mg, 0.02 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.07 mg, 0.08 mg, 0.09 mg, 0.10 mg, 0.11 mg, 0.12 mg, 0.13 mg, 0.14 mg, 0.15 mg, 0.16 mg, 0.17 mg, 0.18 mg, 0.19 mg, 0.20 mg, 0.21 mg, 0.22 mg, 0.23 mg, 0.24 mg, 0.25 mg, 0.26 mg, 0.27 mg, 0.28 mg, 0.29 mg, or 0.30 mg).

[00119] In certain embodiments, the dose range of the alpha-2 adrenergic agonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.0001 mg/kg to about 0.01 mg/kg per day, e.g. may range from about 0.0125 mg to about 0.3 mg per day (e.g. may range from about 0.0125 mg to about 0.16 mg, about 0.16 to about 0.3 mg, about 0.0125 mg to about 0.11 mg, about 0.11 to about 0.20 mg, about 0.20 to about 0.3 mg, about 0.0125 to about 0.08 mg, about 0.08 to about 0.16 mg, about 0.16 to about 0.23 mg, or about 0.23 to about 0.3 mg, about 0.0125 to about 0.23 mg, 0.08 to about 0.3 mg, about 0.08 to about 0.23 mg, or about 0.08 to about 0.3 mg per day).

[00120] In a particular embodiment of a method and a pharmaceutical composition, the human dose range of the opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.1 to about 100 mg per day, e.g. is about 0.25 mg - about 50 mg per day, as described above, and the human the dose range of the alpha-2 adrenergic agonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.01 to about 1 mg, e.g. is about 0.0125 mg to about 0.6 mg or any of the ranges described herein (e.g. about 0.0125 mg, 0.0126 mg, 0.0127 mg, 0.0128 mg, 0.0129 mg, 0.0130 mg, 0.0131 mg, 0.0132 mg, 0.0133 mg, 0.0134 mg, 0.0135 mg, 0.0136 mg, 0.0137 mg, 0.0138 mg, 0.0139 mg, 0.0140 mg, 0.0141 mg, 0.0142 mg, 0.0143 mg, 0.0144 mg, 0.0145 mg, 0.0146 mg, 0.0147 mg, 0.0148 mg, 0.0149 mg, 0.0150 mg, 0.0160 mg, 0.00170 mg, 0.018 mg, 0.019 mg, 0.02 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.07 mg, 0.08 mg, 0.09 mg, 0.10 mg, 0.11 mg, 0.12 mg, 0.13 mg, 0.14 mg, 0.15 mg, 0.16 mg, 0.17 mg, 0.18 mg, 0.19 mg, 0.20 mg, 0.21 mg, 0.22 mg, 0.23 mg, 0.24 mg, 0.25 mg, 0.26 mg, 0.27 mg, 0.28 mg, 0.29 mg, 0.30 mg, 0.31 mg, 0.32 mg, 0.33 mg, 0.34 mg, 0.35 mg, 0.36 mg, 0.37 mg, 0.38 mg, 0.39 mg, 0.40 mg, 0.41 mg, 0.42 mg, 0.43 mg, 0.44 mg, 0.45 mg, 0.46 mg, 0.47 mg, 0.48 mg, 0.49 mg, 0.50 mg, 0.51 mg, 0.52 mg, 0.53 mg, 0.54 mg, 0.55 mg, 0.56 mg, 0.57 mg, 0.58 mg, 0.59 mg or 0.60 mg), wherein said composition is formulated into a single fixed combination dosage form. In a particular embodiment of a method and a pharmaceutical composition, the composition is administered once, twice, three or four times through the day.

[00121] In a particular embodiment of a method and a pharmaceutical composition, the alpha-2 adrenergic agonist is clonidine, or a pharmaceutically acceptable salt or solvate thereof. In a particular embodiment of a method and a pharmaceutical composition, the direct-acting alpha-2 adrenergic agonist is clonidine in a sustained release formulation, or a pharmaceutically acceptable salt or solvate thereof. In a particular embodiment of a method and a pharmaceutical composition, the opioid/TLR4 antagonist is naltrexone or a pharmaceutically acceptable salt or solvate thereof, in a therapeutically effective amount and the direct-acting alpha-2 adrenergic agonist is clonidine, or a pharmaceutically acceptable salt or solvate thereof, in a therapeutically effective amount. In a particular embodiment of a method and a pharmaceutical composition, naltrexone, or a pharmaceutically acceptable salt or solvate thereof, and clonidine, or a pharmaceutically acceptable salt or solvate thereof, are in a weight to weight combination range which corresponds to a synergistic combination range of the order of about 100:1 to about 1:1 parts by weight, e.g. is about 90:1 to about 22.5:1 parts by weight (e.g. about 22.5:1, 23:1, 24:1, 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1, 36:1, 37:1, 38:1, 39:1, 40:1, 41:1, 42:1, 43:1, 44:1, 45:1, 46:1, 47:1, 48:1, 49:1, 50:1, 41:1, 42:1, 43:1, 44:1, 45:1, 46:1, 47:1, 48:1, 49:1, 50:1, 51:1, 52:1,53:1, 54:1, 55:1, 56:1, 57:1, 58:1, 59:1, 60:1, 61:1, 62:1, 63:1, 64:1, 65:1, 66:1, 67:1, 68:1, 69:1, 70:1, 71:1, 72:1, 73:1, 74:1, 75:1, 76:1, 77:1, 78:1, 79:1, 80:1, 81:1, 82:1, 83:1, 84:1, 85:1, 86:1, 87:1, 88:1, 89:1, 90:1).

[00122] In certain embodiments, the weight to weight combination range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, and clonidine, or a pharmaceutically acceptable salt or solvate thereof, are of the order of about 100:1 to about 1:1 parts by weight, e.g. is about 90:1 to about 22.5:1 parts by weight (e.g. may range from about (e.g. may range from about 22.5:1 to about 56:1, about 56:1 to about 90:1, about 22.5:1 to about 45:1, about 45:1 to about 67.5:1, about 67.5:1 to about 90:1, about 22.5:1 to about 40:1, about 40:1 to about 56:1, about 56:1 to about 73:1, about 73:1 about 90:1, about 22.5:1 to about 73:1, 39:1 to about 90:1, about 39:1 to about 73:1, or about 39:1 to about 90:1 parts by weight).

[00123] In a particular embodiment, the naltrexone, or pharmaceutically acceptable salt or solvate thereof, can be administered as explained above in the section entitled "Opioid/TLR4 Antagonists.

[00124] In a particular embodiment of a method and a pharmaceutical composition, the dose range of clonidine, or a pharmaceutically acceptable salt or solvate thereof, is about

0.0001 to about 0.01 mg/kg per day, e.g. is about 0.00018 mg/kg – about 0.0086mg/kg per day (e.g. is about 0.00018 mg/kg, 0.00019 mg/kg, 0.002 mg/kg, 0.0021 mg/kg, 0.0022 mg/kg, 0.0023 mg/kg, 0.0024 mg/kg, 0.0025 mg/kg, 0.0026 mg/kg, 0.0027 mg/kg, 0.0028 mg/kg, 0.0029 mg/kg, 0.003 mg/kg, 0.0031 mg/kg, 0.0032 mg/kg, 0.0033 mg/kg, 0.0034 mg/kg, 0.0035 mg/kg, 0.0036 mg/kg, 0.0037 mg/kg, 0.0038 mg/kg, 0.0039 mg/kg, 0.004 mg/kg, 0.0041 mg/kg, 0.0042 mg/kg, 0.0043 mg/kg, 0.0044 mg/kg, 0.0045 mg/kg, 0.0046 mg/kg, 0.0047 mg/kg, 0.0048 mg/kg, 0.0049 mg/kg, 0.005 mg/kg, 0.0051 mg/kg, 0.0052 mg/kg, 0.0053 mg/kg, 0.0054 mg/kg, 0.0055 mg/kg, 0.0056 mg/kg, 0.0057 mg/kg, 0.0058 mg/kg, 0.0059 mg/kg, 0.006 mg/kg, 0.0061 mg/kg, 0.0062 mg/kg, 0.0063 mg/kg, 0.0064 mg/kg, 0.0065 mg/kg, 0.0066 mg/kg, 0.0067 mg/kg, 0.0068 mg/kg, 0.0069 mg/kg, 0.007 mg/kg, 0.0071 mg/kg, 0.0072 mg/kg, 0.0073 mg/kg, 0.0074 mg/kg, 0.0075 mg/kg, 0.0076 mg/kg, 0.0077 mg/kg, 0.0078 mg/kg, 0.0079 mg/kg, 0.008 mg/kg, 0.0081 mg/kg, 0.0082 mg/kg, 0.0083 mg/kg, 0.0084 mg/kg, 0.0085 mg/kg, or 0.0086 mg/kg).

[00125] In certain embodiments, the dose range of clonidine, or a pharmaceutically acceptable salt or solvate thereof, is about 0.0001 mg/kg to about 0.01 mg/kg per day, e.g. may range from about 0.00018 mg/kg to 0.0086mg/kg per day (e.g. may range from about 0.00018 to about 0.004 mg/kg, about 0.004 to about 0.0086 mg/kg, about 0.00018 to about 0.003 mg/kg, about 0.003 to about 0.006 mg/kg, about 0.006 to about 0.0086 mg/kg, about 0.00018 to about 0.003 mg/kg, about 0.003 to about 0.4 mg/kg, about 0.004 to about 0.006 mg/kg, or about 0.006 to about 0.0086 mg/kg, about 0.00018 to about 0.0006 mg/kg, 0.003 to about 0.0086 mg/kg, about 0.003 to about 0.006 mg/kg, or about 0.003to about 0.0086 mg/kg per day).

[00126] In a particular embodiment of a method and a pharmaceutical composition, the human dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, is about 0.1 to about 100 mg per day, e.g. about 0.25 mg – about 50 mg per day, about 0.25 mg – about 25 mg per day, or about 0.25 mg – about 15 mg per day, as described above.

[00127] In a particular embodiment of a method and a pharmaceutical composition, the human the dose range of clonidine, or a pharmaceutically acceptable salt or solvate thereof, is about 0.01 to about 1.0 mg, e.g. is about 0.0125 mg to about 0.6 mg per day (e.g. about 0.0125 mg, 0.0126 mg, 0.0127 mg, 0.0128 mg, 0.0129 mg, 0.0130 mg, 0.0131 mg, 0.0132 mg, 0.0133 mg, 0.0134 mg, 0.0135 mg, 0.0136 mg, 0.0137 mg, 0.0138 mg, 0.0139 mg, 0.0140 mg, 0.0141 mg, 0.0142 mg, 0.0143 mg, 0.0144 mg, 0.0145 mg, 0.0146 mg, 0.0147 mg, 0.0148 mg, 0.0149 mg, 0.0150 mg, 0.0160 mg, 0.00170 mg, 0.018 mg, 0.019 mg, 0.02

mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.07 mg, 0.08 mg, 0.09 mg, 0.10 mg, 0.11 mg, 0.12 mg, 0.13 mg, 0.14 mg, 0.15 mg, 0.16 mg, 0.17 mg, 0.18 mg, 0.19 mg, 0.20 mg, 0.21 mg, 0.22 mg, 0.23 mg, 0.24 mg, 0.25 mg, 0.26 mg, 0.27 mg, 0.28 mg, 0.29 mg, 0.30 mg, 0.31 mg, 0.32 mg, 0.33 mg, 0.34 mg, 0.35 mg, 0.36 mg, 0.37 mg, 0.38 mg, 0.39 mg, 0.40 mg, 0.41 mg, 0.42 mg, 0.43 mg, 0.44 mg, 0.45 mg, 0.46 mg, 0.47 mg, 0.48 mg, 0.49 mg, 0.50 mg, 0.51 mg, 0.52 mg, 0.53 mg, 0.54 mg, 0.55 mg, 0.56 mg, 0.57 mg, 0.58 mg, 0.59 mg or 0.60 mg per day).

[00128] In a particular embodiment of a method and a pharmaceutical composition, the human the dose range of clonidine, or a pharmaceutically acceptable salt or solvate thereof, is about 0.01 to about 1.0 mg, e.g. is about 0.0125 mg to about 0.6 mg (e.g. may range from about 0.0125 mg to about 0.3 mg, about 0.3 to about 0.6 mg, about 0.0125 mg to about 0.2 mg, about 0.2 to about 0.40 mg, about 0.4 to about 0.6 mg, about 0.0125 to about 0.16 mg, about 0.16 to about 0.3 mg, about 0.3 to about 0.45 mg, or about 0.45 to about 0.6 mg, about 0.0125 to about 0.45 mg, 0.16 to about 0.6 mg, about 0.16 to about 0.45 mg, or about 0.16 to about 0.6 mg per day).

[00129] In a particular embodiment of a method and a pharmaceutical composition, the human the dose range of clonidine, or a pharmaceutically acceptable salt or solvate thereof, is about 0.01 to about 1.0 mg, e.g. is about 0.0125 mg to about 0.3 mg (e.g. about 0.0125 mg, 0.0126 mg, 0.0127 mg, 0.0128 mg, 0.0129 mg, 0.0130 mg, 0.0131 mg, 0.0132 mg, 0.0133 mg, 0.0134 mg, 0.0135 mg, 0.0136 mg, 0.0137 mg, 0.0138 mg, 0.0139 mg, 0.0140 mg, 0.0141 mg, 0.0142 mg, 0.0143 mg, 0.0144 mg, 0.0145 mg, 0.0146 mg, 0.0147 mg, 0.0148 mg, 0.0149 mg, 0.0150 mg, 0.0160 mg, 0.00170 mg, 0.018 mg, 0.019 mg, 0.02 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.07 mg, 0.08 mg, 0.09 mg, 0.10 mg, 0.11 mg, 0.12 mg, 0.13 mg, 0.14 mg, 0.15 mg, 0.16 mg, 0.17 mg, 0.18 mg, 0.19 mg, 0.20 mg, 0.21 mg, 0.22 mg, 0.23 mg, 0.24 mg, 0.25 mg, 0.26 mg, 0.27 mg, 0.28 mg, 0.29 mg or 0.30 mg).

[00130] In certain embodiments, the dose range of clonidine, or a pharmaceutically acceptable salt or solvate thereof, is about 0.0001 mg/kg to about 0.01 mg per day, e.g. may range from about 0.0125 to about 0.3 mg (e.g. may range from about 0.0125 mg to about 0.16 mg, about 0.16 to about 0.3 mg, about 0.0125 mg to about 0.11 mg, about 0.11 to about 0.20 mg, about 0.20 to about 0.3 mg, about 0.0125 to about 0.08 mg, about 0.08 to about 0.16 mg, about 0.16 to about 0.22 mg, or about 0.22 to about 0.3 mg, about 0.0125 to about 0.22 mg, 0.08 to about 0.3 mg, about 0.08 to about 0.22 mg, or about 0.08 to about 0.3 mg per day).

[00131] In a particular embodiment of a method and a pharmaceutical composition, the human dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, is

about 0.1 to about 100 mg per day, e.g. is about 0.25 mg – about 50 mg per day, as described above, and the human the dose range of clonidine, or a pharmaceutically acceptable salt or solvate thereof, is about 0.01 to about 1.0 mg, e.g. is about 0.0125 mg to about 0.6 mg (e.g. may be any of the dose ranges listed above, e.g. may be about 0.0125 mg, 0.0126 mg, 0.0127 mg, 0.0128 mg, 0.0129 mg, 0.0130 mg, 0.0131 mg, 0.0132 mg, 0.0133 mg, 0.0134 mg, 0.0135 mg, 0.0136 mg, 0.0137 mg, 0.0138 mg, 0.0139 mg, 0.0140 mg, 0.0141 mg, 0.0142 mg, 0.0143 mg, 0.0144 mg, 0.0145 mg, 0.0146 mg, 0.0147 mg, 0.0148 mg, 0.0149 mg, 0.0150 mg, 0.0160 mg, 0.00170 mg, 0.018 mg, 0.019 mg, 0.02 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.07 mg, 0.08 mg, 0.09 mg, 0.10 mg, 0.11 mg, 0.12 mg, 0.13 mg, 0.14 mg, 0.15 mg, 0.16 mg, 0.17 mg, 0.18 mg, 0.19 mg, 0.20 mg, 0.21 mg, 0.22 mg, 0.23 mg, 0.24 mg, 0.25 mg, 0.26 mg, 0.27 mg, 0.28 mg, 0.29 mg, 0.30 mg, 0.31 mg, 0.32 mg, 0.33 mg, 0.34 mg, 0.35 mg, 0.36 mg, 0.37 mg, 0.38 mg, 0.39 mg, 0.40 mg, 0.41 mg, 0.42 mg, 0.43 mg, 0.44 mg, 0.45 mg, 0.46 mg, 0.47 mg, 0.48 mg, 0.49 mg, 0.50 mg, 0.51 mg, 0.52 mg, 0.53 mg, 0.54 mg, 0.55 mg, 0.56 mg, 0.57 mg, 0.58 mg, 0.59 mg or 0.60 mg), wherein said composition is formulated into a single fixed combination dosage form. In a particular embodiment of a method and a pharmaceutical composition, the composition is administered once, twice, three or four times through the day.

[00132] In one embodiment, this disclosure teaches using the direct-action alpha-2 adrenergic receptor agonist clonidine to abate the adverse effects caused by the low dose opioid/TLR4 antagonist naltrexone.

Combinations of Opioid.TLR4 Antagonists with Acetyl-Para-Aminophenol (APAP)

[00133] Acetyl-para-aminophenol (APAP) enhances the pain relief action of the opioid/TLR4 antagonist naltrexone. A specific synergistic dose range of the combination is herein presented.

[00134] In a dose finding study the combination of the opioid/TLR4 antagonist, naltrexone and acetyl-para-aminophenol (APAP), acted synergistically, whether administered separately, one right after the other, or administered in combination.

[00135] Acetyl-para-aminophenol (APAP) or acetaminophen (used in the United States Canada, Japan, South Korea, Hong Kong, and Iran) and paracetamol (used elsewhere) both come from a chemical name for the compound: para-acetylaminophenol and para-acetylaminophenol. In some contexts, it is simply abbreviated as APAP, for acetyl-para-aminophenol. Acetyl-para-aminophenol is a widely used over-the-counter analgesic and

antipyretic. Acetyl-para-aminophenol is classified as a mild analgesic. It is commonly used for the relief of headaches and other minor aches and pains and is a major ingredient in numerous cold and flu remedies. In combination with opioid analgesics, acetyl-para-aminophenol can also be used in the management of more severe pain such as post-surgical pain and providing palliative care in advanced cancer patients. Though acetyl-para-aminophenol is used to treat inflammatory pain, it is not generally classified as an NSAID because it exhibits only weak anti-inflammatory activity.

[00136] To date, the mechanism of action of acetyl-para-aminophenol is not completely understood. The main mechanism proposed is the inhibition of cyclooxygenase (COX), and recent findings suggest that it is highly selective for COX-2. While it has analgesic and antipyretic properties comparable to those of aspirin or other NSAIDs, its peripheral anti-inflammatory activity is usually limited by several factors, one of which is the high level of peroxides present in inflammatory lesions. However, in some circumstances, even peripheral anti-inflammatory activity comparable to NSAIDs can be observed.

[00137] Acetyl-para-aminophenol enhances the pain treatment effect of naltrexone by affecting nociceptive pain.

[00138] This disclosure provides a combination, comprising an opioid/TLR4 antagonist and acetyl-para-aminophenol, and pharmaceutically acceptable salts or solvate of any thereof.

[00139] Another embodiment is a combination, comprising an opioid/TLR4 antagonist and acetyl-para-aminophenol. Another embodiment is a combination, comprising an opioid/TLR4 antagonist and acetyl-para-aminophenol, the opioid /TLR4 antagonist is naltrexone as well as pro drugs and all enantiomeric and epimeric forms including, but not limited to, (+)–naltrexone (dextro-naltrexone), as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

[00140] Another embodiment is a combination, comprising an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, and acetyl-para-aminophenol, or a pharmaceutically acceptable salt or solvate thereof. Another embodiment is a combination, comprising an opioid/TLR4 antagonist and acetyl-para-aminophenol in a weight to weight combination range which corresponds to a synergistic combination range of the order of 3:200 parts by weight.

[00141] The dose range of an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, may be about 0.001 mg/kg to about 1.0 mg/kg per day, e.g.

about 0.004 mg/kg-0.71 mg/kg per day, as described above, in combination with acetyl-para-aminophenol, or a pharmaceutically acceptable salt or solvate thereof, at about 1 mg/kg – about 100 mg/kg per day, e.g. about 5mg/kg - about 57mg/kg per day (e.g. about 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, 32 mg/kg, 33 mg/kg, 34 mg/kg, 35 mg/kg, 36 mg/kg, 37 mg/kg, 38 mg/kg, 39 mg/kg, 40 mg/kg, 41 mg/kg, 42 mg/kg, 43 mg/kg, 43 mg/kg, 44 mg/kg, 45 mg/kg, 46 mg/kg, 47 mg/kg, 48 mg/kg, 49 mg/kg, 50 mg/kg, 51 mg/kg, 52 mg/kg, 53 mg/kg, 53 mg/kg, 54 mg/kg, 55 mg/kg, 56 mg/kg or 57 mg/kg).

[00142] In certain embodiments, the dose range of acetyl-para-aminophenol, or a pharmaceutically acceptable salt or solvate thereof, is about 1 mg/kg to about 100 mg/kg per day, e.g. may range from about 5 mg/kg to about 57 mg/kg per day (e.g. may range from about (e.g. may range from about 5 to about 31 mg/kg, about 31 to about 57 mg/kg, about 5 to about 22 mg/kg, about 22 to about 40 mg/kg, about 40 to about 57 mg/kg, about 5 to about 18 mg/kg, about 18 to about 31 mg/kg, about 31 to about 44 mg/kg, about 44 to about 57 mg/kg, about 5 to about 44 mg/kg, 22 to about 57 mg/kg, about 18 to about 44 mg/kg about 31 to about 57 mg/kg, or about 18 to about 57 mg/kg per day).

[00143] Another embodiment is a combination, wherein the human dose range of an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.1 mg to about 100 mg per day, e.g. is about 0.25 mg – about 50 mg per day, about 0.25 mg – about 25 mg per day, or about 0.25 to about 15 mg per day, as described above, and the dose range of acetyl-para-aminophenol, or a pharmaceutically acceptable salt or solvate thereof, is about 100 to about 10,000 mg, e.g. is about 324 mg - 4000 mg (e.g. is about 324 mg, 325 mg, 326 mg, 327 mg, 328 mg,. 329 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 410 mg, 420 mg, 430 mg, 440 mg, 450 mg, 460 mg, 470 mg, 480 mg, 490 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, 2100 mg, 2200 mg, 2300 mg, 2400 mg, 2500 mg, 2600 mg, 2700 mg, 2800 mg, 2900 mg, 3000 mg, 3100 mg, 3200 mg, 3300 mg, 3400 mg, 3500 mg, 3600 mg, 3700 mg, 3800 mg, 3900 mg, 4000 mg). The combination may also comprise an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 0.1 mg to about 100 mg per day, e.g. about 0.25 mg – about 50 mg per day, as described above, and acetyl-para-aminophenol or a pharmaceutically

acceptable salt or solvate thereof, at a dosage range of about 100 mg to about 10,000 mg, e.g. about 324 mg - about 4000mg (e.g. is about 324 mg, 325 mg, 326 mg, 327 mg, 328 mg,. 329 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 410 mg, 420 mg, 430 mg, 440 mg, 450 mg, 460 mg, 470 mg, 480 mg, 490 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, 2100 mg, 2200 mg, 2300 mg, 2400 mg, 2500 mg, 2600 mg, 2700 mg, 2800 mg, 2900 mg, 3000 mg, 3100 mg, 3200 mg, 3300 mg, 3400 mg, 3500 mg, 3600 mg, 3700 mg, 3800 mg, 3900 mg, 4000 mg), wherein said composition is formulated into a single fixed combination dosage form.

[00144] In certain embodiments, the dose range of acetyl-para-aminophenol, or a pharmaceutically acceptable salt or solvate thereof, is about 100 mg to about 10,000 mg, e.g. about 324 mg - about 4000mg (e.g. may range from about 324 to about 2162 mg, about 2162 to about 4000 mg, about 324 to about 1550 mg, about 1550 to about 2776 mg, about 2776 to about 4000 mg, about 324 to about 1240 mg, about 1240 to about 2162 mg, about 2160 to about 3080 mg, about 3080 to about 4000 mg, about 324 to about 3081 mg, 1550 to about 4000 mg, about 1240 to about 3080 mg about 2160 to about 4000 mg, or about 1240 to about 4000 mg per day).

[00145] Another embodiment is a combination, comprising an opioid antagonist and acetyl-para-aminophenol, the opioid /TLR4 antagonist is naltrexone in a sustained release formulation, as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof. Another embodiment is a combination, comprising an opioid antagonist and acetyl-para-aminophenol, the opioid /TLR4 antagonist is (+)–naltrexone (dextro-naltrexone), as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

[00146] Another embodiment is a combination, comprising naltrexone, or a pharmaceutically acceptable salt or solvate thereof, and acetyl-para-aminophenol, or a pharmaceutically acceptable salt or solvate thereof. Another embodiment is a combination, comprising naltrexone and acetyl-para-aminophenol in a weight to weight combination range which corresponds to a synergistic combination range of the order of 3:200 parts by weight.

[00147] The dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, may be about 0.001 mg/kg to about 1.0 mg/kg, e.g. about 0.004 mg/kg-0.71 mg/kg,

as described above, per day in combination with acetyl-para-aminophenol, or a pharmaceutically acceptable salt or solvate thereof, at about 1 mg/kg to about 100 mg/kg per day, e.g. is about 5mg/kg to about about 57mg/kg per day (e.g. may range from about (e.g. may range from about 5 to about 31 mg/kg, about 31 to about 57 mg/kg, about 5 to about 22 mg/kg, about 22 to about 40 mg/kg, about 40 to about 57 mg/kg, about 5 to about 18 mg/kg, about 18 to about 31 mg/kg, about 31 to about 44 mg/kg, about 44 to about 57 mg/kg, about 5 to about 44 mg/kg, 22 to about 57 mg/kg, about 18 to about 44 mg/kg about 31 to about 57 mg/kg, or about 18 to about 57 mg/kg per day; e.g. may be about 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, 32 mg/kg, 33 mg/kg, 34 mg/kg, 35 mg/kg, 36 mg/kg, 37 mg/kg, 38 mg/kg, 39 mg/kg, 40 mg/kg, 41 mg/kg, 42 mg/kg, 43 mg/kg, 43 mg/kg, 44 mg/kg, 45 mg/kg, 46 mg/kg, 47 mg/kg, 48 mg/kg, 49 mg/kg, 50 mg/kg, 51 mg/kg, 52 mg/kg, 53 mg/kg, 53 mg/kg, 54 mg/kg, 55 mg/kg, 56 mg/kg or 57 mg/kg).

[00148] Another embodiment is a combination, wherein the human dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, is about 0.1 to about 100 mg per day, e.g. is about 0.25 mg – about 50 mg per day, about 0.25 mg – about 25 mg per day, or about 0.25 mg – about 15 mg, as described above, per day and the dose range of acetyl-para-aminophenol, or a pharmaceutically acceptable salt or solvate thereof, is about 100 mg to about 10,000 mg, e.g. is about 324 mg to about 4000 mg (e.g. may range from about 324 to about 2162 mg, about 2162 to about 4000 mg, about 324 to about 1550 mg, about 1550 to about 2776 mg, about 2776 to about 4000 mg, about 324 to about 1240 mg, about 1243 to about 2162 mg, about 2160 to about 3080 mg, about 3081 to about 4000 mg, about 324 to about 3080 mg, 1550 to about 4000 mg, about 1240 to about 30801 mg about 2160 to about 4000 mg, or about 1240 to about 4000 mg per day, e.g. is about 324 mg, 325 mg, 326 mg, 327 mg, 328 mg,. 329 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 410 mg, 420 mg, 430 mg, 440 mg, 450 mg, 460 mg, 470 mg, 480 mg, 490 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, 2100 mg, 2200 mg, 2300 mg, 2400 mg, 2500 mg, 2600 mg, 2700 mg, 2800 mg, 2900 mg, 3000 mg, 3100 mg, 3200 mg, 3300 mg, 3400 mg, 3500 mg, 3600 mg, 3700 mg, 3800 mg, 3900 mg, 4000 mg). The combination may also comprise naltrexone, or a pharmaceutically acceptable salt or solvate thereof, at a

dosage range of about 0.1 mg to about 100 mg per day, e.g. is about 0.25 mg – about 50 mg per day, as described above, and acetyl-para-aminophenol or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 100 mg to about 10000 mg, e.g. is about 324 mg to about 4000mg (e.g. may range from about 324 to about 2162 mg, about 2162 to about 4000 mg, about 324 to about 1550 mg, about 1550 to about 2776 mg, about 2776 to about 4000 mg, about 324 to about 1243 mg, about 1243 to about 2162 mg, about 2162 to about 3081 mg, about 3081 to about 4000 mg, about 324 to about 3081 mg, 1550 to about 4000 mg, about 1243 to about 3081 mg about 2162 to about 4000 mg, or about 1243 to about 4000 mg per day; e.g. is about 324 mg, 325 mg, 326 mg, 327 mg, 328 mg,. 329 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 410 mg, 420 mg, 430 mg, 440 mg, 450 mg, 460 mg, 470 mg, 480 mg, 490 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, 2100 mg, 2200 mg, 2300 mg, 2400 mg, 2500 mg, 2600 mg, 2700 mg, 2800 mg, 2900 mg, 3000 mg, 3100 mg, 3200 mg, 3300 mg, 3400 mg, 3500 mg, 3600 mg, 3700 mg, 3800 mg, 3900 mg, 4000 mg), wherein said composition is formulated into a single fixed combination dosage form.

[00149] Described herein is a method of treating neuropathic, nociceptive and migraine pain in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a combination comprising an opioid/TLR4 antagonist and acetyl-para-aminophenol, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment isdescribed a method of treating neuropathic, nociceptive and migraine pain in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a combination comprising naltrexone and acetyl-para-aminophenol, or a pharmaceutically acceptable salt or solvate thereof.

Combinations of Opioid/TLR4 Antagonists with COX inhibitors

[00150] Most nonsteroidal anti-inflammatory drugs (NSAIDs) act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. This inhibition is competitively reversible (albeit at varying degrees of reversibility). COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid. Prostaglandins act as messenger molecules in the process of inflammation. This mechanism of action was elucidated by John

Vane (1927–2004), who received a Nobel Prize for his work. NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present.

[00151] Nonsteroidal anti-inflammatory drug can be classified based on their chemical structure or mechanism of action. Older NSAIDs were known long before their mechanism of action was elucidated and were for this reason classified by chemical structure or origin. Newer substances are more often classified by mechanism of action.

[00152] Several forms of NSAIDs can be selected from groups consisting of Salicylates: Aspirin, Diflunisal, Salsalate; Propionic acid derivatives: Ibuprofen, Dexibuprofen, Naproxen, Fenoprofen, Ketoprofen, Dexketoprofen, Flurbiprofen, Oxaprozin, Loxoprofen; Acetic acid derivatives: Indomethacin, Tolmetin, Sulindac, Etodolac, Ketorolac, iclofenac, Nabumetone; Enolic acid (Oxicam) derivatives: Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam; Fenamic acid derivatives: Mefenamic acid, Meclofenamic acid, Flufenamic acid, Tolfenamic acid; Selective COX-2 inhibitors: Celecoxib, Rofecoxib, Valdecoxib, Parecoxib, Lumiracoxib, Etoricoxib, Firocoxib, Sulphonanilides, Nimesulide, LOX (lipooxygenase); and COX 5-LOX/COX inhibitors: Licofelone, Lysine, clonixinate. Natural: Hyperforin, Figwort, Calcitriol(Vitamin D).

[00153] Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) it is used primarily for fever, pain, dysmenorrhea and inflammatory diseases such as rheumatoid arthritis; it is also used for pericarditis. Ibuprofen is a 'core' medicine in the World Health Organization's Model List of Essential Medicines necessary to meet the minimum medical needs of a basic healthcare system.

[00154] Ibuprofen enhances the pain treatment effect of naltrexone by inhibiting the enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin H2 (PGH2). PGH2, in turn, is converted by other enzymes to several other prostaglandins, which are mediators of pain, inflammation, and fever. The disclosure teaches use of a combination of an opioid/TLR4 antagonist and a cyclooxygenase inhibitor, particularly ibuprofen, for its action on nociception and its anti-inflammatory action. The disclosure teaches that the combination is synergy as far as the effect on pain treatment.

[00155] One embodiment taught by this disclosure is a combination, comprising an opioid/TLR4 antagonist and a cyclooxygenase inhibitor wherein, a cyclooxygenase inhibitor is selected from a group consisting of aspirin, diclofenac, difluinsal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone,

piroxicam, sulindac, tolmetin, zomepirac, and their pharmaceutically acceptable salts or solvates or pharmaceutically acceptable salts or solvates of any thereof. Another embodiment is a combination, comprising an opioid antagonist and a cyclooxygenase inhibitor, the opioid /TLR4 antagonist is naltrexone as well as pro drugs and all enantiomeric and epimeric forms, specifically, (+)–naltrexone (dextro-naltrexone), as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof. Another embodiment is a combination, comprising an opioid antagonist and a cyclooxygenase inhibitor, the opioid /TLR4 antagonist is naltrexone in a sustained release formulation, as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof. Another embodiment is a combination, comprising an opioid antagonist and a cyclooxygenase inhibitor, the opioid /TLR4 antagonist is (+)–naltrexone (dextro-naltrexone), as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

[00156] Another embodiment is a combination, comprising an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, and a COX inhibitor, or a pharmaceutically acceptable salt or solvate thereof. Another embodiment is a combination, comprising an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, and a COX inhibitor, or a pharmaceutically acceptable salt or solvate thereof, in a weight to weight combination range which corresponds to a synergistic combination range of the order of 90:1 parts by weight. Another embodiment is a combination, comprising the dose range of an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.001mg/kg to about 1.0 mg/kg per day, e.g. is about 0.004 mg/kg-0.71 mg/kg per day, as described above, and the COX inhibitor, or a pharmaceutically acceptable salt or solvate thereof, is about 1 mg/kg to about 50 mg/kg per day, e.g. is about 3 mg/kg - 35mg/kg per day (e.g. about 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, 32 mg/kg, 33 mg/kg, 34 mg/kg or 35 mg/kg).

[00157] In an embodiment, the COX inhibitor, or a pharmaceutically acceptable salt or solvate thereof, can be administered in a range of a about 1 mg/kg to about 50 mg/kg per day, e.g. may be administered at a range of about 3 mg/kg to about 35 mg/kg per day (e.g. may

range from about 3 to about 19 mg/kg, about 19 to about 35 mg/kg, about 3 to about 13.7 mg/kg, about 13.7 to about 24.3 mg/kg, about 24.3 to about 35 mg/kg, about 3 to about 11 mg/kg, about 11 to about 19 mg/kg, about 19 to about 27 mg/kg, about 27 to about 35 mg/kg, about 3 to about 27 mg/kg, about 13.7 to about 35 mg/kg, about 11 to about 27 mg/kg about 19 to about 35 mg/kg, or about 11 to about 35 mg/kg per day)

[00158] Another embodiment is a combination, comprising the human dose range of an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, of about 0.1 mg to about 100 mg, e.g. is about 0.25 mg - 50 mg, about 0.25 mg – about 25 mg, or about 0.25 mg – about 15 mg, as described above, per day in combination with a COX inhibitor, or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 100 mg to about 5000 mg per day, e.g. is about 200 mg - about 2400 mg per day (e.g. may range from about 200 to about 1300 mg, about 1300 to about 2400 mg, about 200 to about 933 mg, about 933 to about 1667 mg, about 1667 to about 2400 mg, about 200 to about 750 mg, about 750 to about 1300 mg, about 1300 to about 1850 mg, about 1850 to about 2400 mg, about 200 to about 1850 mg, 933 to about 2400 mg, about 750 to about 1850 mg about 1300 to about 2400 mg, or about 750 to about 2400 mg per day; e.g. is about 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, 2100 mg, 2200 mg, 2300 mg, or 2400 mg).

[00159] Another embodiment is a combination, comprising the human dose range of an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, of about 0.1 mg to about 100 mg, e.g. is about 0.25 mg - 50 mg, as described above, per day and the human the dose range of a COX 2 inhibitor, or a pharmaceutically acceptable salt or solvate thereof, is about 100 to about 5000 mg, e.g. is about 200 mg – about 2400 mg (e.g. may range from about 200 to about 1300 mg, about 1300 to about 2400 mg, about 200 to about 930 mg, about 930 to about 1670 mg, about 1670 to about 2400 mg, about 200 to about 750 mg, about 750 to about 1300 mg, about 1300 to about 1850 mg, about 1850 to about 2400 mg, about 200 to about 1850 mg, 930 to about 2400 mg, about 750 to about 1850 mg about 1300 to about 2400 mg, or about 750 to about 2400 mg per day; e.g. is about 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, 2100 mg, 2200 mg, 2300 mg, or 2400 mg), wherein said composition is formulated into a single fixed combination dosage form. Another embodiment is a combination, comprising naltrexone, or a

pharmaceutically acceptable salt or solvate thereof, and ibuprofen, or a pharmaceutically acceptable salt or solvate thereof. Another embodiment is a combination, comprising naltrexone and ibuprofen in a weight to weight combination range which corresponds to a synergistic combination range of the order of 90:1 parts by weight.

[00160] Another embodiment is a combination, comprising the dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, at about 0.001 mg/kg to about 1.0 mg/kg per day, e.g. at about 0.004 mg/kg-0.71 mg/kg per day, as described above, with ibuprofen, or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 1 mg/kg to about 50 mg/kg per day, e.g. at about 3 mg/kg to about 35mg/kg per day (e.g. in any of the ranges described herein; e.g. about 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, 32 mg/kg, 33 mg/kg, 34 mg/kg or 35 mg/kg). Another embodiment is a combination, comprising the human dose range of naltrexone, at about 0.1 to about 100 mg, e.g. at about 0.25 mg – about 50 mg, about 0.25 mg – about 25 mg, or about 0.25 mg - about 15 mg, as described above, in combination with ibuprofen, or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 100 mg to about 5000 mg per day, e.g. about 200 mg to about 2400 mg per day (e.g. may range from about 200 to about 1300 mg, about 1300 to about 2400 mg, about 200 to about 933 mg, about 933 to about 1670 mg, about 1670 to about 2400 mg, about 200 to about 750 mg, about 750 to about 1300 mg, about 1300 to about 1850 mg, about 1850 to about 2400 mg, about 200 to about 1850 mg, 930 to about 2400 mg, about 750 to about 1850 mg about 1300 to about 2400 mg, or about 750 to about 2400 mg per day; e.g. is about 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, 2100 mg, 2200 mg, 2300 mg, or 2400 mg).

[00161] Another embodiment is a combination, comprising the human dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, is about 0.1 mg to about 100 mg, e.g. is about 0.25 mg - 50 mg, as described above, and the human the dose range of ibuprofen, or a pharmaceutically acceptable salt or solvate thereof, is about 100 mg to about 5000 mg, e.g. is about 200 mg - 2400 mg (e.g. may range from about 200 to about 1300 mg, about 1300 to about 2400 mg, about 200 to about 930 mg, about 930 to about 1670 mg, about 1670 to about 2400 mg, about 200 to about 750 mg, about 750 to about 1300 mg, about 1300

to about 1850 mg, about 1850 to about 2400 mg, about 200 to about 1850 mg, 930 to about 2400 mg, about 750 to about 1850 mg about 1300 to about 2400 mg, or about 750 to about 2400 mg per day; e.g. is about 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, 2100 mg, 2200 mg, 2300 mg, or 2400 mg), wherein said composition is formulated into a single fixed combination dosage form.

Combinations of Opioid/TLR4 Antagonists with Alpha-2-delta Ligands

[00162] An alpha-2-delta ligand including, but not limited to, Gabapentin and pregabalin or a pharmaceutically acceptable salt any thereof, enhances the pain relief action of the opioid/TLR4 antagonists including, but not limited to, naltrexone. A specific synergistic dose range of the combination is herein presented.

[00163] Voltage-dependent calcium channels alpha-2-delta -1 and alpha-2-delta -2 subunits are the binding site of the two anticonvulsant drugs, gabapentin (Neurontin) and pregabalin (Lyrica), that also find use in treating chronic neuropathic pain. Gabapentin (Neurontin) is a pharmaceutical drug, specifically a GABA analog. It was originally developed for the treatment of epilepsy, and currently is also used to relieve neuropathic pain. Gabapentin provides significant pain relief in about a third of people who take it for fibromyalgia or chronic neuropathic pain. Pregabalin is an anticonvulsant drug used for neuropathic pain. Recent studies have shown that pregabalin is effective at treating chronic pain in disorders such as fibromyalgia. In a dose finding study the combination of the opioid/TLR4 antagonist, naltrexone and the calcium channel alpha-2-delta ligands gabapentin and pregabalin, acted synergistically, whether administered separately, one after the other, or administered in combination. Gabapentin and Pregabalin enhance the pain treatment effect of naltrexone by treating pain via another pathway, by binding Voltage-dependent calcium channels alpha-2-delta.

[00164] Based upon this, the disclosure first teaches the use of an opioid/TLR4 antagonist in combination with an alpha-2-delta ligand for their action on neuropathic pain. The disclosure also teaches the use of naltrexone, in combination with an alpha-2-delta ligand such as Gabapentin or Pregabalin, for their action on neuropathic pain. The disclosure teaches that the combination is synergistic as far as the effect on pain.

[00165] Another embodiment is a combination, comprising an opioid/TLR4 antagonist and an alpha-2-delta ligand. The alpha-2-delta ligand inhibitor may be any alpha-2-delta

ligand inhibitor including, but not limited to, Gabapentin or Pregabalin or pharmaceutically acceptable salts or solvates of any thereof. Another embodiment is a combination, comprising an opioid antagonist and an alpha-2-delta ligand, the opioid /TLR4 antagonist is naltrexone as well as pro drugs and all enantiomeric and epimeric forms, specifically, (+)–naltrexone (dextro-naltrexone), as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof. Another embodiment is a combination, comprising an opioid antagonist and an alpha-2-delta ligand, the opioid /TLR4 antagonist is naltrexone in a sustained release formulation, as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

[00166] Another embodiment is a combination, comprising an opioid/TLR4 antagonist and Gabapentin in a weight to weight combination range which corresponds to a synergistic combination range of the order of about 1:50 to about 1:125 parts by weight (e.g. about 1:50, 1:60, 1:70, 1:80, 1:90, 1:100, 1:110, 1:120 or 1:125). Another embodiment is a combination, comprising an opioid/TLR4 antagonist and Pregabalin in a weight to weight combination range which corresponds to a synergistic combination range of the order of order of about 1:10 to about 1:100 parts by weight, e.g. about 1:30- about 1:50 parts by weight (e.g. about 1:30, 1:40, or 1:50). Another embodiment is a combination, comprising the dose range of an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.001 mg/kg to about 1.0 mg/kg per day, e.g. is about 0.004 mg/kg-0.71 mg/kg per day, as described above, with Gabapentin, or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 0.1 mg/kg to about 100 mg/kg per day, e.g. about 1.3 mg/kg to about 26mg/kg per day (e.g. may range from about 1.3 to about 13.6 mg/kg, about 13.6 to about 26 mg/kg, about 1.3 to about 9.5 mg/kg, about 9.5 to about 17.8 mg/kg, about 17.8 to about 26 mg/kg, about 1.3 to about 7.5 mg/kg, about 7.5 to about 13.6 mg/kg, about 13.6 to about 19.8 mg/kg, about 19.8 to about 26 mg/kg, about 1.3 to about 19.8 mg/kg, 9.5 to about 26 mg/kg, about 7.5 to about 19.8 mg/kg about 13.6 to about 26 mg/kg, or about 7.5 to about 26 mg/kg per day; e.g. about 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, 25 mg/kg or 26 mg/kg).

[00167] Another embodiment is a combination, comprising the dose range of an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, is about

0.001 mg/kg to about 1.0 mg/kg per day, e.g. about 0.004 mg/kg- about 0.71 mg/kg per day, as described above, with Pregabalin, or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 0.1 mg/kg to about 10 mg/kg per day, e.g. about 2 mg/kg to about 4 mg/kg per day (e.g. may range from about 2 to about 3 mg/kg, about 3 to about 4 mg/kg, about 2 to about 2.6 mg/kg, about 2.6 to about 3.3 mg/kg, about 3.3 to about 4 mg/kg, about 2 to about 2.5 mg/kg, about 2.5 to about 3 mg/kg, about 3 to about 3.5 mg/kg, about 3.5 to about 4 mg/kg, about 2 to about 3.5 mg/kg, about 2.6 to about 4 mg/kg, about 2.5 to about 3.5 mg/kg about 3 to about 4 mg/kg, or about 2.5 to about 4 mg/kg per day; e.g. about 2 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.7 mg/kg, 2.8 mg/kg, 2.9 mg/kg, 3.0 mg/kg, 3.1 mg/kg, 3.2 mg/kg, 3.3 mg/kg, 3.4 mg/kg, 3.5 mg/kg, 3.6 mg/kg, 3.7 mg/kg, 3.8 mg/kg, 3.9 mg/kg, or 4.0 mg/kg).

[00168] Another embodiment is a combination, comprising an alpha-2-delta ligand with an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, wherein the opioid/TLR4 antagonist is at a dosage range of about 0.1 mg to about 100 mg, e.g. about 0.25 mg to about 50 mg , about 0.25 mg – about 25 mg, or a "low" dose of about 0.25 mg – about 15 mg per day, as described above.

[00169] Another embodiment is a combination, comprising an alpha-2-delta ligand with an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, wherein the opioid/TLR4 antagonist is at a dosage range of about 0.1 mg to about 100 mg, e.g. about 0.25 mg – about 50 mg about 0.25 mg – about 25 mg, or a "low" dose of about 0.25 mg – about 15 mg per day, as described above, and the alpha-2-delta ligand is Gabapentin, or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 1 mg to about 5000 mg per day, e.g. about 100 mg to about 1800 mg per day (e.g. may range from about 100 to about 950 mg, about 950 to about 1800 mg, about 100 to about 670 mg, about 670 to about 1230 mg, about 1230 to about 1800 mg, about 100 to about 520 mg, about 520 to about 950 mg, about 950 to about 1375 mg, about 1375 to about 1800 mg, about 100 to about 1375 mg, about 670 to about 1800 mg, about 525 to about 1375 mg about 950 to about 1800 mg, or about 525 to about 1800 mg per day; e.g. is about 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg or1800 mg).

[00170] Another embodiment is a combination, comprising an alpha-2-delta ligand with an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, wherein the opioid/TLR4 antagonist is at a dosage range of about 0.1 mg to about 100 mg ,

e.g. about 0.25 mg – about 50 mg, about 0.25 mg – about 25 mg, or a "low" dose of about 0.25 mg – about 15 mg per day, as described above, and the alpha-2-delta ligand is Pregabalin, or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 100 mg to about 500 mg per day, e.g. about 150 mg – about 300 mg per day (e.g. may range from about 100 to about 220 mg, about 220 to about 300 mg, about 150 to about 200 mg, about 200 to about 250 mg, about 250 to about 300 mg, about 150 to about 190 mg, about 190 to about 225 mg, about 225 to about 262 mg, about 262 to about 300 mg, about 150 to about 262 mg, about 200 to about 300 mg, about 187 to about 262 mg about 225 to about 300 mg, or about 187 to about 300 mg per day; e.g. is about 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg or 300 mg).

[00171] Another embodiment is a combination, comprising the human dose range of an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.1 mg to about 100 mg, e.g. is about 0.25 mg – about 50 mg, as described above, and the human the dose range of Gabapentin, or a pharmaceutically acceptable salt or solvate thereof, is about 10 mg to about 5000 mg per day, e.g. is about 100 mg to about 1800 mg per day (e.g. may range from about 100 to about 950 mg, about 950 to about 1800 mg, about 100 to about 670 mg, about 670 to about 1230 mg, about 1230 to about 1800 mg, about 100 to about 520 mg, about 520 to about 950 mg, about 950 to about 1375 mg, about 1375 to about 1800 mg, about 100 to about 1375 mg, about 670 to about 1800 mg, about 525 to about 1375 mg about 950 to about 1800 mg, or about 525 to about 1800 mg per day; e.g. is about 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg or1800 mg), wherein said composition is formulated into a single fixed combination dosage form. Another embodiment is a combination, comprising the human dose range of an opioid/TLR4 antagonist, or a pharmaceutically acceptable salt or solvate thereof, is about 0.1 mg to about 100 mg, e.g. is about 0.25 mg – about 50 mg per day, as described above, and the human dose range of pregabalin, or a pharmaceutically acceptable salt or solvate thereof, is about 10 to about 1000 mg per day; e.g. is about 50 mg to about 300 mg per day (e.g. may range from about 50 to about 175 mg, about 175 to about 300 mg, about 50 to about 133 mg, about 217 to about 300 mg, about 217 to about 300 mg, about 50 to about 112 mg, about 112 to about 175 mg, about 175 to about 237 mg, about 237 to about 300 mg, about 50 to about 237 mg, about 133 to about 300 mg, about 112 to about 237 mg about 175 to about 300 mg, or about 112 to about 300 mg per day;

e.g. is about 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg or 300 mg), wherein said composition is formulated into a single fixed combination dosage form.

[00172] Another embodiment is a combination, comprising naltrexone and Gabapentin in a weight to weight combination range which corresponds to a synergistic combination range of the order of about 1:10 to about 1:500 parts by weight, e.g. about 1:50- about 1:125 parts by weight (e.g. about 1:50, 1:60, 1:70, 1:80, 1:90, 1:100, 1:110, 1:120 or 1:125). Another embodiment is a combination, comprising naltrexone and Pregabalin in a weight to weight combination range which corresponds to a synergistic combination range of the order of about 1:1 to about 1:100 parts by weight, e.g. about 1:30- about 1:50 parts by weight (e.g. about 1:30, 1:40, or 1:50).

[00173] Another embodiment is a combination, comprising the dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 0.001 mg/kg to about 1.0 mg/kg per day, e.g. about 0.004 mg/kg- about 0.71 mg/kg per day, about 0.25 mg – about 50 mg, about 0.25 mg – about 25 mg, or a "low" dose of about 0.25 mg – about 15 mg, as described above, per day with Gabapentin, or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 0.1 mg/kg to about 100 mg/kg per day, e.g. about 1.3 mg/kg – about 26mg/kg per day (e.g. may range from about 1.3 to about 13.6 mg/kg, about 13.6 to about 26 mg/kg, about 1.3 to about 9.5 mg/kg, about 9.5 to about 17.8 mg/kg, about 17.8 to about 26 mg/kg, about 1.3 to about 7.4 mg/kg, about 7.4 to about 13.6 mg/kg, about 13.6 to about 19.8 mg/kg, about 19.8 to about 26 mg/kg, about 1.3 to about 19.8 mg/kg, about 9.5 to about 26 mg/kg, about 7.4 to about 19.8 mg/kg about 13.6 to about 26 mg/kg, or about 7.4 to about 26 mg/kg per day; e.g. about 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, 25 mg/kg or 26 mg/kg).

[00174] Another embodiment is a combination, comprising the dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 0.001mg/kg to about 1.0 mg/kg per day, e.g. about 0.004 mg/kg- about 0.71 mg/kg per day, about 0.25 mg – about 50 mg, about 0.25 mg – about 25 mg, or a "low" dose of about 0.25 mg – about 15 mg, as described above, per day with Pregabalin, or a pharmaceutically

acceptable salt or solvate thereof, at a dosage range of about 0.2 mg/kg to about 10 mg/kg per day, e.g. about 2 mg/kg – about 4 mg/kg per day (e.g. may range from about 2 to about 3 mg/kg, about 3 to about 4 mg/kg, about 2 to about 2.7 mg/kg, about 2.7 to about 3 mg/kg, about 3 to about 4 mg/kg, about 2 to about 2.5 mg/kg, about 2.5 to about 3 mg/kg, about 3 to about 3.5 mg/kg, about 3.5 to about 4 mg/kg, about 2 to about 3.5 mg/kg, about 2.7 to about 4 mg/kg, about 2.5 to about 3.5 mg/kg about 3 to about 4 mg/kg, or about 2.5 to about 4 mg/kg per day; e.g. about 2 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.7 mg/kg, 2.8 mg/kg, 2.9 mg/kg, 3.0 mg/kg, 3.1 mg/kg, 3.2 mg/kg, 3.3 mg/kg, 3.4 mg/kg, 3.5 mg/kg, 3.6 mg/kg, 3.7 mg/kg, 3.8 mg/kg, 3.9 mg/kg, or 4.0 mg/kg).

[00175] The combination with the opioid/TLR4 antagonist may also include Gabapentin, or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 1 mg to about 5000 mg per day, e.g. about 100 mg to about 1800 mg per day (e.g. may range from about 100 to about 950 mg, about 950 to about 1800 mg, about 100 to about 670 mg, about 670 to about 1230 mg, about 1230 to about 1800 mg, about 100 to about 525 mg, about 525 to about 950 mg, about 950 to about 1375 mg, about 1375 to about 1800 mg, about 100 to about 1375 mg, about 670 to about 1800 mg, about 525 to about 1375 mg about 950 to about 1800 mg, or about 525 to about 1800 mg per day; e.g. is about 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg or1800 mg). The combination with the opioid/TLR4 antagonist may also include Pregabalin, or a pharmaceutically acceptable salt or solvate thereof, at a dosage range of about 10 mg to about 1000 mg per day, e.g. about 150 mg to about 300 mg per day (e.g., is in a range from about e.g. may range from about 100 to about 225 mg, about 225 to about 300 mg, about 150 to about 200 mg, about 200 to about 250 mg, about 250 to about 300 mg, about 150 to about 187 mg, about 187 to about 225 mg, about 225 to about 262 mg, about 262 to about 300 mg, about 150 to about 262 mg, about 200 to about 300 mg, about 187 to about 262 mg about 225 to about 300 mg, or about 187 to about 300 mg per day; e.g. is about 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg or 300 mg). One embodiment is a combination, comprising the human dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, of about 0.1 mg to about 100 mg per day, e.g. about 0.25 mg – about 50 mg per day, as described above, and the human the dose range of Gabapentin, or a pharmaceutically acceptable salt or solvate thereof, of about 10 mg to about 5000 mg, e.g. about 100 mg to about 1800 mg (e.g. may range from about 100 to about

950 mg, about 950 to about 1800 mg, about 100 to about 670 mg, about 670 to about 1230 mg, about 1230 to about 1800 mg, about 100 to about 525 mg, about 525 to about 950 mg, about 950 to about 1375 mg, about 1375 to about 1800 mg, about 100 to about 1375 mg, about 670 to about 1800 mg, about 525 to about 1375 mg about 950 to about 1800 mg, or about 525 to about 1800 mg per day; e.g. is about 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg or1800 mg), wherein said composition is formulated into a single fixed combination dosage form.

[00176] Another embodiment is a combination, comprising the human dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, of about 0.1 mg to about 100 mg, e.g. about 0.25 mg – about 50 mg per day, as described above, and the human the dose range of pregabalin, or a pharmaceutically acceptable salt or solvate thereof at about 1 mg to about 500 mg per day, e.g. about 50 mg to about 300 mg per day (e.g. may range from about 50 to about 175 mg, about 175 to about 300 mg, about 50 to about 133 mg, about 216 to about 300 mg, about 216 to about 300 mg, about 50 to about 112 mg, about 112 to about 175 mg, about 175 to about 237 mg, about 237 to about 300 mg, about 50 to about 237 mg, about 133to about 300 mg, about 112 to about 237 mg about 175 to about 300 mg, or about 112 to about 300 mg per day; e.g. is about 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg or 300 mg), wherein said composition is formulated into a single fixed combination dosage form.

[00177] Another embodiment comprises administering the combination of an opioid/TLR4 antagonist and an alpha-2-delta ligand once, twice, three or four times through the day. Another embodiment comprising the therapeutically effective dose of the pharmaceutical composition of an opioid/TLR4 antagonist and an alpha-2-delta ligand is administered systemically by such routes including but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical or sublingual routes. Another embodiment comprising, said combination of an opioid/TLR4 antagonist and an alpha-2-delta ligand is in a single dosage form, and said single dosage form is in the form of tablets, lozenges, troches, hard candies, liquid, powders, sprays, creams, salves and suppositories.

[00178] The pharmaceutical composition comprising the combination of an opioid/TLR4 antagonist and an alpha-2-delta ligand may be used for the treatment, prevention and reversal of neuropathic pain, back pain, chronic pain, diabetic neuropathic

pain, trigeminal neuralgia pain, phantom limb pain, complex regional pain syndrome pain, acute herpetic pain, post herpetic pain, causalgia pain, idiopathic pain, inflammatory pain, cancer pain, postoperative pain, fibromyalgia pain, headache pain, migraine pain, allodynia pain, vulvodynia pain, interstitial cystitis pain, irritable bowel syndrome (IBS), arthritic joint pain and tendinitis.

[00179] Another embodiment is a method of treating neuropathic and nociceptive pain with an allodynic component and migraine in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a combination comprising an opioid/TLR4 antagonist and an alpha-2-delta ligand, or pharmaceutically acceptable salts or solvates of any thereof. Another embodiment is a method of treating neuropathic and nociceptive pain with an allodynic component and migraine in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a combination comprising naltrexone and Gabapentin or Pregabalin, or pharmaceutically acceptable salts or solvates of any thereof.

Disease states

[00180] Pain can be classified as either acute or chronic. Acute pain can be caused by damage to tissue and generally has a sudden onset and a limited duration. Chronic pain tends to last longer than acute pain and is usually associated with a long-term illness. It is usually more resistant to treatment, and can be the defining characteristic of a disease (such as fibromyalgia). It can be the result of damaged tissue, but more often is attributed to nerve damage. Pain can also be classified by the kind of damage that causes it. Nociceptive pain is pain caused by tissue damage, while neuropathic pain is pain caused by nerve damage. Nociceptive pain may be further divided into three different sub-categories: visceral, deep somatic, and superficial somatic pain.

[00181] Examples of pain include but are not limited to: acute pain, chronic pain, muscle pain, joint pain, chest pain, neck pain, shoulder pain, hip pain, abdominal pain, carpal tunnel syndrome, knee pain, back pain, myofascial pain syndrome, fibromyalgia, arthritic pain, headache, migraine headache, Piriformis syndrome, whiplash, chronic muscle pain, nociceptive pain, visceral pain, deep somatic pain, superficial somatic pain, neuropathic pain, central pain syndrome, complex regional pain syndrome, diabetic peripheral neuropathy, pain associated with shingles, postherpetic neuralgia, neuralgia, trigeminal neuralgia, sciatica pain, arachnoiditis (spinal pain), central pain syndrome, phantom limb pain, phantom body pain,

neuropathy, compartment syndrome, acute herpetic pain, post herpetic pain, causalgia pain, idiopathic pain, inflammatory pain, cancer pain, postoperative pain, vulvodynia pain, interstitial cystitis pain, irritable bowel syndrome (IBS), tendinitis, breakthrough pain, and incident pain.

[00182] Allodynia is a clinical feature of many painful conditions, including but not limited to: back pain, chronic pain, neuropathic pain, diabetic neuropathic pain, trigeminal neuralgia pain, phantom limb pain, complex regional pain syndrome pain, acute herpetic pain, post herpetic pain, causalgia pain, idiopathic pain, inflammatory pain, cancer pain, postoperative pain, fibromyalgia pain, headache pain, migraine pain, vulvodynia pain, interstitial cystitis pain, irritable bowel syndrome (IBS), arthritic joint pain and tendinitis. It becomes apparent that allodynia plays a role in every kind of pain.

[00183] The disclosure offers a new explanation for the occurrence of allodynia, or "memory pain", connecting the dots of existing knowledge from animal model studies along with the vast information gleaned from the clinical trials disclosed herein, it is now evident that allodynia is caused by abnormal endogenous activation of TLR4 that in turn trigger a pro-inflammatory cascade. The clinical trial for back pain disclosed herein verified that the pain is interrupted by the opioid/TLR4 antagonist naltrexone. Additionally, TLR4 antagonism can play a role in improving nociceptive pain by affecting the allodynic component of nociceptive pain.

[00184] The compositions and methods of use therefore described in this application may be used to prevent, reduce, or eliminate any type of pain, including those types of pain that have an allodynic component. The prevention, reduction, or elimination of pain may be measured in many ways, including (but not limited to): percent relief of pain, decrease in relative severity of the pain, decrease in frequency of breakout pain, reduction in the duration of pain, reduction in the level of pain, reduction in the frequency of night pain, reduction in the patient's Oswestry disability index level, reduction in the patient's Pittsburgh Insomnia scale rating, a decrease in insomnia, a decrease in disability, a decrease in the patient's score on the Roland-Morris low back pain and disability questionnaire, an increase in amount of time patient can stand, an increase in amount of time patient can stand on one leg, an increase in the patient's quality of life, an increase in the patient's energy levels, or an increase in the patient's activity levels.

Pharmaceutical Compositions

[00185] As used herein the term "pharmaceutical composition" refers to a preparation of one or more of the components described herein, or physiologically acceptable salts or prodrugs thereof, with other chemical components such as physiologically suitable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism. The term "prodrug" refers a precursor compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide the active compound.

[00186] The term "excipient" refers to an inert or inactive substance added to a pharmaceutical composition to further facilitate administration of a compound. Non-limiting examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

[00187] The pharmaceutical compositions of the present disclosure comprise an opioid/TLR4 antagonist, dextro enantiomer thereof, pro-drugs, salts, or solvates thereof and may also include one or more additive drugs (e.g., additional active ingredients), such as, but not limited to those listed above that may be suitable for combination therapy.

[00188] One pharmaceutical compositions of the present disclosure comprises an opioid/TLR4 antagonist or pharmaceutically acceptable salts thereof. Another pharmaceutical composition of the present disclosure comprises a dextro-enantiomer of an opioid/TLR4 antagonist or the pharmaceutically acceptable salt thereof.

[00189] The disclosure also provides synergistic compositions comprising an opioid/TLR4 antagonist, dextro enantiomeric mixtures thereof, or pharmaceutically acceptable salts thereof and an alpha-2 adrenergic receptor agonist, acetyl-para-aminophenol (APAP), a cyclooxygenase (COX) inhibitor, and/or an alpha-2-delta ligand. Therefore, the pharmaceutical compositions of the present disclosure also comprise an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with an alpha-2 adrenergic receptor agonist. The pharmaceutical compositions of the present disclosure may also comprise an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with an acetyl-para-aminophenol (APAP). The pharmaceutical compositions of the present disclosure also comprise an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with a cyclooxygenase (COX) inhibitor. The pharmaceutical compositions of the present disclosure also comprise an

opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with an alpha-2-delta ligand.

[00190] Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* vol. 22, pp. 27-55 (1984), occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds when administered alone. Synergy can be in terms of lower cytotoxicity, increased decrease in pain, or some other beneficial effect of the combination compared with the individual components. For example, synergy can encompass the reduction of side effects associated with one or more of the substances in the combination because one or more of the substances can be used at a lower dose while still maintaining or enhancing pharmaceutical effectiveness.

[00191] Furthermore, the pharmaceutical compositions of the present disclosure may comprise an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with an alpha-2 adrenergic receptor agonist and acetyl-para-aminophenol (APAP); an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with an alpha-2 adrenergic receptor agonist and a cyclooxygenase (COX) inhibitor; or an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with an alpha-2 adrenergic receptor agonist and an alpha-2-delta ligand.

[00192] The pharmaceutical compositions of the present disclosure may also comprise an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with acetyl-para-aminophenol (APAP) and a cyclooxygenase (COX) inhibitor, or it may comprise an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with acetyl-para-aminophenol (APAP) and an alpha-2-delta ligand. The pharmaceutical compositions of the present disclosure may also comprise an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with a cyclooxygenase (COX) inhibitor and an alpha-2-delta ligand.

[00193] The pharmaceutical compositions of the present disclosure may also comprise an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically

acceptable salts thereof in combination with a cyclooxygenase (COX) inhibitor in combination with acetyl-para-aminophenol (APAP) and an alpha-2-delta ligand.

[00194] The pharmaceutical compositions of the present disclosure may comprise an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with an alpha-2 adrenergic receptor agonist, acetyl-para-aminophenol (APAP), and a cyclooxygenase (COX) inhibitor. It may also comprise an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with an alpha-2 adrenergic receptor agonist, a cyclooxygenase (COX) inhibitor, and an alpha-2-delta ligand. The pharmaceutical composition may comprise an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with an alpha-2 adrenergic receptor agonist, acetyl-para-aminophenol (APAP), and an alpha-2-delta ligand.

[00195] The pharmaceutical composition may also comprise an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof in combination with an alpha-2 adrenergic receptor agonist, acetyl-para-aminophenol (APAP), an alpha-2 adrenergic receptor agonist, and a cyclooxygenase (COX) inhibitor.

[00196] The term "combination" refers to two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such combination of therapeutic agents may be in the form of a single pill, capsule, or intravenous solution. However, the term "combination" also encompasses the situation when the two or more therapeutic agents are in separate pills, capsules, or intravenous solutions. Likewise, the term "combination therapy" refers to the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, or in separate containers (e.g., capsules) for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner, either at approximately the same time or at different times. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein. The dosage form can be prepared by various conventional mixing, comminution and fabrication techniques readily apparent to those skilled in the chemistry of drug formulations.

[00197] For example, the method of treating a disease according to the invention can comprise (i) administration of the opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or pharmaceutically acceptable salts thereof and (ii) administration of one or more of: an alpha-2 adrenergic receptor agonist, acetyl-para-aminophenol (APAP), and an alpha-2-delta ligand, or any pharmaceutically acceptable salts thereof simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts, *e.g.* in daily or intermittently dosages corresponding to the amounts described herein. The individual combination partners of the combination of the invention can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. Furthermore, the term administering also encompasses the use of a pro-drug of a combination partner that convert *in vivo* to the combination partner as such. The instant invention is therefore to be understood as embracing all such regimens of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

[00198] Frequency of dosage can vary depending on the compound used and the particular condition to be treated or prevented. In general, the use of the minimum dosage that is sufficient to provide effective therapy is preferred. Patients can generally be monitored for therapeutic effectiveness using assays suitable for the condition being treated or prevented, which will be familiar to those of ordinary skill in the art. Different dosage regimens may be used to treat any of the disease states referenced herein. In some embodiments, a daily dosage, such as any of the exemplary dosages described herein, is administered once, twice, three times, or four times a day for three, four, five, six, seven, eight, nine, or ten days. In some embodiments, the compounds described herein may be used on the order of about 10 times per day to about once per six months (e.g., about 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 times per day to about 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 times per month). In some embodiments, dosing frequencies are once per day, once per week, once per two weeks, once per three weeks, and once per month. Depending on the type of disorder treated, a shorter treatment time (e.g., up to five days) may be employed along with a high dosage, or a longer treatment time (e.g., ten or more days, or weeks, or a month, or longer) may be employed along with a low dosage. In some embodiments, the dosing regimen may change over time depending on the condition being treated and the patient's response to the treatment.

[00199] The disclosure provides a composition comprising a compound that is an opioid/TLR4 antagonist, dextro enantiomeric mixture thereof, or a pharmaceutically acceptable salt thereof and its use for the treatment, prevention, and reversal of pain. The disclosure also provides synergistic compositions comprising an opioid/TLR4 antagonist, dextro enantiomeric mixtures thereof, or pharmaceutically acceptable salts thereof and an alpha-2 adrenergic receptor agonist, acetyl-para-aminophenol (APAP), a cyclooxygenase (COX) inhibitor, and/or an alpha-2-delta ligand. The disclosure further provides a method of use of these synergistic compositions for the treatment, prevention, and reversal of pain, particularly neuropathic pain.

[00200] The pharmaceutical compositions of the present disclosure may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, grinding, pulverizing, dragee-making, levigating, emulsifying, encapsulating, entrapping or by lyophilizing processes.

[00201] The compositions for use in accordance with the present disclosure thus may be formulated in conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[00202] The term “administration” or any variation thereof as used herein is meant any way of administration. The one or more opioid/TLR4 antagonists, dextro enantiomers thereof, pro-drugs, salts, or solvates thereof may be administered alone. The one or more opioid/TLR4 antagonists, dextro enantiomers thereof, pro-drugs, salts, or solvates thereof and at least one additional drug may be administered in one therapeutic dosage form or in two or more separate therapeutic dosages such as in separate capsules, tablets or injections. In the case of the two or more separate therapeutic dosages, the administration may be such that the periods between the administrations vary or are determined by the practitioner. The second drug and any other additional drugs may be administered within the therapeutic response time of the first drug. The second drug and any other additional drugs may be also administered after the therapeutic response time of the first drug. The one or more of opioid/TLR4 antagonists, dextro enantiomers thereof, pro-drugs, salts, or solvates thereof and at least one additional drug which may be administered either at the same time, or separately, or sequentially, according to the disclosure, do not represent a mere aggregate of known agents,

but a new combination with the valuable property that the effectiveness of the treatment is achieved at a much lower dosage of said at least one additional drug.

[00203] The pharmaceutical compositions of the present disclosure 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 any other therapeutic agent. Administration can be systemic or local.

[00204] Various delivery systems are known, e.g., encapsulation in liposomes, microparticles, microcapsules, or capsules that may be used to administer the compositions of the disclosure. Methods of administration include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, epidural, oral, sublingual, intranasal, intracerebral, intravaginal, transdermal, rectally (including by suppository or enema), by inhalation, or topically to the cars, nose, eyes, or skin. The mode of administration is left to the discretion of the practitioner, and will depend in part upon the site of the medical condition and the severity of thereof.

[00205] For example, for injection the composition of the disclosure may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants for example DMSO, or polyethylene glycol are generally known in the art.

[00206] For oral administration, the composition can be formulated readily by combining the active components with any pharmaceutically acceptable carriers known in the art. Such “carriers” may facilitate the manufacture of such as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for oral ingestion by a patient. Pharmacological preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carbomethylcellulose, and/or physiologically acceptable polymers such as polyvinylpyrrolidone (PVP). If desired,

disintegrating agents may be added, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[00207] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures.

[00208] Pharmaceutical compositions, which can be used orally, include push-fit capsules made of gelatin as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active ingredients in admixture with filler such as lactose, binders such as starches, lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active components may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols.

[00209] Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active NSAID doses. In addition, stabilizers may be added.

[00210] Pharmaceutical compositions for parenteral administration include aqueous solutions of the active preparation in a water-soluble form. Additionally, suspensions of the active preparation may be prepared as oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acids esters such as ethyl oleate, triglycerides or liposomes. Aqueous injection suspensions may contain substances, which increase the viscosity of the suspension, such as sodium carboxymethyl, cellulose, sorbitol or dextran. Optionally, the suspension may also contain suitable stabilizers or agents, which increase the solubility of the compounds, to allow for the preparation of highly concentrated solutions.

[00211] Alternatively, the composition may be in a powder form for constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water. The exact formulation, route of administration and dosage may be chosen by the physician familiar with the patient's condition. (See for example Fingl, et al., 1975, in “The Pharmacological Basis of Therapeutics”, Chapter I, p. 1). Depending on the severity and responsiveness of the condition treated, dosing can also be a single administration of a slow release composition, with course of treatment lasting from several days to several weeks or until cure is effected or diminution of the disease state is achieved.

[00212] In an embodiment for non-human animal administration the term "pharmaceutical" as used herein may be replaced by "veterinary".

EXAMPLES

[00213] The examples disclosed in the instant application are case studies from clinical trials. These examples are non-limiting and are merely representative.

Example 1: A Pharmaceutical Composition Comprising Naltrexone and Clonidine and Clinical Trials Thereof

[00214] Naltrexone and clonidine were evaluated alone and in combination on a human subject with the purpose of finding whether or not a combination of the two compounds offers synergistic advantage. Two aspects were evaluated for synergy: one aspect was pain treatment effect comparing the amounts used weight to weight, and the other aspect was an assessment of synergy of side effects.

[00215] The components of the combination were administered to a subject in the following manner: naltrexone 4.5mg was given in the morning. The clonidine dose was divided into two doses, a dose of 0.1mg in the morning and a dose of 0.2mg at bedtime. The morning/daytime combination of naltrexone/clonidine 2.25mg/ 0.025mg respectively was given in the morning, and the night/bedtime combination of naltrexone/clonidine of 2.25mg/ 0.05mg and 2.25mg/0.1mg respectively was given at night. The pain treatment effect of naltrexone and clonidine was evaluated after one hour post-dose. Side effects were assessed over the next 24 hours.

[00216] To determine synergy, the amounts of naltrexone and clonidine administered alone were compared to the combination combined amounts. For proper weight to weight (W/W) comparison between naltrexone and clonidine an adjustment for the higher potency of clonidine needed to be made based on the dose of each compound given by itself, where the naltrexone dose was 4.5 mg and the clonidine dose was 0.3 mg. Clonidine is 15 times more potent than naltrexone (4.5/0.3=15). Naltrexone and clonidine were administered at fixed dose ratios of 90:1, 45:1 and 22.5:1 to a human subject afflicted with neuropathic back pain.

[00217] Table 1 illustrates the naltrexone/clonidine ratios that exhibit weight to weight (W/W) synergy in a human subject. The 90:1 combination represents a 2-fold lower dose of naltrexone and 4-fold lower dose of clonidine when administered alone. The 45:1 combination represents a 2-fold lower dose of naltrexone and 2-fold lower dose of clonidine when administered alone.

Table 1: Naltrexone/Clonidine Ratios And Weight to Weight (W/W) Synergy

Ratio	Naltrexone mg	Clonidine mg	Clonidine Potency Adjustment (x15)	% reversal of pain	Total dose Naltrexone + Adjusted clonidine mg	Interaction
4.5:0	4.50	-		100	4.5	-
0:0.3	-	0.300	4.500	50	4.5	-
90:1	2.25	0.025	0.375	100	2.625	synergy
45:1	2.25	0.050	0.750	100	2.25+0.75=3.0	synergy
22.5:1	2.25	0.1	1.500	100	2.25+1.5=3.75	synergy

[00218] The 22.5:1 ratio represents a 2-fold lower dose of naltrexone and the same dose of clonidine when administered alone. The fixed dose ratio of 90:1, 45:1 and 22.5:1 demonstrated weight to weight synergy with neuropathic back pain completely blocked by the doses of 2.25mg/ 0.025mg, 2.25mg/0.05mg and 2.25mg/0.1mg of naltrexone/clonidine respectively.

[00219] Table 2 demonstrates the side effect synergy of the naltrexone/clonidine combination: alertness and anxiety from naltrexone are counteracted by the somnolence and calmness caused by clonidine. Naltrexone administered by itself at a 4.5mg dosage carries a high incidence of alertness, insomnia and anxiety which deters compliance. Clonidine administered by itself at a .3mg dosage at bedtime causes excessive somnolence that carries over through the next day.

Table 2: Synergy of Side Effects for Naltrexone/Clonidine

Ratio	Naltrexone mg	Clonidine mg	Interaction	Side effects
4.5:0	4.5	-	-	Alertness, Insomnia, anxiety
0:0.3	-	0.3	-	Excessive Somnolence, calmness
90:1	2.25	0.025	synergy	No side effects
45:1	2.25	0.05	synergy	Somnolence Rarely
22.5:1	2.25	0.1	synergy	Somnolence Rarely

[00220] The 90:1 ratio is a suitable synergistic ratio for morning/daytime contemplated administration. It embodies a lower adjusted total weight to weight dose of 2.625mg compared to 4.5mg of naltrexone and clonidine alone. Furthermore, it offers balance between the side effects: alertness and anxiety from naltrexone are counteracted by calmness from clonidine.

[00221] The 45:1 ratio is a suitable synergistic ratio for night/bedtime contemplated use. It embodies a lower adjusted total weight to weight dose of 2.35mg compare to 4.5mg of naltrexone and clonidine alone. This ratio provides additional sedation for more restorative night sleep.

[00222] The 22.5:1 ratio is a synergistic ratio for night/bedtime use as it provides additional sedative effect.

[00223] To summarize the naltrexone/clonidine synergistic effect, the disclosure teaches that the optimal contemplated naltrexone, or a pharmaceutically acceptable salt or solvate thereof, to clonidine, or a pharmaceutically acceptable salt or solvate thereof, combination dosage ratio range is between 90:1 and 22.5:1. This dosage ratio range exhibits synergy of weight to weight proportion and of side effect profile.

[00224] The clinical trial described below demonstrated statistically significant improvement of sleep compared to baseline as measured by the Pittsburgh Insomnia Rating Scale (PIRS 20). This suggests that the naltrexone side effects of alertness and insomnia were not only counteracted, but sleep was improved with the co-administration of the clonidine. (See Figure 17, below).

Use of Combination of Opioid/TLR4 Antagonist and direct-acting Alpha-2 Adrenergic Antagonist to treat Lower Back Pain

[00225] A 59 year old female presented with a 15 year history of lower back pain (LBP), leg weakness and pain. Additionally, she had a lifelong history of migraine headaches averaging two headache-days a week with an average intensity of 5 on a scale of 10, where 10 is intolerable pain. Prior to entering the double blind clinical trial, she had used duloxetine, topiramate, and non-steroidal anti-inflammatory drugs (NSAIDs) on a regular basis, all of which were discontinued upon entering the trial.

[00226] Prior to dosing, the subject could not stand on either leg for any length of time. Her baseline average back pain score the week before receiving study drug was 6.5 on a scale of 10, and her headache pain level was rated as 10. Eight minutes after the first dose

combination of naltrexone/clonidine 2.25mg/0.025mg she reported that her headache had begun to resolve. After one hour her migraine pain had resolved to 0; her LBP had become 5 for a 60% improvement by her own report. After six hours, her LBP had fully resolved to a score of 0 out of 10.

[00227] The subject continued the combination of naltrexone/clonidine 2.25mg/0.025mg twice daily for 27 days during which time she reported no lower back pain or migraine pain. At the end of the 27-day treatment period she was able to stand separately on each leg for longer than 20 seconds.

[00228] During an 18-month post-study follow up period with no study medication, the subject was seen on six different occasions and maintained a self-reported long-term 80% improvement of her LBP and migraines compared to the period before receiving the study drug.

[00229] This case study shows that the combination of naltrexone/clonidine at the dose of 2.25mg/0.025mg twice daily is successful in treating acute migraine headache attack and chronic LBP. It also appears to have had a long-term prophylactic impact on migraine headaches. Table 3 tabulates the various pain intensity scores over time and percent relief for the example of lower back pain. The drawing in Figure 1 is a graph of the various pain intensity scores over time in the case of lower back pain. The drawing in Figure 2 is a graph of the percent relief reported by the case of lower back pain over time.

Table 3: An Example of Lower Back Pain

	Baseline										Study Drug																			
Days in Trial	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Worst Pain	5	5	6	6	10	9	9	9	1	1	1	4	1	2		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Least Pain	4	5	4	6	6	6	8	8	1	1	1	4	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Average Pain	5	5	5	5	8	8	8	8	1	1	1	4	1	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Right Now Pain	5	5	6	4	6	6	5	7	1	1	1	4	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Night Pain	8	6	6	6	10	9	8	9	1	0	0	4	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Relief %									70	70	70	50	70	60	60	70	70	70	70	80	80	80	80	90	90	90	90	90	90	90	90	90

Use of Combination of Opioid/TLR4 Antagonist and direct-acting Alpha-2 Adrenergic Antagonist to treat Vulvodynia

[00230] Vulvodynia is a chronic pain syndrome that affects the vulvar area and often occurs without an identifiable cause or visible pathology. A 55 year old female with a six year history of vulvodynia presented with constant pain and sensitivity in the vulva which interfered with her daily living and prevented her from having sexual intercourse. The subject entered open label study for three weeks. She improved dramatically after the first dose. After three days her pain level went from 9 to 0 (on an 11 point pain scale). After taking two capsules the first day, she noticed that she felt aggression, and so she reduced the dose to one capsule a day. One capsule still offered her full relief but without adverse events. Table 4 tabulates the various pain intensity scores over time and percent relief for the example of Vulvodynia. The drawing in Figure 3 is a graph of the various pain intensity scores over time in the case of Vulvodynia pain. The drawing in Figure 4 is a graph of the percent relief reported by the case of Vulvodynia pain over time. This case study demonstrates complete reversal of vulvodynia pain starting after the first dose of ATNC05. The effect was maintained throughout the 30-day treatment period. The patient reported increased energy level, improvement of sleep quality, and resolution of headaches.

Table 4: An Example of Vulvodynia

	Baseline								Treatment with ATNC05										
Treatment Day	-8	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11
Worst Pain	8	10	10	8	8	8	8	8	6	0	6	0	0	0	0	0	0	0	0
Least Pain	3	7	8	6	6	6	6	6	0	0	0	0	0	0	0	0	0	0	0
Average Pain	7	7	8	6	6	6	6	6	0	0	0	0	0	0	0	0	0	0	0
Right-Now Pain	8	7	8	6	6	6	6	6	0	0	0	0	0	0	0	0	0	0	0
Night Pain	6	10	10	8	8	8	8	8	6	0	6	0	0	0	0	0	0	0	0
PGI-I (Percent Relief)									60	100	90	100	100	100	100	100	100	100	100

	Treatment with ATNC05 (Continued)																			
Treatment Day	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	
Worst Pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Least Pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Average Pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Right-Now Pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Night Pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PGI-I (Percent Relief)	1 0 0	1 0 0	100	1 0 0	1 0 0	1 0 0	1 0 0	10 0	10 0	10 0	10 0	10 0	10 0	10 0	10 0	10 0	10 0	10 0	10 0

Use of Combination of Opioid/TLR4 Antagonist and direct-acting Alpha-2 Adrenergic Antagonist to treat Trigeminal Neuralgia

[00231] Trigeminal neuralgia, also known as suicide disease, is a neuropathic disorder characterized by episodes of intense pain in the face, originating from the trigeminal nerve. It has been described as among the most painful conditions known to mankind. This case study is of a 40 year old male with a three month history of trigeminal neuralgia. The patient had a gradual onset of pain in the right side of his face that started six weeks after a root canal. The pain involved the right check, upper jaw and the upper front teeth. The pain was constant and described as burning, stinging and aching. It was aggravated by eating, brushing teeth, flossing, chewing and talking. The subject's pain level on average was 5, but it would peak to 9. Ibuprofen brought the pain level from 9 to 7 for two hours, vicoden brought his pain level from 9 to 5, but relief lasted only three to four hours. The subject entered open label study for 3 weeks. After he was on the study drug at a dose of two capsules a day for one week his pain level fell to 2 and he reported being 90% better than before participating in the study. He stated that one dose had a lasting effect of up to 24 hours, unlike previous medications he had tried. Table 5 tabulates the various pain intensity scores over time and percent relief for the example of Trigeminal Neuralgia. The drawing in Figure 5 is a graph of the various pain intensity scores over time in the case of Trigeminal Neuralgia pain. The drawing in Figure 6 is a graph of the percent relief reported by the case of Trigeminal Neuralgia pain over time.

Table 5: An Example of Trigeminal Neuralgia

	Baseline						Study Drug																						
	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Worst Pain	6	6	6	6	6	6	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1
Least Pain	4	4	4	4	4	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
Average Pain	5	5	5	5	5	5	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1

Right Now Pain	4	4	4	4	4	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
Night Pain	6	6	6	6	6	5	4	2	2	4	4	4	4	3	3	3	4	4	3	3	3	1	1	1	1	1	1	1	1
PGI-I (Percent Relief)							90	90	90	90	90	90	90	90	90	90	90	90	90	90	90	90	96	96	96	96	96	96	96

Use of Combination of Opioid/TLR4 Antagonist and direct-acting Alpha-2 Adrenergic Antagonist to treat Irritable Bowel Syndrome (IBS)

[00232] A 42 year old male had an eight year history of IBS averaging two attacks per year. His present flare-up had persisted for seven days with symptoms include left lower quadrant abdominal pain, cramping and bloating. Physical examination showed tenderness of the left lower quadrant and hyperactive bowel sounds. The subject reported a pain rating of 8. He enrolled in the open label phase of the trial with a baseline pain level of 8, lower back pain of 7. Seventy-five minutes after his initial dose, his pain, cramping, and lower back pain had become zero. Four hours later his pain recurred but was resolved after a second dose was taken. Table 6 tabulates the various IBS symptom intensity scores over time for the example of IBS. The drawing in Figure 7 is a graph of the various IBS symptom intensity scores over time in the case of IBS.

Table 6: An Example of Irritable Bowel Syndrome

An Example of Irritable Bowel Syndrome																			
	Hours Post Dose																		
	0.00	0.25	0.50	0.75	1	3	4	5	6	7	8	9	12	21	22	23	24	25	28
IBS	8	4	2	1	0	3	3	4	5	4	2	0	0	0	0	0	0	0	0
Cramping	8	5	2	0	0	2	3	3		2	0	0	0	3	2	2	2	2	2
Back Pain	7	3	2	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0
Bloating	7	5	2	0	0	2	3	3		2	1	0	0	3	2	2	1		1

Use of Combination of Opioid/TLR4 Antagonist and direct-acting Alpha-2 Adrenergic Antagonist to treat Acute Migraine

[00233] A 45 year old man presented with an acute migraine. His symptoms included pain level of 8 on a 0 to 10 point scale, with 10 being intolerable pain; nausea level of 5; and noise and light disturbance of 6. Seventy-five minutes after administration his nausea was at 3 while all his other symptoms went to zero, and he was able to look directly into the light. He was symptom-free for four hours, after which his headache and other symptoms recurred. He took two additional capsules of study drug and the symptoms resolved completely within one hour. Symptoms did not recur. Table 7 tabulates the various headache parameters

intensity scores over time for the example of migraine. The drawing in Figure 8 is a graph of the various headache parameters intensity scores over time in the case of migraine headache.

Table 7: An Example of Migraine

Migraine Example																			
	Hours Post Dose																		
	0	0.3	0.5	0.8	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Headache	8	8	3	3	2	0	0	0	0	8	0	0	0	0	0	0	0	0	0
Light	6	6	3	3	2	0	0	0	0	6	0	0	0	0	0	0	0	0	0
Noise	6	6	3	3	2	0	0	0	0	6	0	0	0	0	0	0	0	0	0

Use of Combination of Opioid/TLR4 Antagonist and direct-acting Alpha-2 Adrenergic Antagonist to treat Leg Pain

[00234] A 61 year old woman with a ten year history of leg pain and weakness caused by L-5 radiculopathy was incapable of standing for longer than 10 minutes. She was not able to stand on one leg for any length of time on either side without losing balance immediately. The subject of this case had seen eleven spine surgeons, repeatedly told that surgery would not be beneficial for her pain. She tried oral medication such as NSAIDs, anticonvulsants, muscle relaxants, and anti-depressants (bupropion, duloxetine). Aside from some relief from NSAIDs, none of the other medications had any meaningful effect. She received spinal decompression on a DRX 9000 and obtained about 10% relief. An epidural steroid injection provided 5% relief for two weeks, three perispinal injections with botulinum toxin offered 10% relief for two months, and three perispinal Etanercept injections offered 10% relief for two months.

[00235] The subject in this case study has been on naltrexone/clonidine at the dose of 2.25mg/0.025mg twice daily for three years with improvement of up to 80% of her symptoms. Recently she increased the dose to 6 units which she prefers to take at night for the control of night pain and insomnia. With the current regiment her pain level stabilizes at a self-reported score of between 0-3 on a 10-point scale, and she has been able to stand on either leg for longer than 60 seconds. Without medication pain recurs within one to three days.

Clinical Trial Excerpts

[00236] A double-blind, placebo-controlled, randomized, proof-of-concept clinical trial was conducted in order to determine the efficacy and safety of a combination of low dose naltrexone and low dose clonidine (code-named ATNC05) for the treatment of symptoms of back pain. The studies were conducted under the regulatory oversight of the Food and Drug Administration (FDA) and the Independent Institutional Review Board (presently known as Shulman IRB). The subjects were screened to verify the diagnosis of chronic back pain (longer than three months). After a one-week baseline period, during which subjects completed daily pain questionnaires, 78 subjects were enrolled in the study and treated for a three-week Double-Blind treatment period with either placebo or ATNC05 (the first 24 subjects were randomized in a 1:4 ratio, and the remaining were randomized in a 1:1 ratio). Subjects who were non-responders in the Double-Blind were offered the option to continue into the Open-Label extension phase, during which subjects were treated with ATNC05 for three weeks. There were 44 subjects in the ATNC05 group, and 34 subjects in the placebo group. There were 27 subjects who began the Open-Label phase.

Table 8: Demographic Characteristics of Clinical Trial Subjects

	Placebo	ATNC05	Total
N	34	44	78
Age (years)			
Mean(SD)	45.6 (11.4)	48.0 (8.5)	46.9 (9.9)
Median	46	49	47
Range	19-70	21-63	19-70
Gender, n (%)			
Female	24 (70.6)	28 (63.6)	52 (66.7)
Male	10 (29.4)	16 (36.4)	26 (33.3)
Race, n (%)			
White	29 (85.3)	32(72.7)	61(78.2)
Black	1 (2.9)	5(11.4)	6(7.7)
More than One Race	4 (11.8)	7(15.9)	11(14.1)
Ethnicity, n (%)			
Hispanic	24 (70.6)	23(52.3)	47(60.3)
Non-Hispanic	10 (29.4)	21(47.7)	31(39.7)
Weight (Lb)			
Mean(SD)	177.5 (44.5)	177.3 (49.0)	177.4 (46.8)
Median	165	176.5	170.5
Range	106-338	115-352	106-352
Height (inches)			
Mean(SD)	66.0 (3.1)	66.1 (3.3)	66.1 (3.2)
Median	65.5	66	66

	Placebo	ATNC05	Total
Range	60-74	61-77	61-77
Baseline Period Brief Pan Inventory (BPI) Severity Scores – Mean (SD)			
Worst Pain	6.60 (1.14)	6.64 (1.14)	6.62 (1.11)
Least Pain	4.90 (1.40)	4.64 (1.40)	4.75 (1.28)
Average Pain	5.49 (1.02)	5.56 (1.02)	5.53 (1.02)
Right Now Pain	5.42 (1.23)	5.48 (1.23)	5.45 (1.22)
Night Pain	5.74 (1.35)	6.01 (1.35)	5.89 (1.42)
Baseline Period Brief Pan Inventory (BPI) Interference Scores – Mean (SD)			
General Activity	5.46 (1.48)	5.57 (1.48)	5.52 (1.46)
Mood	4.73 (1.62)	4.99 (1.62)	4.88 (1.80)
Walking	5.02 (1.76)	4.97 (1.76)	4.99 (1.91)
Normal Work	5.47 (1.23)	5.62 (1.23)	5.55 (1.42)
Relationships	4.42 (1.72)	4.09 (1.72)	4.24 (2.05)
Sleep	5.77 (1.16)	5.83 (1.16)	5.80 (1.52)
Enjoyment of Life	5.15 (1.53)	5.30 (1.53)	5.23 (1.73)
Standing Ability	5.33 (1.56)	5.22 (1.56)	5.27 (1.81)
Sitting	5.03 (1.70)	5.02 (1.70)	5.03 (1.79)
Office Encounters Measures Scores – Mean (SD)			
CGI-S	5.28 (0.83)	5.32 (0.80)	5.30 (0.82)
Oswestry Disability Index	41.69 (8.56)	42.12 (7.37)	41.36 (9.45)
Roland-Morris Disability	14.83 (4.43)	15.78 (4.50)	14.13 (4.30)
Pittsburgh Insomnia Rating (PIRS-20)	35.42 (7.83)	36.06 (7.28)	34.93 (8.29)
Duration of Subject Back Pain – Mean (SD)			
Duration (Years)*	7.88 (6.16)	9.07 (5.90)	8.67 (5.96)

[00237] The demographic characteristics of the subjects are summarized in Table 8.

[00238] Table 9 shows 23 subjects out of 78 who entered the study for back pain had concomitant migraine or tension headache. This finding represents a higher incidence of headaches than found in the general population. Similarly, table 10 shows 30 out of 78subjects had joint pain, most of which was associated with tendinitis rather than arthritic pain.

Table 9: Baseline Migraine Subject Characteristics

	Placebo Migraine Subjects	ATNC05 Migraine Subjects	All Migraine Subjects
N	10	13	23
Age (years)			
Mean(SD)	41.5 (12.62)	46.2 (8.32)	44.2 (10.42)
Median	39.5	45	43
Range	19 - 70	33 - 59	19 - 70
Gender, n (%)			

Female	10 (100)	10 (76.9)	20 (86.9)
Male	0 (0)	3 (23.1)	3 (13.0)
Race, n (%)			
White	9 (90)	7 (53.8)	15 (65.2)
Black	0 (0)	2 (15.4)	2 (8.6)
More than One Race	1 (10)	4 (30.7)	5 (21.7)
Ethnicity, n (%)			
Hispanic	7 (70)	9 (69.2)	16 (69.5)
Non-Hispanic	3 (30)	4 (30.7)	7 (30.4)

	Duration in Years – Mean (SD)	Average Severity on 11-point scale – Mean (SD)	N
Placebo Migraine Subjects	17.9 (11.23)	6.4 (1.17)	10
ATNC05 Migraine Subjects	23.1 (13.62)	5.8 (1.48)	13
All Migraine Subjects	20.8 (12.64)	6.0 (1.36)	23
Open-Label Migraine Subjects	17.1 (9.87)	6.4 (1.33)	9

Table 10: Baseline Joint Pain (Tendinitis) Characteristics

	Placebo	ATNC05	Total
Joint Pain (Tendinitis)			
N	6	10	16
Average Severity	5.10	5.80	5.53
Average Duration (Years)	3.36	4.58	4.12

[00239] The subjects took 1 capsule containing naltrexone/clonidine 2.25mg/0.025mg respectively or placebo twice daily and were instructed to increase the dose if the pain reduction effect was not sufficient. Subjects who did not respond had the option of continuing in an open label phase, receiving study drug for 3 weeks.

[00240] While in the study the subjects completed a daily pain questionnaire regarding back pain. Subjects who had concomitant headaches and/or joint pain recorded progression of those symptoms as well. The study subjects were evaluated in the office, in person four times during the course of the study and for subjects in open phase six times. Disability and sleep quality questionnaires along with safety data were collected during the office encounters.

Results

[00241] Table 11 presents the daily improvement of pain scores of study drug vs. placebo measured on a scale of 0–10, with 10 being most severe during the blinded study drug period.

Table 11: Daily Improvement of Pain Scores of Study Drug vs. Placebo by Day

Study Day	N of Subjects Receiving Placebo (n of	N of Subjects Receiving	Mean (SE) Average Pain Score for	Mean (SE) Average Pain Score for	Placebo Treatment Effect	ATNC05 Treatment Effect	p-value

	subjects Imputed by BOCF)	ATNC05 (n of subjects Imputed by BOCF)	Placebo Subjects	ATNC05 Subjects			
2	34 (1)	44 (0)	4.77 (0.33)	3.09 (0.29)	-0.72	-2.49	0.00029
3	34 (1)	44 (2)	4.63 (0.33)	3.07 (0.29)	-0.87	-2.51	0.00072
4	34 (1)	44 (2)	4.74 (0.34)	2.77 (0.29)	-0.75	-2.81	0.00003
5	34 (2)	44 (2)	4.59 (0.33)	2.84 (0.31)	-0.90	-2.74	0.00020
6	34 (3)	44 (1)	4.51 (0.35)	2.31 (0.28)	-0.98	-3.27	0.00001
7	34 (3)	44 (2)	4.60 (0.37)	2.48 (0.29)	-0.90	-3.10	0.00003
8	34 (3)	44 (2)	4.83 (0.38)	2.59 (0.32)	-0.66	-2.99	0.00003
9	34 (4)	44 (5)	4.69 (0.37)	2.24 (0.32)	-0.81	-3.33	0.00000
10	34 (4)	44 (3)	4.66 (0.36)	2.14 (0.31)	-0.84	-3.44	0.00000
11	34 (4)	44 (3)	4.66 (0.34)	2.14 (0.32)	-0.84	-3.44	0.00000
12	34 (4)	44 (2)	4.66 (0.36)	1.89 (0.33)	-0.84	-3.69	0.00000
13	34 (4)	44 (2)	4.78 (0.39)	1.86 (0.32)	-0.72	-3.72	0.00000
14	34 (4)	44 (3)	4.86 (0.42)	1.84 (0.33)	-0.63	-3.74	0.00000
15	34 (4)	44 (4)	4.69 (0.41)	1.89 (0.32)	-0.80	-3.69	0.00000
16	34 (4)	44 (5)	4.61 (0.41)	1.82 (0.34)	-0.89	-3.76	0.00000
17	34 (4)	44 (6)	4.69 (0.41)	1.86 (0.35)	-0.80	-3.72	0.00000
18	34 (4)	44 (6)	4.55 (0.39)	1.93 (0.34)	-0.95	-3.65	0.00000
19	34 (4)	44 (7)	4.58 (0.40)	1.84 (0.36)	-0.92	-3.74	0.00000
20	34 (4)	44 (7)	4.43 (0.35)	1.93 (0.37)	-1.07	-3.65	0.00001
21	34 (5)	44 (7)	4.59 (0.39)	1.93 (0.36)	-0.90	-3.65	0.00000
22	26*	36*	4.42 (0.45)	1.14 (0.27)	-1.07	-4.44	0.00000
23	18*	28*	3.28 (0.56)	1.61 (0.39)	-2.22	-3.97	0.02064
24	13*	24*	3.46 (0.69)	1.21 (0.31)	-2.03	-4.37	0.00820

[00242] Table 11 shows that back pain scores were significantly lower in the study drug subjects compared with placebo (P = 0.001) from Day 2 onwards. The drug impact increases as time progressed showing a 5 point improvement.

[00243] Pain intensity scores of study drug vs. placebo, as reported daily by the subjects for Worst Pain, Least Pain, Average Pain, Right-Now Pain, and Night Pain during the previous 24-hours are summarized in the following 5 tables and graphs. The data and graphs show consistent treatment impact on all pain intensity measures. Improvement begins starting the first day. The study drug impact increases as time progresses showing approximately a 5 point (on a scale of 0-10 with 10 being most severe) improvement compared to baseline by the end of the study. The Study Drug group exhibited resolution of pain. Table 12 tabulates the worst pain intensity scores over time for the study drug group

versus placebo group in the clinical trial subjects. The drawing in Figure 9 is a graph of the treatment impact on worst pain by day of study drug group versus placebo group in the clinical trial subjects. Table 13 tabulates the least pain intensity scores over time for the study drug group versus placebo group in the clinical trial subjects. The drawing in Figure 10 is a graph of the treatment impact on least pain by day of study drug group versus placebo group in the clinical trial subjects. Table 14 tabulates the average pain intensity scores over time for the study drug group versus placebo group in the clinical trial subjects. The drawing in Figure 11 is a graph of the treatment impact on average pain by day of study drug group versus placebo group in the clinical trial subjects. Table 15 tabulates the right now pain intensity scores over time for the study drug group versus placebo group in the clinical trial subjects. The drawing in Figure 12 is a graph of the treatment impact on right now pain by day of study drug group versus placebo group in the clinical trial subjects. Table 16 tabulates the night pain intensity scores over time for the study drug group versus placebo group in the clinical trial subjects. The drawing in Figure 13 is a graph of the treatment impact on night pain by day of study drug group versus placebo group in the clinical trial subjects.

Table 12: Worst Pain Scores (Scale: 0-10) By Treatment Group

Double-Blind Mean Worst Pain Scores by Group By Day (BOCF)				
	Placebo		ATNC05	
Treatment Day	N (n BOCF)	Ave.	N (n BOCF)	Ave.
Baseline Period Mean	34	6.60	44	6.62
1*				
2	34 (1)	5.49	44 (0)	4.09
3	34 (1)	5.07	44 (2)	4.01
4	34 (1)	5.27	44 (2)	3.78
5	34 (2)	5.33	44 (2)	3.62
6	34 (3)	5.18	44 (1)	3.02
7	34 (3)	5.29	44 (2)	3.18
8	34 (3)	5.44	44 (2)	3.20
9	34 (4)	5.42	44 (5)	2.78
10	34 (4)	5.24	44 (3)	2.80
11	34 (4)	5.33	44 (3)	2.75
12	34 (4)	5.27	44 (2)	2.45
13	34 (4)	5.51	44 (2)	2.38
14	34 (4)	5.30	44 (3)	2.30
15	34 (4)	5.28	44 (4)	2.48
16	34 (4)	5.16	44 (5)	2.17
17	34 (4)	5.22	44 (6)	2.35
18	34 (4)	5.31	44 (6)	2.30
19	34 (4)	5.28	44 (7)	2.24
20	34 (4)	5.16	44 (7)	2.27
21	34 (5)	5.41	44 (7)	2.46
22	26*	5.15	28*	1.46
23	18*	4.11	24*	2.11
24	13*	4.23	28*	1.75

*Day 1 answers were not tabulated for this question because subjects completed the BPI on Day 1 within hours of their first dose of study drug. Data were not imputed by BOCF during the taper-off periods, days 22-24.

Table 13: Least Pain Scores (Scale: 0-10) By Treatment Group

Double-Blind Mean Least Pain Scores by Group by Day (BOCF)				
	Placebo		ATNC05	
Treatment Day	N (n BOCF)	Ave.	N (n BOCF)	Ave.
Baseline Period Mean	34	4.93	44	4.70
1*				
2	34 (1)	4.29	44 (0)	2.52
3	34 (1)	4.11	44 (2)	2.56
4	34 (1)	4.23	44 (2)	2.33
5	34 (2)	4.15	44 (2)	2.44
6	34 (3)	4.14	44 (1)	2.04
7	34 (3)	4.31	44 (2)	2.03
8	34 (3)	4.31	44 (2)	2.03
9	34 (4)	4.39	44 (5)	1.81
10	34 (4)	4.25	44 (3)	1.73
11	34 (4)	4.07	44 (3)	1.75
12	34 (4)	4.04	44 (2)	1.49
13	34 (4)	4.31	44 (2)	1.40
14	34 (4)	4.34	44 (3)	1.50
15	34 (4)	4.26	44 (4)	1.46
16	34 (4)	4.34	44 (5)	1.34
17	34 (4)	4.26	44 (6)	1.35
18	34 (4)	4.26	44 (6)	1.39
19	34 (4)	4.23	44 (7)	1.42
20	34 (4)	4.08	44 (7)	1.51
21	34 (5)	4.21	44 (7)	1.51
22	26*	4.23	36*	0.97
23	18*	3.17	28*	1.43
24	13*	3.38	24*	1.00

*Day 1 answers were not tabulated for this question because subjects completed the BPI on Day 1 within hours of their first dose of study drug. Data were not imputed by BOCF during the taper-off periods, days 22-24.

Table 14: Average Pain Scores (Scale: 0-10) By Treatment Group

Double-Blind Mean Average Pain Scores by Group by Day (BOCF)				
	Placebo		ATNC05	
Treatment Day	N (n BOCF)	Ave.	N (n BOCF)	Ave.
Baseline Period Mean	34	5.50	44	5.55
1*				
2	34 (1)	4.77	44 (0)	3.09
3	34 (1)	4.63	44 (2)	3.07
4	34 (1)	4.74	44 (2)	2.77
5	34 (2)	4.59	44 (2)	2.84
6	34 (3)	4.51	44 (1)	2.31
7	34 (3)	4.60	44 (2)	2.48
8	34 (3)	4.83	44 (2)	2.59
9	34 (4)	4.69	44 (5)	2.24
10	34 (4)	4.66	44 (3)	2.14
11	34 (4)	4.66	44 (3)	2.14
12	34 (4)	4.66	44 (2)	1.89
13	34 (4)	4.78	44 (2)	1.86
14	34 (4)	4.86	44 (3)	1.84
15	34 (4)	4.69	44 (4)	1.89
16	34 (4)	4.61	44 (5)	1.82
17	34 (4)	4.69	44 (6)	1.86
18	34 (4)	4.55	44 (6)	1.93
19	34 (4)	4.58	44 (7)	1.84

20	34 (4)	4.43	44 (7)	1.93
21	34 (5)	4.59	44 (7)	1.93
22	26*	4.42	36*	1.14
23	18*	3.28	28*	1.61
24	13*	3.46	24*	1.21

*Day 1 answers were not tabulated for this question because subjects completed the BPI on Day 1 within hours of their first dose of study drug. Data were not imputed by BOCF during the taper-off periods, days 22-24.

Table 15 Right Now Pain Scores (Scale: 0-10) By Treatment Group

Double-Blind Mean Right Now Pain Scores by Group by Day (BOCF)				
	Placebo		ATNC05	
Treatment Day	N (n BOCF)	Ave.	N (n BOCF)	Ave.
Baseline Period Mean	34	5.42	44	5.53
1	34	4.65	44	2.77
2	34 (1)	4.58	44 (0)	2.82
3	34 (1)	4.50	44 (2)	2.94
4	34 (1)	4.32	44 (2)	2.76
5	34 (2)	4.38	44 (2)	2.76
6	34 (3)	4.21	44 (1)	2.22
7	34 (3)	4.33	44 (2)	2.35
8	34 (3)	4.64	44 (2)	2.49
9	34 (4)	4.56	44 (5)	2.18
10	34 (4)	4.38	44 (3)	1.94
11	34 (4)	4.50	44 (3)	2.06
12	34 (4)	4.38	44 (2)	1.76
13	34 (4)	4.70	44 (2)	1.69
14	34 (4)	4.59	44 (3)	1.74
15	34 (4)	4.50	44 (4)	1.68
16	34 (4)	4.53	44 (5)	1.72
17	34 (4)	4.35	44 (6)	1.79
18	34 (4)	4.44	44 (6)	1.70
19	34 (4)	4.47	44 (7)	1.75
20	34 (4)	4.41	44 (7)	1.83
21	34 (5)	4.45	44 (7)	1.90
22	26*	4.42	36*	1.03
23	18*	3.22	28*	1.26
24	13*	3.38	24*	1.08

*Day 1 answers were not tabulated for this question because subjects completed the BPI on Day 1 within hours of their first dose of study drug. Data were not imputed by BOCF during the taper-off periods, days 22-24.

Table 16 Night Pain Scores (Scale: 0-10) By Treatment Group

Double-Blind Mean Night Pain Scores by Group by Day (BOCF)				
	Placebo		ATNC05	
Treatment Day	N (n BOCF)	Ave.	N (n BOCF)	Ave.
Baseline Period Mean	34	5.71	44	6.04
1*				
2	34 (1)	4.84	44 (0)	3.43
3	34 (1)	4.78	44 (2)	3.47
4	34 (1)	4.84	44 (2)	3.26
5	34 (2)	4.71	44 (2)	3.26
6	34 (3)	4.44	44 (1)	2.70
7	34 (3)	4.70	44 (2)	2.91
8	34 (3)	4.84	44 (2)	2.81
9	34 (4)	4.60	44 (5)	2.38
10	34 (4)	4.54	44 (3)	2.19
11	34 (4)	4.66	44 (3)	2.49
12	34 (4)	4.60	44 (2)	2.10
13	34 (4)	4.80	44 (2)	2.08
14	34 (4)	4.77	44 (3)	2.03

15	34 (4)	4.66	44 (4)	2.05
16	34 (4)	4.69	44 (5)	1.91
17	34 (4)	4.63	44 (6)	2.05
18	34 (4)	4.72	44 (6)	2.01
19	34 (4)	4.81	44 (7)	2.09
20	34 (4)	4.54	44 (7)	2.11
21	34 (5)	4.63	44 (7)	2.16
22	26*	4.27	36*	1.28
23	18*	3.50	28*	1.64
24	13*	3.54	24*	1.25

*Day 1 answers were not tabulated for this question because subjects completed the BPI on Day 1 within hours of their first dose of study drug. Data were not imputed by BOCF during the taper-off periods, days 22-24.

[00244] The Open Phase enrolled 27 subjects who had not responded to the initial treatment during the Study Drug Phase. Subjects received study drug twice daily for three to four weeks.

[00245] The Open Phase results are summarized in Table 17 and in Figure 14. Table 17 tabulates the daily improvement of pain scores in the open phase and the drawing in Figure 14 graphs the Open Phase Relief by Day. It shows that back pain symptoms were significantly lower in the open phase period compare with baseline measurement. Subjects who did not respond in the blinded study drug period, presumably the subjects who might have received the placebo in the blinded phase of the trial, were given the study drug containing low dose naltrexone and clonidine 2.25mg/0.025mg respectively for three weeks. Improvement begins starting the second day. The drug impact increases as time progress showing approximately a 5 point (on a scale of 0-10 with 10 being most severe) improvement compared to baseline by the end of the study.

Table 17 Daily Improvement of Average Pain Scores Open Phase

Days in Open Phase	Count	Treatment with study drug compare to base line	Standard Deviation	P(Treatment>Placebo)
Day 2 Of Open Phase	22	-3.94	0.18	<.001
Day 3 Of Open Phase	22	-4.05	0.15	<.001
Day 4 Of Open Phase	21	-4.16	0.15	<.001
Day 5 Of Open Phase	21	-4.23	0.15	<.001
Day 6 Of Open Phase	22	-4.27	0.15	<.001
Day 7 Of Open Phase	21	-4.29	0.15	<.001
Day 8 Of Open Phase	21	-4.32	0.15	<.001
Day 9 Of Open Phase	20	-4.35	0.15	<.001
Day10 Of Open Phase	20	-4.42	0.15	<.001

Day11 Of Open Phase	19	-4.50	0.15	<.001
Day12 Of Open Phase	19	-4.57	0.15	<.001
Day13 Of Open Phase	17	-4.62	0.16	<.001
Day14 Of Open Phase	16	-4.65	0.15	<.001
Day15 Of Open Phase	15	-4.71	0.16	<.001
Day16 Of Open Phase	14	-4.73	0.17	<.001
Day17 Of Open Phase	14	-4.73	0.17	<.001
Day18 Of Open Phase	10	-4.72	0.17	<.001
Day19 Of Open Phase	18	-4.71	0.17	<.001
Day20 Of Open Phase	18	-4.69	0.18	<.001
Day21 Of Open Phase	9	-4.68	0.19	<.001
Day22 Of Open Phase	8	-4.69	0.19	<.001
Day23 Of Open Phase	3	-4.68	0.21	<.001
Day24 Of Open Phase	3	-4.69	0.22	<.001
Day25 Of Open Phase	3	-4.71	0.23	<.001
Day26 Of Open Phase	2	-4.74	0.25	<.001
Day27 Of Open Phase	1	-4.78	0.27	<.001
Day28 Of Open Phase	1	-4.80	0.29	<.001
Day29 Of Open Phase	1	-4.82	0.30	<.001

[00246] Figure 14 shows an average 4.5 point drop in pain score during the Open Phase.

[00247] The clinical trial found that the opioid/TLR4 antagonist naltrexone, in combination with the alpha two adrenergic receptor agonist clonidine, treated and reversed chronic pain conditions, including chronic back pain, chronic headaches, including migraines and chronic joint pain. Additionally, the study drug reversed long standing trigeminal neuralgia, tactile allodynia, vulvodynia and IBS.

[00248] The Oswestry Disability Index is considered the gold standard for assessing the disability level of back pain for those, who suffer back pain, to assess their disability level. The drawing in Figure 15 shows the change in the Oswestry Disability Index of the cervical pain over time in the study drug group versus the placebo group. The drawing in Figure 16 shows the change in the Oswestry Disability Index of the lumbar pain over time in the study drug group versus the placebo group.

[00249] The Pittsburgh Insomnia Rating Scale (PIRS) was developed by the University of Pittsburgh's Western Psychiatric Institute and Clinic to assess insomnia. The Total Score is a sum of all nineteen responses to questions on the questionnaire with possible values of zero to sixty. Higher scores indicate greater degree of insomnia. The drawing in Figure 17 shows the change in the Pittsburgh Insomnia Rating Scale over time in the study drug group versus the placebo group. The Study Drug treatment group showed statistically significant improvement over the placebo group in PIRS 20 Total Score at Week 1 and at Week 3.

[00250] The drawing in Figure 18 graphs average the Roland-Morris Low Back Pain and Disability Questionnaire (RMQ) scores for the Study Drug Group and Placebo at Baseline, Week 1, and Week 3. The Roland-Morris Questionnaire is a self-administered disability measure in which greater levels of disability are reflected by higher numbers on a 24-point scale. The RMQ has been shown to yield reliable measurements, which are valid for inferring the level of disability, and to be sensitive to change over time for groups of patients with lower back pain.

[00251] From the clinical trial it is concluded that the opioid/TLR4 antagonist naltrexone, in combination with the alpha-2 adrenergic receptor agonist clonidine, treated and reversed the chronic pain conditions chronic back pain, chronic headaches including migraines and chronic joint pain. Additionally, the study drug reversed long standing trigeminal neuralgia, vulvodynia and irritable bowel syndrome.

Example 2: A Pharmaceutical Composition Comprising Opioid/TLR4 Antagonists and Acetyl-Para-Aminophenol (APAP) for use in treatment of Pain.

[00252] Naltrexone and acetyl-para-aminophenol were evaluated alone and in combination on a human subject with the purpose of finding whether or not a combination of the two compounds offers a synergistic advantage for the pain treatment effect comparing the amounts used weight to weight.

[00253] The components of the combination were administered to a subject as follows, the naltrexone dose administered by itself was 4.5mg and the acetyl-para-aminophenol dose administered by itself was 1000mg, The naltrexone/acetyl-para-aminophenol combination dose was 2.25mg/325 respectively. The pain treatment effect of naltrexone and acetyl-para-aminophenol was evaluated two hours post-dose.

[00254] To determine synergy, the amounts of naltrexone and acetyl-para-aminophenol administered alone were compared to the combination combined amounts. For

proper weight to weight (W/W) comparison between naltrexone and acetyl-para-aminophenol an adjustment for the higher potency of naltrexone was made based on the dose of each compound given by itself. Naltrexone is 222 times more potent than acetyl-para-aminophenol (1000/4.5=222). Naltrexone and acetyl-para-aminophenol were administered at fixed dose ratios of 3:200 to a human subject afflicted with neuropathic back pain.

[00255] Table 18 illustrates the naltrexone/acetyl-para-aminophenol ratio that exhibit weight to weight (W/W) synergy in a human subject. The 3:200 combinations represent a 2-fold lower dose of naltrexone and 3-fold lower dose of acetyl-para-aminophenol when administered together.

Table 18: Naltrexone/acetyl-para-aminophenol Ratio and Weight to Weight (W/W) Synergy

Ratio	Naltrexone mg	acetyl-para-aminophenol e mg	naltrexone Potency Adjustment (x222)	% reversal of pain	Total dose Naltrexone + Adjusted acetyl-para-aminophenol mg	Interaction
4.5:0	4.50	-	1000	100	1000	-
0:800	-	1000		50	1000	-
1:90	2.25	325	500	100	500+325=825	Synergy

[00256] To summarize the naltrexone/acetyl-para-aminophenol synergistic effect, the disclosure teaches that the optimal contemplated naltrexone, or a pharmaceutically acceptable salt or solvate thereof, to acetyl-para-aminophenol, combination dosage ratio range is 3:200, and this dosage ratio exhibits synergy of weight to weight proportion.

Example 3: A Pharmaceutical Composition Comprising Opioid/TLR4 Antagonists and a cyclooxygenase (COX) inhibitor for use in treatment of Pain.

[00257] Naltrexone and ibuprofen were evaluated alone and in combination on a human subject with the purpose of finding whether or not a combination of the two compounds offers a synergistic advantage for the pain treatment effect comparing the amounts used weight to weight.

[00258] The components of the combination were administered to a subject as follows: the naltrexone dose administered alone was 4.5mg, and the ibuprofen dose administered alone was 800mg. The dose of the naltrexone/ibuprofen combination was 2.25mg/200, respectively. The pain treatment effect was evaluated one hour post-dose.

[00259] To determine synergy, the amounts of naltrexone and ibuprofen administered alone were compared to the combination combined amounts. For proper weight to weight (W/W) comparison between naltrexone and ibuprofen an adjustment for the higher potency of naltrexone was made based on the dose of each compound given by itself. Naltrexone is 178 times more potent than ibuprofen (800/4.5=178). Naltrexone and ibuprofen were administered at fixed dose ratios of 1:90 to a human subject afflicted with neuropathic back pain.

[00260] Table 19 illustrates the naltrexone/ibuprofen ratio that exhibit weight to weight (W/W) synergy in a human subject. The 1:90 combinations represent a 2-fold lower dose of naltrexone and 4-fold lower dose of ibuprofen when administered together.

Table 19: Naltrexone/ibuprofen Ratios and Weight to Weight (W/W) Synergy

Ratio	Naltrexone mg	Ibuprofen e mg	Naltrexone Potency Adjustment (x178)	% reversal of pain	Total dose Naltrexone + Adjusted ibuprofen mg	Interaction
4.5:0	4.50	-	800	100	800	-
0:800	-	800		50	800	-
1:90	2.25	200	400.00	100	200+400=600	Synergy

[00261] To summarize the naltrexone/ibuprofen synergistic effect, the disclosure teaches that the optimal contemplated naltrexone to ibuprofen combination dosage ratio is 1:90. This dosage ratio exhibits synergy of weight to weight proportion.

Example 4: A Pharmaceutical Composition Comprising Opioid/TLR4 Antagonists and an Alpha 2 Delta Ligand for use in treatment of Pain.

[00262] Naltrexone and Gabapentin or Pregabalin were evaluated alone and in combination on a human subject with the purpose of finding whether or not a combination of the two compounds offers a synergistic advantage for the pain treatment effect comparing the amounts used weight to weight.

[00263] The components of the combination were administered to a subject as follows: the naltrexone dose administered alone was 4.5mg, and the Gabapentin and pregabalin dose administered alone was 1800mg and 300mg respectively. The dose of the naltrexone/ Gabapentin combination was 2.25mg/300 respectively and the naltrexone/pregabalin

combination was 2.25mg/150 respectively, the pain treatment effect was evaluated one hour post-dose.

[00264] To determine synergy, the amounts of naltrexone and Gabapentin or pregabalin administered alone were compared to the combination combined amounts. For proper weight to weight (W/W) comparison between naltrexone and Gabapentin or pregabalin an adjustment for the higher potency of naltrexone was made based on the dose of each compound given by itself. Naltrexone is 200 times more potent than gabapentin (200/4.5=200). Naltrexone and Gabapentin were administered at fixed dose ratios of 1:50-1:125 to a human subject afflicted with neuropathic back pain. The 1:125 combinations represent a 2-fold lower dose of naltrexone and a 6-fold lower dose of Gabapentin

[00265] Table 20 illustrates the naltrexone/Gabapentin ratio that exhibit weight to weight (W/W) synergy in a human subject. The 1:50 combinations represent a 2-fold lower dose of naltrexone and 18 fold lower dose of Gabapentin. The 1:125 combinations represent a 2-fold lower dose of naltrexone and 6-fold lower dose of Gabapentin.

Table 20: Naltrexone/ Gabapentin Ratios and Weight to Weight (W/W) Synergy

Ratio	Naltrexone mg	Gabapentin mg	Naltrexone Potency Adjustment (x200)	% reversal of pain	Total dose Naltrexone + Adjusted Gabapentin mg	Interaction
4.5:0	4.50	-	900.00	100	900	-
0:900	-	1800	-	50	1800	-
1:50	2.25	100	450.00	100	100+450=550	Synergy
1:125	2.25	300	450.00	100	300+450=850	Synergy

[00266] Table 21 illustrates the naltrexone/pregabalin ratio that exhibit weight to weight (W/W) synergy in a human subject. The 1:30 combinations represent a 2-fold lower dose of naltrexone and 4 fold lower dose of pregabalin when administered together. The 1:50 combinations represent a 2-fold lower dose of naltrexone and 2.4 fold lower dose of Pregalbin when administered together.

Table 21: Naltrexone/pregabalin Ratios and Weight to Weight (W/W) Synergy

Ratio	Naltrexone mg	pregabalin mg	Naltrexone Potency Adjustment (x75)	% reversal of pain	Total dose Naltrexone + Adjusted pregabalin mg	Interaction
4.5:0	4.50	-	300.00	100	300	-

0:900	-	300	-	50	300	-
1:30	2.25	75	150.00	100	150+75=225	Synergy
1:40	2.25	100	150.00	100	150+100=250	Synergy
1:50	2.25	125	150.00	100	150+125=275	Synergy

Example 5: A Pharmaceutical Composition Comprising Opioid/TLR4 Antagonists and Dextro Enantiomers Thereof for use in treatment of Pain.

[00267] The clinical trials demonstrated that adverse effects were minimal and transient with no indication of addiction. There were no reports of tolerance or withdrawal symptoms.

[00268] The following tables and graphs demonstrate safety of naltrexone for the treatment of pain. The data was obtained from a 78 subject clinical trial where naltrexone 2.25 mg/clonidine 0.025 mg were administered twice daily. Table 22 tabulates the change of the pulse from baseline by visit of the study drug group and the placebo group. The drawing in Figure 19 graphs the change in the pulse from baseline of the study drug group versus the placebo group. Table 23 tabulates the change of the systolic blood pressure (BP) from baseline by visit of the study drug group and the placebo group. The drawing in Figure 20 graphs the change in the systolic blood pressure (BP) from baseline of the study drug group versus the placebo group. Table 24 tabulates the change of the diastolic blood pressure (BP) from baseline by visit of the study drug group and the placebo group. The drawing in Figure 21 graphs the change in the diastolic blood pressure (BP) from baseline of the study drug group versus the placebo group The data shows that there were no clinically significant changes in pulse, systolic blood pressure and diastolic blood pressure over a three to four week treatment, either during treatment period or Open Phase (OP).

Table 22 Pulse Change from Baseline by Visit

Mean Change in Pulse From From Pre-Initial Dose In Double-Blind and Open-Label Phase						
	Placebo		ATNC05		Open-Label Phase	
	N	**Mean (SE)**	**N**	**Mean (SE)**	**N**	**Mean (SE)**
Pre-Initial Dose	34	0.00 (0.00)	44	0.00 (0.00)	27	0.00 (0.00)
Post Initial Dose	34	-0.32 (0.71)	44	0.80 (0.80)	28	0.07 (0.83)
Week 1	32	0.81 (0.62)	43	0.98 (1.06)	25	-0.61 (0.93)
Week 3	30	0.07 (1.20)	41	-0.44 (0.86)	23	0.35 (1.07)
End of Taper-Off Phase	31	0.00 (0.00)	42	0.00 (1.10)	24	0.00 (0.00)

Table 23 Systolic BP Change from Baseline by Visit

Mean Change in Systolic Blood Pressure From Pre-Initial Dose In Double-Blind and Open-Label Phase						
	Placebo		ATNC05		Open-Label Phase	
	N	**Mean (SE)**	**N**	**Mean (SE)**	**N**	**Mean (SE)**
Pre-Initial Dose	34	0.00 (0.00)	44	0.00 (0.00)	27	0.00 (0.00)
Post Initial Dose	34	-0.26 (1.18)	44	0.00 (1.63)	28	-1.86 (1.53)
Week 1	32	0.94 (1.56)	43	-1.58 (1.19)	25	-0.87 (2.06)
Week 3	30	1.59 (2.30)	41	-0.39 (1.58)	23	-2.43 (1.94)
End of Taper-Off Phase	4	-9.25 (11.69)	12	-2.83 (3.97)	2	1.00 (15.00)

Table 24 Diastolic Change from Baseline by Visit

Mean Change in Diastolic Blood Pressure From Pre-Initial Dose In Double-Blind and Open-Label Phase						
	Placebo		ATNC05		Open-Label Phase	
	N	**Mean (SE)**	**N**	**Mean (SE)**	**N**	**Mean (SE)**
Pre-Initial Dose	34	0.00 (0.00)	44	0.00 (0.00)	27	0.00 (0.00)
Post Initial Dose	34	0.91 (0.61)	44	0.68 (0.90)	28	0.11 (1.17)
Week 1	32	2.94 (0.90)	43	-0.56 (0.93)	25	0.17 (1.29)
Week 3	30	2.34 (1.66)	41	0.83 (1.09)	23	0.61 (1.16)
End of Taper-Off Phase	4	-3.50 (6.24)	12	-1.83 (2.65)	2	5.00 (5.00)

Example 6: Validation of Use of Dextro Enantiomer of Naltrexone

[00269] The following demonstrates adverse effects in two human subjects who were dosed with naltrexone alone: their experience validates the need to use the dextro enantiomer of naltrexone because of the side effects they experienced.

The Case of a Human Subject using a low dose of Naltrexone (2 mg/12 hours) for treatment of cervical pain.

[00270] A human subject used naltrexone in a low dose of 2 mg twice daily for cervical pain. The subject experienced a significant relief of his pain however he discontinued using the drug after 2 weeks because he was unable to tolerate the side effects that included anxiety and irritability.

[00271] Table 25 tabulates the change of pain and side effects for this patient (on Naltrexone 2mg twice daily) by day. The drawing in Figure 22 graphs the change of pain and side effects over the same period. Table 25 and Figure 22 show naltrexone's effect on pain

and side effects. The pain treatment effect of naltrexone continued for a few days after discontinuation. The side effects resolved within one day of treatment discontinuation.

Table 25 Pain and Side Effects By Day (Naltrexone 2mg/day twice daily)

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Cervical Pain	8	3	3	3	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	4	4	8
Anxiety & Irritability	0	6	6	6	6	6	6	6	6	6	6	6	6	6	6	0	0	0	0	0	0	0	0	0
Naltrexone Daily Dose	0	4	4	4	4	4	4	4	4	4	4	4	4	4	4	0	0	0	0	0	0	0	0	0

The Case of a Human Subject using Naltrexone (12.5 mg/day) for treatment of cervical pain.

[00272] A second subject used 12.5 mg per day of naltrexone for cervical pain. Table 26 tabulates the change of pain and enjoyment of life for this patient (on Naltrexone 12.5mg/day) by day. The drawing in Figure 23 graphs the change of pain and enjoyment of life for this patient by day. As with the subject above (on low-dose Naltrexone), he too experienced relief of his pain, but this patient (on 12.5 mg Naltrexone/day) elected to discontinue the treatment after 10 days because of adverse effects. At this medium dose, naltrexone caused interference with his ability to experience pleasure, particularly from food and alcohol. In addition, his libido was reduced, and he stated that he felt "blah".

Table 26 Example 2 Pain and Side Effects by Day (Naltrexone 12.5mg/day)

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Cervical Pain	6	3	3	3	3	3	3	3	3	3	3	3	3	3
Enjoyment of Life	10	1	1	1	1	1	1	1	1	1	1	1	1	10
Naltrexone Daily Dose	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	0	0

Example 7: Validation of Use of Dextro Enantiomer of Naltrexone

The Investigational product: ATNC05

[00273] ATNC05 is the code name for the investigational product discussed in this application. It consists of capsules containing naltrexone 2.25 mg and clonidine 0.025 mg to be administered orally for neuropathic lower back pain as 1 to 2 capsules taken twice daily.

[00274] Naltrexone was approved for opioid addiction in 1984 and for alcohol dependence in 1995. A dose of 50 mg once daily is recommended for most patients. Clonidine, a direct acting alpha 2 adrenergic agonist and an imidazoline receptor agonist, was

approved for hypertension in 1974 and in an extended release form for the treatment of attention deficit hyperactivity disorder in 2009. The therapeutic doses most commonly employed for clonidine have ranged from 0.2 mg to 0.6 mg per day given in divided doses.

[00275] ATNC05 represents a low dose of naltrexone and clonidine. At the anticipated therapeutic dose of ATNC05, two capsules per day, the dose of naltrexone is 9% of the recommended dose for the approved indication, and the dose of clonidine is 8% (0.05 mg/0.6 mg) of the upper range of the common therapeutic dose for the approved indications. In some cases, as demonstrated by the preliminary data, a higher dose of ATNC05 was needed. At a dose of four capsules per day, the doses of naltrexone and clonidine are 18% and 16% of the approved doses, respectively.

[00276] Dextro-naltrexone ((+)-naltrexone) blocks only the TLR-4 while not blocking the morphine receptors. Therefore, the side effects arising from blocking of the morphine receptors by the racemic naltrexone (a mix of (-)-naltrexone and (+)-naltrexone), which are caused by (-)-naltrexone, are eliminated by use of (+)-naltrexone.

Mechanism of Action and Scientific Rationale of the Investigational Product

Preliminary Clinical Results with ATNC05 for Neuropathic Lower Back Pain

[00277] A Phase II study was conducted using ATNC05 for neuropathic back pain under IND 110491. The Clinical Study Report for this trial was submitted to the Division of Anesthesia, Analgesia, and Addiction Products on July 7, 2013. The study was a 78-subject double-blind placebo-controlled randomized proof-of-concept clinical trial. Following a one-week Baseline period, subjects were administered ATNC05 or placebo for three weeks. The study had an open-label extension phase for non-responders in the double-blind phase, during which all subjects received ATNC05 with no comparator. Missing data were imputed by the Baseline Observation Carried Forward (BOCF) methodology.

Primary Endpoint

[00278] The primary end point for the study was the change from baseline to Week 3 in Average Pain. For the placebo group, pain was reduced by 0.91 points. For the ATNC05 arm, pain was reduced by 3.69 points. The treatment effect size is 2.78 ± 1.351 (99% confidence interval), which is significant, with $p<0.00001$. The analysis is summarized in Table 27.

Table 27: Primary End Point - Change in Average Pain in Week 3

Imputation	Treatment	N	Mean Average Pain Intensity – Week 3

			Baseline	WK3	Change (Standard Error)	p-value
BOCF	Placebo	34	5.50	4.59	-0.91 (0.36)	0.00000
BOCF	ATNC05	44	5.55	1.86	-3.69 (0.34)	

Groups	All Groups in Double Blind Phase
Method	t-Test, 2-sided
P Value	<0.00001
Mean Difference	-2.78
Standard Error	± 0.35
99% Confidence Interval	(-4.131 to -1.429)

Immediate Effect of ATNC05 on Neuropathic Back Pain

[00279] As part of the post-initial dose office assessment, subjects reported their Right Now Pain Severity score one to four hours after the initial dose (on average, two hours). The change from the baseline period mean was compared. For the placebo group, pain was reduced by 1.96. For the ATNC05 arm, pain was reduced by 3.88. The treatment effect size is 1.92 ± 1.488 (99% confidence interval), which is significant, with p<0.00001 (Figure 24, Table 28).

Table 28: Mean change from base line to Post-Initial Dose in Right Now Pain Intensity

			Mean Right Now Pain Intensity – Post-Initial Dose			
Imputation	Treatment	N	Baseline	WK1	Change (Standard Error)	p-value
BOCF	Placebo	34	6.61	4.37	-1.96 (0.39)	0.00000
BOCF	ATNC05	44	6.60	2.44	-3.88 (0.38)	

Groups	All Groups in Double Blind Phase
Method	t-Test, 2-sided
P Value	<0.00001
Mean Difference	-1.92
Standard Error	± 0.39
99% Confidence Interval	(-3.408 to -0.432)

[00280] This indicates that ATNC05 causes immediate significant relief of neuropathic back pain. By contrast, other treatments for neuropathic lower back pain take weeks to provide relief.

Subject Global Impression of Improvement (PGI-I)

[00281] The Patient Global Impression – Improvement (PGI-I) asks subjects to report "what percent [pain] relief has the study medication provided," compared to the subject's pain before treatment. The item is scored on a percentage scale, where 0% corresponds to no relief, and 100% corresponds to total relief. Subjects with missing data were not imputed because there was no baseline measure of PGI-I.

[00282] Figure 25 shows the response rates as measured by PGI-I during Week 3 during both the double-blind and open-label phases. The sections on the x-axis indicate ranges of improvement. The columns in the charts are a histogram of the number of subjects with a mean PGI-I in Week 3 in each range. The lines indicate the cumulative distribution of the subjects; it shows the percentage of subjects whose score is in that range or one greater.

[00283] Table 29 shows the response rates across study phases. The percent indicates the percentage of subjects reporting improvement of the threshold or greater.

Table 29: Summary of Response Rates based on Week 3 PGI-I

Response Threshold of Improvement	ATNC05 Response Rate (n=40)	Placebo Response Rate (n=30)	Open-Label Response Rate (n=23)
50%	35/40 (87.50%)	6/30 (20.00%)	22/23 (95.70%)
70%	33/40 (82.50%)	6/30 (20.00%)	20/23 (87.00%)
90%	28/40 (70.00%)	6/30 (20.00%)	12/23 (52.20%)

[00284] ATNC05 subjects had a high improvement in PGI-I. 7 out of 10 of ATNC05 subjects reported 90% or greater improvement, 8 out of 10 subjects reported 70% or greater improvement, and nearly 9 out of 10 subjects reported of 50% or greater improvement during Week 3 of the double-blind phase. Subjects showed even stronger improvement in the Open-Label phase, where nearly 9 out of 10 subjects reported 70% or greater improvement, and 95.7% of subjects reported improvement of 50% or greater. By comparison, 2 out of 10

placebo subjects reported 70% or greater improvement, consistent with the placebo effect size observed in other studies.

[00285] Of the 40 ATNC05 subjects who completed the double-blind phase, 4 subjects were non-responders. Three of these subjects responded to ATNC05 in the open-label phase. It is likely that these subjects would have had a faster response to ATNC05 with a higher dose.

[00286] All 18 placebo subjects (non-responders in the double-blind phase) who completed the open-label phase responded to ATNC05. This indicates a response rate of 98.2% (57/58) among the subjects who completed a three-week treatment period with ATNC05 in either double-blind or open-label phase.

Brief Pain Inventory Measures

[00287] The following tables and charts are excerpted from the Clinical Study Report in order to demonstrate that ATNC05 has a significant treatment effect and represents a substantial improvement when compared to published data on available therapies.

BPI-Severity Measures

[00288] The groups had nearly identical Baseline Period Mean Average Pain Scores; 5.50 for placebo subjects and 5.55 for ATNC05 subjects. On the second day of the treatment period, subjects receiving ATNC05 already showed a large and statistically significant improvement in Average Pain scores. On every day of the treatment period, subjects on ATNC05 reported a statistically significant treatment effect compared to the placebo group. On each day during the main treatment period of Study Days 2-21, the p-value was less than 0.0001.

[00289] Table 30 shows the daily self-reported mean Average Pain Scores for subjects starting on Study Day 2 during the Double-Blind phase (Average Pain is measured over the previous 24 hours, and taking this measure on Day 1 would have included time in the Baseline Period; Day 1 data were discussed earlier). The p-value column shows the result of a Student's t-test comparing the Placebo Treatment Effect and the ATNC05 Treatment Effect. Please note that data were not imputed by BOCF during the taper-off periods (days 22-24).

[00290] Figure 26 shows the daily mean Average Pain Scores by day with standard error bars. The Baseline Period Mean is shown on the chart as Day 0.

[00291] Table 31 shows the mean weekly pain scores for each of the five back pain severity measures. For each pain measurement and period, the p-value is based on a Student's t-test comparing the groups' mean change in the score from the Baseline Period Mean for that score. For all groups in all time-frames, ATNC05 subjects had significantly greater improvement than the placebo subjects. In the main treatment period (Week 1, Week 2, and Week 3), the improvement has a p-value of <0.00001.

[00292] Figure 27 shows the summary of weekly pain severity scores in graphical form for subjects in the placebo treatment group. It shows the five severity measures for each week of the treatment period.

[00293] Figure 28 shows the same summary graph for subjects receiving ATNC05. As illustrated, placebo group subjects do not show a strong trend of improvement, while the ATNC05 subjects show a strong downward trend in all the pain severity measures.

Table 30: Mean Average Pain Scores of ATNC05 and Placebo by Day (BOCF)

Study Day	N of Subjects Receiving Placebo (n of subjects Imputed by BOCF)	N of Subjects Receiving ATNC05 (n of subjects Imputed by BOCF)	Mean (SE) Average Pain Score for Placebo Subjects	Mean (SE) Average Pain Score for ATNC05 Subjects	Placebo Treatment Effect	ATNC05 Treatment Effect	p-value
2	34 (1)	44 (0)	4.77 (0.33)	3.09 (0.29)	-0.72	-2.49	0.00029
3	34 (1)	44 (2)	4.63 (0.33)	3.07 (0.29)	-0.87	-2.51	0.00072
4	34 (1)	44 (2)	4.74 (0.34)	2.77 (0.29)	-0.75	-2.81	0.00003
5	34 (2)	44 (2)	4.59 (0.33)	2.84 (0.31)	-0.90	-2.74	0.00020
6	34 (3)	44 (1)	4.51 (0.35)	2.31 (0.28)	-0.98	-3.27	0.00001
7	34 (3)	44 (2)	4.60 (0.37)	2.48 (0.29)	-0.90	-3.10	0.00003
8	34 (3)	44 (2)	4.83 (0.38)	2.59 (0.32)	-0.66	-2.99	0.00003
9	34 (4)	44 (5)	4.69 (0.37)	2.24 (0.32)	-0.81	-3.33	0.00000
10	34 (4)	44 (3)	4.66 (0.36)	2.14 (0.31)	-0.84	-3.44	0.00000
11	34 (4)	44 (3)	4.66 (0.34)	2.14 (0.32)	-0.84	-3.44	0.00000
12	34 (4)	44 (2)	4.66 (0.36)	1.89 (0.33)	-0.84	-3.69	0.00000
13	34 (4)	44 (2)	4.78 (0.39)	1.86 (0.32)	-0.72	-3.72	0.00000
14	34 (4)	44 (3)	4.86 (0.42)	1.84 (0.33)	-0.63	-3.74	0.00000
15	34 (4)	44 (4)	4.69 (0.41)	1.89 (0.32)	-0.80	-3.69	0.00000
16	34 (4)	44 (5)	4.61 (0.41)	1.82 (0.34)	-0.89	-3.76	0.00000
17	34 (4)	44 (6)	4.69 (0.41)	1.86 (0.35)	-0.80	-3.72	0.00000
18	34 (4)	44 (6)	4.55 (0.39)	1.93 (0.34)	-0.95	-3.65	0.00000
19	34 (4)	44 (7)	4.58 (0.40)	1.84 (0.36)	-0.92	-3.74	0.00000
20	34 (4)	44 (7)	4.43 (0.35)	1.93 (0.37)	-1.07	-3.65	0.00001
21	34 (5)	44 (7)	4.59 (0.39)	1.93 (0.36)	-0.90	-3.65	0.00000

22	26*	36*	4.42 (0.45)	1.14 (0.27)	-1.07	-4.44	0.00000
23	18*	28*	3.28 (0.56)	1.61 (0.39)	-2.22	-3.97	0.02064
24	13*	24*	3.46 (0.69)	1.21 (0.31)	-2.03	-4.37	0.00820

Table 31: Summary of Back Pain Severity Measures by Week (BOCF)

		Baseline	Week 1	Week 2	Week 3	Taper-Off
Worst Pain	Placebo	6.61	5.19	5.36	5.25	4.89
	ATNC05	6.65	3.33	2.65	2.28	1.84
	p-value		0.00000	0.00000	0.00000	0.00000
Least Pain	Placebo	4.91	4.19	4.25	4.23	4.08
	ATNC05	4.64	2.16	1.66	1.41	0.93
	p-value		0.00000	0.00000	0.00000	0.00001
Average Pain	Placebo	5.50	4.62	4.72	4.59	4.19
	ATNC05	5.55	2.57	2.08	1.86	1.30
	p-value		0.00000	0.00000	0.00000	0.00003
Right Now Pain	Placebo	6.61	4.37	4.52	4.44	4.41
	ATNC05	6.60	2.44	1.98	1.72	1.08
	p-value		0.00000	0.00000	0.00000	0.00066
Night Pain	Placebo	6.61	4.68	4.68	4.66	4.33
	ATNC05	6.65	2.94	2.28	2.02	1.32
	p-value		0.00000	0.00000	0.00000	0.00000

BPI-Interference Measures

[00294] Table 32 shows the mean weekly pain scores for each of the nine back pain interference measures. For each pain measurement and period, the p-value is based on a Student's t-test comparing the groups' mean change in the score from the Baseline Period Mean for that score.

[00295] Figure 29 shows the summary of weekly pain interference scores in graphical form for subjects in the placebo treatment group. Figure 30 shows the same summary graph for subjects receiving ATNC05. As illustrated, placebo group subjects do not show a strong trend of improvement, while the ATNC05 subjects show a strong downward trend in all the pain interference measures.

Table 32: Summary of Back Pain Interference Measures by Week (BOCF)

		Baseline	Week 1	Week 2	Week 3	Taper-Off
General Activity	Placebo	6.61	4.56	4.63	4.71	4.64
	ATNC05	6.61	2.52	1.91	1.70	0.90
	p-value		0.00000	0.00000	0.00000	0.00018
Mood	Placebo	6.61	3.81	3.83	3.92	4.37
	ATNC05	6.67	2.10	1.58	1.41	0.77
	p-value		0.00000	0.00005	0.00002	0.00021
Walking Ability	Placebo	5.02	4.17	4.18	4.28	4.49
	ATNC05	4.97	2.44	1.84	1.69	0.75
	p-value		0.00000	0.00001	0.00000	0.00000
Normal Work, Including House Work	Placebo	5.47	4.41	4.46	4.47	4.58
	ATNC05	5.62	2.58	1.95	1.68	0.89
	p-value		0.00000	0.00000	0.00000	0.00001
Relationships with Other People	Placebo	6.61	3.35	3.63	3.61	4.16
	ATNC05	6.52	1.78	1.35	1.23	0.98
	p-value		0.00591	0.00008	0.00003	0.00074
Sleep Quality	Placebo	5.77	4.46	4.41	4.38	4.54
	ATNC05	5.85	2.71	2.07	1.80	1.18
	p-value		0.00000	0.00000	0.00000	0.00044
Enjoyment of Life	Placebo	5.15	4.00	4.18	4.33	4.65
	ATNC05	5.30	2.13	1.68	1.58	1.35
	p-value		0.00000	0.00001	0.00000	0.00104
Standing Ability	Placebo	6.61	4.31	4.33	4.38	4.38
	ATNC05	6.63	2.30	1.71	1.60	1.11
	p-value		0.00000	0.00000	0.00000	0.00081
Sitting Ability	Placebo	5.03	4.25	4.24	4.33	4.36
	ATNC05	5.03	2.37	1.69	1.53	1.11
	p-value		0.00000	0.00000	0.00000	0.00000

Oswestry Disability Index Results

[00296] The Oswestry Disability Index (ODI) is a 10 item questionnaire which measures permanent functional disability caused by back pain. It was measured during each office visit, and is measured on a scale of 0 to 100.

[00297] Figure 31 shows the average ODI score for each treatment group during the Baseline Period, and at the Week 1 and Week 3 visits. The Open-Label results are shown for Week 1 and Week 3. Double-Blind period were imputed by BOCF when needed. During the baseline period, both Placebo and ATNC05 subjects had mean scores around 40 points. By

Week 3, placebo subjects improved by 4.9 points, while ATNC05 subjects dropped by 27.5 points. In both Week 1 and Week 3, the difference between the placebo and ATNC05 groups was statistically significant, with p-values of 0.00005 and <0.00001, respectively.

Roland-Morris Low Back Pain and Disability Questionnaire Results

[00298] The Roland-Morris Low Back Pain and Disability Questionnaire is a 24 item questionnaire which asks the subjects to choose statements about back pain which apply to them. The statements cover a variety of impairments caused by back pain. It was measured during each office visit, and is measured on a scale of 0 to 24 (where each statement the subject agrees with increases the score by one).

[00299] Figure 32 shows the average Roland-Morris score for each treatment group during the Baseline Period, and at the Week 1 and Week 3 visits. The Open-Label results are shown for Week 1 and Week 3. Double-Blind period were imputed by BOCF when needed. In the baseline period, placebo subjects scored a mean of 15.75, while ATNC05 subjects scored a mean of 14.18. In Week 3, the Placebo subjects scored a mean of 14.98, a change of 0.77. The ATNC05 subjects had a Week 3 mean of 3.85, a change of 10.33 points from their baseline period. In the third week of the Open-Label phase, subjects scored a mean of 1.89 points. In both Week 1 and Week 3, the difference between the placebo and ATNC05 groups was statistically significant, with p-values of <0.00001.

Pittsburgh Insomnia Scale Results

[00300] The Pittsburgh Insomnia Scale (PIRS-20) is a 20 item questionnaire which measures the difficulty subjects have with sleeping due to pain. It was measured during each office visit and is measured on a sale of 0 to 60.

[00301] Figure 33 shows the average PIRS-20 score for each treatment group during the Baseline Period, and at the Week 1 and Week 3 visits. The Open-Label results are shown for Week 1 and Week 3. Double-Blind period were imputed by BOCF when needed. In the baseline period, placebo subjects scored a mean of 36.05, while ATNC05 subjects scored a mean of 34.81. In Week 3, the Placebo subjects scored a mean of 30.57, a change of 5.48. The ATNC05 subjects had a Week 3 mean of 12.88, a change of 21.93 points from their baseline period. In the third week of the Open-Label phase, subjects scored a mean of 6.96

points. In both Week 1 and Week 3, the difference between the placebo and ATNC05 groups was statistically significant, with p-values of 0.00010 and <0.00001, respectively.

Ability to Stand on One Leg Results

[00302] Part of the evaluation of back pain included the length of time subjects are able stand on one leg. This was measured during office visits. The investigator postulates that involvement of the Lumbar 5 dermatome results in difficulty with standing on one leg; the Lumbar 5 dermatome innervates the superior gluteal nerve supplying the musculature involved in standing. The particular muscles involved with standing are the gluteus minimus, gluteus medius, and the tensor fasciae latae. The investigator hypothesizes that ATNC05 will improve the duration that subjects are able to stand on one leg. This measure was taken only for subjects who had difficulty standing on one leg during the Baseline Period office visits (N=20).

[00303] Figure 34 shows the average length of time these subjects were able to stand on one leg, in seconds. During the baseline period, both groups have a similar ability to stand on one leg. While the placebo group never exceeds 5 seconds of standing on one leg, by the end of the first week, ATNC05 subjects are able to stand on one leg for over 24 seconds on average. By the end of the open-label period, subjects are able to stand on one leg for over 59 seconds on average.

Open-Label Phase Results

[00304] The study had an Open-Label Extension phase, during which subjects who did not respond to the medication (either true non-responders who received ATNC05 or placebo subjects) were given the opportunity to receive ATNC05 for three weeks. 27 subjects entered the Open-Label phase, and 21 completed.

[00305] Figure 35 and Figure 36 show the weekly mean BPI-Severity and BPI-Interference scores, respectively, for subjects during the Open-Label extension phase. Since most of the subjects in the Open-Label extension were originally randomized placebo, the Baseline Period Means are shown for the placebo group for the various BPI measures.

Use of Other Pain Medications

[00306] Subjects on ATNC05 took fewer doses of other pain medications than placebo subjects throughout the treatment period. In Week 3, ATNC05 subjects took a mean of 0.5 doses, a reduction from baseline of 4.16 doses, while placebo subjects took 2.87 doses, a

reduction from baseline of 0.95 doses. Table 33 shows both the total number of doses taken and the number per subject as a table. Figure 37 shows the mean number of doses taken per week. This indicates that ATNC05 relieved the subjects' symptoms, so they did not need to take other pain medications.

Table 33: Doses of Concomitant Analgesics and/or Muscle Relaxants by Week

		Baseline	Week 1	Week 2	Week 3
Total Doses	Placebo	130	60	68	86
	ATNC05	205	81	35	20
Doses per Subject	Placebo	3.82	1.88	2.13	2.87
	ATNC05	4.66	1.88	0.88	0.5

Post-Treatment Sustained Effect of ATNC05

[00307] Table 34 shows the results of post-study questionnaires, collected by in-person and telephone interviews with subjects after the treatment period. 60 or more days after treatment ended. Of 58 patients who completed a treatment with ATNC05, 32 were available for this follow up. These data were collected outside of the original protocol. Responders analysis was done as a percentage of patients who had the post-study follow-up and as a percentage of all ATNC05 treated patients. Reversal is defined as 70% or more improvement in the Patient Global Impression of Improvement (PGI-I).

[00308] 40 ATNC05 subjects completed a three-week treatment period in the double-blind phase (5 of those subjects also completed the open-label phase). In the open-label phase, 18 subjects who had previously received placebo completed the open-label with ATNC05. In total, 58 (40+18) subjects completed a three-week treatment period with ATNC05, with 5 subjects completing two three-week treatment periods.

[00309] Post-study data gathering was not part of the original protocol and was collected on an ad hoc basis. A conservative estimate, taking post-study responders as a percentage of all subjects who ever completed a course ATNC05 (N=58), gives a response rate of 43% who were 70% or more improved 60 days or more after they finished their three-week treatment with ATNC05.

[00310] Taking response rate as the percentage of subjects who answered post-study questionnaires (N=32) who were responders gives a response rate of 78%.

[00311] Eleven subjects reported a 100% improvement in back pain more than two months after they stopped taking ATNC05. This is a response rate of 19% (11/58). While

further study would be required to establish this definitively, this hints toward ATNC05 being a potential cure for some neuropathic pain syndromes.

Table 34: Responders Analysis of Mean Subject Improvement (PGI-I) 61 or more day post-treatment

	Number of Long-term Reversal Patients	Long-term Reversal Patients as a Percent of Patients who Reported Post-Study Follow-up Scores (N=32)	Long-term Reversal Patients as a Percentage of Patients who completed a three-week treatment with ATNC05 (N=58)
70% or more improvement	25	78.13%	43.10%
100% improvement	11	34.38%	18.97%

Safety Evaluation

[00312] In the clinical trial for neuropathic back pain, ATNC05 did not cause serious adverse events or death. Mild and transient nausea, dizziness, and dry mouth were the most commonly observed side effects in the study. A full safety analysis is available in Section 12 (pp. 136–153) of the Clinical Study Report dated July 7, 2013.

[00313] Four subjects in the double-blind phase had adverse events that were distressing enough to cause subjects to withdraw. Two of these subjects were placebo subjects and two were ATNC05 subjects. This corresponds to a dropout rate of 4.5% (2/44) for the ATNC05 group and 5.8% (2/34) in the placebo group. Additionally, two subjects withdrew for adverse events during the open-label phase, corresponding to a dropout rate of 7.4% (2/27) for all subjects entering the open-label phase. At the worst case, the dropout rate is 7.4%, based on the study. The adverse symptoms resolved within two days of ceasing the medication, and did not require medical attention. The impact on other vital signs and laboratory parameters is minimal to nonexistent.

[00314] The components of ATNC05 have separately been demonstrated to be safe in decades of clinical use, and it may be concluded from this study that they are safe in combination. Naltrexone and clonidine are present in ATNC05 in a low dose of less than

10% of their approved doses for other indications. The mean dose of ATNC05 was 2.18 capsules per day in the double-blind phase, and 2.13 capsules per day when the taper-off period is included. Information on doses taken in the study is found on pages 128–131 of the Clinical Study Report. Dose-dependent adverse effects are therefore less pronounced in ATNC05.

[00315] ATNC05 is a product which consists of a low dose of two approved medications. It has a low adverse events profile and the preliminary data show it to be well-tolerated.

Comparison of ATNC05 and other Neuropathic Pain Treatments

Efficacy Comparison

[00316] The data from the Phase II trial showed treatment effect more than four times larger than drugs recently investigated for neuropathic pain. If data from the open-label extension phase is examined, the effect may be as large as six times greater than that of the comparable medications for neuropathic pain.

[00317] Table 35 shows the effect size for ATNC05 compared to two other recently studied medications approved for neuropathic pain: Cymbalta (duloxetine) and Lyrica (pregabalin). The data are taken from reviewer's analyses from statistical reviews published by the Center for Drug Evaluation and Research.

[00318] In all four studies cited in the table, missing data were imputed by the very conservative method, Baseline Observation Carried Forward (BOCF). Cymbalta showed an effect size of 0.5 points on a pain scale. Lyrica showed effect sizes of 0.6 and 0.9 points. ATNC05 showed an effect size of 2.8, more than 4.5 times larger than the mean effect size of the other treatments.

[00319] In the open-label extension phase of the ATNC05 Back Pain Study, during which all subjects received ATNC05, the subjects showed a mean improvement of 4.6 points at the primary endpoint (Week 3). The open-label extension phase consisted of subjects who were non-responders in the Double-Blind phase (most subjects in the extension phase received placebo during the Double-Blind phase); 27 subjects began the open-label extension phase and 22 subjects were evaluated for the primary end point. Of the subjects who left the open-label extension phase, two left due to adverse effects, while three were lost to follow up. When compared to the improvement experienced by the placebo group, the effect size of ATNC05 becomes 3.7 points, over six times more than the mean for Lyrica and Cymbalta.

[00320] It is the position of the applicant that the open-label results more accurately reflect the true net effect of ATNC05. Seven subjects receiving ATNC05 left the study during the double-blind phase. However, most of these subjects did not leave due to adverse events; they were lost to follow up. Prior to their departing the study, these subjects showed similar improvement to the subjects who completed the treatment period, and had they remained in the study, the resulting effect size would have been larger. While the open-label phase did not have a direct placebo comparator, most of the subjects in the open-label extension phase were randomized to the placebo group in the Double-Blind phase, so their results provide a good proxy for any placebo effects they may have experienced.

Table 35: Efficacy of ATNC05 compared to existing treatments for neuropathic pain

	Placebo Subjects	Active Drug Subjects	Placebo Improvement	Active Drug Improvement	Effect Size	p-value
Cymbalta (duloxetine)[1] – Chronic low back pain	128	128	-1.5	-2.0	0.5	0.004
Lyrica (pregabalin)[2] – Neuropathic Pain Associated with Spinal Cord Injury	67	70	-0.3	-1.2	0.9	<0.001
Lyrica[3] – Neuropathic Pain Associated with Spinal Cord Injury	108	111	-1.1	-1.7	0.6	0.014
ATNC05[4] – Neuropathic Back Pain	34	44	-0.9	-3.7	2.8	0.00000
ATNC05 (Open-Label Phase)[5] – Neuropathic Back Pain	34	22	-0.9	-4.6	3.7	

[1] Reviewer's Primary Efficacy Analysis, BOCF, HMGC Study in Summary Review for Regulatory Action, page 11

[2] Reviewer's Primary Efficacy Analysis, BOCF, Study 125 in Statistical Review and Evaluation, page 9

[3] Reviewer's Primary Efficacy Analysis, BOCF, Study 1107 in Statistical Review and Evaluation, page 15

[4] Double-blind phase primary endpoint, from Clinical Study Report dated July 7, 2013, "ATNC05, a composition to reduce back pain, A Proof-of-Concept, Randomized, Double-Blind, and Placebo controlled study with an Open Label Phase extension". Table 11-17, page 40.

[5] During open-label extension phase, missing data were not imputed. Open-label extension phase is compared to the placebo group from the Double-Blind phase.

Safety Comparison

[00321] It is well established that treatments currently available for neuropathic pain have limitations. Opioid drugs cause tolerance, dependence and side effects sufficiently serious to prompt recent action by the FDA to further restrict the drugs. NSAIDs, taken for a prolonged periods of time, are known to cause gastro-intestinal bleeding as well as toxicity to the liver, kidneys and other organs. Newly approved treatments, like the calcium channel alpha-2-delta ligands gabapentin and pregabalin and the serotonin and norepinephrine reuptake inhibitors milnacipran and duloxetine, require high doses to show nominal effectiveness, have a high dropout rate and carry many side effects.

[00322] In the Phase II trial, ATNC05 was tested for subjects with moderate chronic pain (4 points to 8 points on an 11-point scale). Currently available treatments for moderate neuropathic pain are NSAIDs, APAP, alpha-2-delta ligands, and serotonin and norepinephrine reuptake inhibitors. ATNC05 is more effective than NSAIDs and has fewer adverse effects. The same is true for APAP, alpha-2-delta ligands, and serotonin and norepinephrine reuptake inhibitors. ATNC05 has fewer negative impacts compared to opioids used for moderate pain.

Opioid Use and Chronic Neuropathic Back Pain

[00323] The FDA has cited overuse of opioid medication as a serious health issue. According to Sharon Hertz, MD, deputy director of FDA's Division of Anesthesia, Analgesia and Addiction Products, "There are a limited number of options available for the treatment of pain. Opioids are one option, but they carry a significant risk of misuse, abuse, overdose and death (FDA Works to Reduce Risk of Opioid Pain Relievers, 2012)."

[00324] Martell et al. (2007) conducted a meta-analysis of opioid use in chronic back pain and found that the current prevalence of opioid use disorder associated with chronic back pain ranges between 3% and 43%, with a mean of 21%. The differences in these rates depend on the criteria used for assessing opioid misuse. Based on these rates and the estimated prevalence of chronic neuropathic back pain (estimated as 13.5 million people in an earlier section), it is estimated that between 405,000 and 5.8 million people in the United States misuse opioids due to chronic neuropathic back pain, with a mean estimate of 2.8 million people.

[00325] Approximately 21% of people with chronic back pain misuse opioids. Opioids carry a significant risk of misuse, abuse, overdose and death. By offering a non-narcotic alternative for moderate chronic neuropathic lower back pain, ATNC05 has the potential to

greatly reduce the risks linked to narcotic medication used in chronic neuropathic lower back pain.

Conclusion: ATNC05 as a Breakthrough Therapy

[00326] Chronic neuropathic back pain is a serious condition, and is one of the leading causes of disability in the world, as measured by the WHO. The treatment effect size of ATNC05 is 4.5 times larger than recently approved treatments for neuropathic pain (duloxetine and pregabalin). Most importantly, by offering an effective non-narcotic treatment for chronic neuropathic lower back pain of moderate severity, ATNC05 has the potential to greatly reduce the risks linked to narcotic medication used in chronic neuropathic lower back pain because of the lack of effective non-narcotic treatment options.

[00327] Preliminary data for ATNC05 show reversal of pain after a three-week course of treatment, and at least 43% of ATNC05 subjects still had 70% or more relief of their back pain two months after ending the three-week treatment course.

[00328] There is a large public health benefit to be realized from meeting the current unmet need for an effective non-narcotic treatment for pain.

[00329] Unlike other available treatments for neuropathic back pain, ATNC05 shows reversal and a "cure" in at least 43% of the subjects in the Phase II trial, showing 70% or more improvement of their back pain more than two months after the end of their three-week treatment course with ATNC05. This may indicate that the novel mechanism of action of ATNC05, TLR-4 antagonism, has a relationship to the pathophysiology of chronic neuropathic back pain and has the ability to "switch off" the cycle that perpetuates the chronicity of neuropathic pain.

[00330] ATNC05 has the potential to revolutionize the treatment of neuropathic lower back pain, and alleviate the suffering and economic impact. ATNC05 has the potential to be a game-changer for the treatment of back pain and may eliminate the need for lengthy and costly treatments with marginal benefit, such as physical therapy and chiropractic treatment. Additionally, ATNC05 will most likely reduce the prevalence of spinal surgical procedures.

[00331] ATNC05 represents an inexpensive treatment option for three primary reasons. First, it is administered at home and does not have to be administered by a medical professional. Second, ATNC05 provides substantial relief after a short course of treatment, and this relief endures even after ceasing treatment. Third, even if needed to be taken for a

long term, the components of ATNC05 are available generically, so when ATNC05 is commercialized, the prices will need to be competitive with compounding variations.

[00332] The applicant states: a) chronic neuropathic back pain is a serious condition, b) ATNC05 is superior in efficacy and safety profile to current treatments (e.g., APAP, NSAIDs, alpha-2-delta ligands, and antidepressants) and begins to work within hours of the initial dose, rather than taking several weeks to reach an effect, c) ATNC05 has a novel mechanism of action, TLR-4 antagonism, which "switches off" the underlying cause of neuropathic pain, d) ATNC05 will be an inexpensive treatment option, since its components are generically available, significantly reducing the direct and indirect costs of chronic neuropathic back pain, and e) will greatly reduce the need for opioids for chronic neuropathic back pain of moderate severity.

Example 8: Preliminary Clinical Results with ATNC05 for Migraine Prevention

[00333] A study was conducted using ATNC05 for neuropathic back pain under IND 110491. The study was a 78-subject double-blind placebo-controlled randomized proof-of-concept clinical trial. Following a one-week Baseline period, subjects were administered ATNC05 or placebo for three weeks. The study had an open-label extension phase for back pain non-responders in the double-blind phase, during which all subjects received ATNC05 with no comparator. The Clinical Study Report for this trial was submitted to FDA on July 7, 2013 and is available upon request. Because this was a proof-of-concept study, data on concomitant migraine were collected.

[00334] 23 subjects met the criteria set forth by the International Headache Society for migraine (moderate to severe intensity [4 points or greater on an 11-point scale], occurring three or more days per month). Ten of these subjects were randomized to receive placebo, and 13 were randomized to ATNC05. Nine migraine subjects continued into the open-label phase (8 of them were originally randomized placebo, and one was ATNC05). They were classified by the investigator's assessment of the IHS criteria during the initial screening process.

[00335] These subjects had a mean duration of migraine diagnosis of 20.8 years and a mean severity of 6 points on an 11-point scale, with no significant difference between the treatment groups. Table 36 shows the demographic summary of the migraine subjects. Table 37 shows the duration and severity of these subjects' migraine diagnosis.

[00336] During the study, subjects completed daily questionnaires on which they recorded headache incidence and intensity. The analysis only considers migraine days, which are days where headache intensity was four points or more on an 11-point pain scale.

Table 36: Demographics of Migraine Subjects

	Placebo Migraine Subjects	ATNC05 Migraine Subjects	All Migraine Subjects
N	10	13	23
Age (years)			
Mean(SD)	41.5 (12.62)	46.2 (8.32)	44.2 (10.42)
Median	39.5	45	43
Range	19 - 70	33 - 59	19 - 70
Gender, n (%)			
Female	10 (100)	10 (76.9)	20 (86.9)
Male	0 (0)	3 (23.1)	3 (13.0)
Race, n (%)			
White	9 (90)	7 (53.8)	15 (65.2)
Black	0 (0)	2 (15.4)	2 (8.6)
More than One Race	1 (10)	4 (30.7)	5 (21.7)
Ethnicity, n (%)			
Hispanic	7 (70)	9 (69.2)	16 (69.5)
Non-Hispanic	3 (30)	4 (30.7)	7 (30.4)

Table 37: Migraine History at Screening – Duration of Condition and Average Severity

	Duration in Years – Mean (SD)	Average Severity on 11-point scale – Mean (SD)	N
Placebo Migraine Subjects	17.9 (11.23)	6.4 (1.17)	10
ATNC05 Migraine Subjects	23.1 (13.62)	5.8 (1.48)	13
All Migraine Subjects	20.8 (12.64)	6.0 (1.36)	23
Open-Label Migraine Subjects	17.1 (9.87)	6.4 (1.33)	9

Migraine Frequency Data from Daily Questionnaire

[00337] Based on the daily questionnaire data, a subject was classified as having a Migraine Day on all days upon which the subject reported a headache intensity of 4 points or more on an 11-point pain scale (the frequency is filtered by severity). During the baseline

period, subjects in the placebo group reported 2.6 migraine days, and ATNC05 subjects reported 3.85 migraine days.

[00338] In the first week of the treatment period, placebo subjects reported 1.3 migraine days, a decrease of 1.3 from baseline, and ATNC05 subjects reported 0.15, a decrease of 3.44 from baseline (Table 38). The difference in the changes from baseline was not significant, with p=0.091. This is not because the ATNC05 group did not improve (indeed, ATNC05 subjects went from 3.85 to 0.15, a 96% decrease), but because the placebo group included two subjects who had a large placebo effect. This distortion is less likely to occur in a larger study. ATNC05 started working in the first week.

[00339] In the second week of the treatment period, placebo subjects reported 1.7 migraine days, an increase from baseline of 0.40, and ATNC05 subjects reported 0.15 migraine days, a decrease from baseline of 3.43 (or 96%). The difference in the changes from baseline was highly statistically significant, with p=0.00038 (Table 39).

[00340] In the third week of the treatment period, placebo subjects reported 1.5 migraine days, a decrease from baseline of 1.10, while ATNC05 subjects reported 0.0 migraine days, a 100% improvement. The difference in the changes from baseline in Week 3 is significant with p=0.043 (Table 40).

[00341] Over entire three-week treatment period, placebo subjects reported 2.0 migraine days per week, a decrease of 1.10 migraine days per week from baseline, and ATNC05 subjects reported 0.1 migraine days per week, a decrease from baseline of 3.74 migraine days per week. The number of migraine days in the treatment period was converted to weekly frequency by dividing by 3. The difference in the changes from baseline in the Treatment Period is significant with p=0.049 (Table 41, Figure 38).

Table 38: Analysis of Change from Baseline in Weekly Frequency To Week 1 In Migraine Subjects

Treatment	N	Weekly Frequency of Migraine Days			
		Baseline	Wk 1	Change (Standard Error)	p-value
Placebo	10	2.60	1.30	1.30 (1.09)	0.09127
ATNC05	13	3.85	0.15	3.44 (0.82)	

Groups	All Subjects Migraine Subjects
Method	t-Test, 2-sided
P Value	0.09127
Mean Difference	0.091272445

Standard Error	± 0.46
95% Confidence Interval	(-1.957 to 1.775)

Table 39: Analysis of Change from Baseline in Weekly Frequency To Week 2 In Migraine Subjects

Treatment	N	Weekly Frequency of Migraine Days			
		Baseline	Wk 2	Change (Standard Error)	p-value
Placebo	10	2.60	1.70	-0.40 (0.34)	0.00038
ATNC05	13	3.85	0.15	3.43 (0.82)	

Groups	All Subjects Migraine Subjects
Method	t-Test, 2-sided
P Value	0.00038
Mean Difference	0.091272445
Standard Error	± 0.56
95% Confidence Interval	(-2.066 to 1.884)

Table 40: Analysis of Change from Baseline in Weekly Frequency To Week 3 In Migraine Subjects

Treatment	N	Weekly Frequency of Migraine Days			
		Baseline	WK3	Change (Standard Error)	p-value
Placebo	10	2.60	1.50	1.10 (0.85)	0.04284
ATNC05	13	3.85	0.00	3.85 (0.90)	

Groups	All Migraine Subjects
Method	t-Test, 2-sided
P Value	0.04284
Mean Difference	-2.75
Standard Error	± 0.88
95% Confidence Interval	(-0.050 to 5.550)

Table 41: Analysis of Change from Baseline in Weekly Frequency in Entire Treatment Period in Migraine Subjects

Treatment	N	Weekly Frequency of Migraine Days			
		Baseline	Treatment Period Mean	Change (Standard Error)	p-value
Placebo	10	2.60	2.00	1.10 (0.92)	0.04989
ATNC05	13	3.85	0.10	3.74 (0.86)	

Groups	All Migraine Subjects
Method	t-Test, 2-sided
P Value	0.04989
Mean Difference	-2.64
Standard Error	± 0.89
95% Confidence Interval	(-0.209 to 5.489)

Table 42: Migraine Day Incidence Data from Daily Questionnaire, Expressed As Monthly (Four-Week) Frequency

	Baseline	Week 1	Week 2	Week 3
Placebo (N=10)	10.40	5.20	6.80	6.00
ATNC05 (N=13)	15.38	0.62	0.62	0.00
Open-Label (N=9)		2.22	0.00	0.00

[00342] Converting the weekly frequencies to a monthly basis, the evidence shows that the ATNC05 migraine subjects went from a mean 15.38 migraine days per month to nearly zero throughout three weeks of treatment (Table 42). The reduction started immediately in the first week and persisted through the entire treatment period. The placebo subjects showed some reduction, attributable mainly to two subjects with a strong placebo effect. These subjects showed a strong placebo effect in the back pain parameters in the study as well.

[00343] Even with the relatively small sample in this study, this represents a statistically significant improvement, and reflects the potential of ATNC05 to be an effective treatment for chronic migraine prevention. The applicant believes that the data represents true and compelling findings.

[00344] As referenced earlier in this section, current treatments for migraine prevention tend to only reduce migraine frequency by about 40% in half of patients. The preliminary evidence shows that ATNC05 has a larger effect than these therapies, providing complete remission of migraine. As part of this project, a meta-analysis will be undertaken to

compare the efficacy data from the proposed study and data from studies of other current treatments for chronic migraine prevention.

MIDAS

[00345] The Migraine Disability Assessment Test (MIDAS) was used to measure the number of migraine days in the three months before the study period and the three-week treatment period. It was administered to subjects reporting frequent and severe migraines (n=12 ATNC05 subjects). This is a less reliable methodology than daily questionnaires, since it depends on subjects' memory, which may be biased.

[00346] Six subjects with ≥15 headache days per month before the study went from a mean of 25.7 headache days per month to a mean of 3.6. Nine subjects with ≥10 headache days per month went from a mean of 21.1 headache days per month to mean of 2.4. Twelve subjects with ≥6 headache days per month went from a mean of 15.2 headache days per month to a mean of 1.8. Subjects with migraine assessed by MIDAS showed significant reduction in headache days during the treatment period. This data is in Table 43.

Potential Limitations of the MIDAS Data

[00347] The MIDAS was used on the most severe migraine subjects. The number of subjects assessed with MIDAS was too small for statistical analysis (placebo n=4 and ATNC05 n=12). However, the reliability of the MIDAS is supported by the fact that, for the baseline period, the frequency of migraine reported on the daily questionnaire (15.38 migraine days per month) and the frequency reported by MIDAS (15.28 migraine days per month) differ by only 0.1 days for ATNC05 subjects. The memory bias of the subjects is practically non-existent. The applicant believes that the data represent true and compelling findings.

Table 43: Summary of Midas-Assessed Subjects with Concomitant Migraine

	MIDAS-Assessed Subjects receiving ATNC05		
	Subjects with 6 or more headache days per month prior to the study	10 or more headache days per month prior to the study	15 or more headache days per month prior to the study
N of Subjects	12	9	6
Mean Monthly Frequency in Three Months Prior to Study	15.28	21.11	25.67
Mean Monthly Frequency during Study Period*	1.78	2.37	3.56

Percent Improvement in Study Period	88.3%	88.8%	86.1%
Number of subjects reporting zero headache days while receiving ATNC05	10	6	4

* The number of headache days reported during the three-week study period was multiplied by 1.33 to get the monthly frequency.

Conclusion of Preliminary Clinical Experience with ATNC05 in Migraine Prevention

[00348] The preliminary study enrolled 23 migraine subjects in the double-blind phase (placebo n = 10, ATNC05 n = 13), with nine of these subjects continuing to the open-label phase. Despite the small size of the migraine group (who were a subset of subjects in a larger study on back pain), the number of subjects was large enough to determine statistical significance of the effect size. ATNC05 provides a statistically significant reduction in migraine frequency, compared to placebo.

[00349] Based on the daily questionnaire data, subjects had a reduction of 96% in migraine frequency in their first and second weeks on ATNC05, and a 100% reduction in their third week on ATNC05. The MIDAS assessment shows that migraine subjects had reduction of nearly 90% in migraine frequency during the treatment period, compared to the three months before the trial.

[00350] In addition to the preventive effect of ATNC05, the investigator observed complete resolution of acute migraine upon administration of the first dose of ATNC05.

Comparison of ATNC05 and other Chronic Migraine Treatments

[00351] A review in Rev. Neurol. (Spain) states that there are only two treatments which show efficacy in the prevention of chronic migraine: topiramate (Topamax) and pericranial infiltrations of Onabotulinumtoxin A (Botulinum Toxin Type A, Botox) (Pascual).Please see Table 44.

[00352] Studies by Silberstein, Lipton, Dodick et al. and Diener et al. for the treatment of chronic migraine with topiramate show an effect size of 1.7 and 3.7 fewer migraine days per month, respectively. The completion rates in the active treatment group were 55.8% and 75%, respectively.

[00353] Silberstein, Lipton, Dodick et al. reported that 28.7% of subjects who discontinued use of topiramate did so due to lack of efficacy, and 25% of topiramate

discontinuations were due to adverse events. A breakdown of reasons for discontinuation was not available from Diener et al.

[00354] Silberstein, Blumenfeld, Cady, et al. studied Onabotulinumtoxin A in chronic migraine subjects and found an effect size of 2.0 fewer migraine days per month. The treatment was well tolerated.

[00355] ATNC05 showed an effect size of 10.56 fewer migraine days per month. ATNC05 migraine subjects had a 92% completion rate, with only one migraine subject discontinuing the study early (on day 15 of the 21-day treatment period) due to lack of sexual interest.

[00356] The preliminary study with ATNC05 showed an effect size of 10.56 fewer migraine days per month for subjects with migraine and chronic migraine. This is compared with effect sizes of 1.7 and 3.7 fewer migraine days in topiramate, and 2.0 with Onabotulinumtoxin A, the current Standard of Care for chronic migraine prevention.

[00357] ATNC05 produced fewer side effects than topiramate. In the topiramate studies, the completion rate was between 55% and 75%. ATNC05 had a 92% completion rate for migraine subjects, which indicates that ATNC05 is well-tolerated and effective compared to topiramate. Onabotulinumtoxin A has to be administered by a trained professional. By contrast, ATNC05 is administered orally at home. The components of ATNC05 are available generically, so ATNC05 represents an inexpensive treatment option.

Table 44: Review of Efficacy Studies for Chronic Migraine

	Treatment	N Active	N Placebo	Active Completion Rate	Placebo Completion Rate	Treatment length	Improvement from Baseline in Migraine Days (per month) - Active	Improvement from Baseline in Migraine Days per Month - Placebo	Net Effect Size	p-value	AE Dropout Rate – Active
Silberstein, Lipton, Dodick et al	Topiramate (with and without Medication Overuse)	153	153	55.8%	55.2%	16 week	5.6±6.0	4.1±6.1	1.7	0.032	10.9%
Diener et al.	Topiramate (with and without Medication Overuse)	32	27	75%	52%	16 week	3.5±6.3	-0.2±4.1	3.7	<0.05	
Silberstein, Blumenfeld, Cady, et al	Onabotulinumtoxin A (with Medication Overuse)	445	459			24-week	8.2	6.2	2.0	<0.001	

Toledano[6] - Migraine	ATNC05	13	10	92%	100%	3-week	14.96±3.44	4.4±3.68	10.56	0.049	0%

[00358] The efficacy of ATNC05 on neuropathic back pain is shown in Table 45. In the 78-subject study, ATNC05 showed an effect size of 2.78 points (on an 11-point scale) in Week 3 of the treatment period.

Table 45: Summary of Results from Phase II Study For Neuropathic Back Pain

Study	Treatment	N Active	N Placebo	Active Completion Rate	Placebo Completion Rate	Treatment length	Improvement from Baseline in Average Back Pain Severity at Week 3 - Active	Improvement from Baseline in Average Back Pain Severity at Week 3 - Placebo	Net Effect Size	p-value	AE Dropout Rate – Active
Toledano[7] - Neuropathic Back Pain (BOCF)	ATNC05	44	34	93.2%	88.2%	3-week	3.32±0.33 (11-point scale)	1.42±0.33 (11-point scale)	2.78 (11-point scale)	<0.0001	4.5%

[00359] The studies above show that there is an unmet medical need that the current available treatments for chronic migraine prevention do not adequately address. ATNC05 provides a large effect size of 10.56 fewer migraine days per month, compared to 1.7-3.7 for topiramate, and 2.0 for Onabotulinumtoxin A. ATNC05 is tolerated much better than topiramate, as evidenced by the low dropout rate. ATNC05 has a quick onset of action, starting immediately (1-2 hours) after the first dose and persisting throughout the treatment period. The components of ATNC05 are available generically, so ATNC05 represents an inexpensive treatment option.

Opioid Use and Chronic Migraine

[00360] The FDA has cited overuse of opioid medication as a serious health issue. According to Sharon Hertz, MD, deputy director of FDA's Division of Anesthesia, Analgesia and Addiction Products, "There are a limited number of options available for the treatment of

[6] This analysis is based on the subset of migraine subjects in the back pain study.

[7] This summary is of all subjects in the neuropathic back pain study. Missing data were imputed by Baseline Observation Carried Forward (BOCF)

pain. Opioids are one option, but they carry a significant risk of misuse, abuse, overdose and death (FDA Works to Reduce Risk of Opioid Pain Relievers, 2012)."

[00361] Buse et al. (2012) studied opioid use and dependence among persons with migraine and found 15.9% of migraine sufferers use opioids for acute migraine symptoms. Of these, 16.6% meet the standard for opioid dependence. Opioid users reported greater disability due to migraine and greater frequency of migraine. Based on the prevalence figures cited earlier, it is estimated that between 683,000 and one million people (15.9% of people with chronic migraine) in the United States use opioids for chronic migraine, and between 113,494 and 180,000 of these people (16.6% of chronic migraine patients who use opioids) are dependent on opioids. 15.9% of people with migraine use opioids. Opioids carry a significant risk of misuse, abuse, overdose and death. By offering a non-narcotic alternative for chronic migraine prevention, ATNC05 has the potential to greatly reduce the risks linked to narcotic medication used in chronic migraine.

Example 9: Concomitant Joint Pain in Back Pain Clinical Trials with ATMC05

[00362] Figure 41 shows the mean joint pain (for subjects who reported concomitant joint pain) during the back pain study. Subjects on ATNC05 reported significant reductions in joint pain; subjects reported no joint pain at all during the third week of the Open-Label phase.

Example 10: Long-term Pain Relief

[00363] Table 46 shows the results of post-study questionnaires, collected from the daily questionnaire forms and telephone interviews. For this analysis, a subject is classified as having responded to the treatment if they report 70% or more improvement in the Patient Global Impression of Improvement (PGI-I).

[00364] 40 ATNC05 subjects completed a three-week treatment period in the double-blind phase (5 of those subjects also completed the open-label phase). In the open-label phase, 18 subjects who had previously received placebo completed the open-label with ATNC05. In total, 58 (40+18) subjects completed a three-week treatment period with ATNC05, with 5 subjects completing two three-week treatment periods.

[00365] Post-study data gathering was not part of the original protocol and was collected on a voluntary basis (Table 47, Figure 42). 25 subjects reported 70% or more improved 60 days or more after they finished their three-week treatment with ATNC05. This

number as a percentage of all subjects who completed a course of ATNC05 (N=58) gives a response rate of 43%. The response rate as the percentage of subjects who answered post-study questionnaires (N=32) is 78%. Accordingly, the post-study reversal of symptoms greater than 70% is between 43% and 78%.

[00366] At least 43% of subjects reported 70% or greater improvement of their back pain 60 days or more after finishing their three-week treatment period with ATNC05.

[00367] Eleven subjects reported a 100% reversal of back pain more than two months after they stopped taking ATNC05. This is a post-treatment response rate of 19% (11/58). While further study would be required to establish this definitively, this hints toward ATNC05 being a potential cure for some neuropathic pain syndromes.

Table 46: Responders Analysis of Mean Subject Improvement (PGI-I) 61 or more day post-treatment

	Number of Responders	Responders as a Percent of Subjects who Reported Post-Study Follow-up Scores (N=32)	Responders as a Percentage of Subjects who completed a three-week treatment with ATNC05 (N=58)
70% or more improvement	25	78.13%	43.10%
100% improvement	11	34.38%	18.97%

Table 47: Responders Analysis of Mean Subject Improvement (PGI-I) during Post-Study Period

	30-60 Days Post end of Study Drug	61 or More Days Post end of Study Drug
Total Subjects answering Post-Study Questionnaire	27	32
Number of Subjects classified as Responders*	23	27
Responders as a Percent of Subjects who Reported Post-Study Follow-up Scores	85.19%	84.38%
Responders as a Percent of Initially Randomized Subjects (N=78)	29.49%	34.62%
Responders as a Percentage of Subjects who Received ATNC during Double-Blind or Open-Label Phases (n=71)	37.10%	43.55%

Example 11: Energy and Activity Levels Results

[00368] In the daily pain questionnaire, subjects were asked to respond if their energy levels had changed from before the treatment period (options were Increased, Decreased, and Stayed the Same). They were also asked to rate if they had been more or less active in the 24 hours prior to the questionnaire, as compared to before starting the study drug (subjects provided a percentage increase or decrease, which was converted to trinary increase/decrease/stayed the same results).

[00369] Figure 39 shows the subjects' reported change in energy level during the treatment period. The percentage is the percentage of questionnaires with the response in each group (i.e., the percentage of subject-days reporting the given energy level). Subjects on ATNC05 reported increased levels of energy on 70% of subject days, compared to 10% for subjects in the placebo treatment group.

[00370] Figure 40 shows the subjects' reported change in activity level during the treatment period. The percentage is the percentage of questionnaires with the response in each group (i.e., the percentage of subject-days reporting the given energy level). Subjects on ATNC05 reported an increase in activity of 68% of subject-days during the Double-Blind phase and of 75% during the Open-Label phase, compared to 35% for subjects in the placebo treatment group. ATNC05 subjects reported a mean percentage increase in activity level of more than 50%, while subjects on the placebo reported an increase of 16.78%.

CLAIMS

That which is claimed is:

1. A composition for treatment of pain in a mammal comprising a synergistic ratio of (a) an opioid/TLR4 antagonist, or pharmaceutically acceptable salts or solvates thereof and (b) a direct-acting alpha-2 adrenergic agonist, or pharmaceutically acceptable salts or solvates thereof.

2. A composition comprising the formulation of claim 1, wherein the opioid/TLR4 antagonist is selected from a group consisting of: naltrexone, norbinaltorphimine, nalmefene, naloxone, nalorphine, methylnaltrexone, samidorphan, cyprodime, naltrindole, amentoflavone, naltriben, norbinaltorphimine, 6-ß-naltrexol, metabolites and pro drugs thereof, including all enantiomeric and epimeric forms as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

3. A composition comprising the formulation of claim 1, wherein the opioid/TLR4 antagonist is naltrexone, enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, pro drugs thereof, or any pharmaceutically acceptable salts or solvates of any thereof.

4. A composition comprising the formulation of claim 3, wherein the opioid/TLR4 antagonist is naltrexone in a sustained release formulation, as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

5. A composition comprising the formulation of claim 3, wherein the opioid/TLR4 antagonist is (+)–naltrexone (dextro-naltrexone) as well as appropriate mixtures thereof, as well as pro drugs thereof, or pharmaceutically acceptable salts or solvates thereof.

6. A composition comprising the formulation of claim 1, wherein the direct-acting alpha 2 adrenergic agonist is selected from a group consisting of apraclonidine, brimonidine, clonidine, detomidine, dexmedetomidine, guanabenz, guanfacine, lofexidine, medetomidine, romifidine, tizanidine, tolonidine, xylazine and fadolmidine, or pharmaceutically acceptable salts or solvates of any thereof.

7. A composition comprising the formulation of claim 1, wherein the direct-acting alpha-2 adrenergic agonist is clonidine, or pharmaceutically acceptable salts or solvates thereof.

8. A composition comprising the formulation of claim 1, wherein the direct-acting alpha-2 adrenergic agonist is clonidine in a sustained release formulation, or pharmaceutically acceptable salts or solvates thereof.

9. A composition according to claim 1, wherein the opioid/TLR4 antagonist is naltrexone, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount and the direct-acting alpha-2 adrenergic agonist is clonidine, or pharmaceutically acceptable salts or solvates thereof, in therapeutically effective amount.

10. A composition according to claim 9, wherein naltrexone and clonidine, or pharmaceutically acceptable salts or solvates of any thereof, are in a weight to weight combination range which corresponds to a synergistic combination range of the order of 90:1 to 22.5:1 parts by weight.

11. A composition according to claim 10, wherein the dose range of naltrexone, or pharmaceutically acceptable salts or solvates thereof, is about 0.004 mg/kg-0.71 mg/kg. And wherein, the dose range of clonidine, or pharmaceutically acceptable salts or solvates thereof, is about 0.00018 mg/kg - 0.0086mg/kg per day.

12. A composition according to claim 10, wherein the human dose range of naltrexone is 0.25 mg - 50 mg per day. And wherein, the human the dose range of clonidine is 0.0125 mg - 0.6 mg, wherein said composition is formulated into a single fixed combination dosage form.

13. A composition according to claim 10, wherein the human dose range of naltrexone is 0.25 mg - 15 mg per day. And wherein, the human the dose range of clonidine is 0.0125 mg - 0.3 mg, wherein said composition is formulated into a single fixed combination dosage form.

14. A composition according to claim 10, wherein the composition is administered once, twice, three or four times through the day.

15. A composition of claim 10, wherein the therapeutically effective dose of the pharmaceutical composition is administered systemically, including but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical or sublingual routes.

16. A composition according to claim 10, wherein said combination is in a single dosage form, and wherein, said single dosage form is in the form of tablets, lozenges, troches, hard candies, liquid, powders, sprays, creams, salves and suppositories.

17. A composition according to claim 1 for treating, preventing and reversing pain.

18. A composition according to claim 1 for treating pain wherein said pain is back pain.

19. A composition according to claim 1 for treating pain wherein said pain is neuropathic pain.

20. A composition according to claim 1 for treating pain wherein said pain is migraine headache.

21. A composition according to claim 1 for treating pain wherein said pain is trigeminal neuralgia.

22. A composition according to claim 1 for treating pain wherein said pain is vulvodynia.

23. A composition according to claim 1 for treating pain wherein said pain is irritable bowel syndrome.

24. A composition according to claim 1 for treating pain wherein said pain is post herpetic neuralgia.

25. A composition according to claim 1 for treating pain wherein said pain is diabetic neuropathy.

26. A composition according to claim 1 for treating pain wherein said pain is nociceptive pain with an allodynic component.

27. A composition for treatment of pain in a mammal comprising a synergistic ratio of (a) an opioid/TLR4 antagonist, or pharmaceutically acceptable salts or solvates thereof and (b) a acetyl-para-aminophenol, or pharmaceutically acceptable salts or solvates thereof.

28. A composition comprising the formulation of claim 27, wherein the opioid/TLR4 antagonist is selected from a group consisting of naltrexone, norbinaltorphimine, nalmefene, naloxone, nalorphine, methylnaltrexone, samidorphan, cyprodime, naltrindole, amentoflavone, naltriben, norbinaltorphimine, 6-ß-naltrexol, metabolites and pro drugs thereof, including all enantiomeric and epimeric forms as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

29. A composition comprising the formulation of claim 27, wherein the opioid/TLR4 antagonist is naltrexone as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

30. A composition comprising the formulation of claim 29, wherein the opioid/TLR4 antagonist is naltrexone in a sustained release formulation, as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

31. A composition comprising the formulation of claim 29, wherein the opioid/TLR4 antagonist is (+)–naltrexone (dextro-naltrexone),as well as appropriate mixtures thereof, as well as pro drugs thereof, or pharmaceutically acceptable salts or solvates thereof.

32. A composition comprising the formulation of claim 27, wherein acetyl-para-aminophenol or pharmaceutically acceptable salts or solvates thereof, is the second compound.

33. A composition according to claim 27, wherein the opioid/TLR4 antagonist is naltrexone, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount and the acetyl-para-aminophenol is in therapeutically effective amount.

34. A composition according to claim 27, wherein naltrexone and acetyl-para-aminophenol, or pharmaceutically acceptable salts or solvates of any thereof, are in a weight to weight combination range which corresponds to a synergistic combination of 3:200 parts by weight.

35. A composition according to claim 34, wherein the dose range of naltrexone, or pharmaceutically acceptable salts or solvates thereof, is about 0.004 mg/kg-0.71 mg/kg. And wherein, the dose range of acetyl-para-aminophenol, or pharmaceutically acceptable salts or solvates thereof, is about 5 mg/kg - 57mg/kg per day.

36. A composition according to claim 34, wherein the human dose range of naltrexone is 0.25 mg - 50 mg per day. And wherein, the human the dose range of acetyl-para-aminophenol is 325 mg - 4000 mg, wherein said composition is formulated into a single fixed combination dosage form.

37. A composition according to claim 34, wherein the human dose range of naltrexone is 0.25 mg - 15 mg per day. And wherein, the human the dose range of acetyl-para-aminophenol is 325 mg - 4000 mg, wherein said composition is formulated into a single fixed combination dosage form.

38. A composition according to claim 34, wherein the composition is administered once, twice, three or four times through the day.

39. A composition of claim 34, wherein the therapeutically effective dose of the pharmaceutical composition is administered systemically, including but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical or sublingual routes.

40. A composition according to claim 34, wherein naltrexone and acetyl-para-aminophenol are in a single dosage form, and wherein said single dosage form is in the form of tablets, lozenges, troches, hard candies, liquid, powders, sprays, creams, salves and suppositories.

41. A composition according to claim 27 for treating, preventing and reversing pain.

42. A method of treating neuropathic pain, nociceptive pain, nociceptive pain with an allodynic component, migraine, inflammation, osteoarthritis, rheumatoid arthritis, psoriatic arthritis, trigeminal neuralgia, vulvodynia, irritable bowel syndrome, post herpetic neuralgia, or diabetic neuropathy in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a combination according to Claim 34.

43. A composition for treatment of pain in a mammal comprising a synergistic ratio of an opioid/TLR4 antagonist, or pharmaceutically acceptable salts or solvates thereof and a cyclooxygenase (COX) inhibitor, or pharmaceutically acceptable salts or solvates thereof.

44. A composition comprising the formulation of claim 43, wherein the opioid/TLR4 antagonist is selected from a group consisting of naltrexone, norbinaltorphimine, nalmefene, naloxone, nalorphine, methylnaltrexone, samidorphan, cyprodime, naltrindole, amentoflavone, naltriben, norbinaltorphimine, 6-ß-naltrexol, metabolites and pro drugs thereof, including all enantiomeric and epimeric forms as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

45. A composition comprising the formulation of claim 43, wherein, the opioid/TLR4 antagonist is naltrexone as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

46. A composition comprising the formulation of claim 45, wherein, the opioid/TLR4 antagonist is naltrexone in a sustained release formulation, as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

47. A composition comprising the formulation of claim 45, wherein, the opioid/TLR4 antagonist is (+)–naltrexone (dextro-naltrexone),as well as appropriate mixtures thereof, as well as pro drugs thereof, or pharmaceutically acceptable salts or solvates thereof.

48. A composition comprising the formulation of claim 43, wherein the cyclooxygenase (COX) inhibitor is selected from a group consisting of aspirin diflunisal, salsalate. ibuprofen, dexibuprofen, naproxen, fenoprofen, ketoprofen, dexketoprofen, flurbiprofen, oxaprozin, loxoprofen. indomethacin, tolmetin, ,sulindac, etodolac, ketorolac, iclofenac, nabumetone. piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam. mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid. celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricoxib, firocoxib, sulphonanilides, nimesulide, licofelone, lysine, clonixinate, hyperforin, figwort, calcitriol or pharmaceutically acceptable salts or solvates of any thereof.

49. A composition comprising the formulation of claim 43, wherein the cyclooxygenase (COX) inhibitor is ibuprofen, or pharmaceutically acceptable salts or solvates thereof.

50. A composition according to claim 43, wherein the opioid/TLR4 antagonist is naltrexone, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount and the cyclooxygenase (COX) inhibitor is ibuprofen, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount.

51. A composition according to claim 50, wherein naltrexone and ibuprofen, or pharmaceutically acceptable salts or solvates of any thereof, are in a weight to weight combination range which corresponds to a synergistic combination of 1:90 parts by weight.

52. A composition according to claim 50, wherein the dose range of naltrexone, or pharmaceutically acceptable salts or solvates thereof, is about 0.004 mg/kg-0.71 mg/kg. And wherein, the dose range of ibuprofen, or pharmaceutically acceptable salts or solvates thereof, is about 3 mg/kg - 35mg/kg per day.

53. A composition according to claim 50, wherein the human dose range of naltrexone is 0.25 mg - 50 mg per day. And wherein, the human the dose range of ibuprofen is 200 mg - 2400 mg, wherein said composition is formulated into a single fixed combination dosage form.

54. A composition according to claim 50, wherein the human dose range of naltrexone is 0.25 mg - 15 mg per day. And wherein, the human the dose range of ibuprofen is 200 mg - 2400 mg, wherein said composition is formulated into a single fixed combination dosage form.

55. A composition according to claim 50, wherein the composition is administered once, twice, three or four times through the day.

56. A composition of claim 50, wherein the therapeutically effective dose of the pharmaceutical composition is administered systemically, including but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical or sublingual routes.

57. A composition according to claim 50, wherein said combination is in a single dosage form, and wherein, said single dosage form is in the form of tablets, lozenges, troches, hard candies, liquid, powders, sprays, creams, salves and suppositories.

58. A composition according to claim 43 for treating, preventing, and reversing pain.

59. A method of treating neuropathic pain, nociceptive pain, nociceptive pain with an allodynic component, migraine, trigeminal neuralgia, vulvodynia, irritable bowel syndrome, post herpetic neuralgia, or diabetic neuropathy in a mammal in need thereof, comprising administering to the mammal in a therapeutically effective amount of a combination according to Claim 50.

60. A composition for treatment of pain in a mammal comprising a synergistic ratio of (a) an opioid/TLR4 antagonist, or pharmaceutically acceptable salts or solvates thereof and (b) an alpha-2-delta ligand, or pharmaceutically acceptable salts or solvates thereof.

61. A composition comprising the formulation of claim 60, wherein the opioid/TLR4 antagonist is selected from a group consisting of naltrexone, norbinaltorphimine, nalmefene, naloxone, nalorphine, methylnaltrexone, samidorphan, cyprodime, naltrindole, amentoflavone, naltriben, norbinaltorphimine, 6-alpha-naltrexol, 6-beta-naltrexol metabolites and pro drugs thereof, including all enantiomeric and epimeric forms as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

62. A composition comprising the formulation of claim 60, wherein the opioid/TLR4 antagonist is naltrexone as well as pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

63. A composition comprising the formulation of claim 62, wherein the opioid/TLR4 antagonist is naltrexone in a sustained release formulation, as well as metabolites and pro drugs thereof or any enantiomeric and epimeric forms thereof, as well as the appropriate mixtures thereof, or pharmaceutically acceptable salts or solvates of any thereof.

64. A composition comprising the formulation of claim 62, wherein the opioid/TLR4 antagonist is (+)–naltrexone (dextro-naltrexone), as well as appropriate mixtures thereof, as well as metabolites or pro drugs thereof, or pharmaceutically acceptable salts or solvates thereof.

65. A composition comprising the formulation of claim 60, wherein the alpha-2-delta ligand is selected from Gabapentin or Pregabalin or pharmaceutically acceptable salts or solvates of any thereof.

66. A composition comprising the formulation of claim 60, wherein the alpha-2-delta ligand inhibitor is Gabapentin, or pharmaceutically acceptable salts or solvates thereof.

67. A composition comprising the formulation of claim 60, wherein the alpha-2-delta ligand inhibitor is pregabalin, or pharmaceutically acceptable salts or solvates thereof.

68. A composition according to claim 60, wherein the opioid/TLR4 antagonist is naltrexone, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount and the alpha-2-delta inhibitor is Gabapentin or Pregabalin, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount.

69. A composition according to claim 60, wherein the opioid/TLR4 antagonist is dextro naltrexone, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount and the alpha-2-delta inhibitor is Gabapentin or Pregabalin, or pharmaceutically acceptable salts or solvates thereof, in a therapeutically effective amount.

70. A composition according to claim 68, wherein naltrexone and alpha-2-delta ligand, or pharmaceutically acceptable salts or solvates of any thereof, are in a weight to weight combination range which corresponds to a synergistic combination of 1:30-1:125 parts by weight.

71. A composition according to claim 69, wherein the dose range of naltrexone, or pharmaceutically acceptable salts or solvates thereof, is about 0.004 mg/kg-0.71 mg/kg.

72. A composition according to claim 69, wherein the human dose range of naltrexone is 0.25 mg - 50 mg per day.

73. A composition according to claim 69, wherein the human dose range of naltrexone is 0.25 mg - 25 mg per day.

74.. A composition according to claim 68, wherein the human dose range of naltrexone is 0.25 mg - 15 mg per day.

75. A composition according to claim 69, wherein said composition is formulated into a single fixed combination dosage form and wherein, the composition is administered once, twice, three or four times through the day.

76. A composition of claim 69, wherein the therapeutically effective dose of the pharmaceutical composition is administered systemically, including but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical or sublingual routes.

77. A composition according to claim 69, wherein said combination is in a single dosage form, and wherein, said single dosage form is in the form of tablets, lozenges, troches, hard candies, liquid, powders, sprays, creams, salves and suppositories.

78. A composition according to claim 60 for treating, preventing and reversing pain.

79. A method of treating neuropathic pain, nociceptive pain with an allodynic component, migraine, trigeminal neuralgia, vulvodynia, irritable bowel syndrome, post herpetic neuralgia, or diabetic neuropathy in a mammal in need thereof, comprising administering to the mammal in a therapeutically effective amount of a combination according to Claims 69.

80. A method for the treatment of pain in a mammal comprising administration to said mammal a therapeutically effective amount of a composition comprising an opioid/TLR4 antagonist, or a dextro enantiomer of the opioid/TLR4 antagonist or a racemic mixture thereof, or a pharmaceutically acceptable salt or solvate thereof.

81. A method of claim 80 for the treatment of pain in a mammal comprising administration to said mammal a therapeutically effective amount of a composition predominantly comprising a dextro enantiomer of an opioid/TLR4 antagonist or a pharmaceutically acceptable salt or solvate thereof.

82. A method of claim 80 for the treatment of pain in a mammal comprising administration of a composition comprising a therapeutically effective amount of an opioid/TLR4 antagonist. The opioid/TLR4 antagonist is selected from a group consisting of naltrexone, norbinaltorphimine, nalmefene, naloxone, nalorphine, methylnaltrexone, samidorphan, cyprodime, naltrindole, amentoflavone, naltriben, norbinaltorphimine, 6-beta-naltrexol, and 6-alpha-naltrexol, including all enantiomeric and epimeric forms as well as the

appropriate mixtures thereof, as well as pro drugs or metabolites thereof or pharmaceutically acceptable salts or solvates of any thereof.

83. A method of claim 80 for treatment of pain in a mammal comprising administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of naltrexone, naloxone or nalmefene, or a predominantly dextro enantiomeric mixture of naltrexone, naloxone or nalmefene, or a pharmaceutically acceptable salt or solvate of any thereof.

84. A method of claim 80 for treatment of pain in a mammal comprising administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of naltrexone or a pharmaceutically acceptable salt or solvate thereof.

85. A method of claim 80 for treatment of pain in a mammal comprising administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt or solvate thereof.

86. A method of claim 80 for treatment of pain in a mammal comprising administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of nalmefene or a pharmaceutically acceptable salt or solvate thereof.

87. A method of claim 81 for treatment of pain in a mammal comprising administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of predominantly dextro naltrexone mixture or a pharmaceutically acceptable salt or solvate thereof.

88. A method of claim 81 for treatment of pain in a mammal comprising administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of predominantlydextro naloxone mixture or a pharmaceutically acceptable salt or solvate thereof.

89. A method of claim 81 for treatment of pain in a mammal comprising administration to said mammal a pharmaceutical composition containing a therapeutically effective amount of predominantly dextro nalmefene mixture or a pharmaceutically acceptable salt or solvate thereof.

90. A method of claim 80 for treatment of pain wherein the amount of the opioid/TLR4 antagonist varies from about 0.004mg/kg to about 4.3mg/kg, preferably from about

0.004mg/kg to about 0.71mg/kg, and most preferably from about 0.004mg/kg to about 0.21 mg/kg.

91. A method of claim 80 for treatment of pain wherein the amount of naltrexone varies from about 0.004mg/kg to about 4.3mg/kg, preferably from about 0.004mg/kg to about 0.71mg/kg, and most preferably from about 0.004mg/kg to about 0.21 mg/kg.

92. A method of claim 81 for treatment of pain wherein the amount of dextro naltrexone varies from about 0.004mg/kg to about 4.3mg/kg, preferably from about 0.004mg/kg to about 0.71mg/kg, and most preferably from about 0.004mg/kg to about 0.21 mg/kg.

93. A method of claim 80 for treatment of pain wherein the human dose range of naltrexone, or a pharmaceutically acceptable salt or solvate thereof, varies from about 0.25mg - 50mg per day, preferably from about 0.25mg - 25mg per day, most preferably from about 0.25 mg – 15 mg per day wherein said dose is formulated into a single dosage form.

94. The method of claim 81 wherein the composition comprises greater than 50% to 60% dextro enantiomer.

95. The method of claim 81 wherein the composition comprises greater than 60% dextro enantiomer.

96. The method of claim 81 wherein the composition comprises greater than 70% dextro enantiomer.

97. The method of claim 81 wherein the composition comprises greater than 80% dextro enantiomer.

98. The method of claim 81 wherein the composition comprises greater than 90% dextro enantiomer.

99. A method of claim 80 for treatment of pain wherein the single fixed dosage form is administered once, twice, three or four times through the day.

100. A method of claim 80 for treatment of pain wherein a therapeutically effective dose is administered systemically, via routes of mucosal, nasal, oral, parenteral, gastrointestinal, tropical or sublingual.

101. A method of claim 80 for treatment of pain wherein said composition is in a single dosage form, and said single dosage form is in the form of tablets, lozenges, troches, hard candies, liquid, powders, sprays, creams, salves and suppositories.

102. A method of claim 80 for treatment of pain wherein the pharmaceutical composition is used for the treatment, prevention and reversal of neuropathic pain, back pain, chronic pain, diabetic neuropathic pain, trigeminal neuralgia pain, phantom limb pain, complex regional pain syndrome pain, post herpetic pain, causalgia pain, idiopathic pain, inflammatory pain, cancer pain,postoperative pain, fibromyalgia pain, headache pain, migraine pain, allodynia pain, vulvodynia pain, interstitial cystitis pain, irritable bowel syndrome (IBS), arthritic joint pain and tendinitis.

103. A method of claim 80 wherein the pharmaceutical composition is used for the treatment, prevention and reversal of nociceptive pain with an allodynic component.

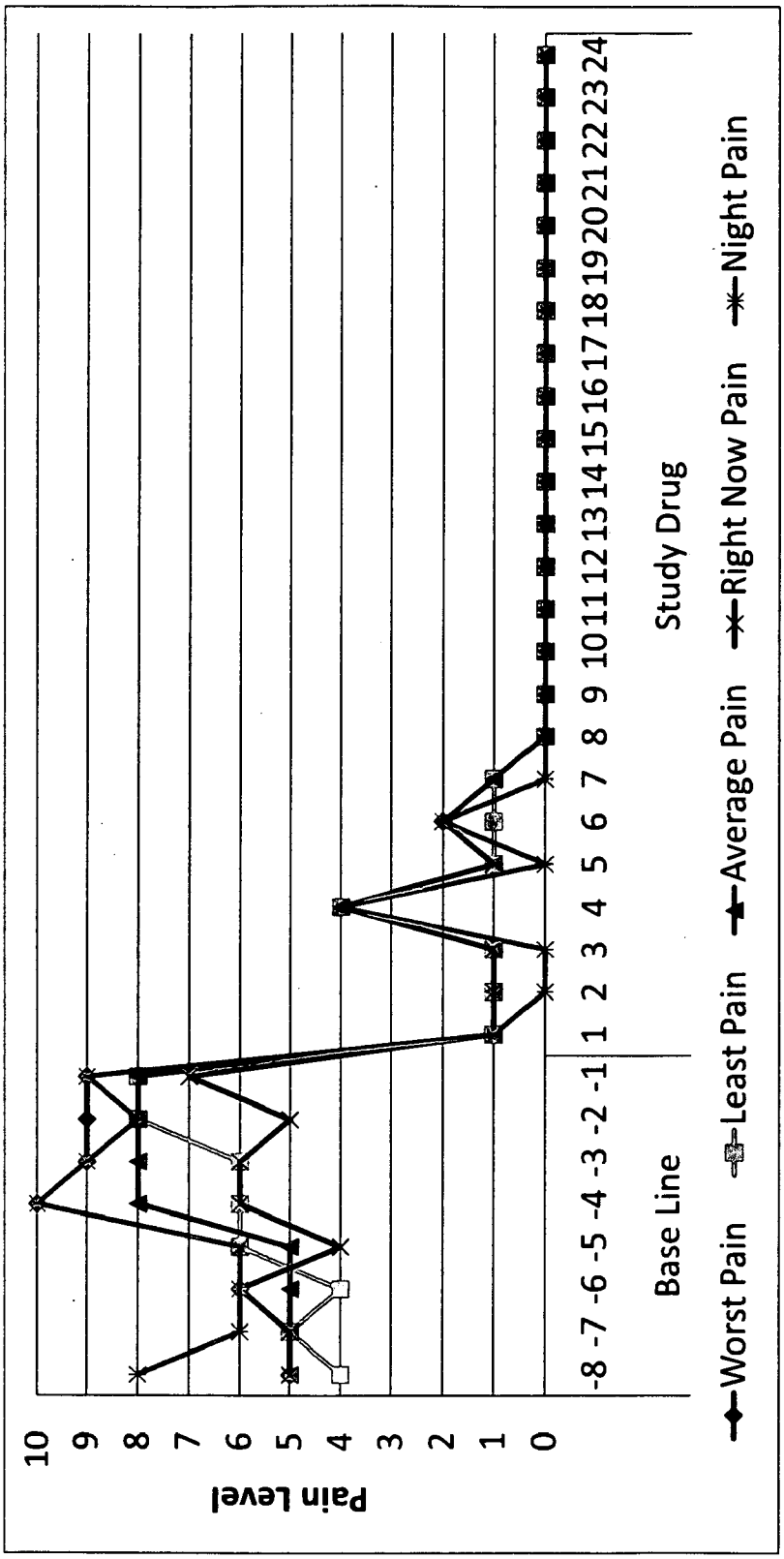

Figure 1

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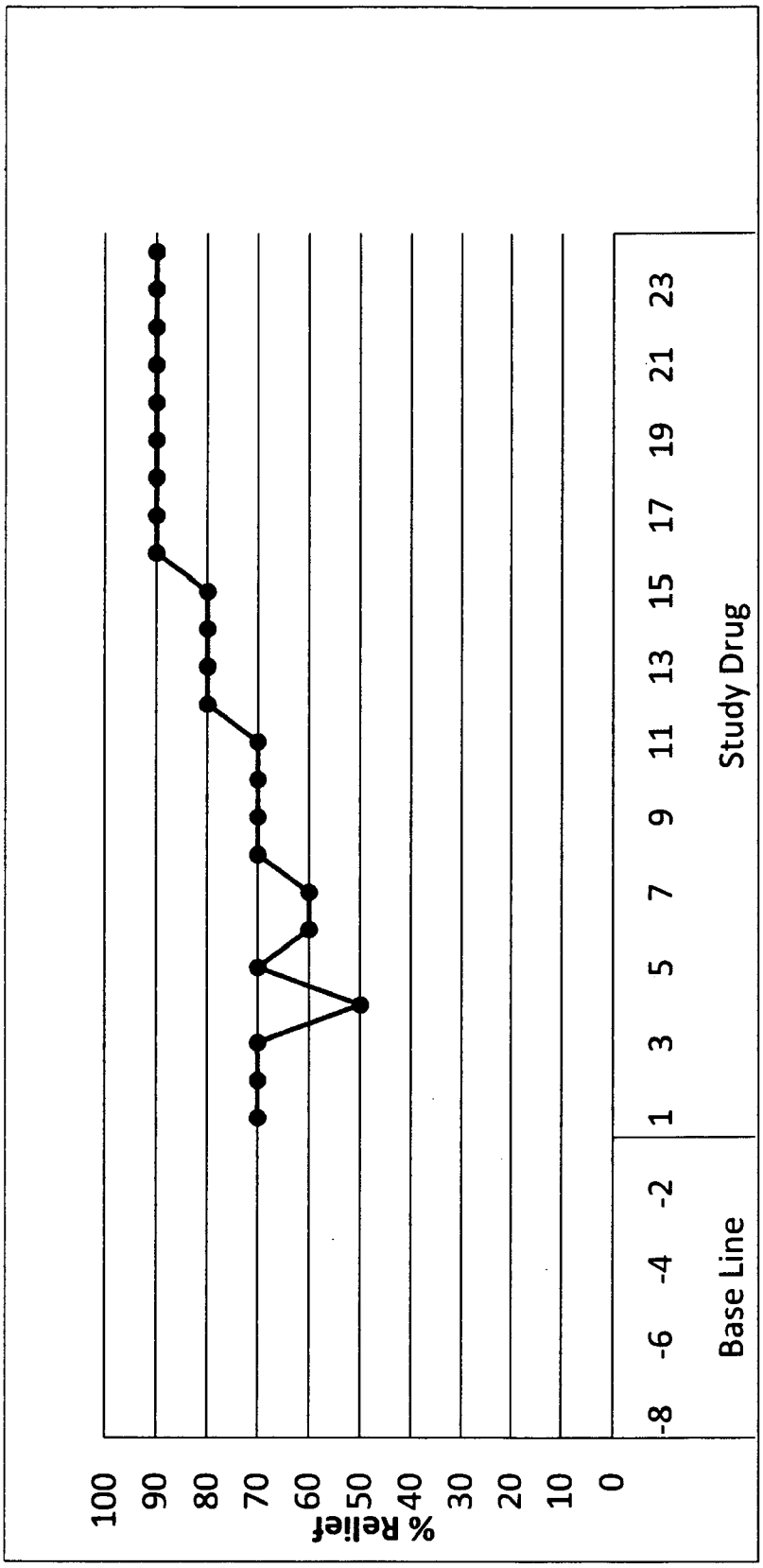

Figure 2

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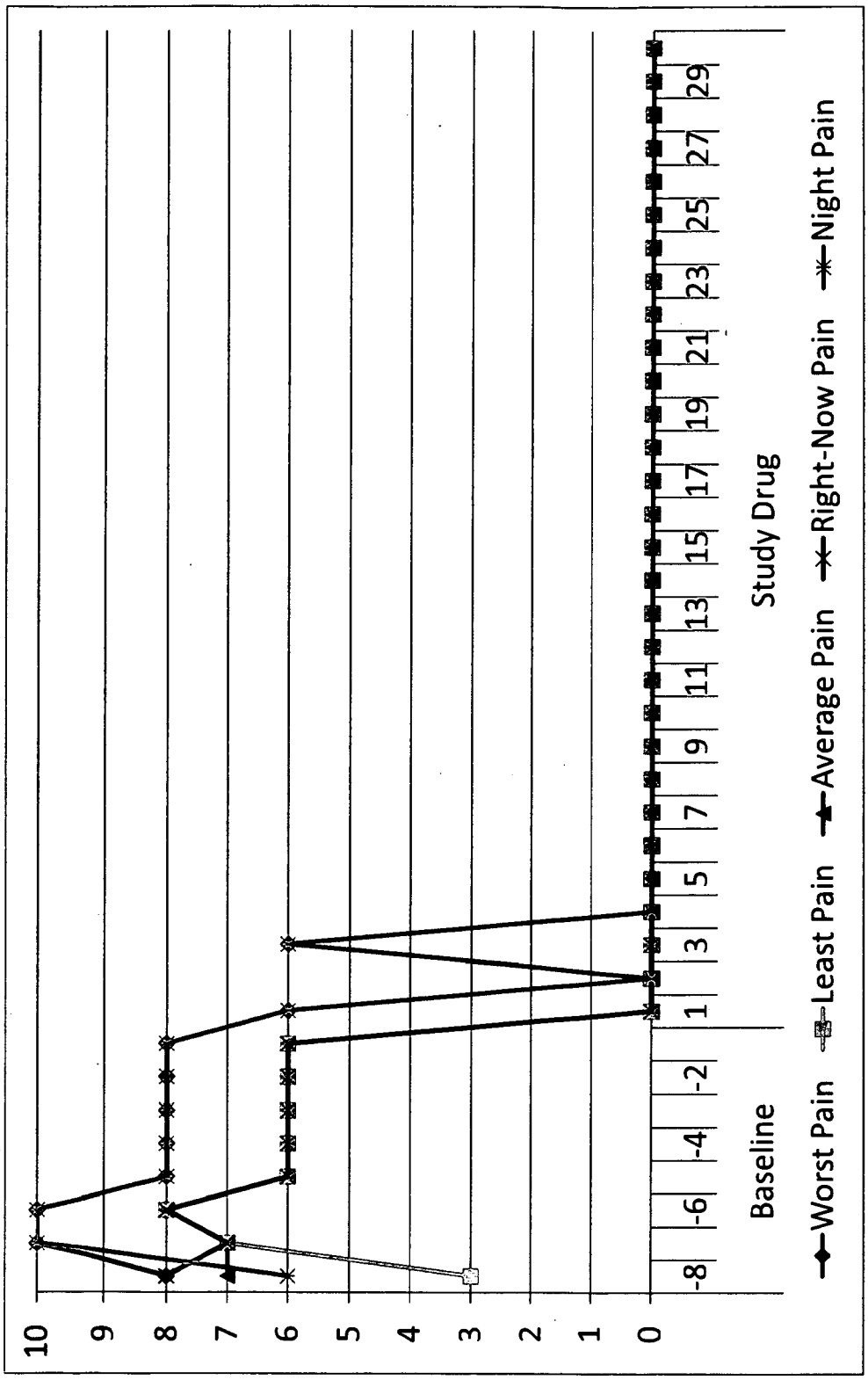

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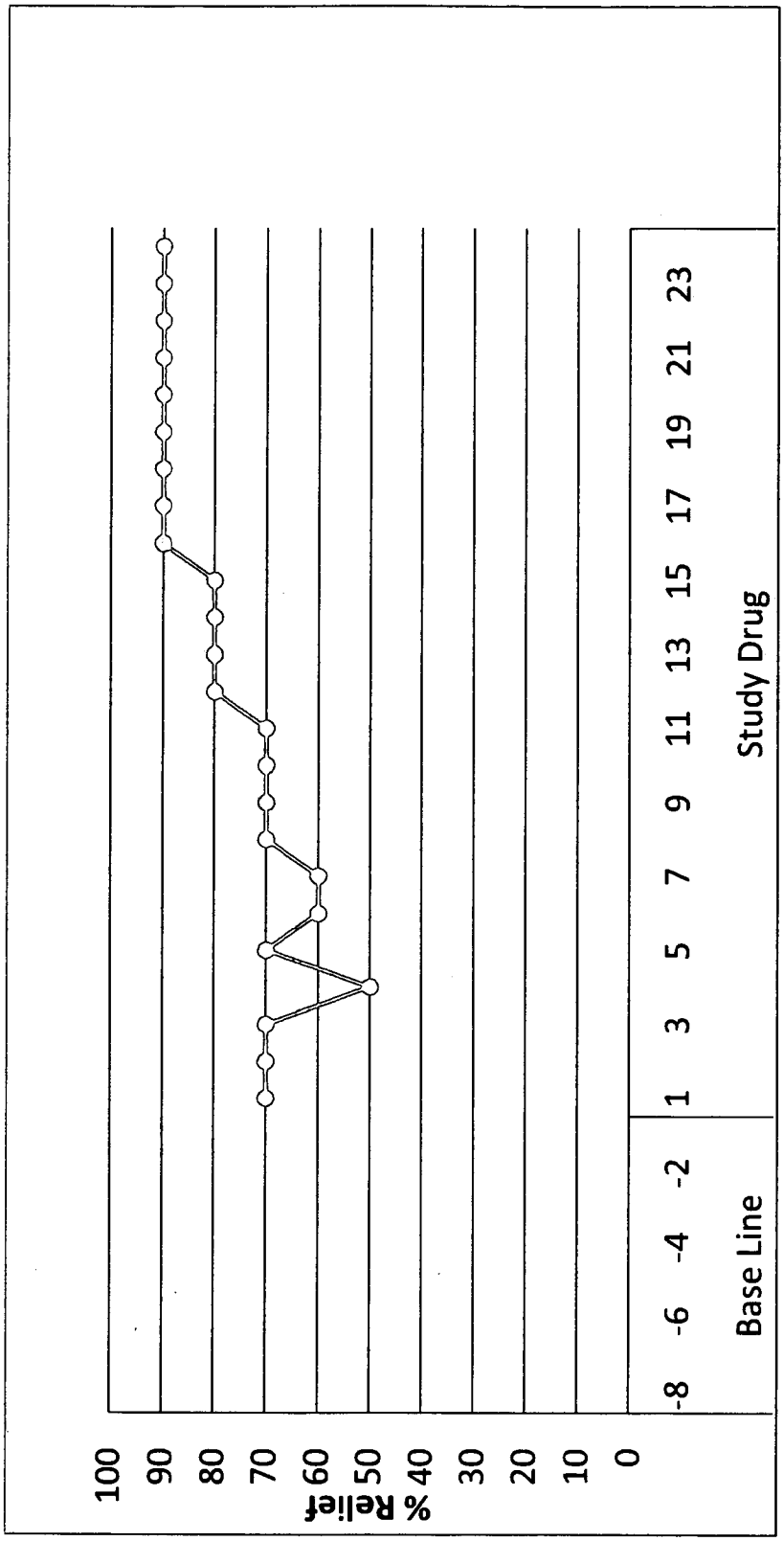

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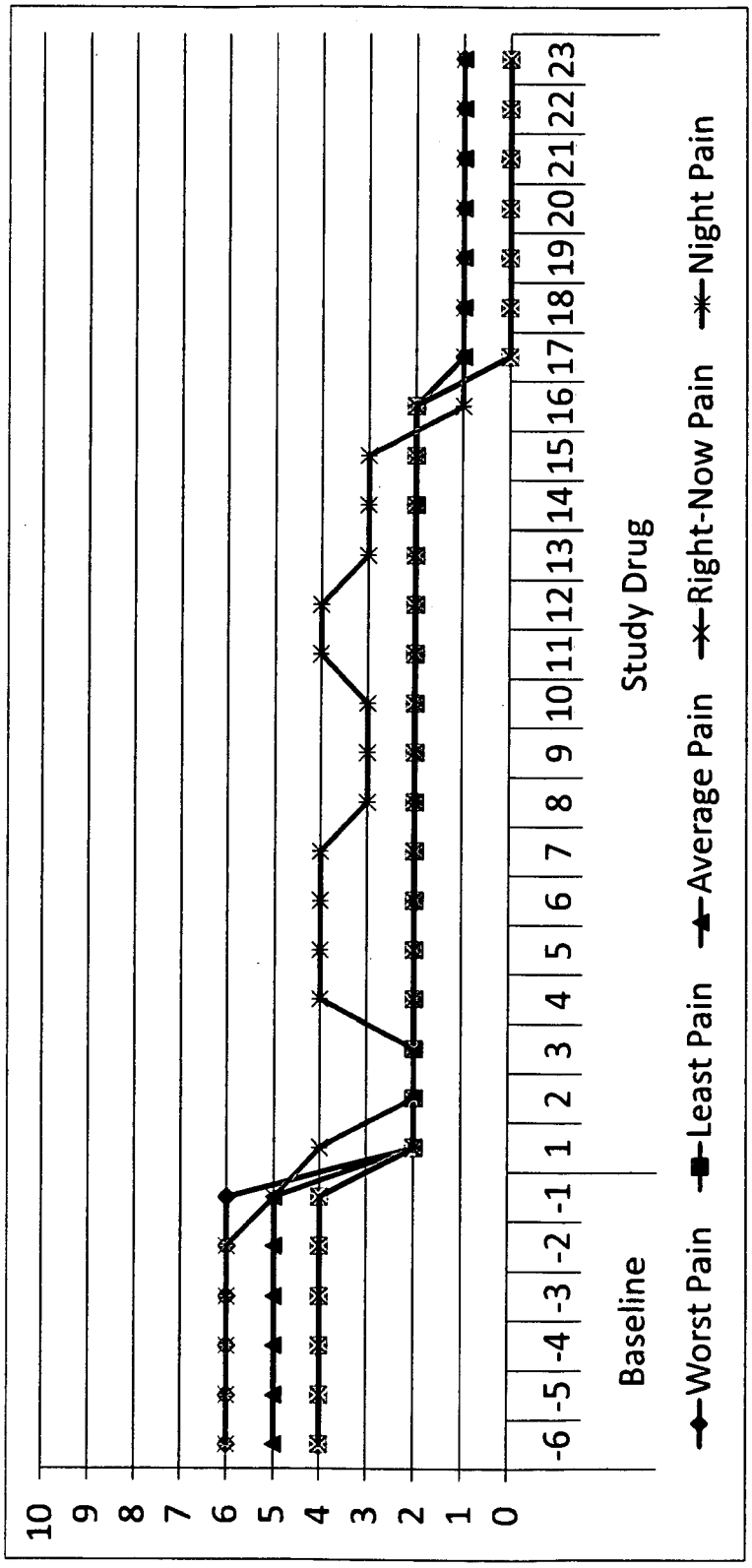

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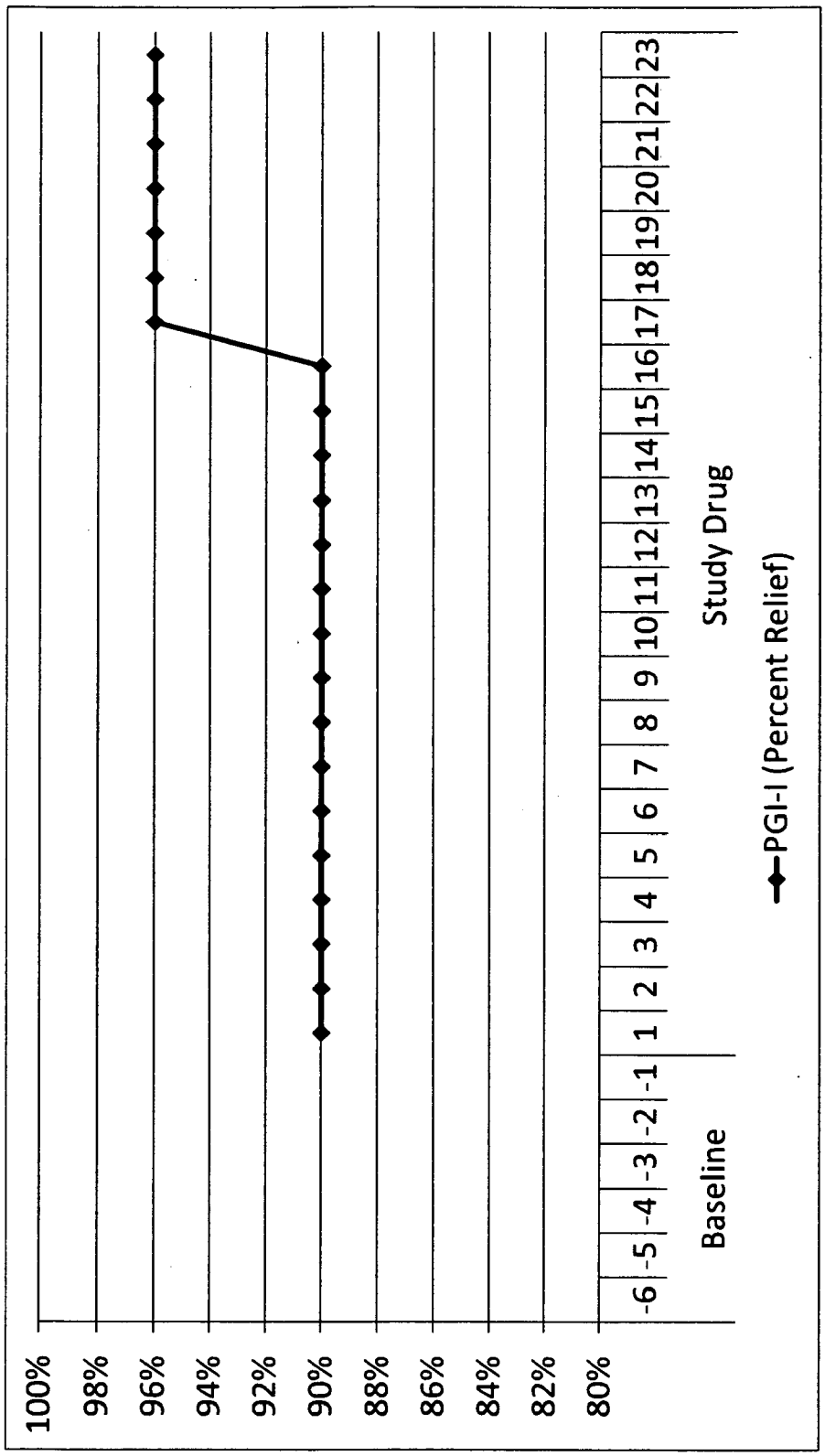

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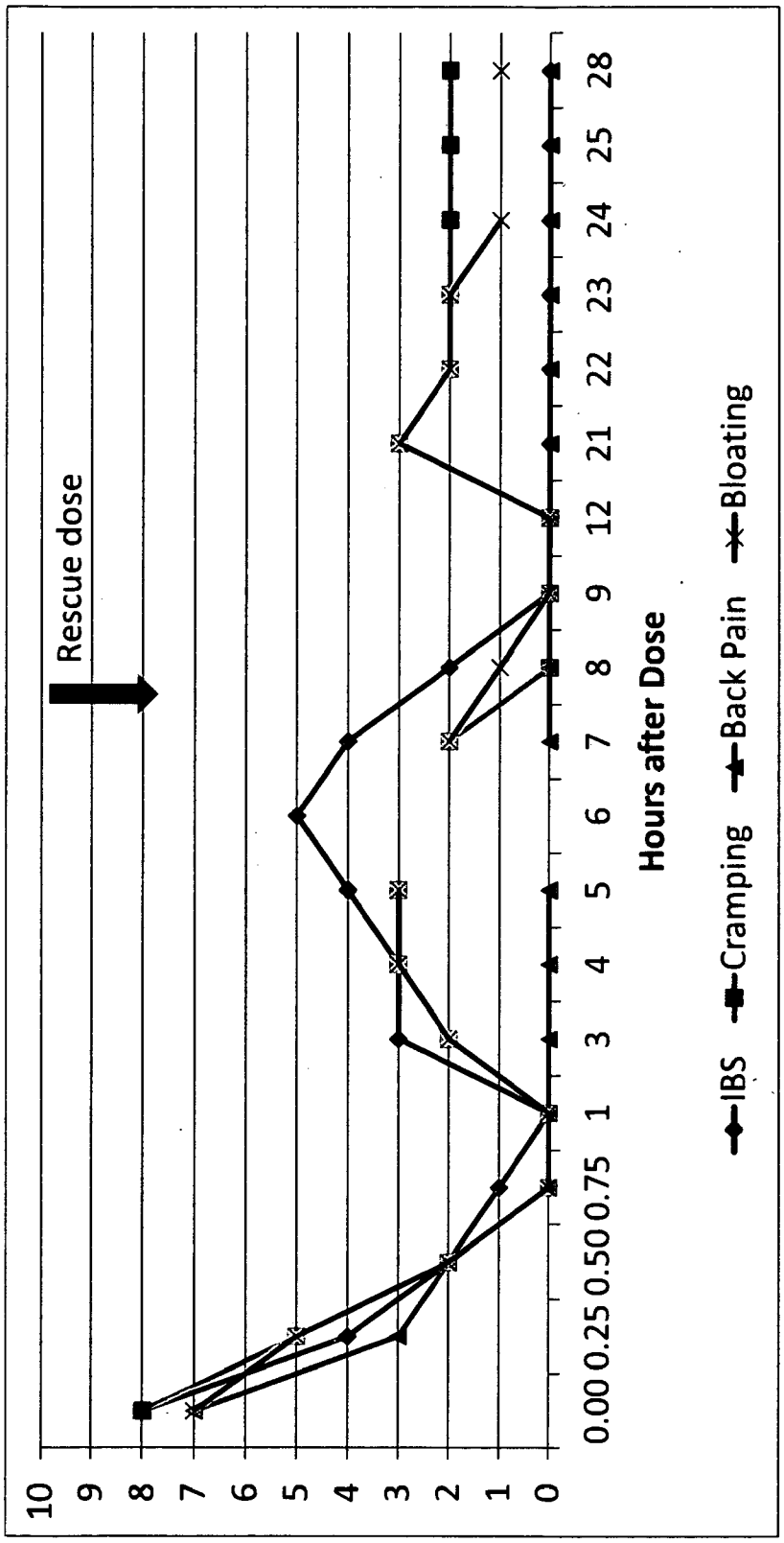

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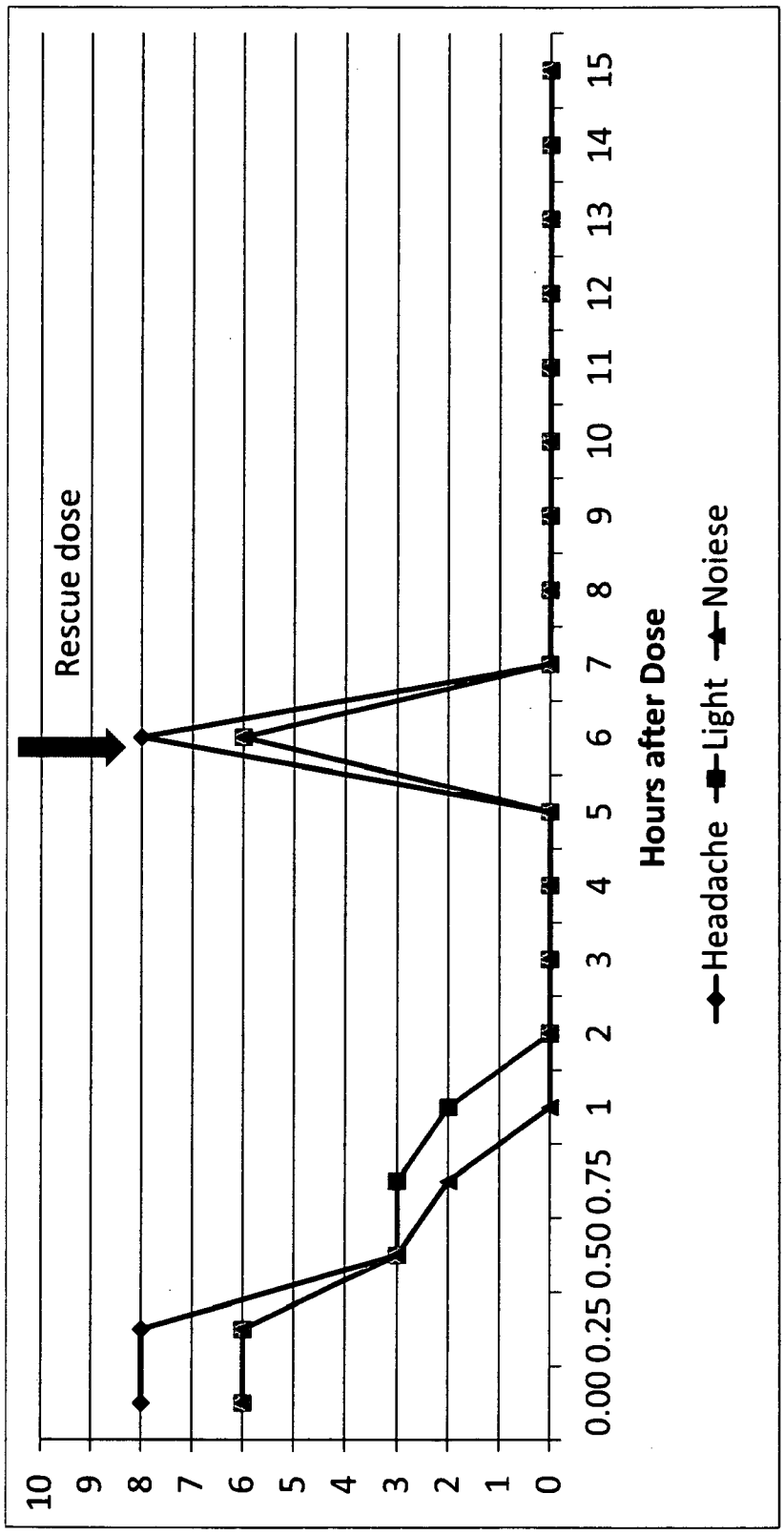

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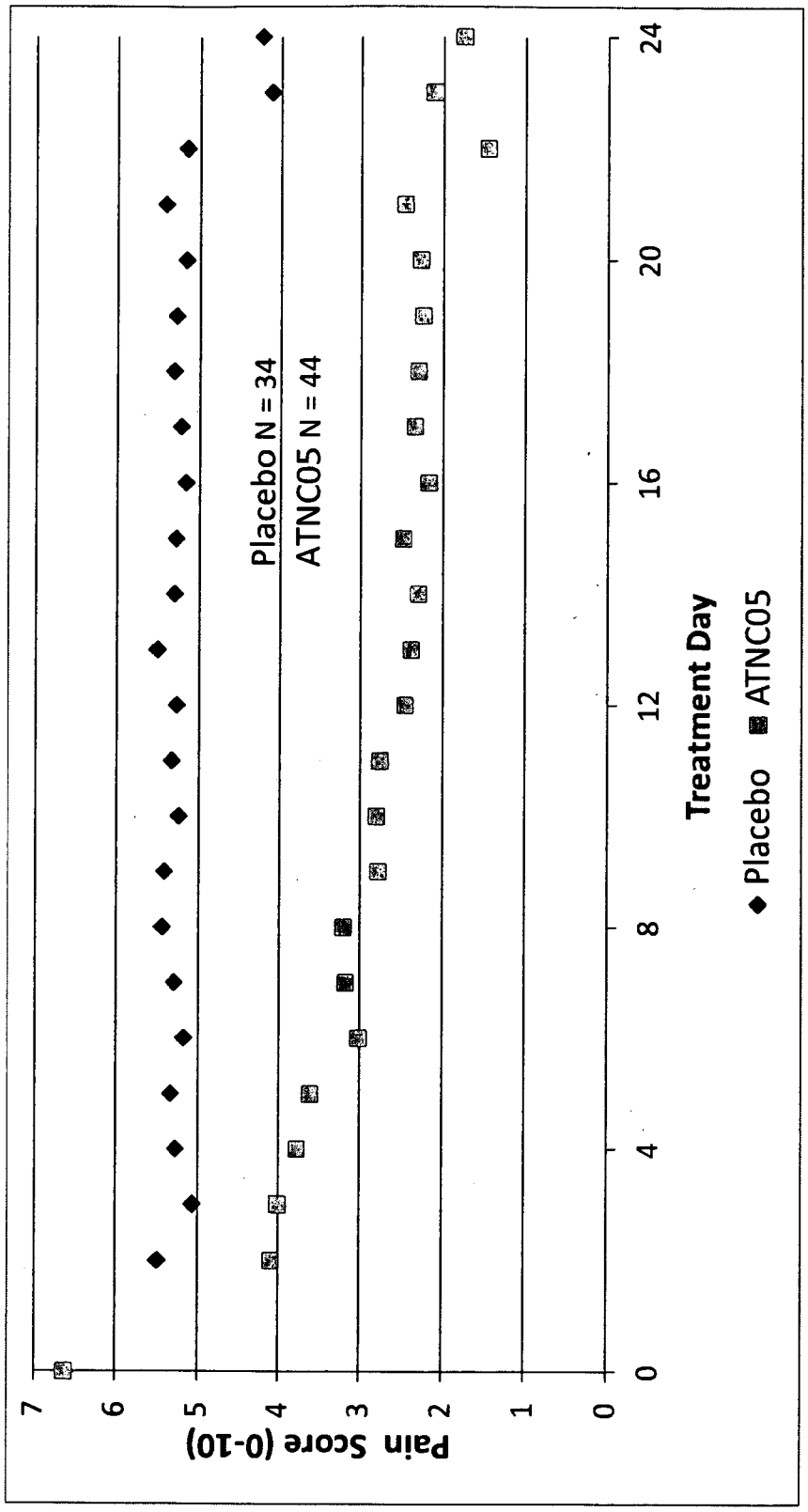

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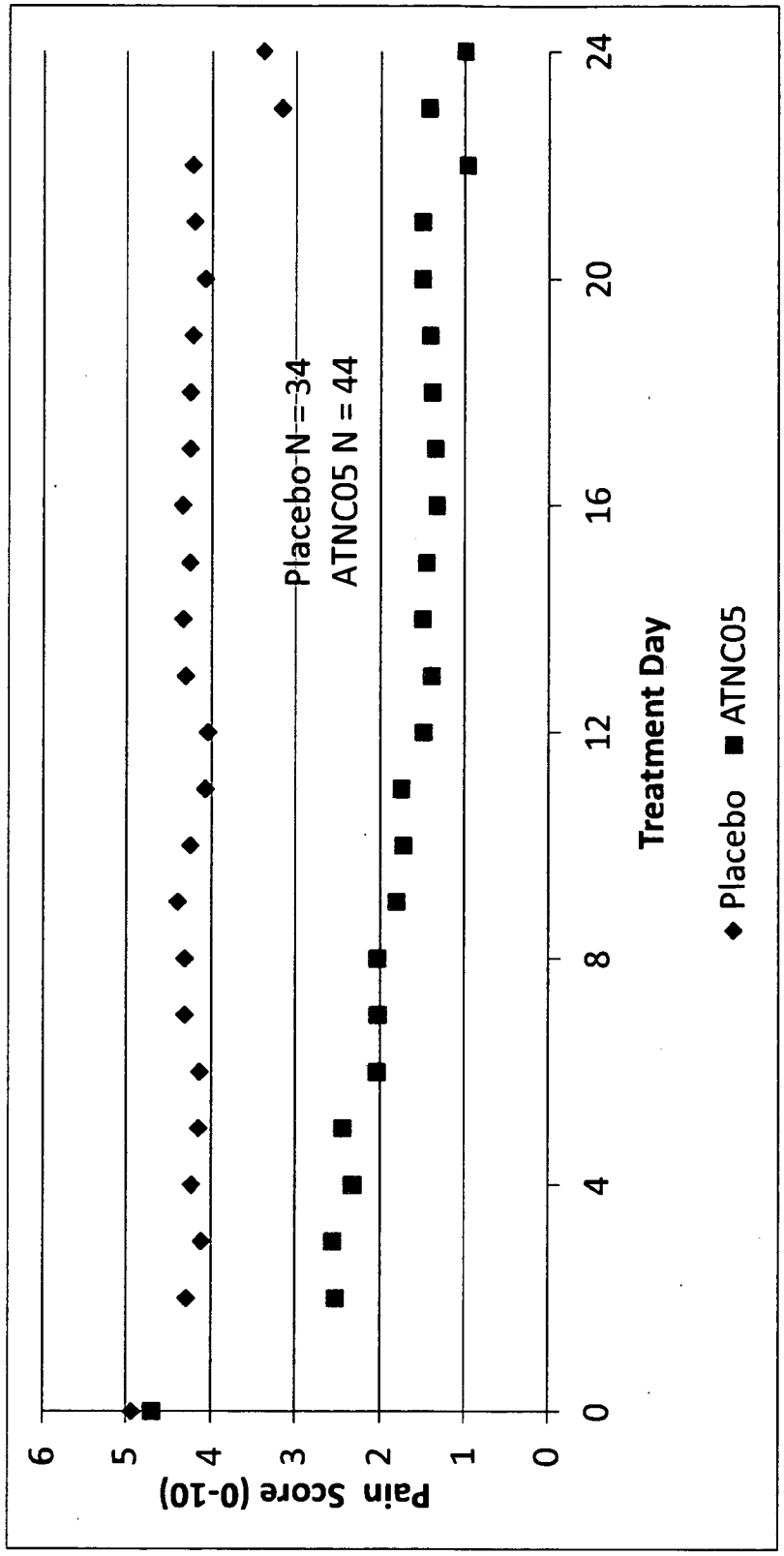

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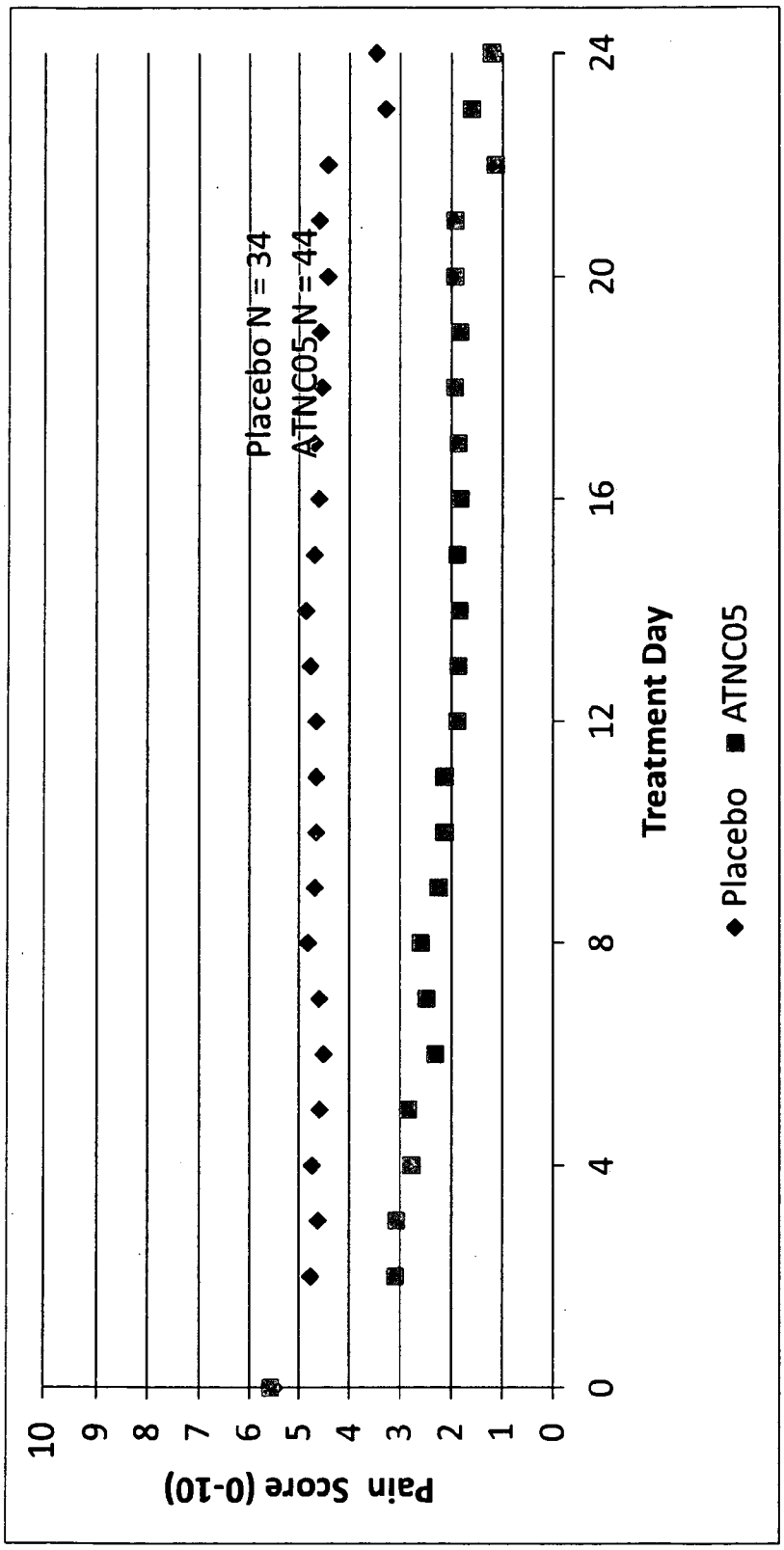

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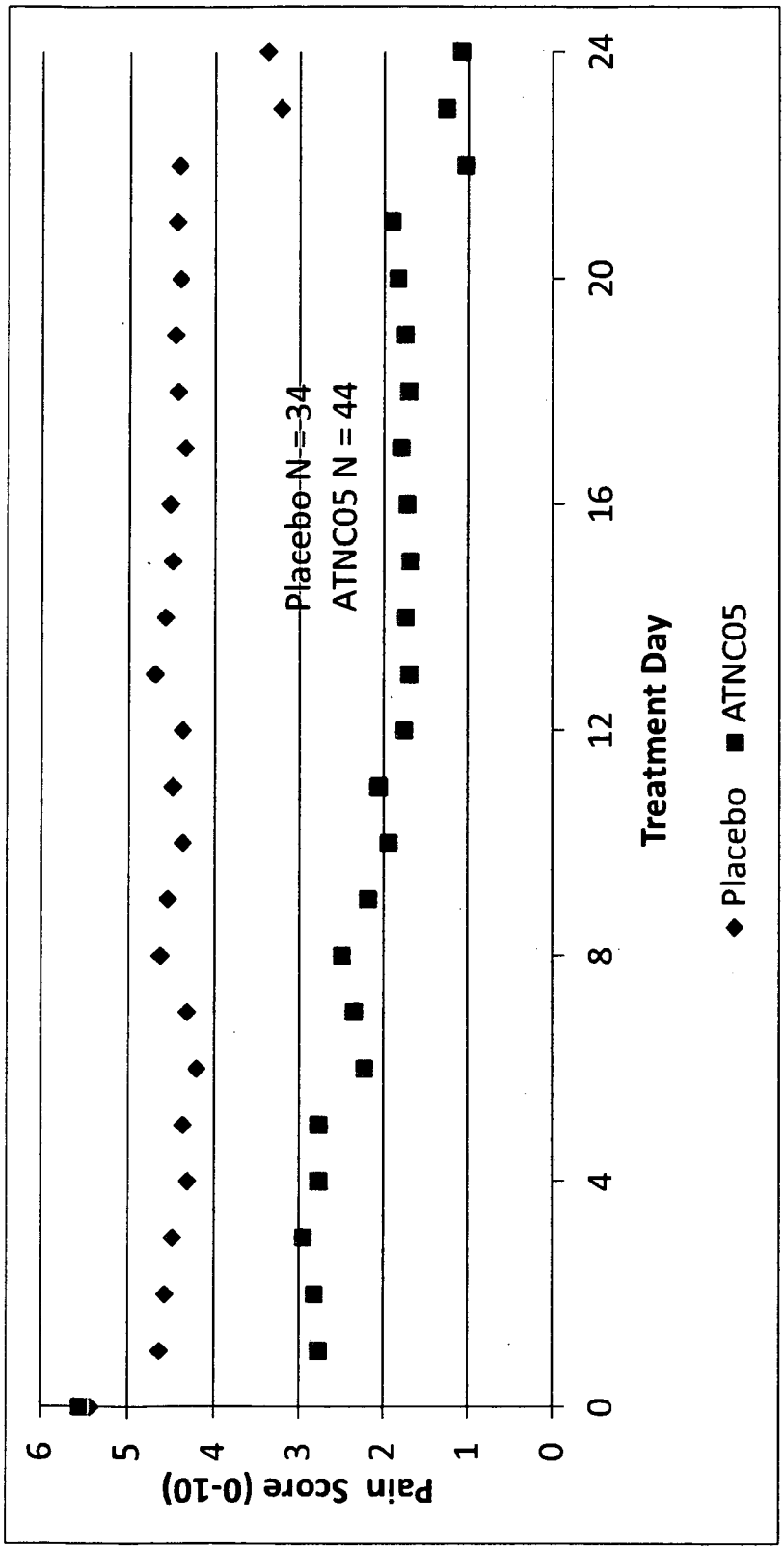

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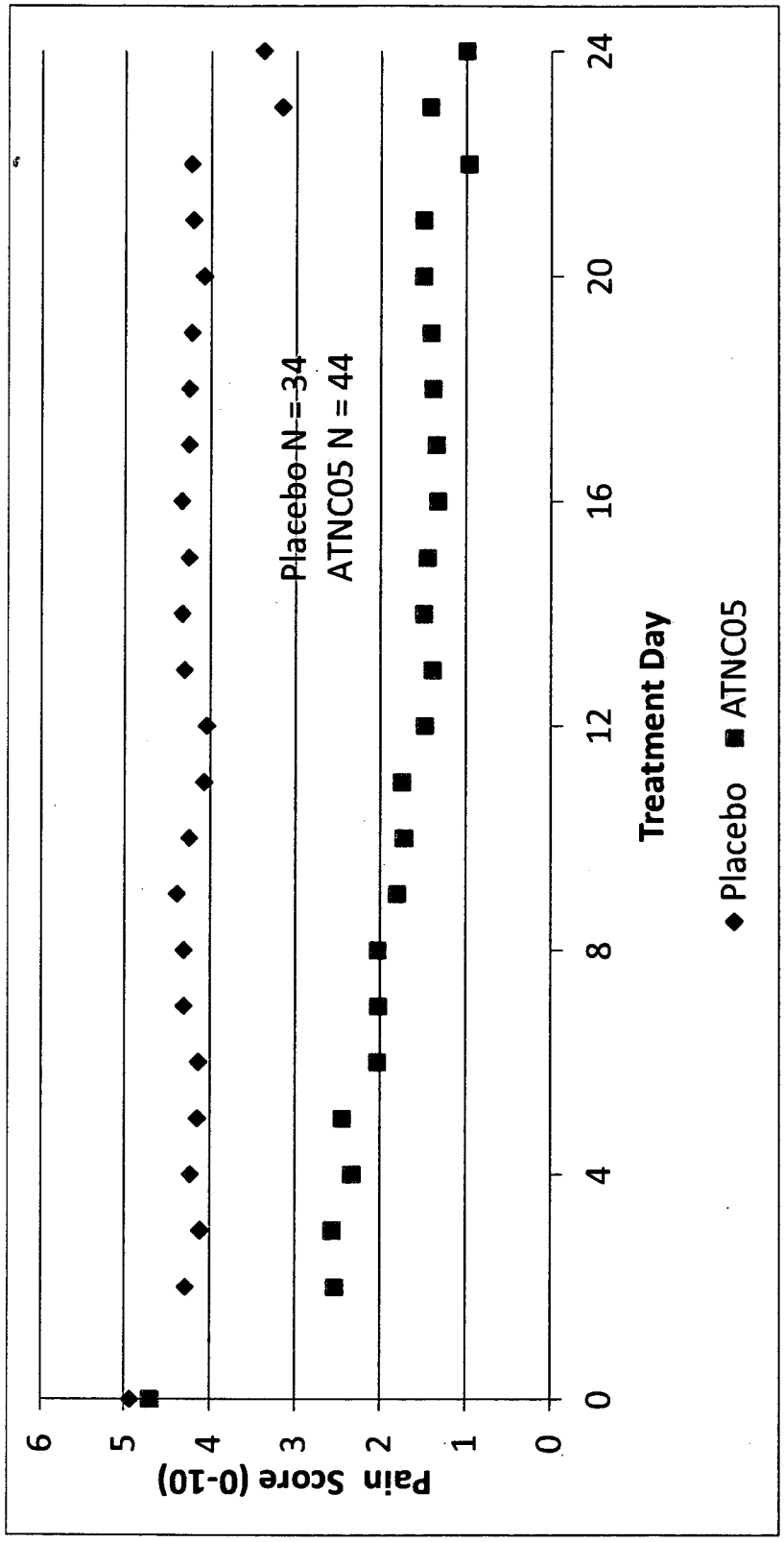
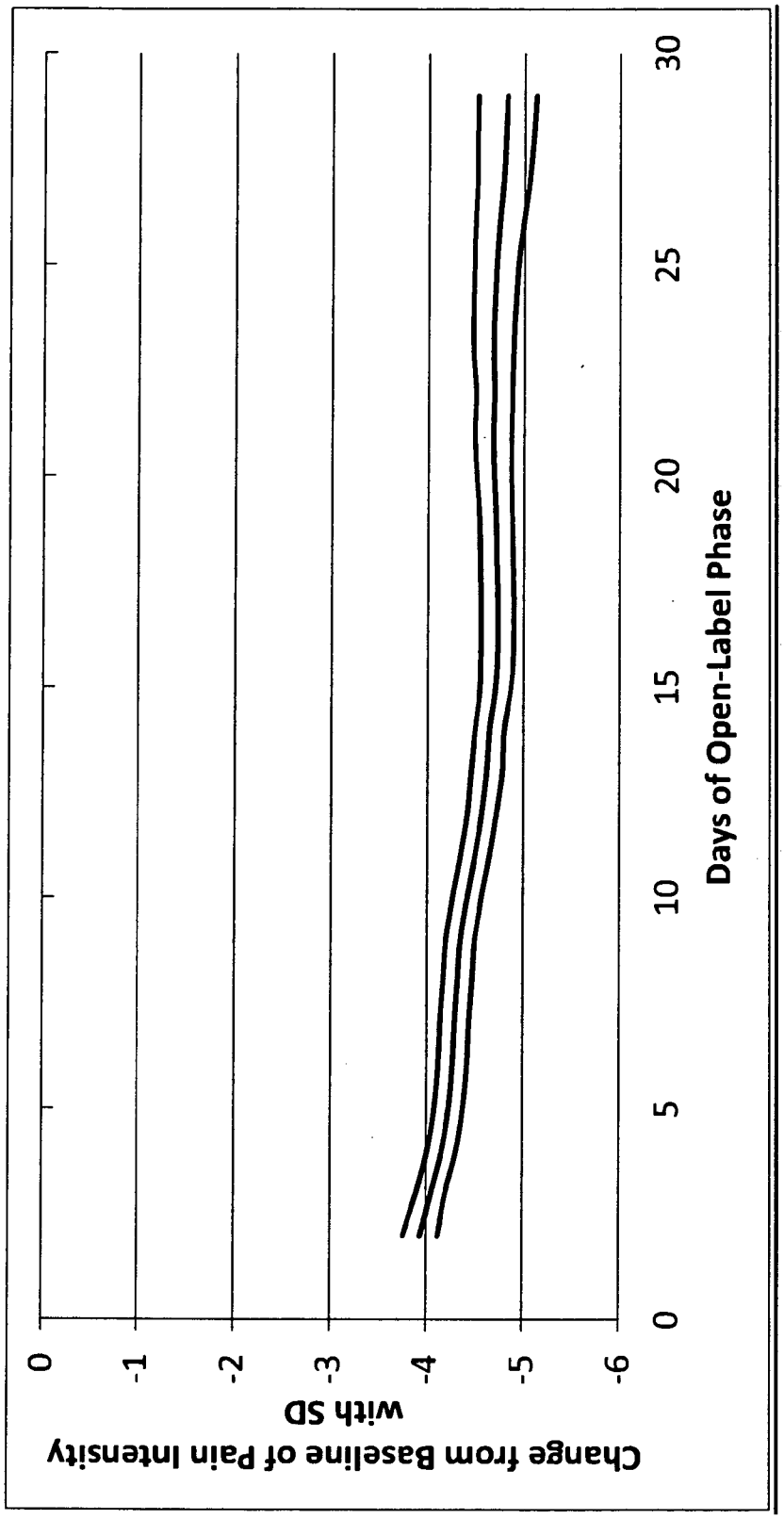


Figure 13



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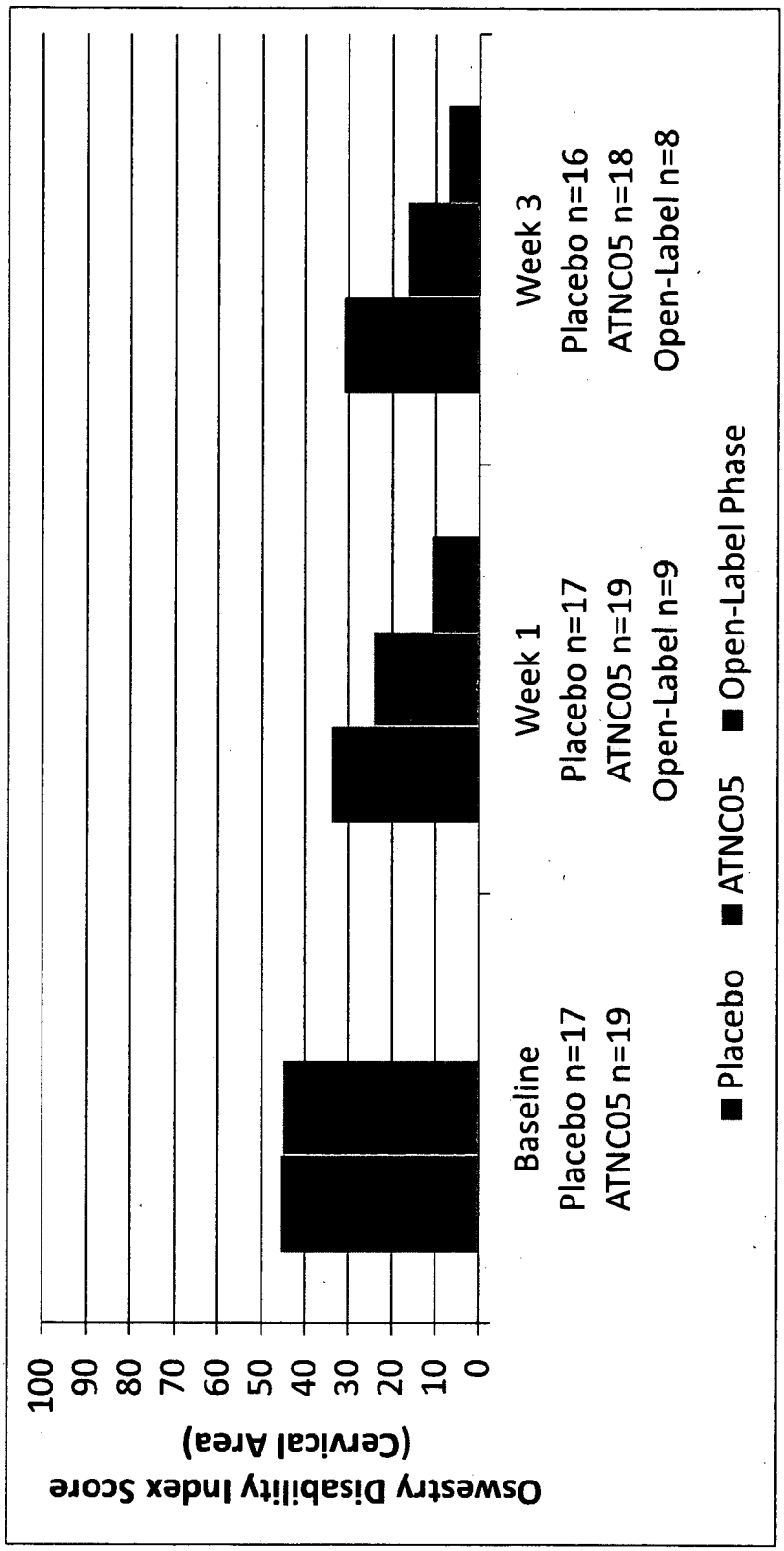

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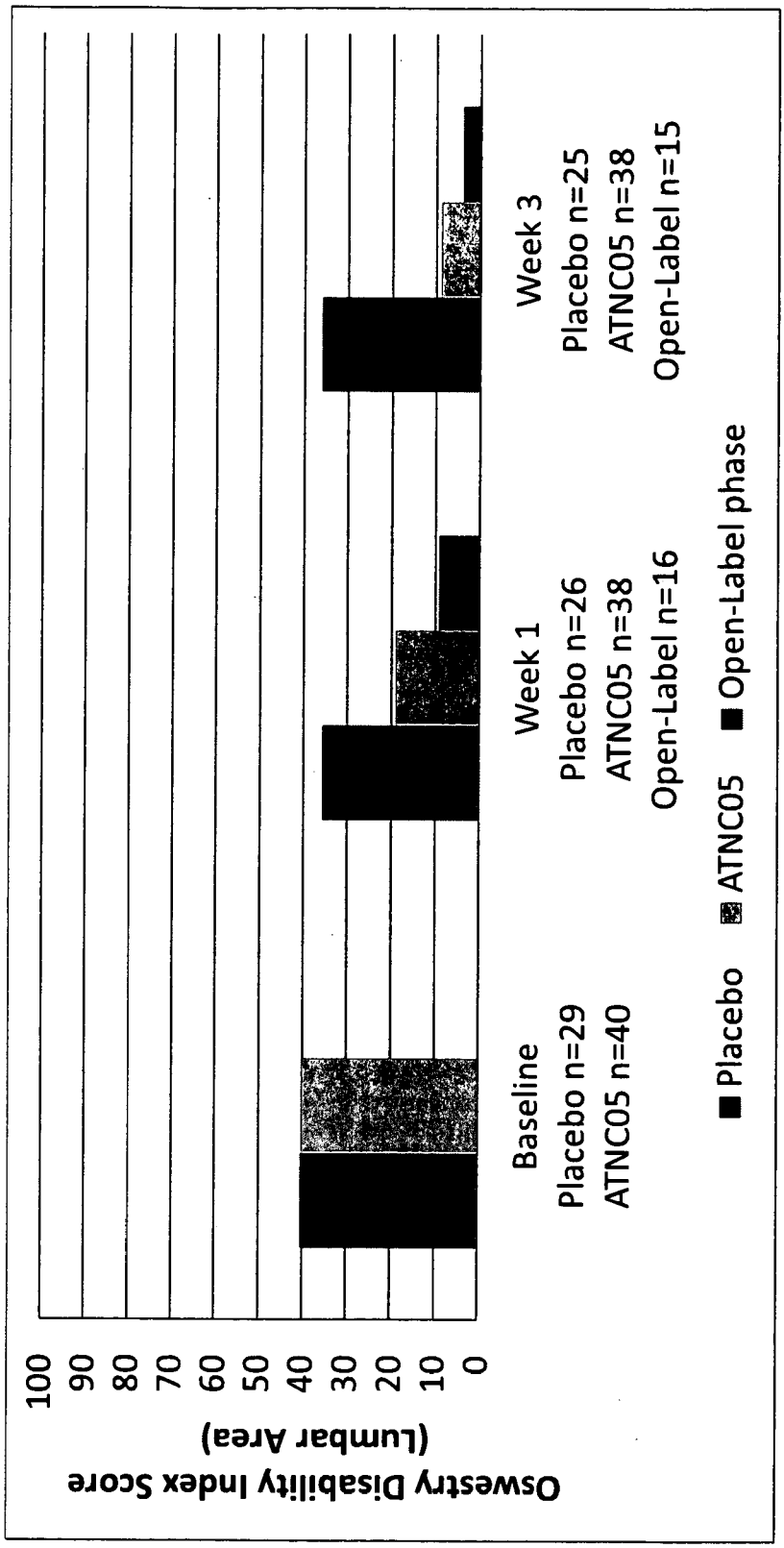

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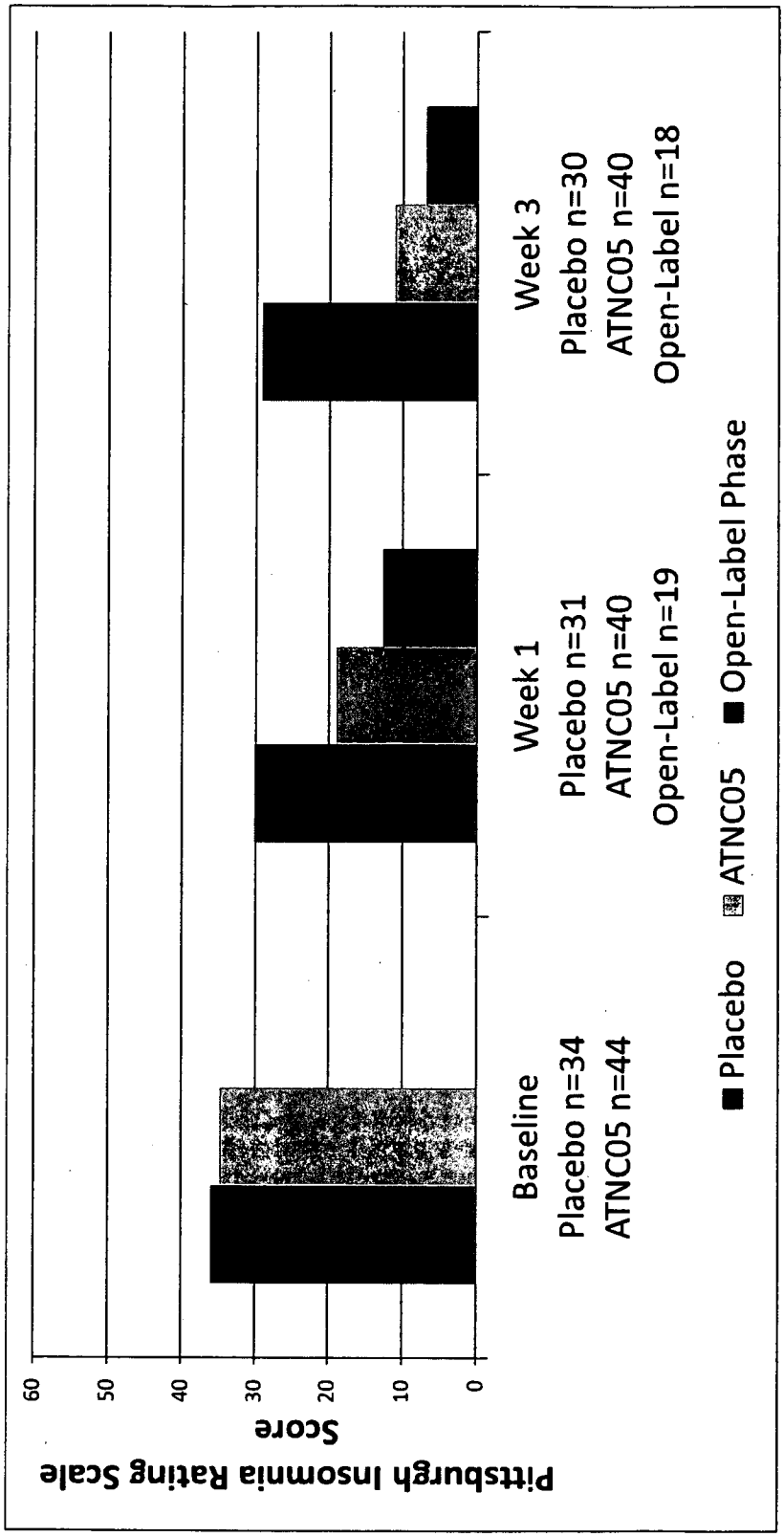

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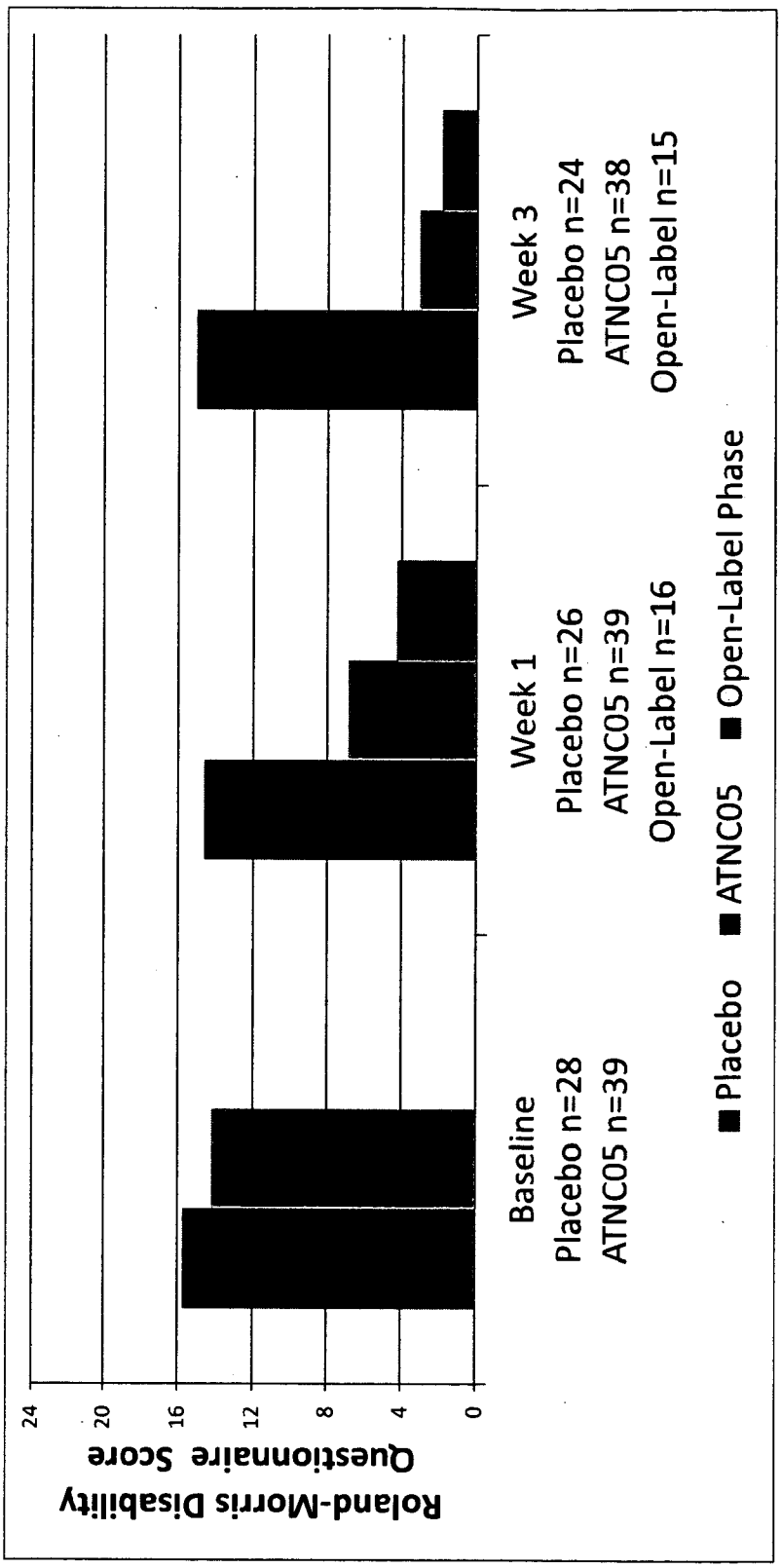

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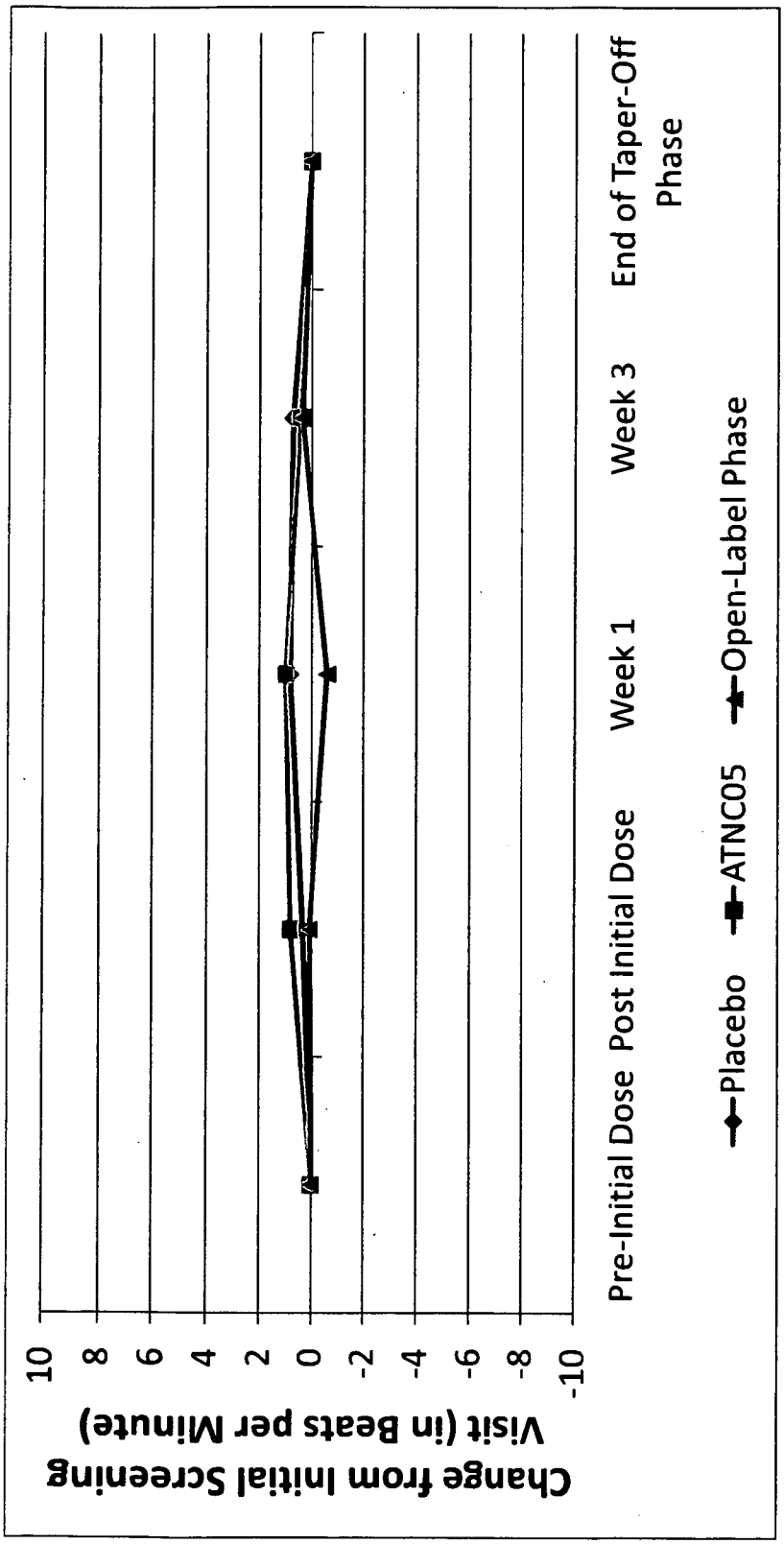

Figure 19

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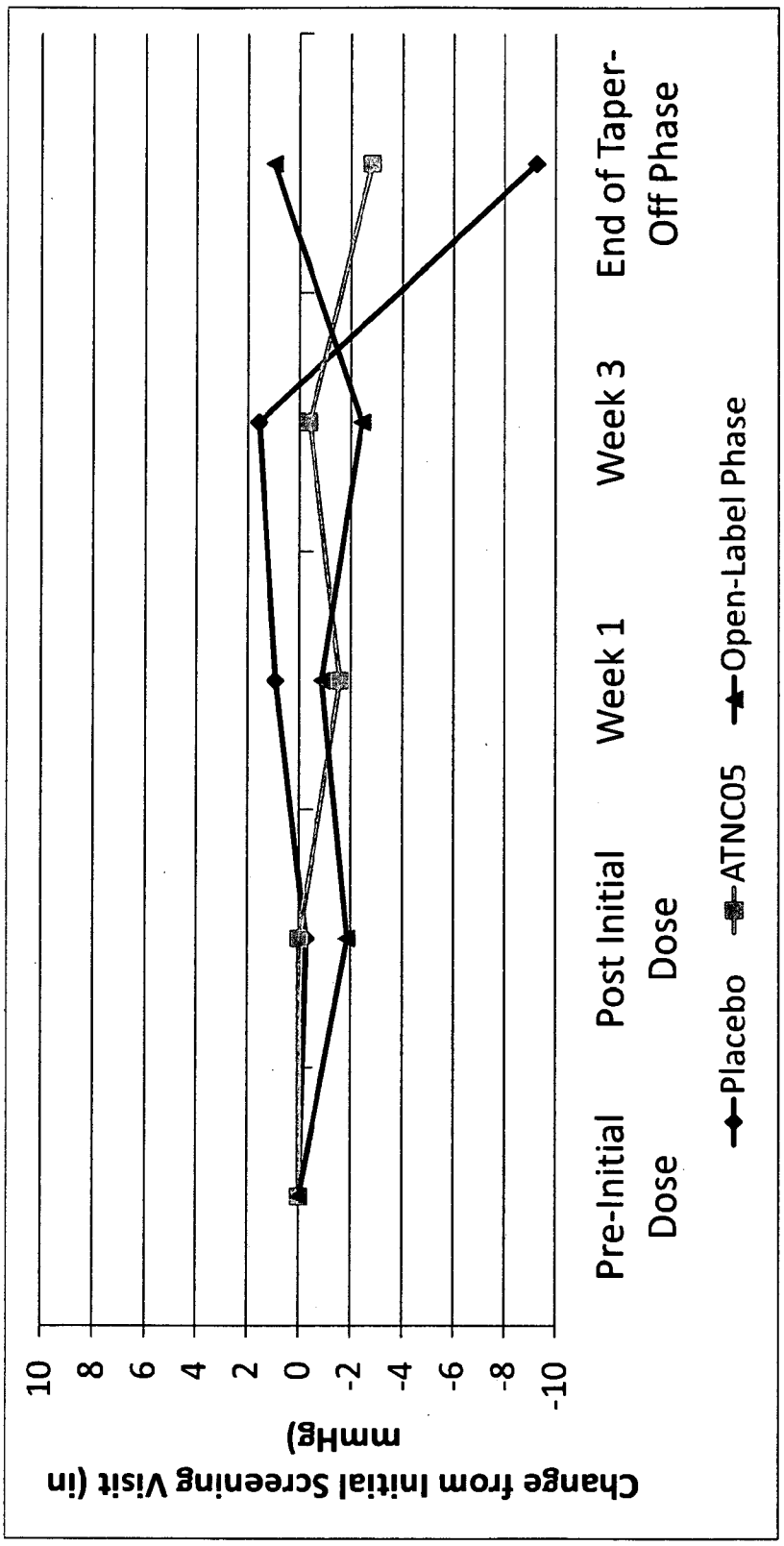

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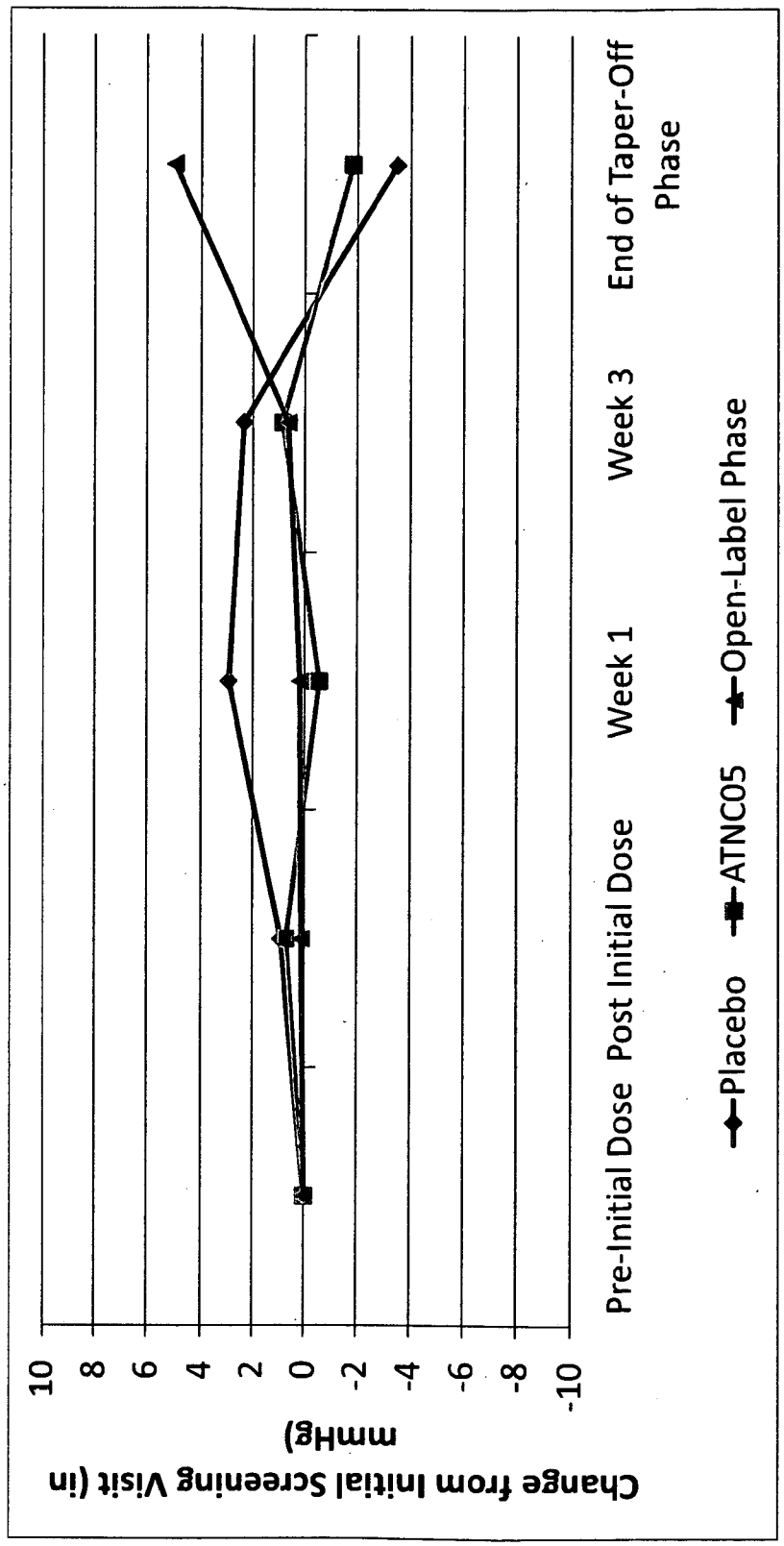

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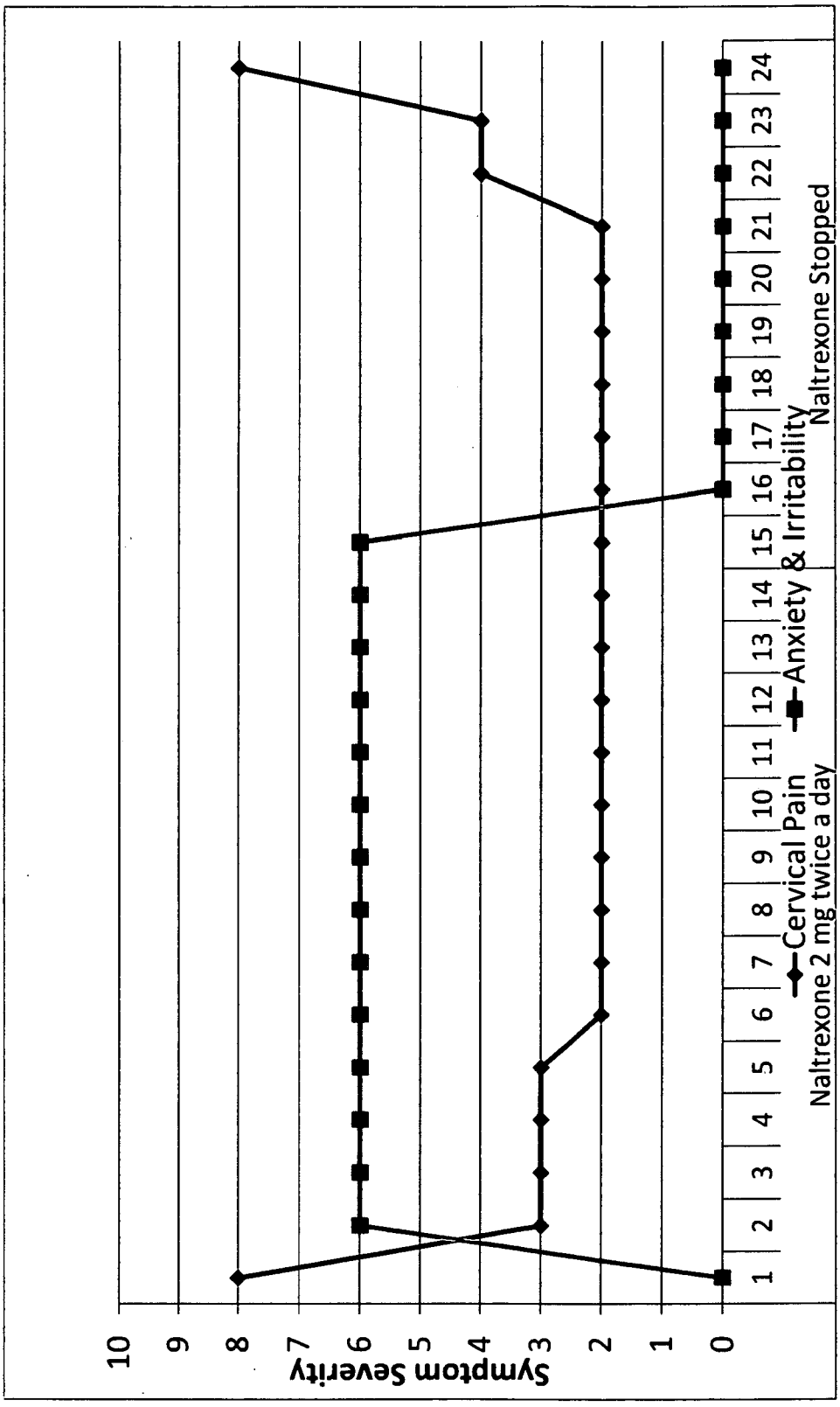

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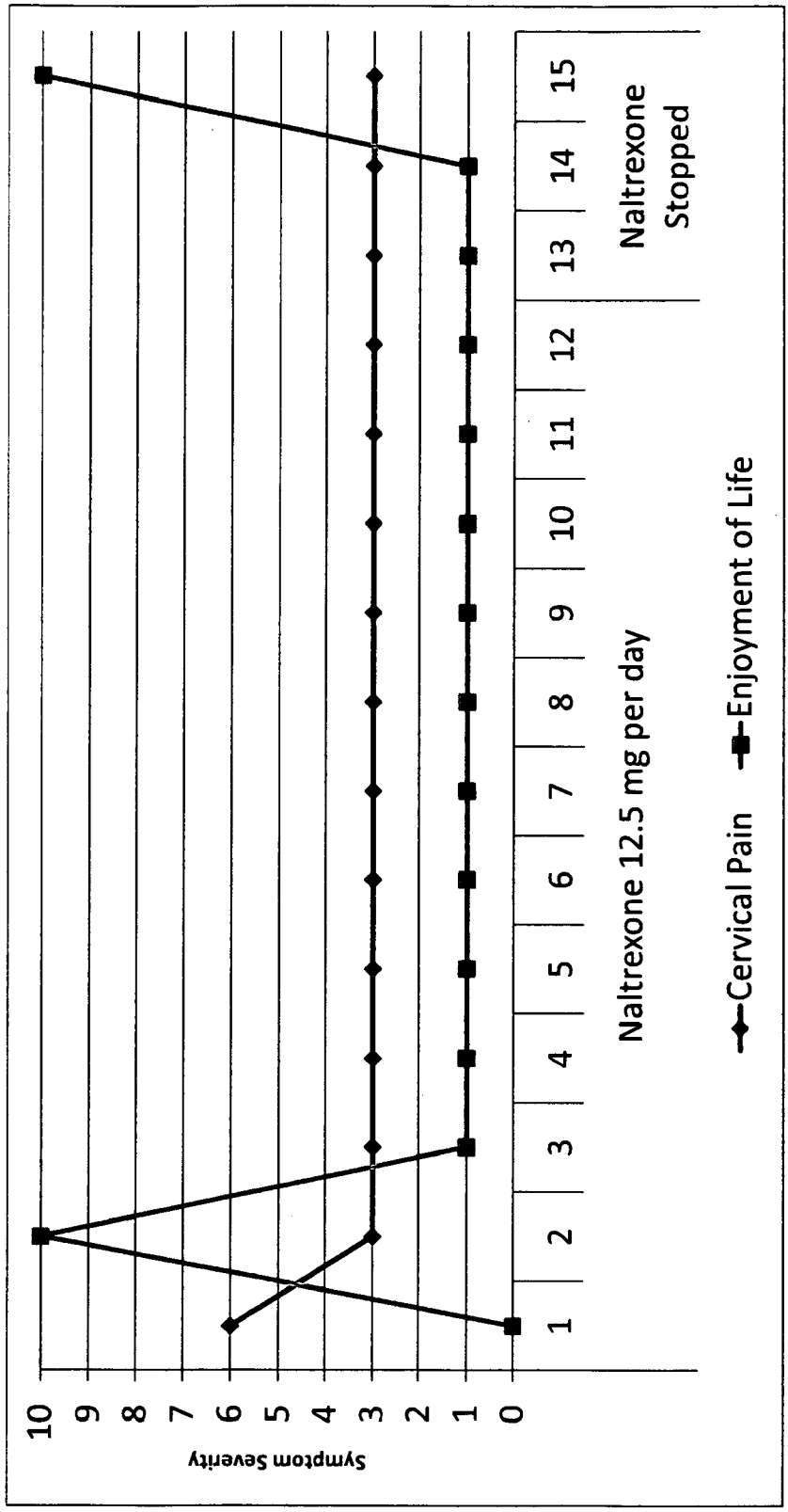

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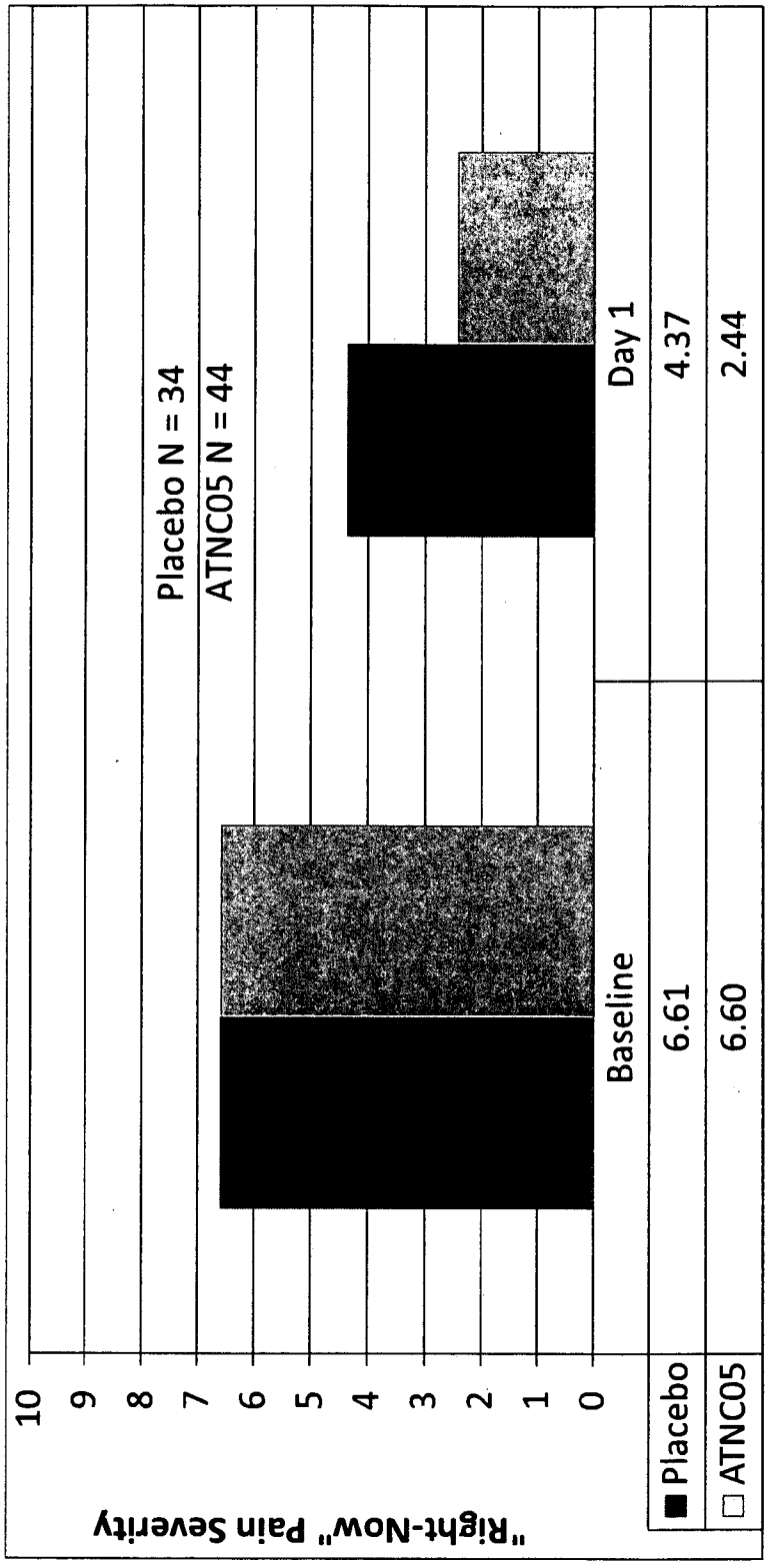

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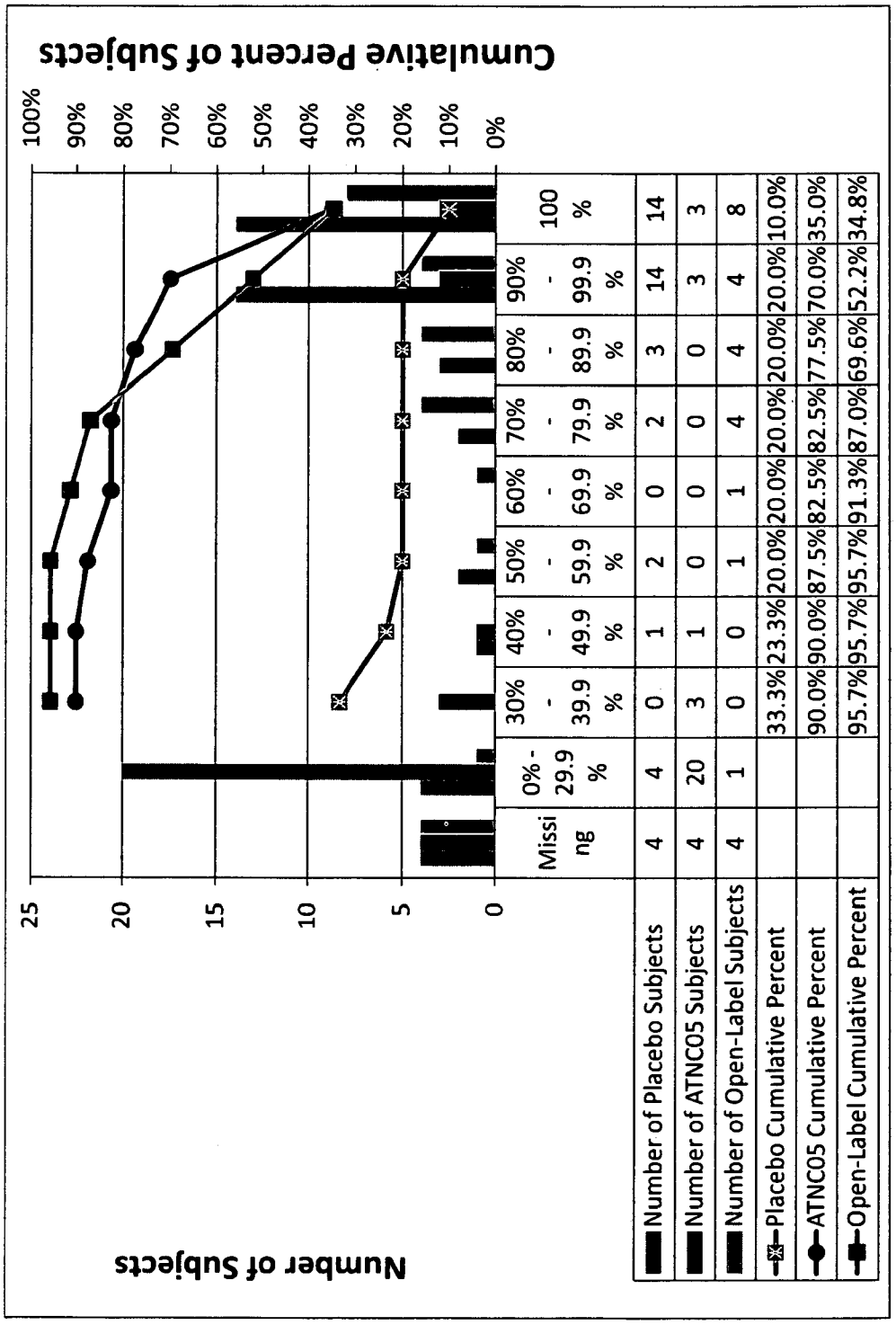

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Number of Placebo Subjects	4	4	0	1	2	0	2	3	14	14	
Number of ATNC05 Subjects	4	20	3	1	0	0	0	0	3	3	
Number of Open-Label Subjects	4	1	0	0	1	1	4	4	4	8	
Placebo Cumulative Percent			33.3%	23.3%	20.0%	20.0%	20.0%	20.0%	20.0%	10.0%	
ATNC05 Cumulative Percent			90.0%	90.0%	87.5%	82.5%	82.5%	77.5%	70.0%	35.0%	
Open-Label Cumulative Percent			95.7%	95.7%	95.7%	91.3%	87.0%	69.6%	52.2%	34.8%	

Replacement Sheets

Figure 25

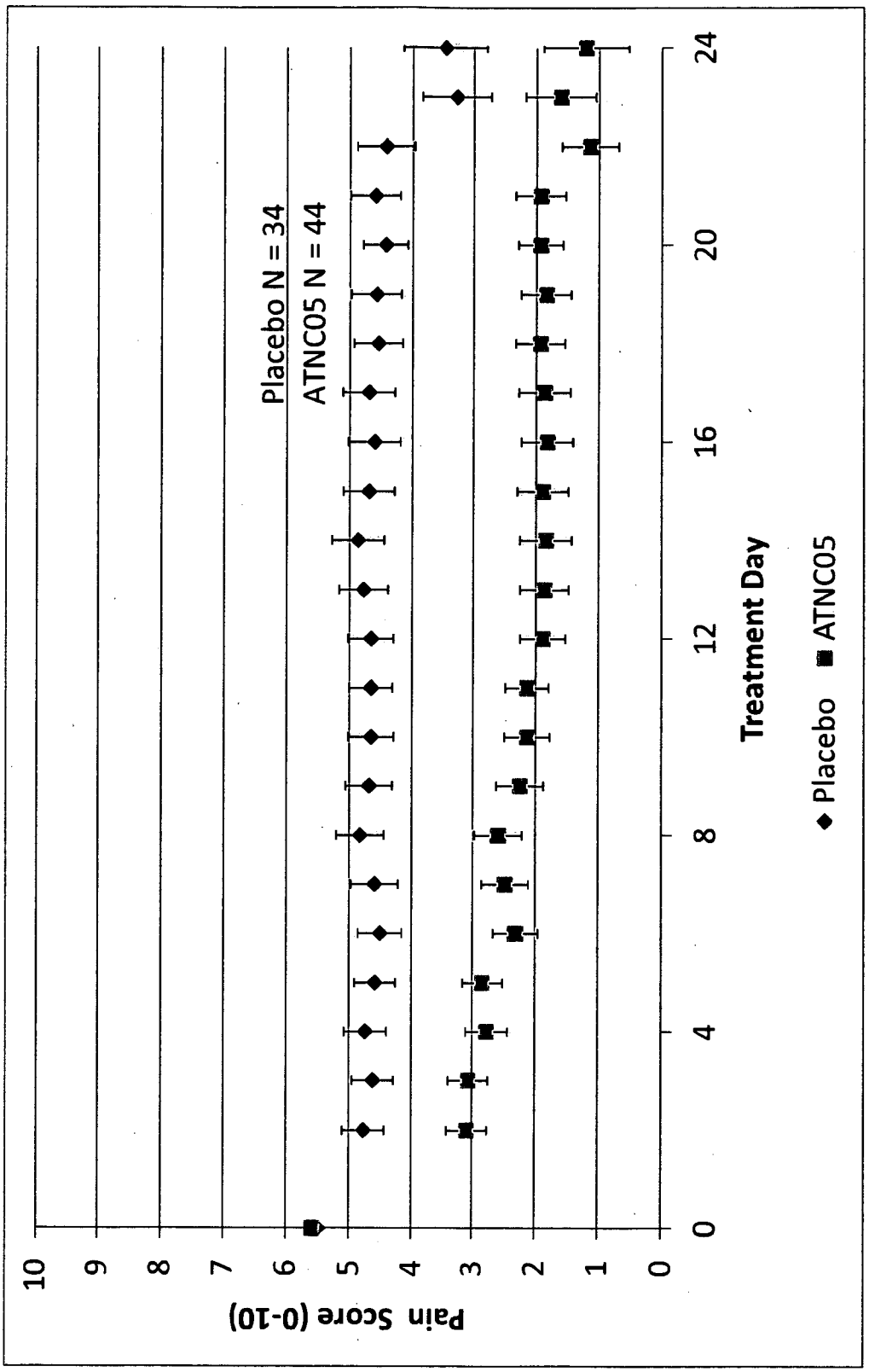
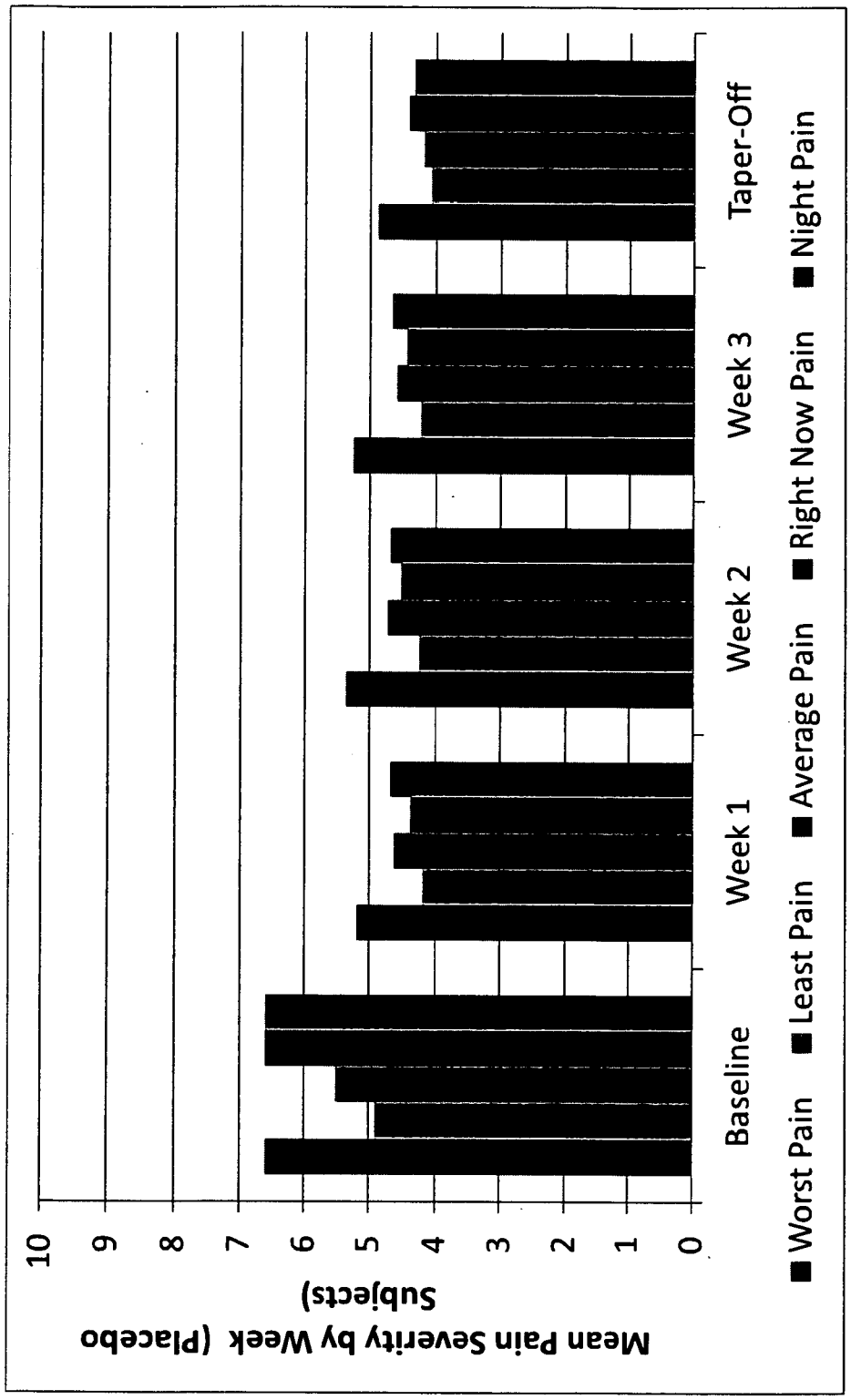


Figure 26



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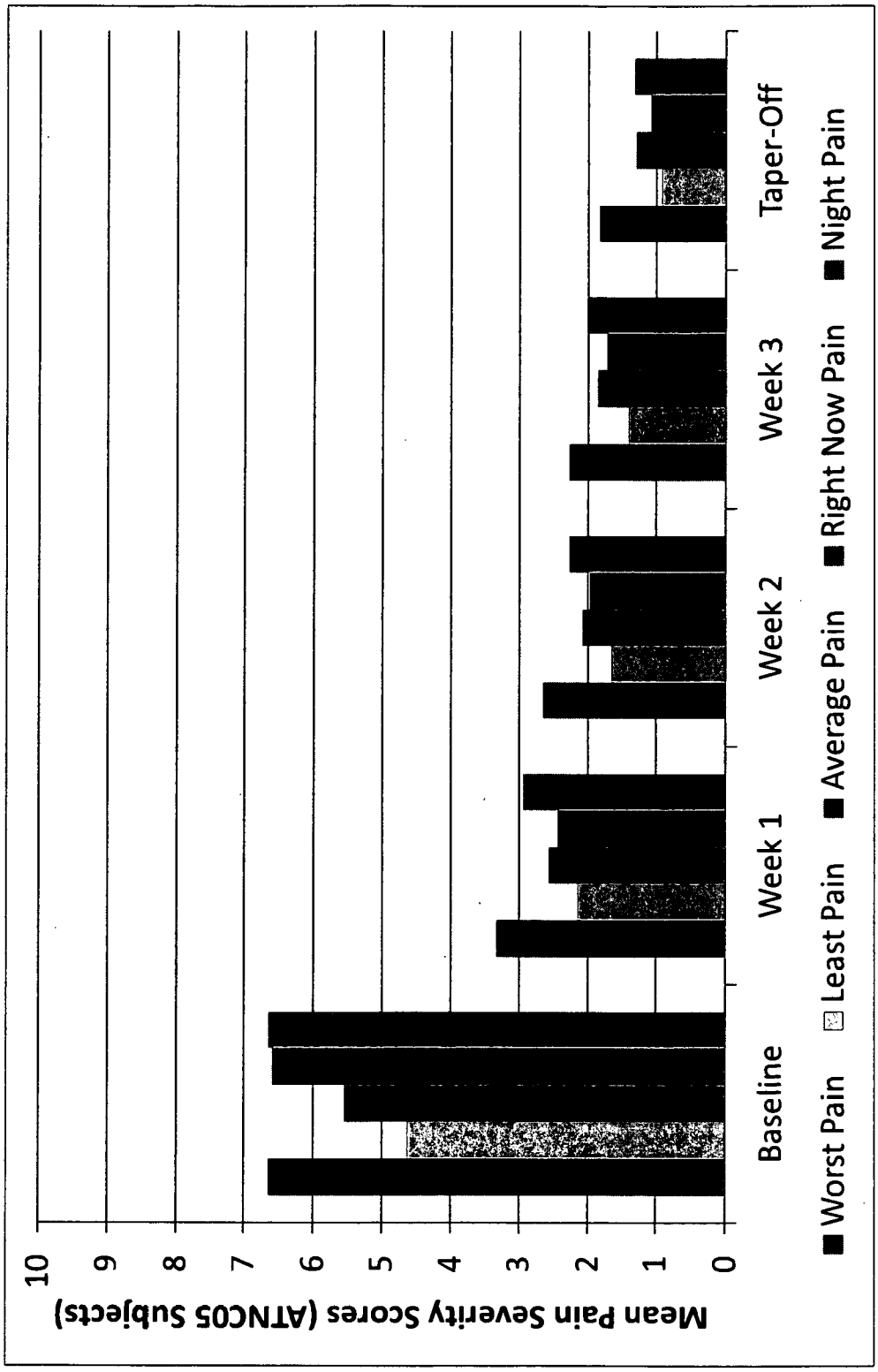

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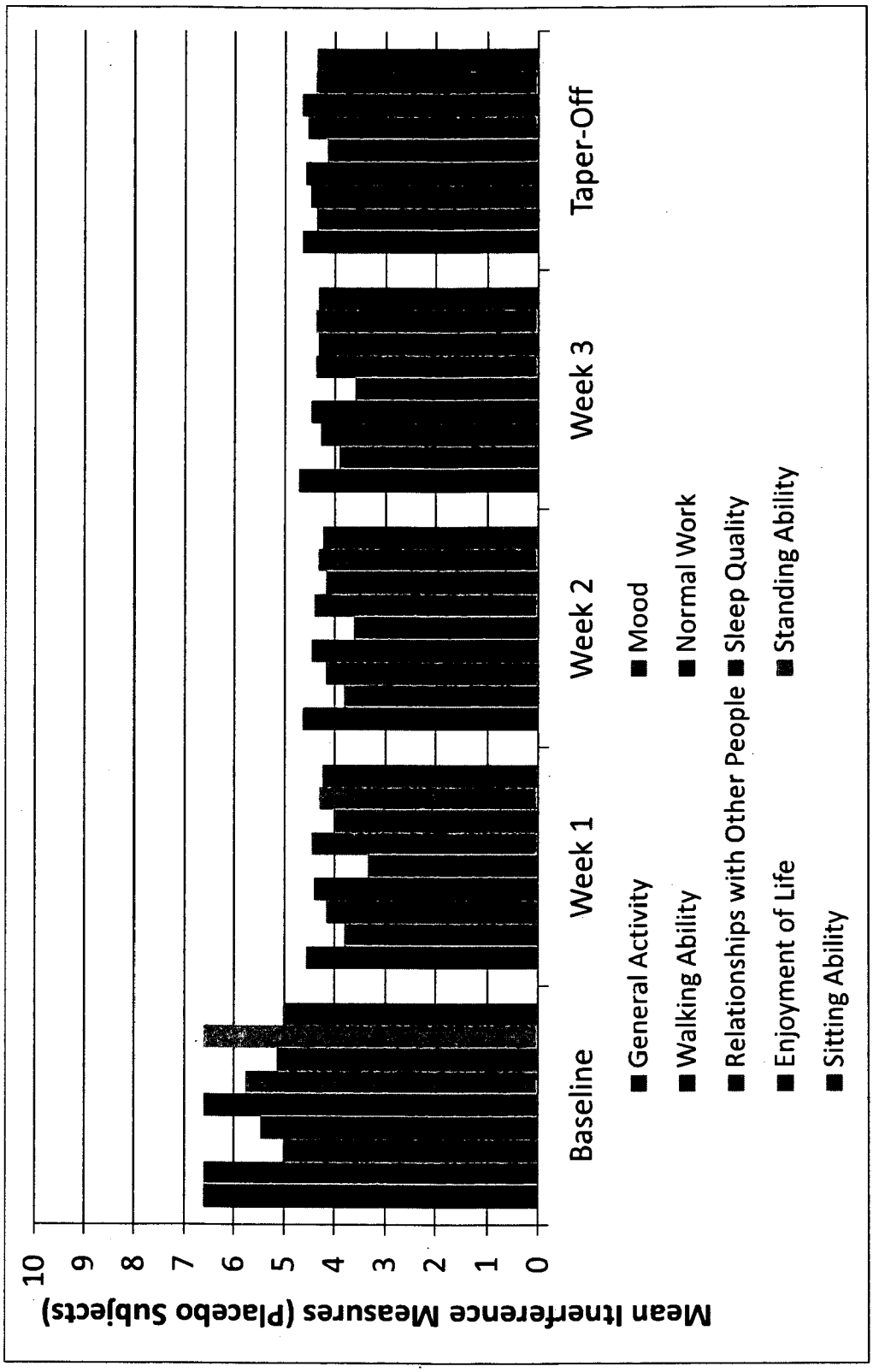

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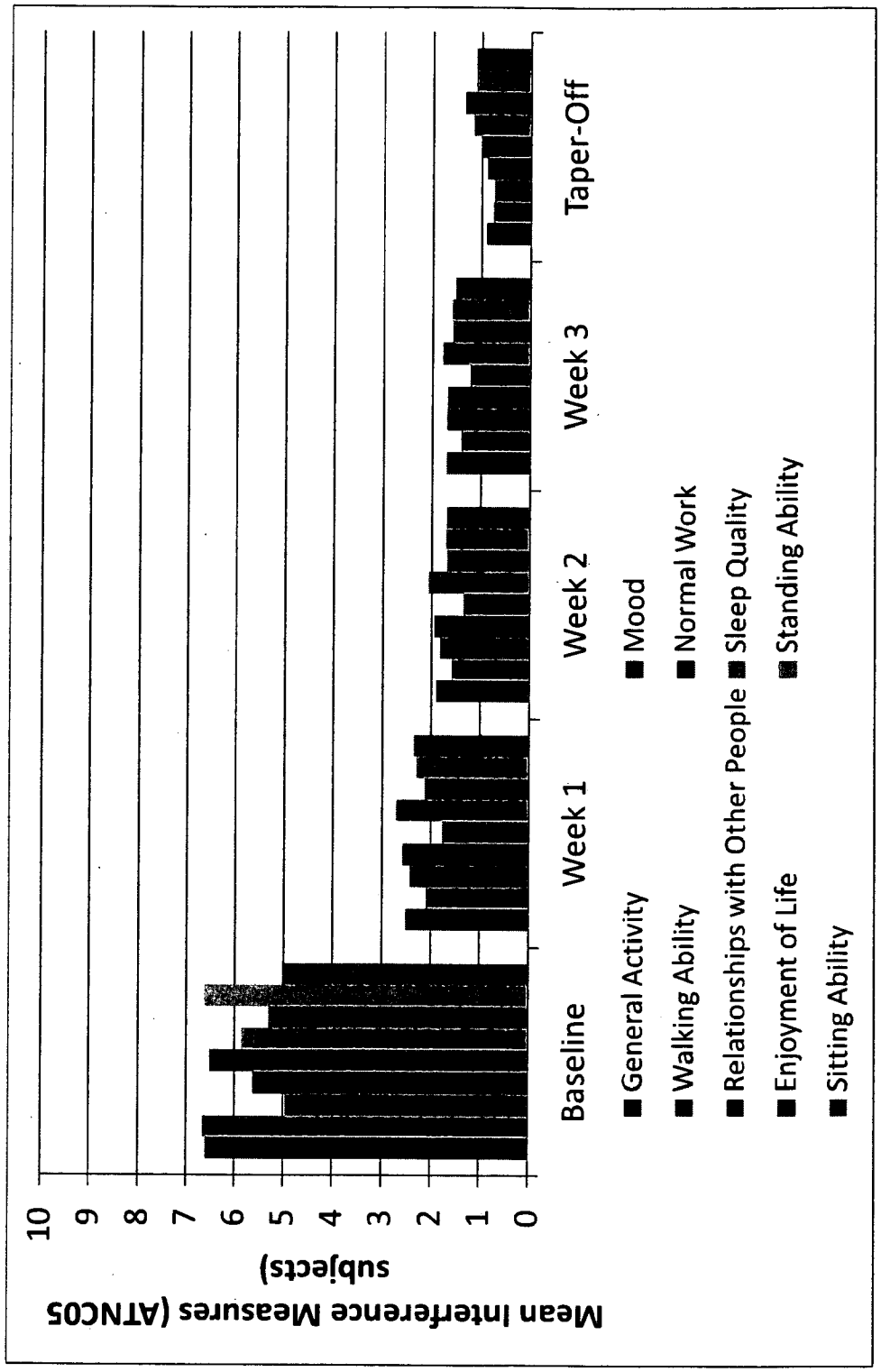

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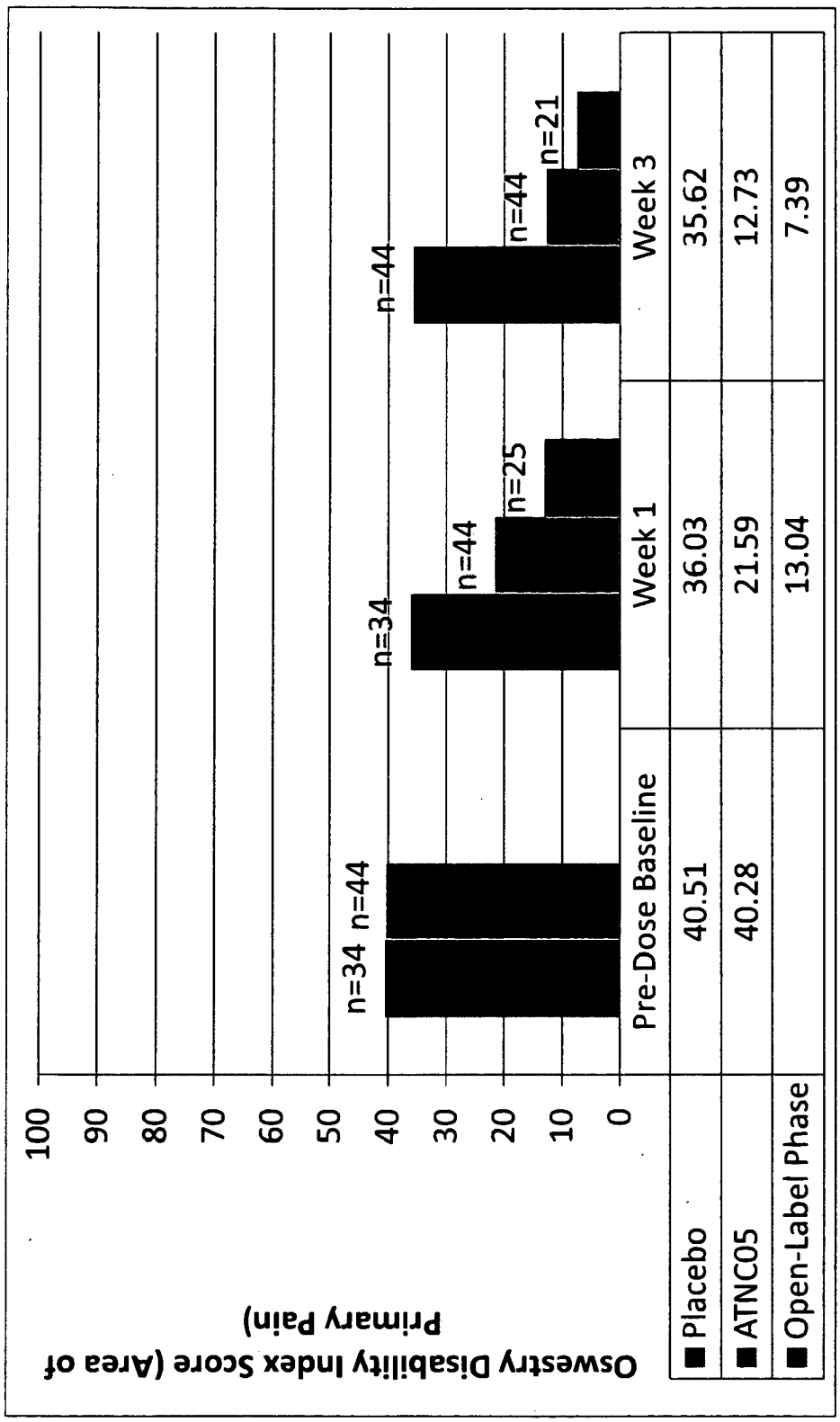

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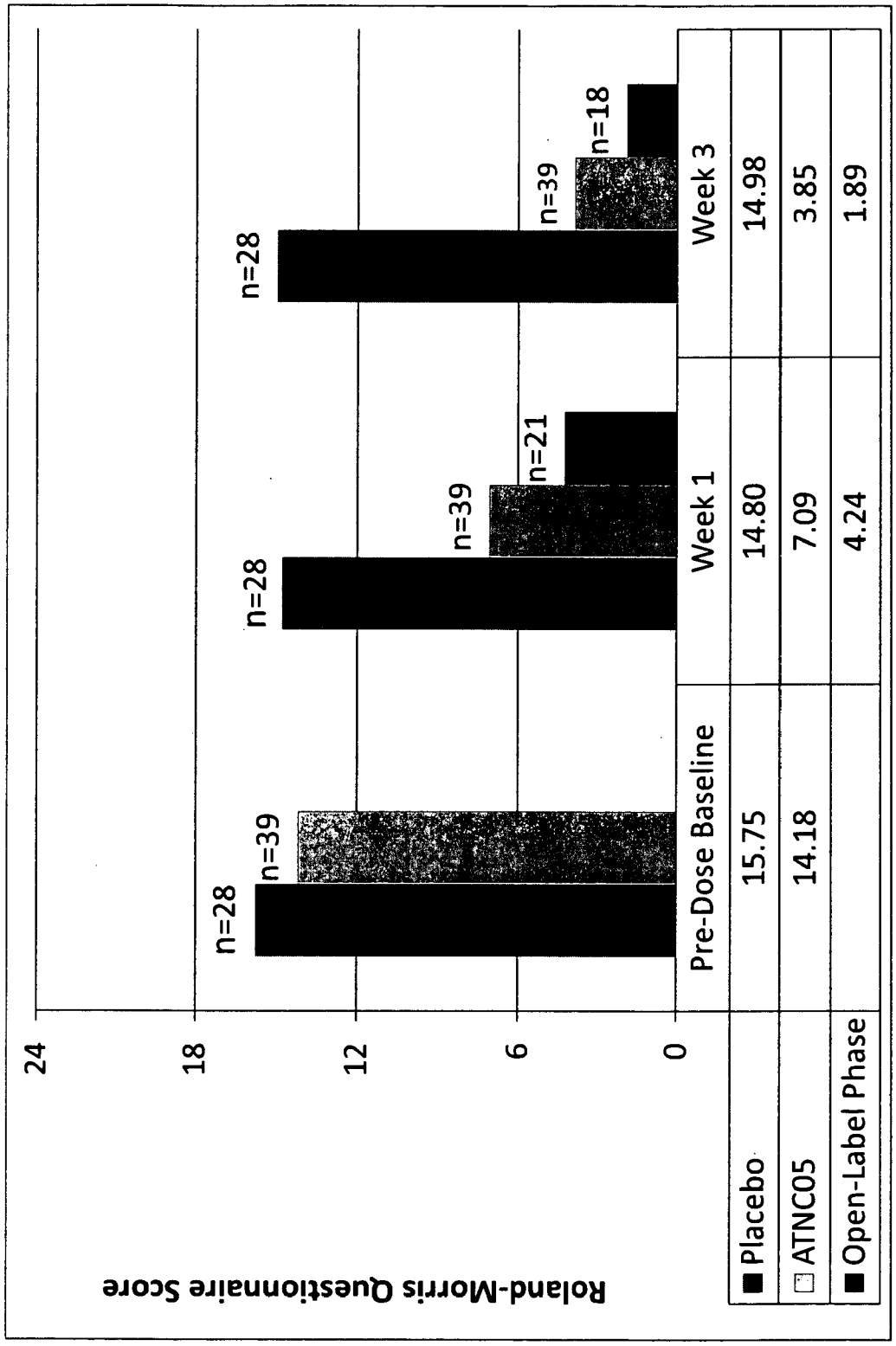

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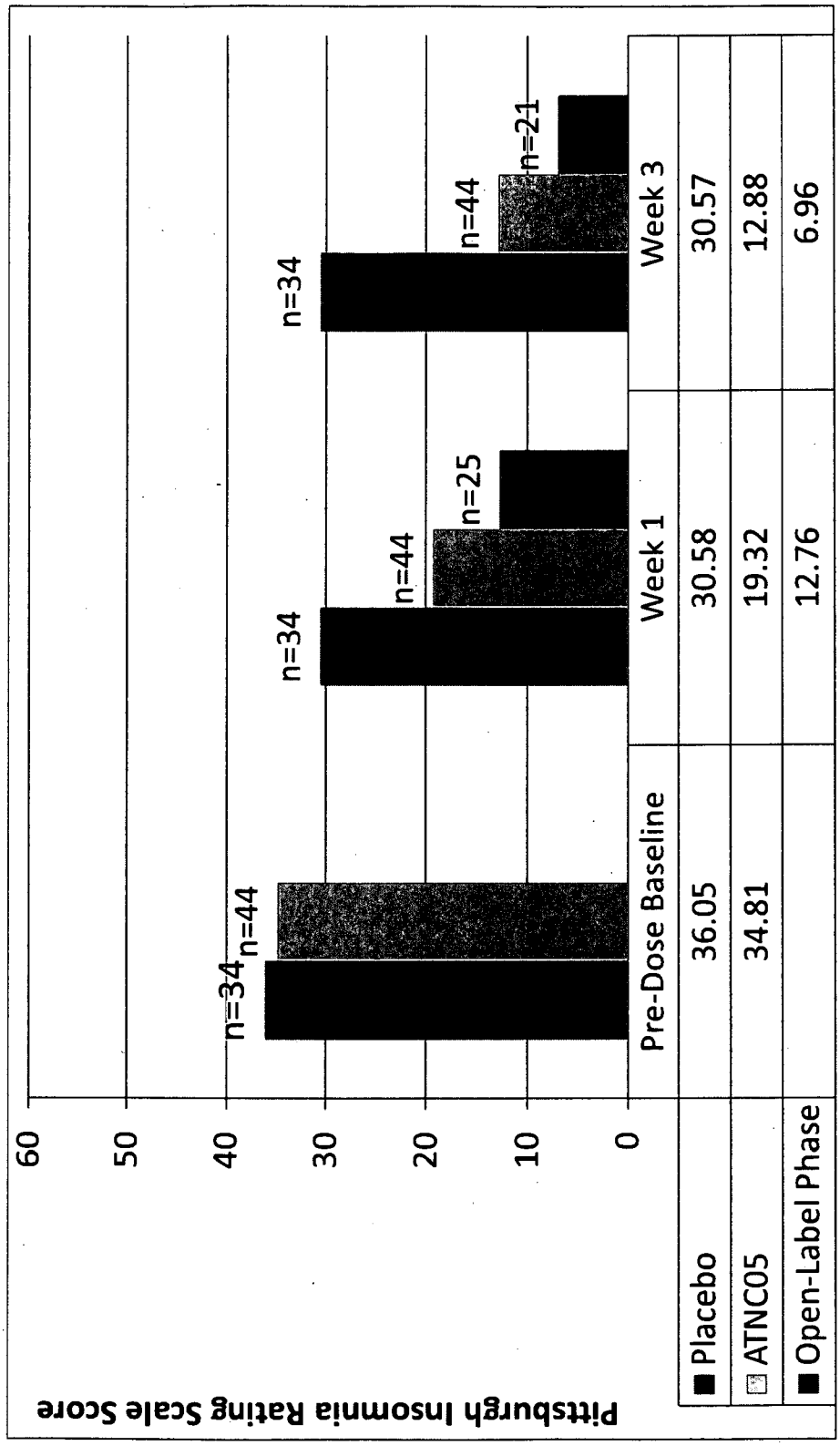

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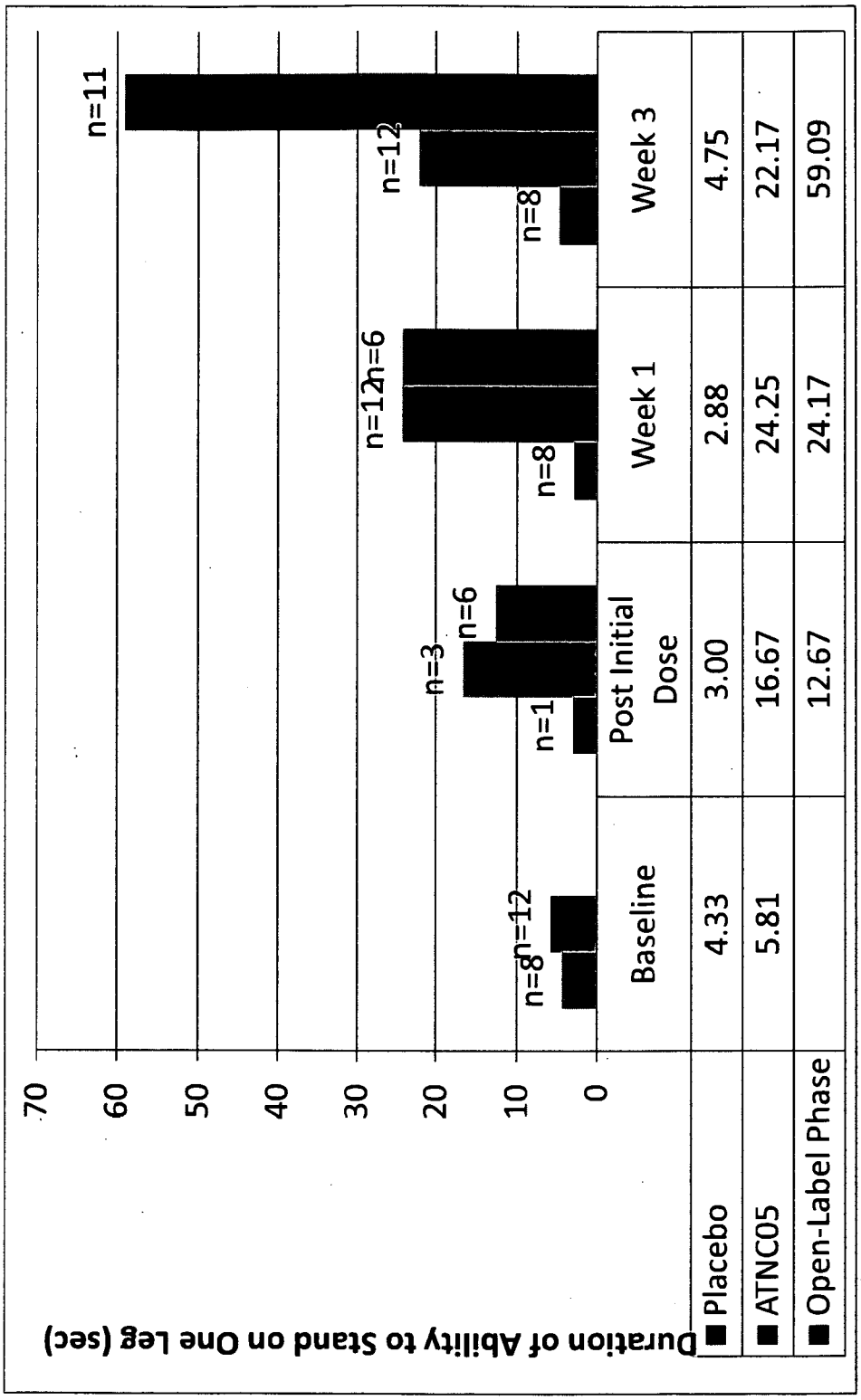

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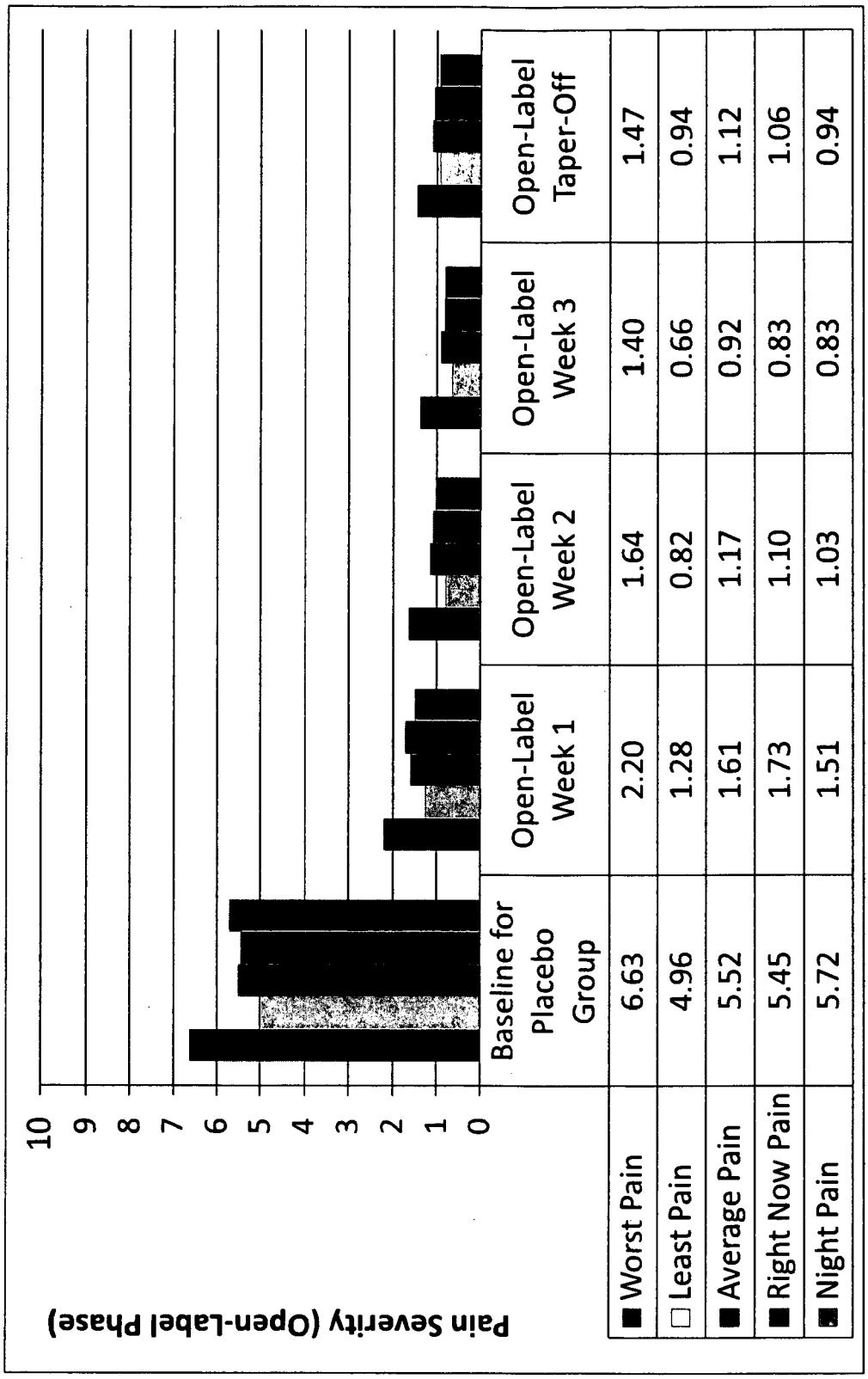

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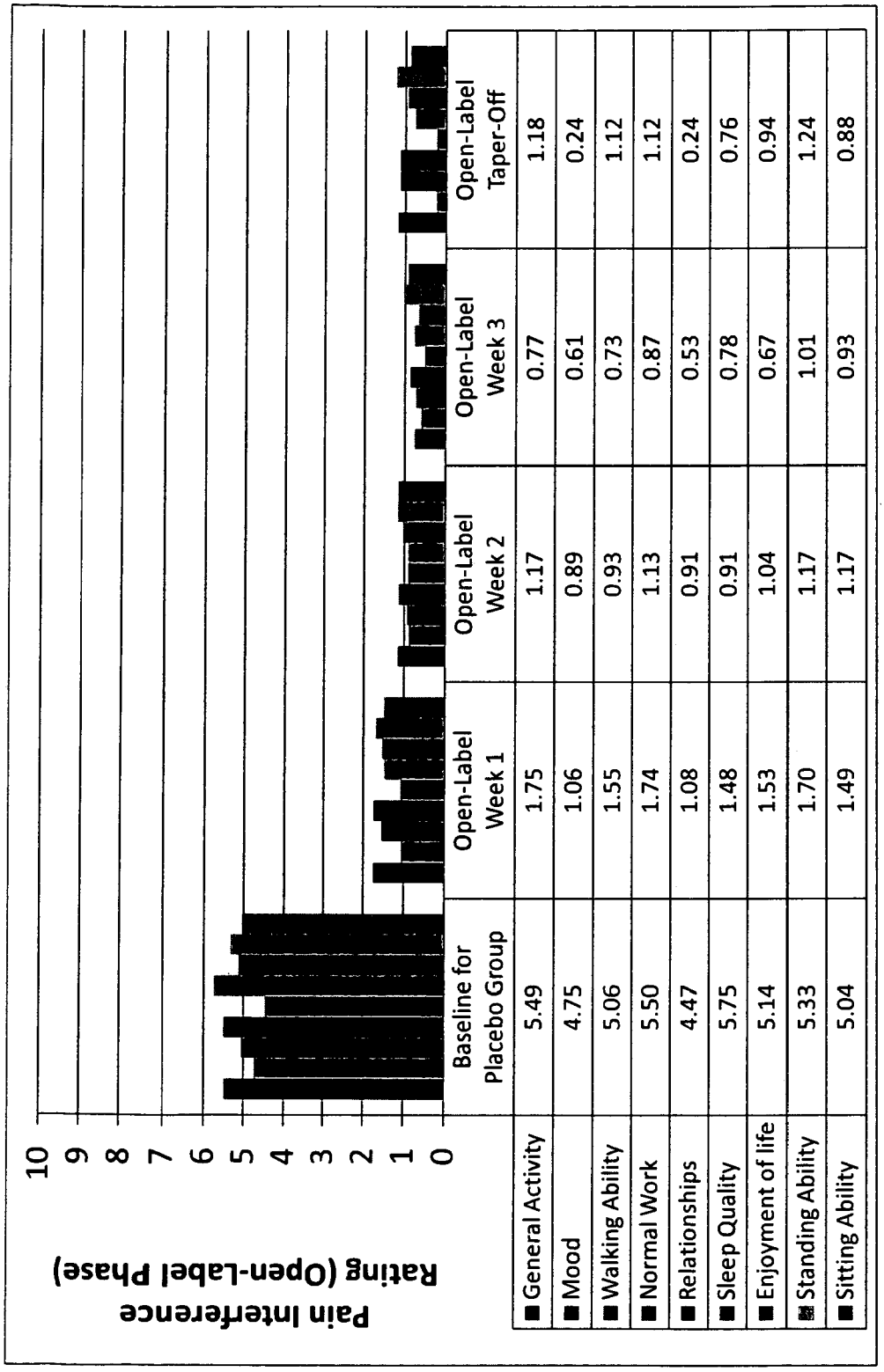


	Baseline for Placebo Group	Open-Label Week 1	Open-Label Week 2	Open-Label Week 3	Open-Label Taper-Off
General Activity	5.49	1.75	1.17	0.77	1.18
Mood	4.75	1.06	0.89	0.61	0.24
Walking Ability	5.06	1.55	0.93	0.73	1.12
Normal Work	5.50	1.74	1.13	0.87	1.12
Relationships	4.47	1.08	0.91	0.53	0.24
Sleep Quality	5.75	1.48	0.91	0.78	0.76
Enjoyment of life	5.14	1.53	1.04	0.67	0.94
Standing Ability	5.33	1.70	1.17	1.01	1.24
Sitting Ability	5.04	1.49	1.17	0.93	0.88

Figure 36

Replacement Sheets

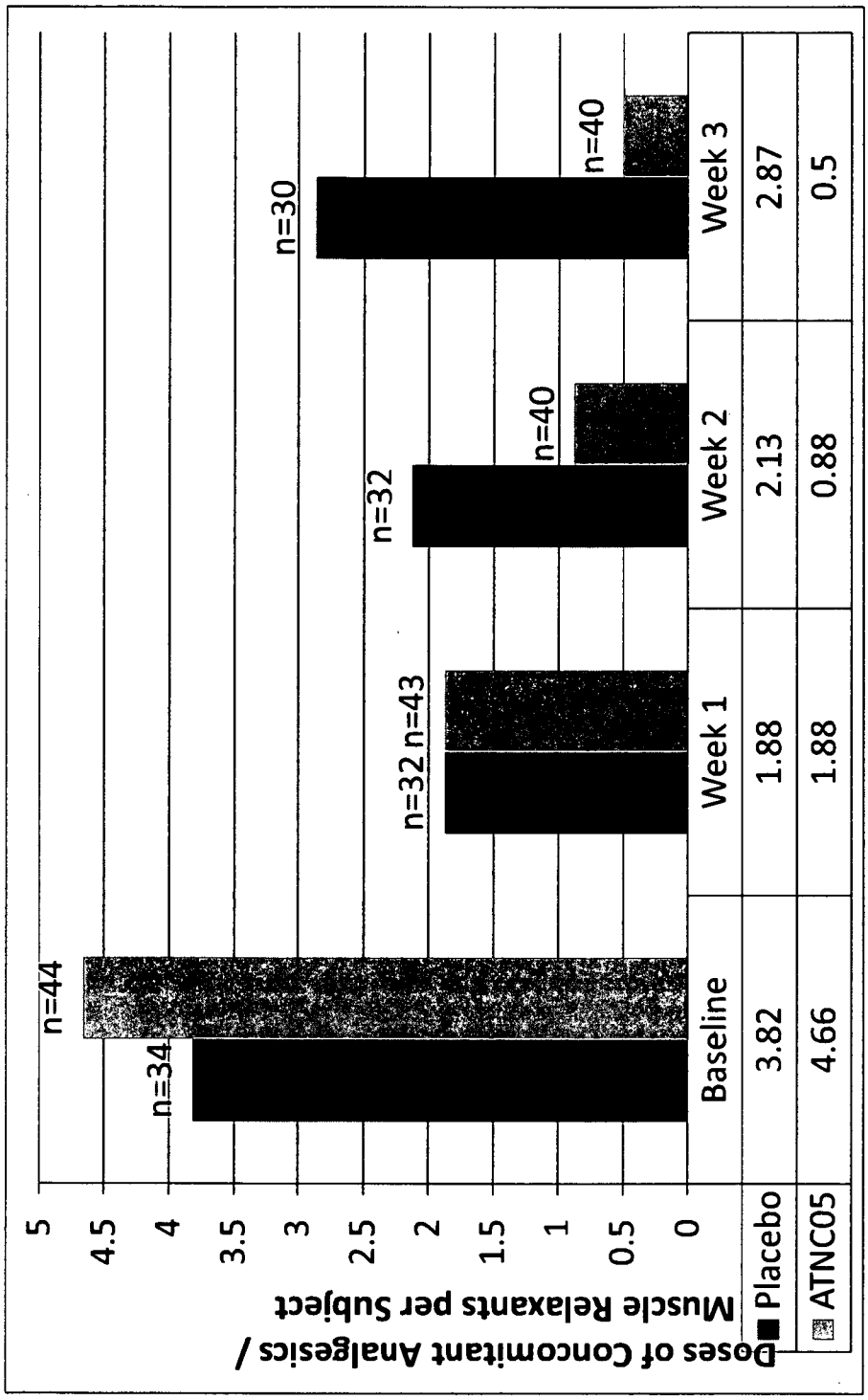


Figure 37

Replacement Sheets

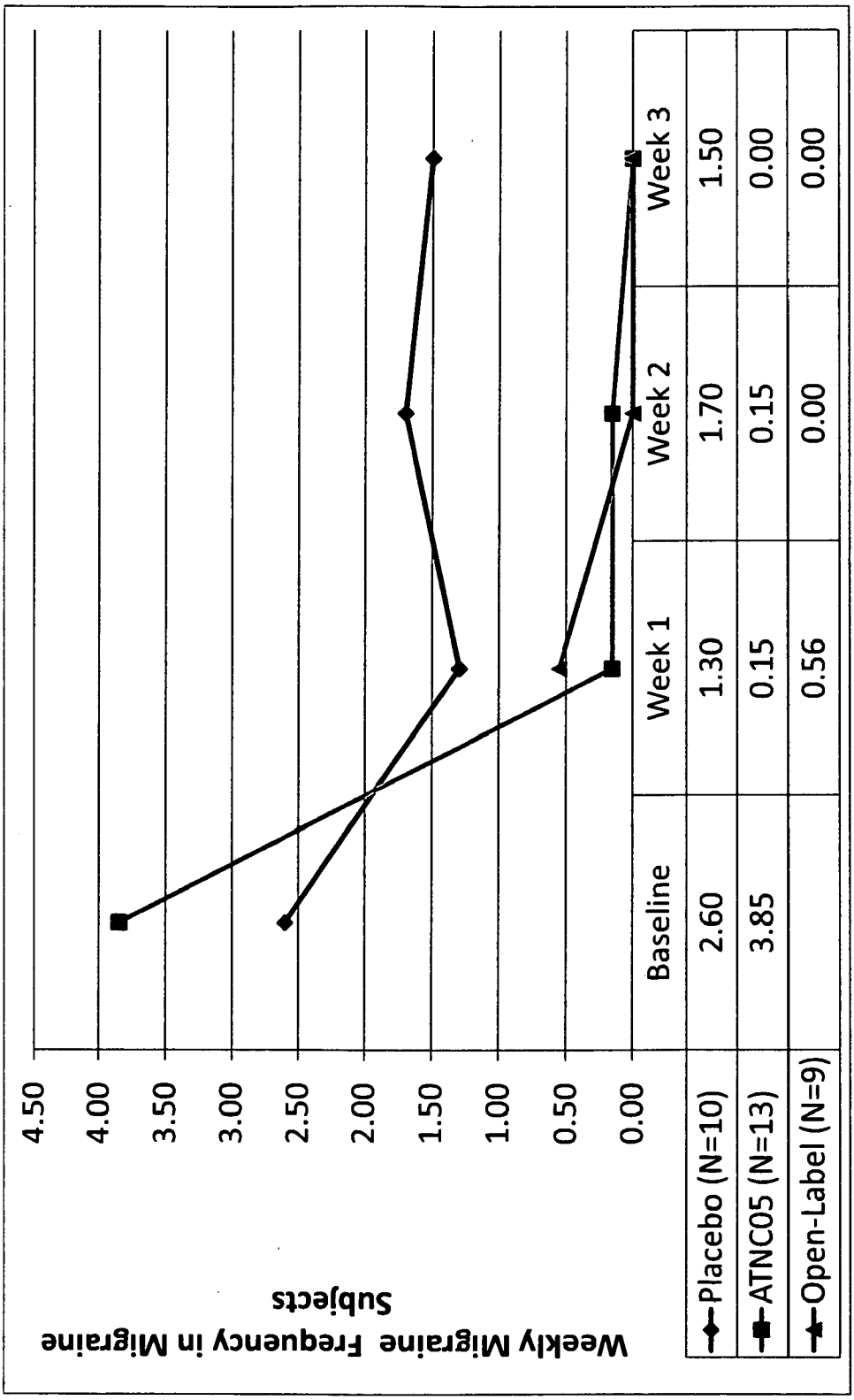


Figure 38

Replacement Sheets

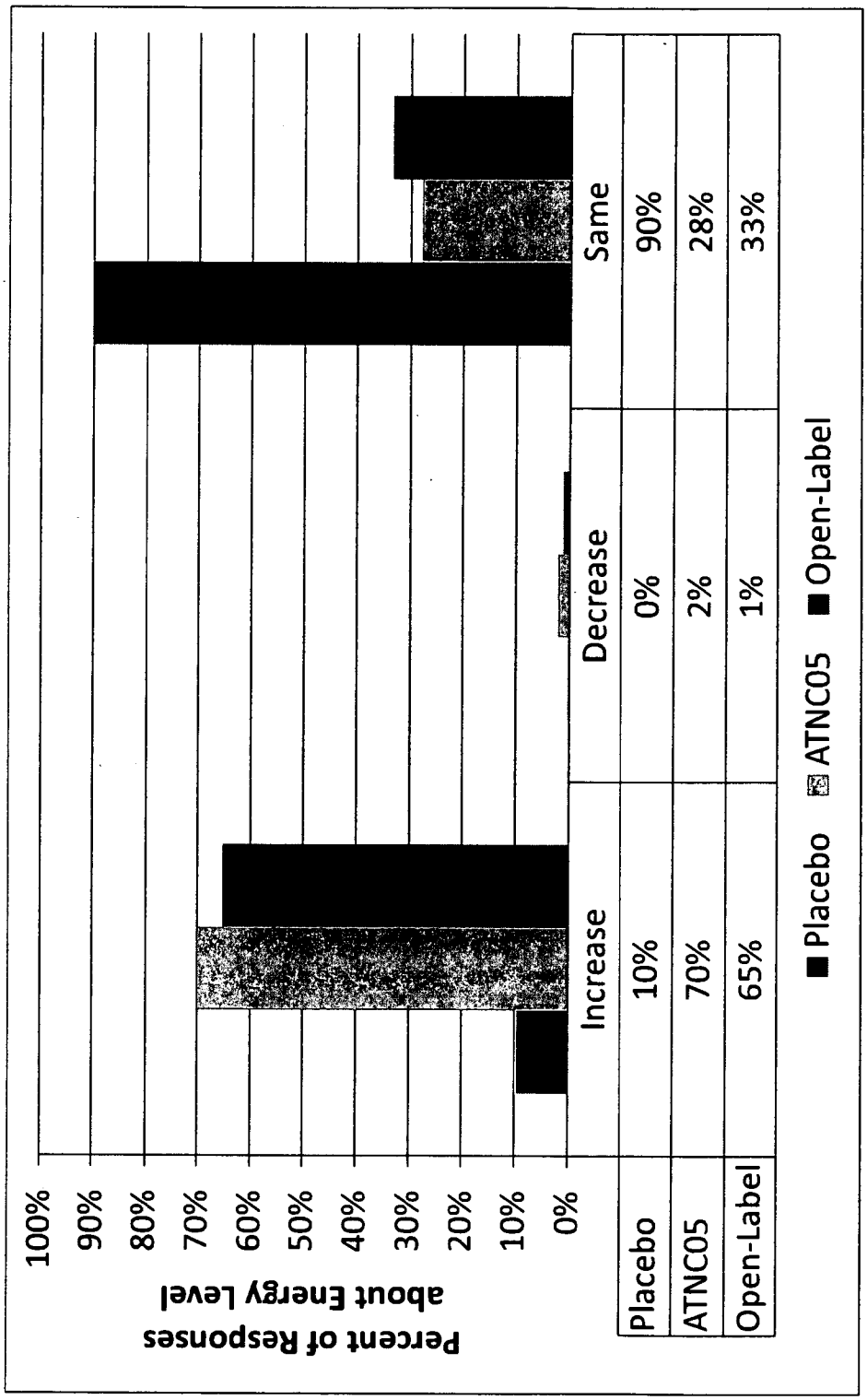


Figure 39

Replacement Sheets

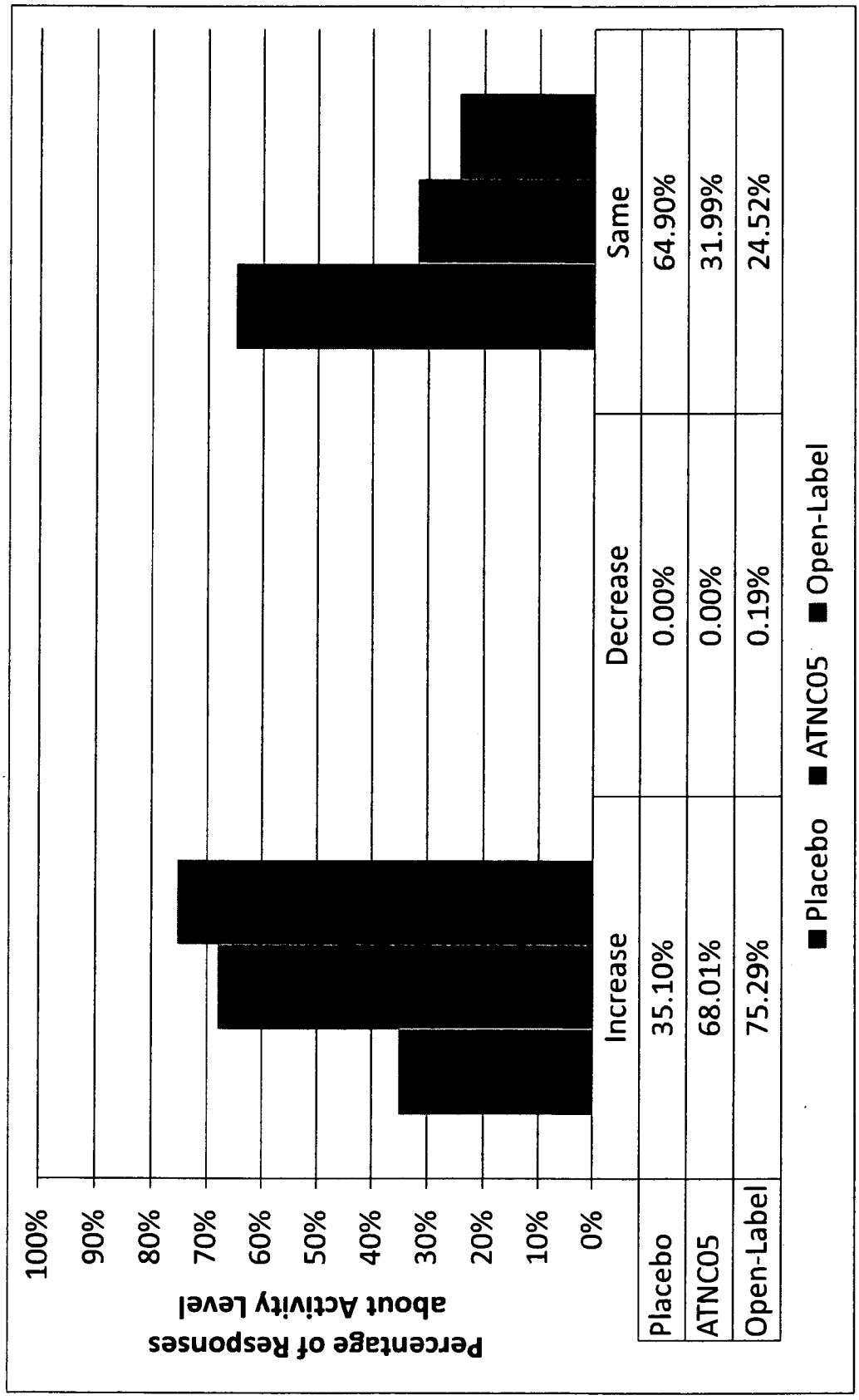
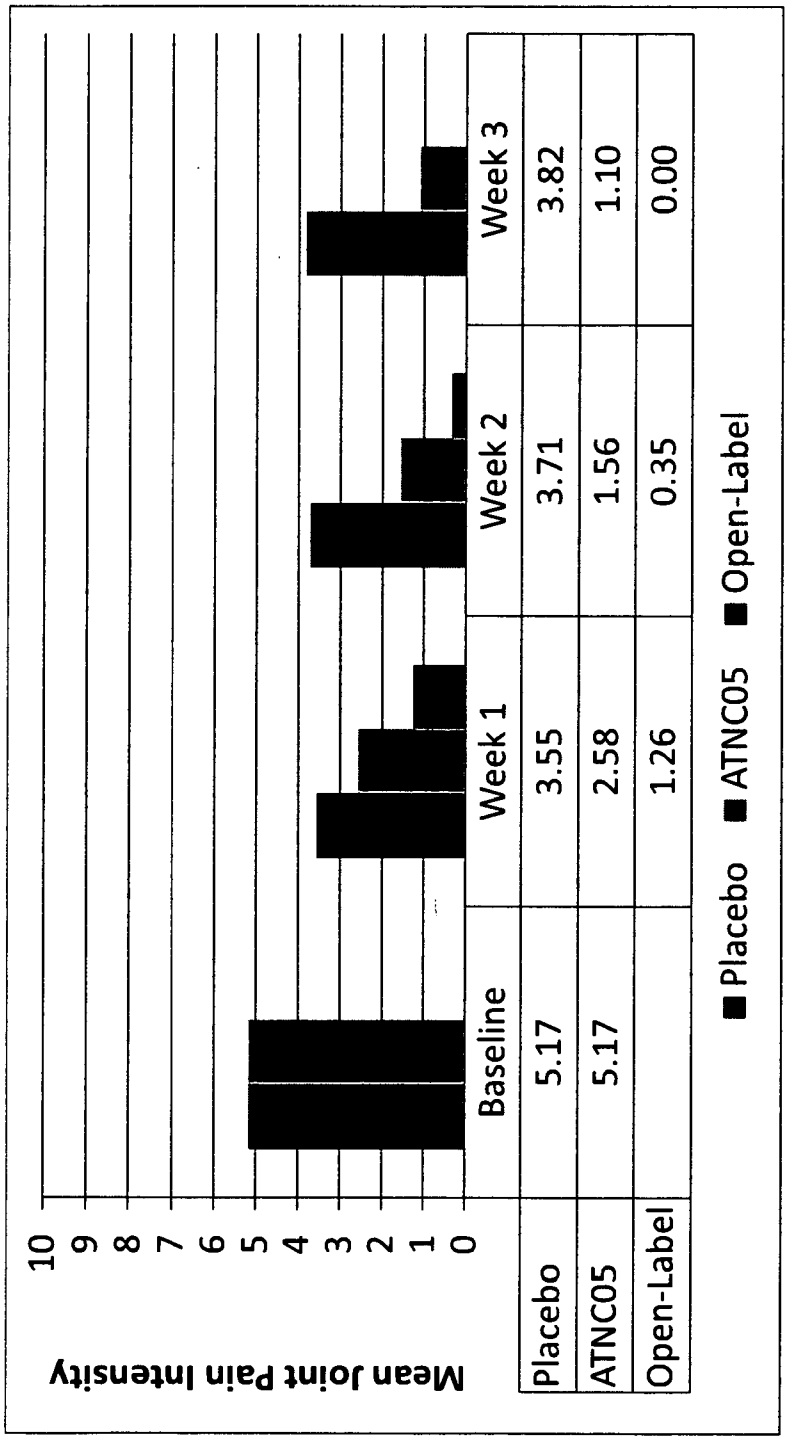


Figure 40

Replacement Sheets



	Baseline	Week 1	Week 2	Week 3
Placebo	5.17	3.55	3.71	3.82
ATNC05	5.17	2.58	1.56	1.10
Open-Label		1.26	0.35	0.00

Figure 41

Replacement Sheets

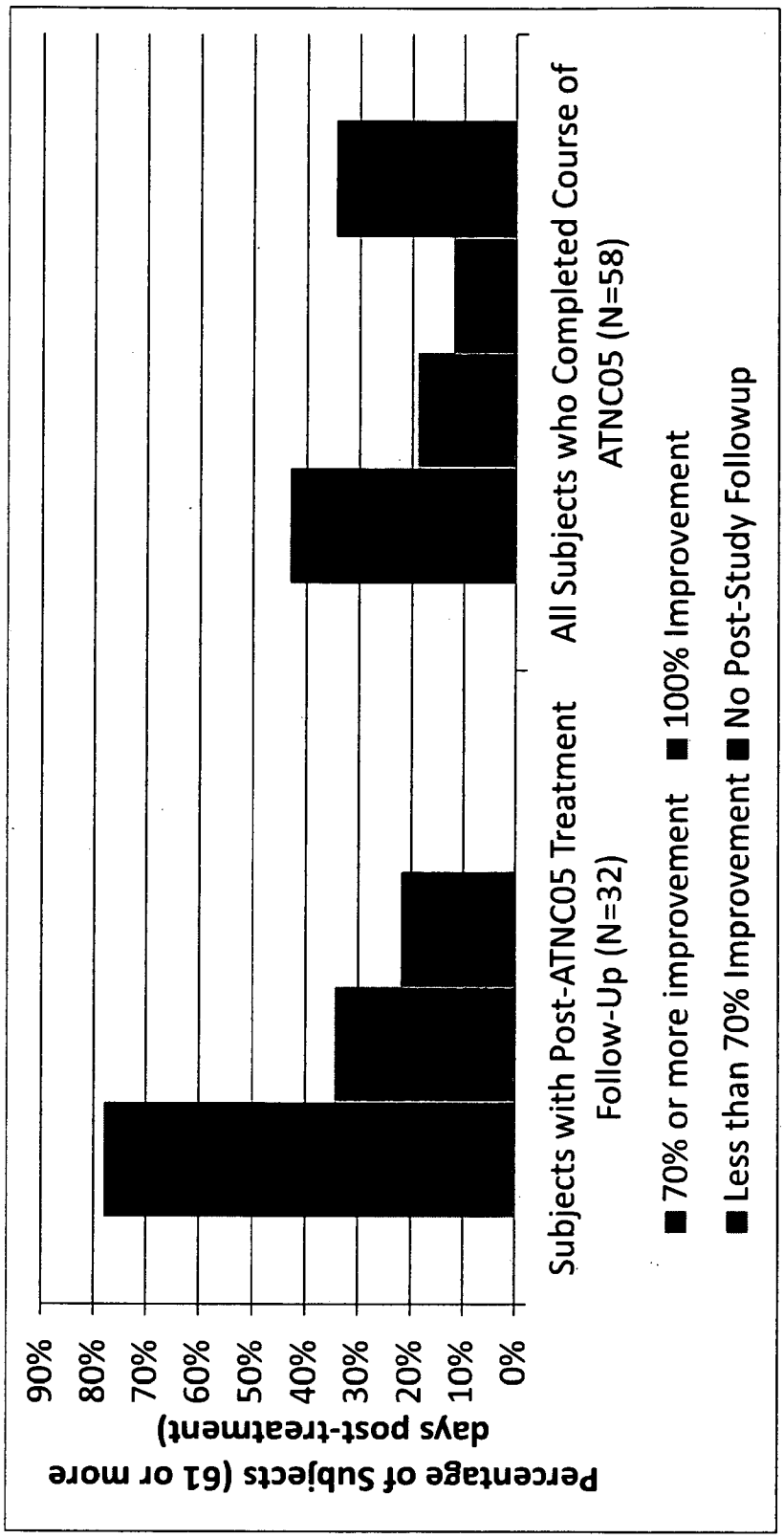


Figure 42

Replacement Sheets