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(54) **METHODS USEFUL FOR THE TREATMENT OF PAIN, ARTHRITIC CONDITIONS OR INFLAMMATION ASSOCIATED WITH A CHRONIC CONDITION**

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(57) **ABSTRACT**

Methods, including those for administering novel pharmaceutical compositions, dosage forms containing an opioid active pharmaceutical ingredient, are useful for treating pain, arthritic conditions and/or inflammation associated with a chronic condition, including pain from arthritis and inflammation.

METHODS USEFUL FOR THE TREATMENT OF PAIN, ARTHRITIC CONDITIONS OR INFLAMMATION ASSOCIATED WITH A CHRONIC CONDITION

FIELD OF THE INVENTION

[0001] The present invention relates to methods, including novel methods of administration, useful for the treatment of pain, arthritic conditions, and/or inflammation associated with a chronic condition, using opioid compositions. The methods provide human subjects with an alleviation of one or more symptoms or signs of pain, an arthritic condition or inflammation associated with a chronic condition, including, for example, reduced pain, reduced stiffness and/or improved physical function.

BACKGROUND OF THE INVENTION

[0002] Opioids are a broad class of drugs used clinically in the management of pain, but their use is limited by a constellation of undesirable side effects, including their potential for dependence and abuse. The principle actions and therapeutic value of opioids are analgesia and sedation. The precise mechanisms of action for these effects are unknown; however, specific central nervous system opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord, and likely play a role in the analgesic effects of opioid drugs.

[0003] Controlled-release formulations of opioids, such as oxycodone, have several advantages over immediate-release formulations. Lower peak concentrations of opioids in the blood may allow for decreased dose-dependent opioid-related adverse events (AEs). In controlled release formulations, if blood levels of opioids, such as oxycodone, are sustained over longer periods, this should allow for more convenient dosing regimens. However, marketed versions of controlled-release oxycodone have been the subject of intense media scrutiny due to an epidemic of misuse, abuse and diversion. For example, OxyContin introduced dosage strengths that contained much higher amounts of oxycodone than previously available to the market. Abusers can easily disrupt the controlled-release mechanism of OxyContin by crushing, chewing or dissolving tablets or capsules in alcohol, leading to an immediate surge in oxycodone blood levels, which can produce a sense of euphoria but can also lead to respiratory depression and even death.

SUMMARY OF THE INVENTION

[0004] The present invention provides methods, including novel methods of administration, useful for the treatment of pain (e.g., chronic pain), arthritic conditions and/or inflammation associated with a chronic condition using a novel oral opioid pharmaceutical composition. Methods of the invention provide treatment for pain, including wherein the pain is moderate to severe and including pain from cancer, arthritic conditions and/or inflammation. Methods of the present invention provide subjects with alleviation of one or more symptoms or signs of the pain, arthritic condition, inflammation associated with a chronic condition, including, for example, alleviation of pain, alleviation of stiffness and/or improvement of physical function. Methods of the invention comprising administration of the oral opioid composition may optionally include one or more additional therapeutic agents.

[0005] Methods are provided for treating pain in a subject that comprise administering to a subject a pharmaceutical composition for oral administration. The pharmaceutical composition comprises: an opioid active pharmaceutical ingredient (API), a sucrose acetate isobutyrate liquid carrier material, triacetin, isopropyl myristate, cellulose acetate butyrate, hydroxyethyl cellulose, colloidal silicon dioxide and butylated hydroxytoluene, wherein one or more symptoms or signs associated with the pain is alleviated.

[0006] Methods are also provided for treating an arthritic condition in a subject that comprise administering to the subject a pharmaceutical composition for oral administration that comprises: an opioid API, sucrose acetate isobutyrate, triacetin, isopropyl myristate, cellulose acetate butyrate, hydroxyethyl cellulose, colloidal silicon dioxide and butylated hydroxytoluene, wherein one or more symptoms or signs associated with the arthritic condition are alleviated.

[0007] Methods are provided for treating inflammation in a subject that comprise administering to the subject a pharmaceutical composition for oral administration that comprises: an opioid API, sucrose acetate isobutyrate, triacetin, isopropyl myristate, cellulose acetate butyrate, hydroxyethyl cellulose, colloidal silicon dioxide and butylated hydroxytoluene, wherein one or more symptoms or signs associated with inflammation are alleviated.

[0008] In some embodiments, the opioid API is in the form of a free base. In some embodiments, the opioid is in the form of a salt. In some embodiments, the opioid is micronized. Preferred opioids include oxycodone, oxymorphone, hydrocodone and hydromorphone. Particularly preferred is oxycodone.

[0009] In some embodiments, the subject is a human.

[0010] In some embodiments, the pain is chronic pain. Chronic pain may result from various abnormal or compromised states (e.g., diseased), including but not limited to osteoarthritis, rheumatoid arthritis, psoriatic arthritis, back pain, cancer, injury or trauma.

[0011] In some embodiments, the chronic pain is associated with an arthritic condition. In some embodiments, the chronic pain results from osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enteropathric spondylitis, juvenile arthropathy, juvenile ankylosing spondylitis, reactive arthropathy, infectious or post-infectious arthritis, gonoccocal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphlitic arthritis, Lyme disease, calcium crystal deposition arthropathies, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis, carpal tunnel syndrome, a repetitive use injury, neuropathic joint disease, hemarthrosis, Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, or multicentric reticulohistiocytosis. In some embodiments, the chronic pain results from an arthritis associated with a vasculitic syndrome, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, surcoilosis, hemochromatosis, sickle cell disease or another hemoglobinopathry, hyperlipo proteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, lupus, systemic lupus erythematosis, hemophilia, or relapsing polychondritis.

[0012] In some embodiments, the chronic pain is associated with a joint, hip, knee, back, neck, or lower back of the subject. In some embodiments, the pain is measured as pain intensity. In some embodiments, the pain intensity is attenu-

ated as compared to a pain intensity baseline of the subject. In some embodiments the pain is measured on the pain subscale of the WOMAC Osteoarthritis Index. In some embodiments, the pain measurement of the subject is improved with administration of the opioid as compared to baseline pain measurement of the subject on the WOMAC pain subscale baseline of the subject.

[0013] In some embodiments, the pain is measured by a patient or physician assessment. In some embodiments, the pain is measured on an 11-point numerical scale. In some embodiments, the pain is reduced by at least 1 point with administration of the opioid, as compared to the pain where a subject is administered a placebo.

[0014] In some embodiments, the pain felt by the subject when walking on a flat surface, when going up or down stairs, at night while in bed, that disturbs the sleep of the subject, while sitting or lying down, or while standing is attenuated.

[0015] In some embodiments, the methods further comprise administering to the subject an additional therapeutic agent that is a non-steroidal anti-inflammatory drug, cytokine inhibitor, corticosteroid, anti-rheumatic drug, anticonvulsant agent, tricyclic antidepressant agent, anti-dynorphin agent, or glutamate receptor antagonist agent. In some embodiments, the additional therapeutic agent is a TNF-α inhibitor, corticosteroid, anti-rheumatic drug, non-steroidal anti-inflammatory drug, celecoxib, ropecoxib, valdecoxib, etanercept, infiximab, anti-TNF-α, D2E7 human Mab, CDP-870, CDP-571, humicade, PEGylated soluble TNF-α Receptor-1, TBP-1, PASSTNF-alpha, AGT-1, ienercept, CytoTAB, TACE, small molecule TNF mRNA synthesis inhibitor, PEGylated p75TNFR Fc mutein (Immunex), TNF-α antisense inhibitor, methotrexate, leflunomide, D-Penicillamine, sulfasalazine, a gold composition, minocycline, azathioprine, hydroxychloroquine, an antimalarial drug, cyclosporine, or a biologic agent that designed to either inhibit or supplement a cytokine.

[0016] In some embodiments, the methods further comprise administering to the subject an opioid antagonist, including, for example, naloxone, naltrexone or nalmefene.

[0017] In some embodiments, the oral pharmaceutical composition is administered no more than twice in a 24-hour period. In some embodiments, the oral pharmaceutical composition is provided as a solid oral dosage form or as a liquid oral dosage form.

[0018] In some embodiments, the arthritic condition is osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, juvenile arthropathy, juvenile ankylosing spondylitis, reactive arthropathy, infectious or post-infectious arthritis, gonoccocal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphlitic arthritis, Lyme disease, calcium crystal deposition arthropathies, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis, carpal tunnel syndrome, a repetitive use injury, neuropathic joint disease, hemarthrosis, Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, or multicentric reticulohistiocytosis. In some embodiments, the arthritic condition is an arthritis associated with a vasculitic syndrome, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, surcoilosis, hemochromatosis, sickle cell disease or another hemoglobinopathry, hyperlipo proteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, lupus, systemic lupus erythematosis, hemophilia, or relapsing polychondritis. In some embodiments, the arthritic condition is associated with a joint, hip, knee, back, neck, or lower back of the subject.

[0019] In some embodiments, progression of the arthritic condition is inhibited. In some embodiments, damage associated with an arthritic condition is reversed.

[0020] In some embodiments, tissue or cellular damage resulting from inflammation associated with a chronic condition is inhibited. In some embodiments, tissue or cellular damage resulting from inflammation associated with a chronic condition is reversed

[0021] The pharmaceutical compositions that are provided for oral administration to a subject comprise an opioid API (e.g., oxycodone), sucrose acetate isobutyrate, triacetin, isopropyl myristate, cellulose acetate butyrate, hydroxyethyl cellulose, colloidal silicon dioxide or butylated hydroxytoluene).

[0022] Particular pharmaceutical compositions that are provided for oral administration to a subject comprise: 5.13% opioid (e.g., oxycodone), 40.98% sucrose acetate isobutyrate, 27.32% triacetin, 14.23% isopropyl myristate, 4.74% cellulose acetate butyrate, 5.69% hydroxyethyl cellulose, 1.90% colloidal silicon dioxide and 0.02% butylated hydroxytoluene.

[0023] The pharmaceutical compositions may be encapsulated, including, for example, in hard gelatin capsules or soft gelatin capsules.

[0024] One or more symptoms and signs of pain, arthritic conditions or inflammation associated with chronic conditions are alleviated (e.g., ameliorated, attenuated, reduced, diminished, blocked, inhibited or prevented), by methods of the invention, for example, as measured by an alleviation (e.g., amelioration, attenuation, reduction, diminishment, blockage, inhibition or prevention) of pain, stiffness, or difficulty in physical function.

[0025] The present invention is directed to the use of novel pharmaceutical compositions, provided as novel dosage forms, kits, and other materials comprising an opioid API for use in or with the foregoing methods including, for example, methods for alleviating one or more symptoms or signs associated with pain (e.g., chronic pain), an arthritic condition and/or inflammation associated with a chronic condition, wherein the amount of the opioid that is administered is effective for alleviating one or more symptoms or signs associated with pain, an arthritic condition, or inflammation associated with a chronic condition.

[0026] Symptoms and signs of arthritic conditions and inflammation resulting from chronic conditions are alleviated (e.g., ameliorated, attenuated, reduced, diminished, blocked, inhibited or prevented) by practice of the methods of the invention, for example, as measured by an alleviation (e.g., amelioration, attenuation, reduction, diminishment, blockage, inhibition or prevention) of pain, stiffness, and/or difficulty in physical function.

[0027] Advantages of methods of the invention include enhanced and prolonged analgesia, prevention of tolerance and continued protection against tolerance even with chronic administration, reversal of opioid-induced hyperalgesia, prevention of physical dependence or withdrawal, decreased rewarding/euphoric side effect, and/or decreased potential for relapse/addiction.

POINTS OF THE INVENTION

[0028] 1. A method for treating pain comprising administering to a subject a pharmaceutical composition for oral administration that comprises:

[0029] (a) an opioid;

[0030] (b) sucrose acetate isobutyrate;

[0031] (c) triacetin;

[0032] (d) isopropyl myristate;

[0033] (e) cellulose acetate butyrate;

[0034] (f) hydroxyethyl cellulose;

[0035] (g) colloidal silicon dioxide; and

[0036] (h) butylated hydroxytoluene,

[0037] wherein one or more symptoms or signs associated with the pain is alleviated.

[0038] 2. The method of point 1, wherein the opioid is in the form of a free base.

[0039] 3. The method of point 1, wherein the opioid is in the form of a salt.

[0040] 4. The method of point 1, wherein the opioid is micronized.

[0041] 5. The method of any one of points 1, 2, 3 or 4, wherein the opioid is oxycodone, oxymorphone, hydrocodone or hydromorphone.

[0042] 6. The method of any one of points 1, 2, 3 or 4, wherein the opioid is oxycodone.

[0043] 7. The method of point 1, wherein the pharmaceutical composition is encapsulated.

[0044] 8. The method of point 1, wherein the subject is a human.

[0045] 9. The method of point 1, wherein the pain is associated with cancer.

[0046] 10. The method of point 1, wherein the pain is chronic pain.

[0047] 11. The method of point 10, wherein the chronic pain is associated with an arthritic condition.

[0048] 12. The method of point 10, wherein the chronic pain results from osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, juvenile arthropathy, juvenile ankylosing spondylitis, reactive arthropathy, infectious or post-infectious arthritis, gonoccocal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphlitic arthritis, Lyme disease, calcium crystal deposition arthropathies, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis, carpal tunnel syndrome, a repetitive use injury, neuropathic joint disease, hemarthrosis, Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, or multicentric reticulohistiocytosis.

[0049] 13. The method of point 10, wherein the chronic pain results from an arthritis associated with a vasculitic syndrome, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, surcoilosis, hemochromatosis, sickle cell disease or another hemoglobinopathry, hyperlipo proteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, lupus, systemic lupus erythematosis, hemophilia, or relapsing polychondritis.

[0050] 14. The method of point 10, wherein the chronic pain is associated with a joint, hip, knee, back, neck, or lower back of the subject.

[0051] 15. The method of point 10 wherein the pain is measured as pain intensity.

[0052] 16. The method of point 15, wherein the pain intensity is attenuated as compared to a pain intensity baseline of the subject.

[0053] 17. The method of point 10, wherein the pain is measured on the pain subscale of the WOMAC Osteoarthritis Index.

[0054] 18. The method of point 17, wherein the pain measurement of the subject is improved as compared to baseline pain measurement of the subject on the WOMAC pain subscale baseline of the subject.

[0055] 19. The method of point 10, wherein the pain is measured by a patient or physician assessment.

[0056] 20. The method of point 10, wherein the pain is measured on an 11-point numerical scale.

[0057] 21. The method of point 20, wherein the pain is reduced by at least 1 point, as compared to the pain where a human subject is administered a placebo.

[0058] 22. The method of point 10, wherein the pain felt by the subject when walking on a flat surface, when going up or down stairs, at night while in bed, that disturbs the sleep of the subject, while sitting or lying down, or while standing is attenuated.

[0059] 23. The method of point 1 further comprising administering to the subject an additional therapeutic agent that is a non-steroidal anti-inflammatory drug, cytokine inhibitor, corticosteroid, anti-rheumatic drug, anticonvulsant agent, tricyclic antidepressant agent, anti-dynorphin agent, or glutamate receptor antagonist agent.

[0060] 24. The method of point 23, wherein the additional therapeutic agent is a TNF-α inhibitor, corticosteroid, anti-rheumatic drug, non-steroidal anti-inflammatory drug, celecoxib, ropecoxib, valdecoxib, etanercept, infiximab, anti-TNF-α, D2E7 human Mab, CDP-870, CDP-571, humicade, PEGylated soluble TNF-α Receptor-1, TBP-1, PASSTNF-alpha, AGT-1, ienercept, CytoTAB, TACE, small molecule TNF mRNA synthesis inhibitor, PEGylated p75TNFR Fc mutein (Immunex), TNF-α antisense inhibitor, methotrexate, leflunomide, D-Penicillamine, sulfasalazine, a gold composition, minocycline, azathioprine, hydroxychloroquine, an antimalarial drug, cyclosporine, or a biologic agent that designed to either inhibit or supplement a cytokine.

[0061] 25. The method of points 1, wherein the pharmaceutical composition is administered no more than twice in a 24-hour period.

[0062] 26. The method of point 1, wherein the oral dosage form is a solid oral dosage form or a liquid oral dosage form.

[0063] 27. A method for treating an arthritic condition in a subject comprising administering to the subject a pharmaceutical composition for oral administration that comprises:

[0064] (a) an opioid;

[0065] (b) sucrose acetate isobutyrate;

[0066] (c) triacetin;

[0067] (d) isopropyl myristate;

[0068] (e) cellulose acetate butyrate;

[0069] (f) hydroxyethyl cellulose;

[0070] (g) colloidal silicon dioxide; and

[0071] (h) butylated hydroxytoluene,

[0072] wherein one or more symptoms or signs associated with the arthritic condition are alleviated.

[0073] 28. The method of point 27, wherein the opioid is in the form of a free base.

[0074] 29. The method of point 27, wherein the opioid is in the form of a salt.

[0075] 30. The method of point 27, wherein the opioid is micronized.

[0076] 31. The method of any one of points 27, 28, 29 or 30, wherein the opioid is oxycodone, oxymorphone, hydrocodone or hydromorphone.

[0077] 32. The method of any one of points 27, 28, 29 or 30, wherein the opioid is oxycodone.

[0078] 33. The method of point 27, wherein the pharmaceutical composition is encapsulated.

[0079] 34. The method of point 27, wherein the subject is a human.

[0080] 35. The method of point 27, wherein the arthritic condition is osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, juvenile arthropathy, juvenile ankylosing spondylitis, reactive arthropathy, infectious or post-infectious arthritis, gonoccocal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphlitic arthritis, Lyme disease, calcium crystal deposition arthropathies, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis, carpal tunnel syndrome, a repetitive use injury, neuropathic joint disease, hemarthrosis, Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, or multicentric reticulohistiocytosis.

[0081] 36. The method of point 27, wherein the arthritic condition is an arthritis associated with a vasculitic syndrome, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, surcoilosis, hemochromatosis, sickle cell disease or another hemoglobinopathry, hyperlipo proteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, lupus, systemic lupus erythematosis, hemophilia, or relapsing polychondritis.

[0082] 37. The method of point 36, wherein the arthritic condition is associated with a joint, hip, knee, back, neck, or lower back of the subject.

[0083] 38. The method of point 37, wherein the symptom or sign is pain.

[0084] 39. The method of point 38, wherein the pain is measured as pain intensity.

[0085] 40. The method of point 39, wherein the pain intensity measurement is attenuated as compared to a pain intensity baseline measurement of the subject.

[0086] 41. The method of point 40, wherein the pain is measured on the pain subscale of the WOMAC Osteoarthritis Index.

[0087] 42. The method of point 41, wherein the pain measurement of the subject is improved as compared to a baseline pain measurement of the subject on the WOMAC pain subscale.

[0088] 43. The method of point 40, wherein the pain is measured by a patient or physician assessment.

[0089] 44. The method of point 40, wherein the pain is measured on an 11-point numerical scale.

[0090] 45. The method of point 44, wherein the pain is reduced by at least 1 point, as compared to the pain where a human subject is administered a placebo.

[0091] 46. The method of point 38, wherein the pain felt by the subject when walking on a flat surface, when going up or down stairs, while in bed, disturbs the sleep of the subject, while sitting or lying down, or while standing, is attenuated.

[0092] 47. The method of point 27, wherein the symptom or sign is stiffness.

[0093] 48. The method of point 47, wherein the stiffness is attenuated, as compared to a stiffness baseline of the subject.

[0094] 49. The method of point 48, wherein the stiffness is measured by a patient or physician assessment.

[0095] 50. The method of point 49, wherein the stiffness is measured on the stiffness subscale of the WOMAC Osteoarthritis index.

[0096] 51. The method of point 50, wherein the stiffness measurement of the subject is improved as compared to a baseline stiffness measurement of the subject on the WOMAC stiffness subscale.

[0097] 52. The method of point 47, wherein the stiffness felt by the patient after the subject first wakes up in the morning, after sitting or lying down later in the day, or while resting later in the day, is attenuated.

[0098] 53. The method of point 27, wherein the symptom or sign is difficulty in physical function had by the subject.

[0099] 54. The method of point 53, wherein the difficulty in physical function is attenuated, as compared to a baseline physical function measurement of the subject.

[0100] 55. The method of point 53, wherein the difficulty in physical function is measured by a patient or physician assessment.

[0101] 56. The method of point 53 wherein the difficulty in physical function is measured on the physical function subscale of the WOMAC Osteoarthritis index.

[0102] 57. The method of point 56, wherein the physical function measurement of the subject is improved, as compared to a baseline physical function measurement of the subject on the WOMAC physical function subscale.

[0103] 58. The method of point 53, wherein the difficulty had by the subject when going down stairs, when going up stairs, when getting up from a sitting position, while standing, when bending to the floor, when walking on a flat surface, when getting in or out of a car or bus, while going shopping, when getting out of bed, when putting on socks or panty hose or stockings, while lying in bed, when getting in or out of the bathtub, while sitting, when getting on or off the toilet, while doing heavy household chores, or while doing light household chores, is attenuated.

[0104] 59. The method of point 27, wherein the total score of the subject on the WOMAC Osteoarthritis Index is attenuated.

[0105] 60. The method of point 27, wherein progression of the arthritic condition is inhibited.

[0106] 61. A method for treating inflammation in a subject comprising administering to the subject a pharmaceutical composition for oral administration that comprises:

[0107] (a) an opioid;

[0108] (b) sucrose acetate isobutyrate;

[0109] (c) triacetin;

[0110] (d) isopropyl myristate;

[0111] (e) cellulose acetate butyrate;

[0112] (f) hydroxyethyl cellulose;

[0113] (g) colloidal silicon dioxide; and

[0114] (h) butylated hydroxytoluene,

[0115] wherein one or more symptoms or signs associated with inflammation are alleviated.

[0116] 62. The method of point 61, wherein the opioid is in the form of a free base.

[0117] 63. The method of point 61, wherein the opioid is in the form of a salt.

[0118] 64. The method of point 61, wherein the opioid is micronized.

[0119] 65. The method of any one of points 61, 62, 63 or 64, wherein the opioid is oxycodone, oxymorphone, hydrocodone or hydromorphone.

[0120] 66. The method of any one of points 61, 62, 63 or 64, wherein the opioid is oxycodone.

[0121] 67. The method of point 61, wherein the pharmaceutical composition is encapsulated.

[0122] 68. The method of point 61, wherein the subject is a human.

[0123] 69. The method of point 61, wherein the inflammation is associated with an arthritic condition.

[0124] 70. The method of point 69, wherein the arthritic condition is osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, juvenile arthropathy, juvenile ankylosing spondylitis, reactive arthropathy, infectious or post-infectious arthritis, gonoccocal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphlitic arthritis, Lyme disease, calcium crystal deposition arthropathies, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis, carpal tunnel syndrome, a repetitive use injury, neuropathic joint disease, hemarthrosis, Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, or multicentric reticulohistiocytosis.

[0125] 71. The method of point 70, wherein the arthritic condition is an arthritis associated with a vasculitic syndrome, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, surcoilosis, hemochromatosis, sickle cell disease or another hemoglobinopathry, hyperlipo proteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, lupus, systemic lupus erythematosis, hemophilia, or relapsing polychondritis.

[0126] 72. The method of point 69, wherein the arthritic condition is associated with a joint, hip, knee, back, neck, or lower back of the subject.

[0127] 73. The method of point 61, wherein the symptom or sign is pain.

[0128] 74. The method of point 73, wherein the pain is measured as pain intensity.

[0129] 75. The method of point 74, wherein the pain intensity measurement is attenuated as compared to a pain intensity baseline measurement of the subject.

[0130] 76. The method of point 75, wherein the pain is measured on the pain subscale of the WOMAC Osteoarthritis Index.

[0131] 77. The method of point 76, wherein the pain measurement of the subject is improved as compared to a baseline pain measurement of the subject on the WOMAC pain subscale.

[0132] 78. The method of point 75, wherein the pain is measured by a patient or physician assessment.

[0133] 79. The method of point 75, wherein the pain is measured on an 11-point numerical scale.

[0134] 80. The method of point 79, wherein the pain is reduced by at least 1 point, as compared to the pain where a human subject is administered a placebo.

[0135] 81. The method of point 73, wherein the pain felt by the subject when walking on a flat surface, when going up or down stairs, while in bed, disturbs the sleep of the subject, while sitting or lying down, or while standing, is attenuated.

[0136] 82. The method of point 67, wherein the symptom or sign is stiffness.

[0137] 83. The method of point 82, wherein the stiffness is attenuated, as compared to a stiffness baseline of the subject.

[0138] 84. The method of point 83, wherein the stiffness is measured by a patient or physician assessment.

[0139] 85. The method of point 84, wherein the stiffness is measured on the stiffness subscale of the WOMAC Osteoarthritis index.

[0140] 86. The method of point 85, wherein the stiffness measurement of the subject is improved as compared to a baseline stiffness measurement of the subject on the WOMAC stiffness subscale.

[0141] 87. The method of point 82, wherein the stiffness felt by the patient after the subject first wakes up in the morning, after sitting or lying down later in the day, or while resting later in the day.

[0142] 88. The method of point 61, wherein the symptom or sign is difficulty in physical function had by the subject.

[0143] 89. The method of point 88, wherein the difficulty in physical function is attenuated, as compared to a baseline physical function measurement of the subject.

[0144] 90. The method of point 88, wherein the difficulty in physical function is measured by a patient or physician assessment.

[0145] 91. The method of point 88, wherein the difficulty in physical function is measured on the physical function subscale of the WOMAC Osteoarthritis index.

[0146] 92. The method of point 91, wherein the physical function measurement of the subject is improved, as compared to a baseline physical function measurement of the subject on the WOMAC physical function subscale.

[0147] 93. The method of point 88, wherein the difficulty had by the subject when going down stairs, when going up stairs, when getting up from a sitting position, while standing, when bending to the floor, when walking on a flat surface, when getting in or out of a car or bus, while going shopping, when getting out of bed, when putting on socks or panty hose or stockings, while lying in bed, when getting in or out of the bathtub, while sitting, when getting on or off the toilet, while doing heavy household chores, or while doing light household chores, is attenuated.

[0148] 94. The method of point 61, wherein the total score of the subject on the WOMAC Osteoarthritis index is attenuated.

[0149] 95. A pharmaceutical composition for oral administration to a human subject, the pharmaceutical composition comprising:

[0150] (a) an opioid;

[0151] (b) sucrose acetate isobutyrate;

[0152] (c) triacetin;

[0153] (d) isopropyl myristate;

[0154] (e) cellulose acetate butyrate;

[0155] (f) hydroxyethyl cellulose;

[0156] (g) colloidal silicon dioxide; and

[0157] (h) butylated hydroxytoluene.

[0158] 96. A pharmaceutical composition for oral administration to a human subject, the pharmaceutical composition comprising:

[0159] (a) 5.13% opioid;

[0160] (b) 40.98% sucrose acetate isobutyrate;

[0161] (c) 27.32% triacetin;

[0162] (d) 14.23% isopropyl myristate;
[0163] (e) 4.74% cellulose acetate butyrate;
[0164] (f) 5.69% hydroxyethyl cellulose;
[0165] (g) 1.90% colloidal silicon dioxide; and
[0166] (h) 0.02% butylated hydroxytoluene.
[0167] 97. The pharmaceutical composition of any one of points 95 or 96, wherein the opioid is in the form of a free base.
[0168] 98. The pharmaceutical composition of any one of points 95 or 96, wherein the opioid is in the form of a salt.
[0169] 99. The pharmaceutical composition of any one of points 95 to 98, wherein the opioid is micronized.
[0170] 100. The pharmaceutical composition of any one of points 95 to 99, wherein the opioid is oxycodone, oxymorphone, hydrocodone or hydromorphone.
[0171] 101. The pharmaceutical composition of any one of points 95 to 100, wherein the opioid is oxycodone.
[0172] 102. The pharmaceutical composition of any one of points 95 to 101 wherein the composition is encapsulated.
[0173] 103. The pharmaceutical composition of any one of points 95 to 102 wherein the composition comprises:
[0174] (a) 5.0 mg micronized oxycodone base;
[0175] (b) 40.0 mg sucrose acetate isobutyrate;
[0176] (c) 26.6 mg triacetin;
[0177] (d) 13.9 mg isopropyl myristate;
[0178] (e) 4.6 mg cellulose acetate butyrate;
[0179] (f) 5.5 mg hydroxyethyl cellulose;
[0180] (g) 1.8 mg colloidal silicon dioxide; and
[0181] (h) 0.02 mg butylated hydroxytoluene.
[0182] 104. The pharmaceutical composition of any one of points 95 to 102, wherein the composition comprises:
[0183] (a) 10.0 mg micronized oxycodone base;
[0184] (b) 79.9 mg sucrose acetate isobutyrate;
[0185] (c) 53.3 mg triacetin;
[0186] (d) 27.7 mg isopropyl myristate;
[0187] (e) 9.2 mg cellulose acetate butyrate;
[0188] (f) 11.1 mg hydroxyethyl cellulose;
[0189] (g) 3.7 mg colloidal silicon dioxide; and
[0190] (h) 0.04 mg butylated hydroxytoluene.
[0191] 105. The pharmaceutical composition of any one of points 95 to 102, wherein the composition comprises:
[0192] (a) 20.0 mg micronized oxycodone base;
[0193] (b) 159.8 mg sucrose acetate isobutyrate;
[0194] (c) 106.5 mg triacetin;
[0195] (d) 55.5 mg isopropyl myristate;
[0196] (e) 18.5 mg cellulose acetate butyrate;
[0197] (f) 22.2 mg hydroxyethyl cellulose;
[0198] (g) 7.4 mg colloidal silicon dioxide; and
[0199] (h) 0.08 mg butylated hydroxytoluene.
[0200] 106. The pharmaceutical composition of any one of points 95 to 102, wherein the composition comprises:
[0201] (a) 30.0 mg micronized oxycodone base;
[0202] (b) 239.7 mg sucrose acetate isobutyrate;
[0203] (c) 159.8 mg triacetin;
[0204] (d) 83.2 mg isopropyl myristate;
[0205] (e) 27.8 mg cellulose acetate butyrate;
[0206] (f) 33.3 mg hydroxyethyl cellulose;
[0207] (g) 11.1 mg colloidal silicon dioxide; and
[0208] (h) 0.12 mg butylated hydroxytoluene.
[0209] 107. The pharmaceutical composition of any one of points 95 to 102, wherein the composition comprises:
[0210] (a) 40.0 mg micronized oxycodone base;
[0211] (b) 319.6 mg sucrose acetate isobutyrate;
[0212] (c) 213.1 mg triacetin;
[0213] (d) 111.0 mg isopropyl myristate;
[0214] (e) 37.0 mg cellulose acetate butyrate;
[0215] (f) 44.4 mg hydroxyethyl cellulose;
[0216] (g) 14.8 mg colloidal silicon dioxide; and
[0217] (h) 0.16 mg butylated hydroxytoluene.

DETAILED DESCRIPTION OF THE INVENTION

[0218] The present invention provides for the use of novel long-acting, that is, controlled release compositions, formulations and/or dosage forms containing an opioid API such as oxycodone and that are formulated to resist common physical and chemical challenges that attempt to defeat the long-acting feature of the dosage form and thereby lead to rapid release and absorption of a potentially fatal dose of the opioid. Such abuse-resistant compositions, formulations and dosage forms can prevent accidental overdose or intentional misuse that occur with currently marketed long-acting opioid pharmaceuticals, such as long-acting oxycodone formulations.
[0219] The pharmaceutical compositions (the controlled release formulations and dosage forms/kits containing such formulations) that are used herein comprise an opioid API, such as oxycodone, provided in a controlled release formulation that includes a sucrose acetate isobutyrate ("SAIB", a high viscosity liquid controlled release material), triacetin, isopropyl myristate, cellulose acetate butyrate, hydroxyethyl cellulose, colloidal silicon dioxide and butylated hydroxytoluene. Such compositions may be encapsulated, for example, in a gelatin capsule dosage form. When administered, the gelatin capsule dissolves and the opioid API is delivered from the long-acting controlled release matrix by diffusion as the dosage form transits the GI tract. In addition to controlling the rate of opioid release, the components in the controlled release matrix provide the material properties that impart abuse-resistance to the compositions, formulations and dosage forms.
[0220] The present invention provides methods, including the use or administration of novel pharmaceutical compositions, formulations and/or dosage forms containing an opioid API that are useful for the treatment of pain, arthritic conditions and/or inflammation associated with a chronic condition. The methods of the invention provide human subjects with alleviation of one or more of such symptoms or signs including, for example, reduced pain, reduced stiffness and/or improved physical function. The methods of the invention further comprise administration of a pharmaceutical composition comprising an opioid and, optionally, one or more additional active pharmaceutical ingredient (therapeutic agents).
[0221] The present invention provides methods, including the use or administration of novel pharmaceutical compositions, formulations and/or dosage forms containing an opioid API for treating pain, arthritic conditions and/or inflammation associated with chronic conditions in a human subject. For example, the pharmaceutical compositions that are administered to the subject contain an amount of an opioid API that is effective for alleviating one or more symptoms or signs associated with pain, an arthritic condition and/or inflammation associated with a chronic condition, for example, symptoms or signs such as pain, stiffness or difficulty in physical function.
[0222] The present invention provides methods, including the use or administration of novel pharmaceutical compositions, formulations and/or dosage forms containing an opioid API for inhibiting progression of an arthritic condition or

inflammation associated with chronic conditions in a human subject. For example, the amount of the opioid API in the pharmaceutical composition that is administered to the subject is effective for inhibiting progression of the arthritic condition or chronic conditions associated with inflammation. The present invention thus provides methods and materials for inhibiting the change or progression in a subject from a normal or uncompromised state (e.g., healthy) to an abnormal or compromised state (e.g., diseased), as indicated, for example, by a symptom or sign associated with an arthritic condition, inflammation from a chronic condition or chronic pain. The progression of an arthritic condition or inflammation associated with a chronic condition can be measured by a variety of methods, including by radiography, by measuring levels of cytokines and/or by measuring B cell and T cell subtype ratios.

[0223] The present invention provides methods, including the use or administration of novel pharmaceutical compositions, formulations and/or dosage forms containing an opioid API for reversing damage associated with an arthritic condition or inflammation associated with chronic conditions in a human subject. For example, the amount of the opioid in the composition is an amount effective for reversing damage due to the arthritic condition or inflammation associated with chronic conditions. The present invention thus provides methods for reversing the change or progression in a subject from a normal or uncompromised state to an abnormal or compromised state as indicated, for example, by a symptom or sign associated with an arthritic condition, inflammation from a chronic condition or chronic pain. The progression of the arthritic condition or inflammation associated with chronic conditions can be measured by a variety of methods, including by radiography, by measuring levels of cytokines and/or by measuring B cell and T cell subtype ratios.

[0224] The present invention provides methods, including the use of novel pharmaceutical compositions, formulations and/or dosage forms containing an opioid API for treating pain (e.g., chronic pain), such as wherein a pharmaceutical composition comprising an opioid API is administered to a human subject suffering from chronic pain. Chronic pain can include pain that is headache, lower back pain, cancer pain, arthritis pain, infection pain, neurogenic pain or psychogenic pain. The methods of the invention are effective for the treatment of moderate to severe pain and particularly severe pain. For example, the amount of the opioid API in the pharmaceutical compositions is an amount effective for alleviating chronic pain. The pain intensity of the chronic pain is thereby alleviated (e.g., ameliorated, attenuated, reduced, diminished, blocked, inhibited or prevented).

[0225] In the treatment of chronic pain, an arthritic condition and/or inflammation associated with a chronic condition, a pharmaceutical composition containing an opioid can be administered at least once or twice daily for at least one week, alternatively at least once or twice daily for at least two weeks, at least once or twice daily for at least three weeks, or at least once or twice daily for a longer time. The method for treating pain, treating an arthritic condition or treating inflammation associated with a chronic condition may comprise administering the pharmaceutical composition no more than once or twice daily for at least one week, alternatively no more than once or twice daily for at least two weeks, alternatively no more than once or twice daily for at least three weeks, or no more than once or twice daily for a longer time. The method for treating pain, treating an arthritic condition and/or treating inflammation associated with a chronic condition, may comprise administering to the subject a sufficient number or strength of dosage form to provide a daily amount of the opioid API that is less than or equal to 80 mg, alternatively less than or equal to 60 mg, alternatively less than or equal to 40 mg, alternatively less than or equal to 30 mg, alternatively less than or equal to 20 mg or alternatively less or equal to than 10 mg.

[0226] It is contemplated that the present methods may be employed for the treatment of inflammation associated with chronic conditions (including inhibiting progression of and/or reversing damage associated with inflammation), including chronic conditions associated with inflammation in and around joints, muscles, bursae, tendons vertebrae, or fibrous tissue. Such methods provide reduced pain, reduced stiffness and/or improved physical function.

[0227] It is also contemplated that the present methods may be employed for the treatment of chronic conditions (including inhibiting progression of and/or reversing damage associated with chronic conditions). Chronic conditions include, for example, arthritic conditions such as osteoarthritis, rheumatoid arthritis, and psoriatic arthritis. For example, the present methods may be used to treat one or more symptoms or signs of osteoarthritis of the joint, (such as a hip or knee) or the back (for example, the lower back). Chronic conditions also include, for example, conditions associated with or resulting from pain such as chronic pain, including pain associated with or arising from cancer, from infection or from the nervous system (e.g., neurogenic pain such as peripheral neurogenic pain following pressure upon or stretching of a peripheral nerve or root or having its origin in stroke, multiple sclerosis or trauma, including of the spinal cord). Chronic conditions also include, for example, conditions associated with or arising from psychogenic pain (e.g., pain not due to past disease or injury or visible sign of damage inside or outside the nervous system).

[0228] The present methods may also be employed for the treatment of other arthritic conditions, including gout and spondylarthropathris (including ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, juvenile arthropathy or juvenile ankylosing spondylitis, and reactive arthropathy). The present methods may be used for the treatment of infectious or post-infectious arthritis (including gonoccocal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphlitic arthritis, and Lyme disease).

[0229] Additionally, the present methods may be used for the treatment of arthritis associated with various syndromes, diseases, and conditions, such as arthritis associated with vasculitic syndrome, arthritis associated with polyarteritis nodosa, arthritis associated with hypersensitivity vasculitis, arthritis associated with Luegenec's granulomatosis, arthritis associated with polymyalgin rheumatica, and arthritis associated with joint cell arteritis. Other preferred indications contemplated for employing the methods disclosed herein include calcium crystal deposition arthropathies (such as pseudo gout), non-articular rheumatism (such as bursitis, tenosynomitis, epicondylitis, carpal tunnel syndrome, and repetitive use injuries), neuropathic joint disease, hemarthrosis, Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, and multicentric reticulohistiocytosis. Other preferred indications contemplated for employing the methods herein include arthritic conditions associated with surcoilosis, hemochromatosis, sickle cell disease and other hemoglobino-

pathries, hyperlipo proteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, lupus (including systemic lupus erythrematosis), hemophilia, and relapsing polychondritis.

[0230] The methods for treating pain, arthritic conditions, or inflammation associated with chronic conditions alleviate (e.g., ameliorate, attenuate, reduce, diminish, block, inhibit or prevent) at least one symptom or sign of pain, an arthritic condition or inflammation associated with a chronic condition. For example, the methods herein may alleviate one or more of pain intensity, stiffness, or difficulty in physical functions. The methods may attenuate one or more symptoms or signs of pain, an arthritic condition, or inflammation associated with a chronic condition, wherein the sign or symptom after administration of the pharmaceutical composition is ameliorated as compared to the sign or symptom before administration of the pharmaceutical composition.

[0231] The present invention is directed to administration of novel pharmaceutical compositions, formulations, dosage forms, and kits (e.g., blister packs) containing an opioid API, wherein the amount of the opioid is effective to alleviate (e.g., ameliorate, attenuate, reduce, diminish, block, inhibit or prevent) one or more symptoms or signs of pain, an arthritic condition, or inflammation associated with a chronic condition. Optionally, the present methods may comprise administration of an additional therapeutic agent, either in the same pharmaceutical composition or in combination therewith.

[0232] The present invention also provides methods for treating a subject with pain from an arthritic condition or inflammation associated with a chronic condition, comprising administering a pharmaceutical composition containing an amount of an opioid API to the subject, preferably a human, in need thereof, whereby the pain is alleviated.

[0233] The present invention also provides methods for treating an arthritic condition or inflammation associated with chronic conditions. The methods comprise administering to a human subject a pharmaceutical composition containing an amount of an opioid that is effective to alleviate one or more symptoms or signs of an arthritic condition or inflammation associated with a chronic condition, including for example, as measured by a suitable index, scale or measure. The attenuation of one or more symptoms or signs of an arthritic condition or of inflammation associated with a chronic condition may be measured on the WOMAC Osteoarthritis Index or one of its subscales (in other words, the pain, stiffness, or physical function subscales of the WOMAC Osteoarthritis Index). Any suitable version of the WOMAC OA Index may be used, including, for example, Version 3.0 or Version 3.1. Any suitable scale may be used as well. The WOMAC OA Index is available in Likert and Visual Analog scaled formats, either of which may be employed in the present methods. WOMAC values can be considered as surrogate markers for the diagnosis, prognosis, monitoring or treatment of an arthritic condition, inflammation from a chronic condition, and/or chronic pain. The WOMAC values represent a subjective surrogate marker. Alternatively or additionally, the attenuation of one or more symptoms or signs may be measured on another suitable index, scale or measure, such the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index or the Osteoarthritis Global Index (OGI). The AUSCAN 3.0 Index and User Guide are currently available from http://www.womac.org/contact/index.cfm, as are the WOMAC 3.1 Osteoarthritis Index and User Guide. Another suitable measure of attenuation is the Definition of Improvement in Rheumatoid Arthritis described in Felson et al (1995), *Arthritis & Rheumatism* 38:727-735 incorporated herein by reference. This measure, which also may be designated as the ACR (American College of Rheumatology) 20 improvement, is a composite defined as both improvement of 20% in the number of tender and number of swollen joints, and a 20% improvement in three of the following five: patient global, physician global, patient pain, patient function assessment, and C-reactive protein (CRP). Another suitable measure is described by Paulus et al (1990) *Arthritis & Rheumatism* 33:477-484 incorporated herein by reference. Paulus et al. provides a definition of improvement based on a set of measures that discriminate between active second-line drug treatment and placebo. These include a 20% improvement in morning stiffness, erythrocyte sedimentation rate (ESR), joint tenderness score, and joint swelling score and improvement by at least 2 grades on a 5-grade scale (or from grade 2 to grade 1) for patient and physician global assessments of current disease severity. Current disease severity can be measured in a variety of ways, including patient or physician global assessments, patient or physician assessments of joint tenderness, joint swelling stiffness, pain, or physical function, cytokine levels, B-cell or T-cell subtype ratios, erythrocyte sedimentation rate (ESR), or C-reactive protein. Suitable measures of attenuation of one or more symptoms or signs, of inhibiting the progression of an arthritic condition or chronic condition, or of reversing tissue or cellular damage include measuring current disease severity. Other indexes, definitions, measures, or scales may also be used for measuring attenuation of one or more symptoms or signs, inhibition of progression, or reversal of tissue or cellular damage.

[0234] The present invention provides methods for alleviating pain associated with arthritic conditions or inflammation associated with chronic conditions. For example, the amount of the opioid API in the novel compositions that are administered to the subject may be effective to attenuate (e.g., ameliorate, alleviate, reduce, diminish, block, inhibit or prevent) (1) the pain felt by the subject when walking on a flat surface; (2) the pain felt by the subject when going up or down stairs; (3) the pain felt by the subject at night while in bed; (4) the pain felt by the subject that disturbs the sleep of the subject; (5) the pain felt by the subject while sitting or lying down; and/or (6) the pain felt by the subject while standing.

[0235] Alternatively or additionally, the present invention provides methods for alleviating stiffness associated with arthritic conditions or inflammation associated with chronic conditions. For example, the amount of the opioid API in the novel compositions that are administered to the subject may be effective to attenuate (e.g., ameliorate, alleviate, reduce, diminish, block, inhibit or prevent) (1) the severity of the stiffness felt by the patient after the subject first woke up in the morning; (2) the severity of the stiffness felt by the subject after sitting or lying down later in the day; and/or (3) the severity of the stiffness felt by the subject while resting later in the day.

[0236] Alternatively or additionally, the present invention provides methods and materials for alleviating difficulty in physical function associated with arthritic conditions or inflammation associated with chronic conditions. For example, the amount of the opioid API in the novel compositions that are administered to the subject may be effective to attenuate (e.g., ameliorate, alleviate, reduce, diminish, block, inhibit or prevent) (1) the difficulty had by the subject when going down stairs; (2) the difficulty had by the human subject

when going up stairs; (3) the difficulty had by the subject when getting up from a sitting position; (4) the difficulty had by the subject while standing; (5) the difficulty had by the subject when bending to the floor; (6) the difficulty had by the patient when walking on a flat surface; (7) the difficulty had by the human subject when getting in or out of a car or bus; (8) the difficulty had by the subject while going shopping; (9) the difficulty had by the patient when getting out of bed; (10) the difficulty had by the subject when putting on socks, or panty hose or stockings; (11) the difficulty had by the subject while lying in bed; (12) the difficulty had by the subject when getting in or out of the bathtub; (13) the difficulty had by the subject while sitting; (14) the difficulty had by the patient when getting on or off the toilet; (15) the difficulty had by the subject while doing heavy household chores; and/or (16) the difficulty had by the subject while doing light household chores.

[0237] An "effective amount to alleviate" (e.g., ameliorate, attenuate, reduce, diminish, block, inhibit or prevent) symptom or sign of an arthritic condition or inflammation associated with chronic conditions refers to the amount of opioid API contained in the pharmaceutical composition (with or without one or more additional therapeutic agents) which elicits alleviation (e.g., amelioration, attenuation, reduction, diminishment, blockage, inhibition or prevention) of at least one symptom or sign of an arthritic condition or inflammation associated with chronic conditions (e.g., pain) upon administration to a subject (e.g., patient) in need thereof. The amount of the opioid or another therapeutic agent can refer to the weight of the salt or the weight of the free base of such opioid or agent.

[0238] Opioids refer to compounds or compositions, including metabolites of the compounds or compositions, that bind to specific opioid receptors and have agonist (activation) or antagonist (inactivation) effects at the opioid receptors. Preferred opioids include oxycodone, oxymorphone, hydrocodone and hydromorphone. Particularly preferred is oxycodone.

[0239] Inhibitory opioid receptors refer to opioid receptors that mediate inhibitory opioid receptor functions, such as analgesia.

[0240] Opioid receptor agonist or opioid agonist refers to an opioid compound or composition, including any active metabolite of such compound or composition, that binds to and activates opioid receptors on neurons that mediate pain.

[0241] An opioid receptor antagonist or opioid antagonist refers to an opioid compound or composition, including any active metabolite of such compound or composition, that binds to and blocks opioid receptors on neurons that mediate pain. An opioid antagonist attenuates (e.g., blocks, inhibits, prevents, or competes with) the action of an opioid agonist. Preferred opioid antagonists include naloxone, naltrexone and nalmefene.

[0242] Pharmaceutically acceptable refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications, commensurate with a reasonable benefit/risk ratio.

[0243] Pharmaceutically acceptable salts refer to derivatives of the disclosed compounds wherein the compounds are modified by making at least one acid or base salt thereof, and includes inorganic and organic salts.

[0244] An analgesic amount of an opioid API refers to an amount of the opioid that causes analgesia in a subject, and includes standard doses of the opioid which are typically administered in commercially available dosage forms to cause analgesia (e.g. mg doses).

[0245] A subanalgesic amount of opioid refers to an amount which does not cause analgesia in a subject administered that amount of the opioid.

[0246] An effective antagonistic amount of opioid refers to an amount that effectively attenuates (e.g. ameliorates, reduces, diminishes, blocks, inhibits, prevents, or competes with) the analgesic activity of an opioid.

[0247] A therapeutically effective amount of a pharmaceutical composition refers to a composition containing an amount of the API that elicits alleviation (e.g., amelioration, attenuation, reduction, diminishment, blockage, inhibition or prevention) of at least one sign or symptom of an arthritic condition, inflammation associated with a chronic condition, or pain, including chronic pain, upon administration to a patient in need thereof.

[0248] Potency may refer to the strength of an active pharmaceutical ingredient (or treatment employing such API) in producing desired effects, for example, improved pain relief, improved pain control, reduced stiffness, and/or improved physical function. Potency also may refer to the effectiveness or efficacy of a treatment in eliciting desired effects, for example, improved pain relief, improved pain control, reduced stiffness, and/or improved physical function. For example, enhanced potency may refer to the lowering of a dose in achieving desired effects or to an increased therapeutic benefit including that not previously seen. In therapeutics, for example, potency may refer to the relative pharmacological activity of a compound or a composition.

[0249] In the pharmaceutical compositions for use in methods according to the present invention, the opioid may be present in its original form or in the form of a pharmaceutically acceptable salt. The opioid APIs that may be used in methods according to the present invention include: alfentanil, allylprodine, alphaprodine, anileridine, apomorphine, apocodeine, benzylmorphine, bezitramide, butorphanol, clonitazene, codeine, cyclazocine, cyclorphen, cyprenorphine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxyaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydroxymethylmorphinan, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, methylmorphine, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, ohmefentanyl, opium, oxycodone, oxymorphone, papavereturn, phenadoxone, phenomorphan, phenazocine, phenoperidine, pholcodine, piminodine, piritramide, propheptazine, promedol, profadol, properidine, propiram, propoxyphene, remifentanyl, sufentanyl, tramadol, tilidine, salts thereof, mixtures of any of the foregoing, mixed mu-agonists/antagonists, mu-antagonist combinations, or others known to those skilled in the art. Preferred opioids for use in methods according to the present invention include morphine, hydrocodone, oxycodone, codeine, fentanyl (and its relatives), hydromorphone, meperidine, methadone, oxymorphone, propoxyphene or tramadol,

or mixtures thereof. More preferred opioids include oxycodone, oxymorphone, hydrocodone and hydromorphone. Opioids include exogenous or endogenous opioids. Endogenous opioids include endorphin, beta-endorphin, enkephalin, met-enkephalin, dynorphin, orphanin FQ, neuropeptide FF, nociceptin, endomorphin, endormorphin-1, endormorphin-2.

[0250] The opioid API may be present in the pharmaceutical composition in an amount that is analgesic or subanalgesic (e.g., non-analgesic) in the human subject. The subject compositions may be administered in dosage forms containing from about 5 mg to about 40 mg of the opioid API. The opioid is included in the dosage form in an amount sufficient to produce the desired effect upon the process or condition of pain, including inflammatory pain, such as alleviation (e.g., amelioration, attenuation, reduction, diminishment, blockage, inhibition or prevention) of at least one symptom of pain, including inflammatory pain. Symptoms and signs include, for example, pain (including chronic pain), stiffness or difficulty in physical function.

[0251] Optimized amounts of an opioid administered separately or in combination with one or more additional active pharmaceutical ingredient will of course depend upon the particular opioid and API(s) used, the particular components of the composition, the route of administration, and/or the pharmacokinetic properties of the subject being treated. Effective administration levels of opioid and other API will vary upon the state and circumstances of the subject being treated. As those skilled in the art will recognize, many factors that modify the action of an active pharmaceutical ingredient will be taken into account by a treating physician, such as the age, body weight, sex, diet, and condition of the subject, the lapse of time between the condition or injury and the administration of the present compositions, and the administration technique. A person of ordinary skill in the art will be able to ascertain the optimal dosage for a given set of conditions in view of the disclosure herein.

[0252] The opioid API can be present in the present pharmaceutical compositions, formulations and/or dosage forms as an acid, base, or pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" embraces inorganic or organic salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts. The pharmaceutically acceptable salts include the conventional non-toxic salts made, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfonic, sulfamic, phosphoric, nitric and others known to those skilled in the art; and the salts prepared from organic acids such as amino acids, acetic, propionic, succinic, glycolic, stearic, lactic, malic, malonic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, glucuronic, and other acids. Other pharmaceutically acceptable salts and variants include mucates, phosphate (dibasic), phosphate (monobasic), acetate trihydrate, bi(heptafluorobutyrate), bi(methylcarbamate), bi(pentafluoropropionate), mesylate, bi(pyridine-3-carboxylate), bi(trifluoroacetate), bitartrate, chlorhydrate, and sulfate pentahydrate. An oxide, though not usually referred to by chemists as a salt, is also a "pharmaceutically acceptable salt" for the purposes of the present invention. For acidic compounds, the salt may include an amine-based (primary, secondary, tertiary or quaternary amine) counter ion, an alkali metal cation, or a metal cation. Lists of suitable salts are found in texts such as *Remington's Pharmaceutical Sciences,* 18th Ed. (Alfonso R. Gennaro, ed.; Mack Publishing Company, Easton, Pa., 1990); *Remington: the Science and Practice of Pharmacy* 19th Ed. (Lippincott, Williams & Wilkins, 1995); *Handbook of Pharmaceutical Excipients,* 3rd Ed. (Arthur H. Kibbe, ed.; Amer. Pharmaceutical Assoc., 1999); the *Pharmaceutical Codex Principles and Practice of Pharmaceutics* 12th Ed. (Walter Lund ed.; Pharmaceutical Press, London, 1994); The United States Pharmacopeia: The National Formulary (United States Pharmacopeial Convention); and *Goodman and Gilman's: the Pharmacological Basis of Therapeutics* (Louis S. Goodman and Lee E. Limbird, eds.; McGraw Hill, 1992), the disclosures of which are all incorporated herein by reference. Additional representative salts include hydrobromide, hydrochloride, mucate, succinate, n-oxide, sulfate, malonate, acetate, phosphate dibasic, phosphate monobasic, acetate trihydrate, bi(heplafluorobutyrate), maleate, bi(methylcarbamate), bi(pentafluoropropionate), mesylate, bi(pyridine-3-carboxylate), bi(trifluoroacetate), bitartrate, chlorhydrate, fumarate, and sulfate pentahydrate.

[0253] The methods of the invention may further comprise administering to the subject another therapeutic agent, for example, non-steroidal anti-inflammatory agents or local anesthetic and/or analgesic agents, TNF-α antagonists, corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs), anticonvulsant agents, tricyclic antidepressant agents, anti-dynorphin agents, glutamate receptor antagonist agents. In particularly, it is specifically completed that, in addition to the opioid, the subject may be administered TNF-α antagonists, P38 inhibitors, and cytokines inhibitors (including but not limited to IL-2, IL-6, IL-8, and GM-CSF). The opioid and other therapeutic agent may be administered to the subject in a combined dosage form or in separate dosage forms. If in separate dosage forms, the opioid and other therapeutic agent may be administered together or before or after the administration of the other.

[0254] An NSAID refers to a non-steroidal anti-inflammatory drug and includes anti-inflammatory drugs such as aspirin, members of the cycloxygenease I, II and III inhibitors, and includes naproxen sodium, diclofenac and misoprostol, valdecoxib, diclofenac, celecoxib, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, meloxicam, ibuprofen, naproxen, mefenamic acid, nabumetone, ketorolac, choline or magnesium salicylates, rofecoxib, tolmetin sodium, phenylbutazone, oxyphenbutzone, meclofenamate sodium or diflusenal.

[0255] In an embodiment, the pharmaceutical compositions comprise an opioid API and at least one non-narcotic analgesic, such as a nonsteroidal anti-inflammatory agent (NSAID). Representative nonsteroidal anti-inflammatory agents include aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxican, sulindac, tolmetin, and zomepirac. NSAIDs include Celebrex®, Vioxx®, Anaprox®, Arthrotec®, Bextra®, Cataflam®, Clinoril®, DayPro®, Dolobid®, Feldene®, Indocin®, Mobic®, Motrin®, Negprelen®, Naprosyn®, Ponstel®, Relafen® and Toradol®.

[0256] In another embodiment, the pharmaceutical compositions may further comprise an analgesic, antipyretic, and/or

anti-inflammatory therapeutic agent. For example, the composition may further comprise one or more of aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, sulfasalazine, olsalazine, acetaminophen, indomethacin, sulindac, tolmetin, diclofenac, ketorolac, ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin, mefenamic acid, meclofenamic acid, piroxicam, meloxicam, nabumetone, refecoxib, celecoxib, etodolac, and nimesulide.

[0257] With regard to dosage levels, the non-narcotic analgesic may be present in a pain-alleviating amount, or in an amount that is not pain-alleviating alone but is pain-alleviating in combination with the opioid API. This amount is at a level corresponding to the generally recommended adult human dosages for a particular non-narcotic analgesic. An effective pain-alleviating amount of the opioid can be present at a level that potentiates the pain-alleviating effectiveness of the non-narcotic analgesic. Specific dosage levels for the non-narcotic analgesic that can be used herein as given, inter alia, in the "Physicians' Desk Reference", 2003 Edition (Medical Economics Data Production Company, Montvale, N.J.) as well as in other reference works including Goodman and Gilman's "*The Pharmaceutical Basis of Therapeutics*" and "*Remington's Pharmaceutical Sciences*," the disclosures of all are incorporated herein by reference. As is well known to one of ordinary skill in the art, there can be a wide variation in the dosage level of the non-narcotic analgesic, wherein the dosage level depends to a large extent on the specific non-narcotic analgesic being administered. These amounts can be determined for a particular drug combination by employing routine experimental testing.

[0258] In yet another embodiment, the pharmaceutical compositions may further comprise at least one inhibitor of TNF-α. Inhibitors of TNF-α may also be designated TNF-α antagonists. TNF-α antagonists are compounds that are capable of, directly or indirectly, counteracting, reducing or inhibiting the biological activity of TNF-α, or the activation of receptors therefor. Tumor necrosis factor (TNF) is a key proinflammatory cytokine released by a number of cell types, particularly activated macrophages and monocytes. Two forms of TNF are released—TNF-α and TNF-beta. TNF-α is a soluble homotrimer of 17 kD protein subunits (Smith et al. (1987) *J. Biol. Chem.* 262:6951-6954. A membrane-bound 26 kD precursor form of TNF also exists as a pro-protein and must be cleaved to produce the 17 kD TNF. (Kriegler, et al. (1988) *Cell,* 53:45-53). Without limitation, the TNF-α antagonist can be a compound that affects the synthesis of TNF-α, or one that affects the maturation of TNF-α, or one that inhibits the binding of TNF-α with a receptor specific for TNF-α, or one that interferes with intracellular signaling triggered by TNFα binding with a receptor. Additional details regarding the manufacture and use of TNF-α antagonists are available in U.S. Patent Application Publication No. US 2003/0157061 A1, which is incorporated herein by reference.

[0259] Preferred TNF-α antagonists for the present invention include ENBREL® (etanercept) from Wyeth-Ayerst Laboratories/Immunex; REMICADE®, infiximab, which is an anti-TNF chimeric Mab (Centocor; Johnson & Johnson); anti-TNF-α, D2E7 human Mab (Cambridge Antibody Technology) and HUMIRA® (Abbott); CDP-870, which is a PEGylated antibody fragment (Celltech); CDP-571; Humicade, which is a humanized Mab described in U.S. Pat. No. 5,994,510 (Celltech); PEGylated soluble TNF-α Receptor-1 (Amgen); TBP-1, which is a TNF binding protein (Ares Serono); PASSTNF-alpha®, which is an anti-TNF-α polyclonal antibody (Verigen); AGT-1, which is a mixture of three anti-cytokine antibodies to IFN-alpha, IFN-gamma, and TNF (Advanced Biotherapy Concepts); TENEFUSE®, ienercept, which is a TNFR-Ig fusion protein (Roche); CytoTAB® (Protherics); TACE, which is a small molecule TNF-α converting enzyme inhibitor (Immunex); small molecule TNF mRNA synthesis inhibitor (Nereus); PEGylated p75TNFR Fc mutein (Immunex); and TNF-α antisense inhibitor.

[0260] With regard to dosage levels, the TNF-α antagonist is present at an amount effective to inhibit progression or reduce damage from an arthritic condition or a chronic condition associated with inflammation. Alternatively, the TNF-α antagonist is present in an amount that is not effective to inhibit progression or reduce damage alone but is effective to inhibit progression or reduce damage in combination with an opioid according to the invention. This amount is at a level corresponding to the generally recommended adult human dosages for a particular TNF-α antagonist. The effective pain-alleviating amount of the opioid can be present at a level that potentiates the effectiveness of a TNF-α antagonist. Specific dosage levels for TNF-α antagonists that can be used herein as given, inter alia, are included, for example, in the "Physicians' Desk Reference", 2003 Edition (Medical Economics Data Production Company, Montvale, N.J.) as well as in other reference works including Goodman and Gilman's "*The Pharmaceutical Basis of Therapeutics*" and "*Remington's Pharmaceutical Sciences,*" the disclosure of all are incorporated herein by reference. As is well known to one of ordinary skill in the art, there can be a wide variation in the dosage level of the TNF-α antagonist, wherein the dosage level depends to a large extent on the specific TNF-α antagonist being administered. These amounts can be determined for a particular drug combination by employing routine experimental testing.

[0261] In another embodiment, the pharmaceutical compositions may further comprise at least one anti-rheumatic drug. Anti-rheumatic drugs include those referred to as Disease-modifying antirheumatic drugs (DMARDs). Anti-rheumatic drugs include methotrexate (RHEUMATREX, TREXALL), leflunomide (ARAVA), D-Penicillamine, sulfasalazine, gold therapy, minocycline, azathioprine, hydroxychloroquine (PLAQUENIL) and other antimalarials, cyclosporine and biologic agents. Biologic response modifiers, often referred to as biologic agents or simply biologics, are designed to either inhibit or supplement immune system components called cytokines. Cytokines play a role in either fueling or suppressing the inflammation that causes damage in RA and some other diseases. The four biologics currently approved for rheumatoid arthritis all work by inhibiting inflammatory cytokines. Adalimumab (HUMIRA), etanercept (ENBREL) and infliximab (REMICADE) work to inhibit a cytokine called tumor necrosis factor (TNF). Anakinra (KINERET) blocks the action of the cytokine interleukin-1 (IL-1).

[0262] With regard to dosage levels, the anti-rheumatic drug is present at an amount that attenuates a symptom or sign of rheumatism or an amount that does not attenuate such a symptom or sign alone but does attenuate such a symptom or sign in combination with an opioid according to the invention. This amount is at a level corresponding to the generally recommended adult human dosages for a particular anti-rheumatic drug. The effective amount of the opioid API can be present at a level that potentiates the effectiveness of the anti-rheumatic drug. Specific dosage levels for anti-rheu-

matic drugs that can be used herein as given, inter alia, are included, for example, in the "Physicians' Desk Reference", 2003 Edition (Medical Economics Data Production Company, Montvale, N.J.) as well as in other reference works.

[0263] In an embodiment, the present compositions further comprise at least one anticonvulsant or anti-epileptic agent. Any therapeutically effective anticonvulsant may be used according to the invention. For extensive listings of anticonvulsants, see, e.g., Goodman and Gilman's "*The Pharmaceutical Basis Of Therapeutics*", 8th ed., McGraw-Hill, Inc. (1990), pp. 436-462, and "Remington's Pharmaceutical Sciences", 17th ed., Mack Publishing Company (1985), pp. 1075-1083 (the disclosures of which are incorporated herein by reference). Representative anticonvulsants that can be used herein include lamotrigine, gabapentin, valproic acid, topiramate, famotodine, phenobarbital, diphenylhydantoin, phenytoin, mephenytoin, ethotoin, mephobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phensuximide, trimethadione, benzodiazepine, phenacemide, acetazolamide, progabide, clonazepam, divalproex sodium, magnesium sulfate injection, metharbital, paramethadione, phenytoin sodium, valproate sodium, clobazam, sulthiame, dilantin, diphenylan and L-5-hydroxytryptophan. Currently marketed anticonvulant/anti-epileptic drugs include Keppra®, Lamictol®, Neurontin®, Tegretol®, Carbatrol®, Topiramate®, Trileptal®, and Zonegran®.

[0264] With regard to dosage levels, the anticonvulsant is present at a pain-alleviating amount or an amount that is not pain-alleviating alone but is pain-alleviating in combination with the opioid API administered according to the invention. This amount is at a level corresponding to the generally recommended adult human dosages for a particular anticonvulsant. The effective pain-alleviating amount of the opioid can be present at a level that potentiates the pain-alleviating effectiveness of the anticonvulsant. Specific dosage levels for anticonvulsants that can be used herein as given, inter alia, are included, for example, in the "Physicians' Desk Reference", 2003 Edition (Medical Economics Data Production Company, Montvale, N.J.) as well as in other reference works including Goodman and Gilman's "*The Pharmaceutical Basis of Therapeutics*" and "*Remington's Pharmaceutical Sciences,*" the disclosure of all are incorporated herein by reference. As is well known to one of ordinary skill in the art, there can be a wide variation in the dosage level of the anticonvulsant, wherein the dosage level depends to a large extent on the specific anticonvulsant being administered. These amounts can be determined for a particular drug combination by employing routine experimental testing.

[0265] The following examples are provided for illustrative purposes and are not to be construed to limit the scope of the invention in any manner whatsoever.

EXAMPLES

Example 1

Evaluation of the Efficacy and Safety of an Oral Opioid Pharmaceutical Composition

[0266] A clinical trial of an exemplary oral opioid pharmaceutical composition was conducted as follows. The "study drug" used in the clinical trial is a controlled release oral formulation containing oxycodone as the API. The clinical trial was conducted in subjects with moderate to severe chronic pain due to osteoarthritis of the hip or knee. A primary objective of the clinical trial was to study the efficacy and safety of the study drug in these subjects. A secondary objective of the clinical trial was to compare quality of life measures in these subjects with moderate to severe chronic pain due to osteoarthritis of the hip or knee who receive the study drug as compared with those who receive placebo.

[0267] For this clinical trial, a multicenter, randomized, double-blind, placebo-controlled, phase III study was conducted in approximately four hundred subjects with moderate to severe chronic pain due to osteoarthritis of the hip or knee. The study evaluated the efficacy and safety of the study drug relative to placebo over a twelve week double-blind treatment period. Subjects that met eligibility criteria enter a two week open-label titration phase in which subjects are administered 5 mg study drug titrated up to 20 mg study drug. Approximately four hundred subjects were selected that tolerate 20 mg study drug (e.g., no unacceptable adverse events). The selected subjects were randomized in a 1:1 ratio to receive the study drug or placebo with dose adjustments allowed during the first four weeks of the double-blind treatment period. The randomization schedule was generated using a permuted block algorithm and randomly allocated study medication to randomization numbers. The randomization numbers were assigned sequentially through a central IVRS system as subjects are entered into the study.

[0268] Prior to the open-label titration period, subjects were put through a four to ten day washout period during which they stopped taking all pain medication other than acetaminophen (500 mg every four to six hours PRN [a maximum of 3000 mg/day] was permitted). A daily diary (via touch tone phone system) is utilized to record each of the subjects overall pain intensity (PI) each day during the washout period.

[0269] Subjects were permitted to enter the open-label titration period if the mean value of the diary PI over the last two days of the washout period (Baseline PI) is ≥5; if IVRS diary compliance was ≥75%; and, if the subject continued to meet all inclusion/exclusion criteria. Baseline functional assessments were conducted using the Short Form 12 Question Health Survey (SF-12) (Table 1 below) and the Western Ontario and MacMaster Universities Osteoarthritis Index (WOMAC) (Table 2 below).

Table 1

The SF-12v2™ Health Survey

Instructions for Completing the Questionnaire

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

EXAMPLE

This is for your review. Do not answer this question. The questionnaire begins with the section ***Your Health in General*** below.

For each question you will be asked to fill in a bubble in each line:

1. **How strongly do you agree or disagree with each of the following statements?**

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
a) I enjoy listening to music.	○	●	○	○	○

The SF-12v2™ Health Survey

b) I enjoy reading magazines.	●	○	○	○	○

Please begin answering the questions now.

Your Health in General

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor	
O_1	O_2	O_3	O_4	O_5	GH1

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all	
a) **Moderate activities**, such as moving a table, pushing a vacuum	O_1	O_2	O_3	PF02
b) Climbing **several** flights of stairs	O_1	O_2	O_3	PF04

3. **During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
a) **Accomplished less** than you would like	O_1	O_2	O_3	O_4	O_5	RP2
b) Were limited in the **kind** of work or other	O_1	O_2	O_3	O_4	O_5	RP3

4. **During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or**

The SF-12v2™ Health Survey

anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
a) **Accomplished less** than you would like	O_1	O_2	O_3	O_4	O_5	RE2
b) Did work or other activities **less carefully than usual**	O_1	O_2	O_3	O_4	O_5	RE3

5. **During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely	
O_1	O_2	O_3	O_4	O_5	BP2

6. **These questions are about how you feel and how things have been with you <u>during the past week</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past week</u>...**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
a) have you felt calm and peaceful?	O_1	O_2	O_3	O_4	O_5	MH3
b) did you have a lot of energy?	O_1	O_2	O_3	O_4	O_5	VT2
c) have you felt downhearted and depressed?	O_1	O_2	O_3	O_4	O_5	MH4

The SF-12v2™ Health Survey

7. **During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
O_1	O_2	O_3	O_4	O_5

SF2

***THANK YOU* FOR COMPLETING THIS QUESTIONNAIRE!**

Table 2

WOMAC OSTEOARTHRITIS INDEX

Directions: Please refer to the instructions provided to you for completion of the following questions.

Section A

PAIN

Think about the pain you felt in your _____ (study joint) caused by your arthritis during the **last 48 hours**. (Please mark your answers with an "x").

QUESTION: **How much pain have you had ...**	STUDY COORDINATOR USE ONLY
1. when walking on a flat surface? No Pain ——— Extreme Pain	___ ___ ___ mm
2. when going up or down stairs? No Pain ——— Extreme Pain	___ ___ ___ mm
3. at night while in bed? (that is – pain that disturbs your sleep) No Pain ——— Extreme Pain	___ ___ ___ mm
4. while sitting or lying down? No Pain ——— Extreme Pain	___ ___ ___ mm
5. while standing? No Pain ——— Extreme Pain	___ ___ ___ mm

WOMAC OSTEOARTHRITIS INDEX

Section B

STIFFNESS

Think about the stiffness (not pain) you felt in your _____ (study joint) caused by your arthritis during the **last 48 hours**. Stiffness is a sensation of **decreased** ease in moving your joint. (Please mark your answers with an "x").

6. How **severe** has your stiffness been after **you first woke up** in the morning?

No Stiffness ——— Extreme Stiffness

___ ___ ___ mm

7. How **severe** has your stiffness been after sitting or lying down, or while resting **later in the day**?

No Stiffness ——— Extreme Stiffness

Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by your arthritis in your _____ (study joint) during the **last 48 hours**. By this we mean **your ability to move around and take care of yourself.** (Please mark your answers with an "x").

QUESTION: **How much difficulty have you had ...**

STUDY COORDINATOR USE ONLY

8. when going down the stairs?

No Difficulty ——— Extreme Difficulty

___ ___ ___ mm

WOMAC OSTEOARTHRITIS INDEX	
9. when going up the stairs? No Difficulty ——— Extreme Difficulty	___ ___ ___ mm
10. when getting up from a sitting position? No Difficulty ——— Extreme Difficulty	___ ___ ___ mm
11. while standing? No Difficulty ——— Extreme Difficulty	___ ___ ___ mm
12. when bending to the floor? No Difficulty ——— Extreme Difficulty	___ ___ ___ mm
13. when walking on a flat surface? No Difficulty ——— Extreme Difficulty	___ ___ ___ mm
14. getting in or out of a car, or getting on or off a bus? No Difficulty ——— Extreme Difficulty	___ ___ ___ mm

WOMAC OSTEOARTHRITIS INDEX

15. while going shopping?

No Difficulty ——— Extreme Difficulty

___ ___ ___ mm

Think about the difficulty you had in doing the following daily physical activities caused by your arthritis in your _____ (study joint) during the **last 48 hours**. By this we mean **your ability to move around and take care of yourself**. (Please mark your answers with an "x").

QUESTION: **How much difficulty have you had ...**

STUDY COORDINATOR USE ONLY

16. when putting on your socks or panty hose or stockings?

No Difficulty ——— Extreme Difficulty

___ ___ ___ mm

17. when getting out of bed?

No Difficulty ——— Extreme Difficulty

___ ___ ___ mm

18. when taking off your socks or panty hose or stockings?

No Difficulty ——— Extreme Difficulty

___ ___ ___ mm

19. while lying in bed?

No Difficulty ——— Extreme Difficulty

___ ___ ___ mm

WOMAC OSTEOARTHRITIS INDEX	
20. when getting in or out of the bathtub? No Difficulty ——— Extreme Difficulty	___ ___ ___ mm
21. while sitting? No Difficulty ——— Extreme Difficulty	___ ___ ___ mm
22. when getting on or off the toilet? No Difficulty ——— Extreme Difficulty	___ ___ ___ mm
23. while doing heavy household chores? No Difficulty ——— Extreme Difficulty	___ ___ ___ mm
24. while doing light household chores? No Difficulty ——— Extreme Difficulty	___ ___ ___ mm

[0270] During the open-label titration period, subjects were titrated from 5 mg study drug to 20 mg study drug over two weeks as follows:

Week	Day	Dose of Study Drug
Week 1 Open-Label	Days 1-3 Days 4-7	5 mg 10 mg
Week 2 Open-Label	Days 1-3 Days 4-7	15 mg 20 mg

[0271] Subjects were instructed to take a dose of study drug with breakfast and with dinner, to administer doses at least eight hours apart and to take the study drug with meals. Additionally, subjects recorded their overall PI every twenty-four hours by calling in their daily diary information (via touch tone phone) immediately before bedtime.

[0272] At the end of each week during the open-label titration period, subjects returned to the study center and opioid toxicity assessments, adverse events, concomitant medications, drug accountability, and vital signs are performed.

[0273] At the end of the open-label titration period, subjects were enrolled in the double-blind placebo-controlled study if the subjects were able to tolerate 20 mg study drug (e.g., no unacceptable adverse events) and if IVRS diary compliance is ≥75%. Approximately 400 subjects selected from the open-label titration period are randomized in a 1:1 ratio to receive the study drug or placebo. Randomization of the subjects was stratified by both baseline PI (<7.5 vs. ≥7.5) and by the average PI over the last two days of the open-label titration period (<5 vs. ≥5). During the first four weeks of the double-blind treatment period, subjects were titrated (up or down) to analgesic effect. At the conclusion of four weeks, the dose was fixed for an additional 8 weeks.

[0274] The patient characteristics of the 558 patients that enrolled in the open label study are shown in Table 3.

TABLE 3

PATIENT CHARACTERISTICS
OPEN-LABEL TITRATION PERIOD
ANALYSIS POPULATION: OPEN-LABEL SAFETY POPULATION

	OXY BID (N = 558)
AGE (YEARS)	
MEAN (SD)	58.9(8.23)
MEDIAN	59.1
MIN, MAX	40.4, 75.7
N	558
<=60	301(53.9%)
>60	257(46.1%)
SEX	
FEMALE	387(69.4%)
MALE	171(30.6%)
TOTAL	558(100.0%)
ETHNICITY	
HISPANIC OR LATINO	35(6.3%)
NOT HISPANIC OR LATINO	521(93.4%)

TABLE 3-continued

PATIENT CHARACTERISTICS
OPEN-LABEL TITRATION PERIOD
ANALYSIS POPULATION: OPEN-LABEL SAFETY POPULATION

	OXY BID (N = 558)
RACE	
AMERICAN INDIAN OR ALASKA NATIVE	5(0.9%)
ASIAN	1(0.2%)
BLACK OR AFRICAN AMERICAN	83(14.9%)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0(0.0%)
WHITE	469(84.1%)
HEIGHT(CM)	
MEAN (SD)	167.5(9.58)
MEDIAN	165.6
MIN, MAX	137.2, 208.3
N	556
WEIGHT (KG)	
MEAN (SD)	94.2(19.55)
MEDIAN	93.8
MIN, MAX	50.4, 136.2
N	558
PRIOR OPIOID USE WITHIN 30 DAYS OF FIRST DOES OF OPEN-LABEL STUDY DRUG	
YES	152(27.2%)
NO	406(72.8%)
TARGET JOINT	
HIP	122(21.9%)
KNEE	436(78.1%)
WASHOUT PERIOD ACETAMINOPHEN USAGE	
YES	532(95.3%)
NO	26(4.7%)
SCREENING CLINIC PI	
MEAN (SD)	7.0(1.40)
MEDIAN	7.0
MIN, MAX	4.0, 10.0
N	558
BASELINE PI	
MEAN(SD)	7.5(1.33)
MEDIAN	7.5
MIN, MAX	5.0, 10.0
N	558
<7.5	255(45.7%)
>=7.5	303(54.3%)
PRE-RANDOMIZATION PI	
MEAN(SD)	5.3(2.15)
MEDIAN	5.5
MIN, MAX	0.0, 10.0
N	412
<5	145(26.MCNI0%)
>=5	267(47.8%)

NOTE:
OPEN-LABEL SAFETY POPULATION - ALL PATIENTS WHO TAKE AT LEAST ONE DOSE OF STUDY MEDICATION IN OPEN-LABEL PERIOD.

[0275] All subjects enrolled in the open-label titration period received study drug BID as shown in Table 4. Subjects that tolerated the study drug were randomized to receive study drug BID or placebo BID for the remainder of the clinical trial.

TABLE 4

ENROLLMENT AND RANDOMIZATION STATUS

	PLACEBO BID	OXY BID	TOTAL
OPEN-LABEL SAFETY [1]		58	558
DOUBLE-BLIND SAFETY [2]	207	205	412
ITT [3]	207	203	410

[1] OPEN-LABEL SAFETY POPULATION - ALL PATIENTS WHO TAKE AT LEAST ONE DOSE OF STUDY MEDICATION IN OPEN-LABEL PERIOD.
[2] DOUBLE-BLIND SAFETY POPULATION - ALL PATIENTS WHO TAKE AT LEAST ONE DOSE OF STUDY MEDICATION IN DOUBLE-BLIND PERIOD.
[3] INTENT TO TREAT POPULATION - ALL RANDOMIZED PATIENTS WHO TAKE ANY STUDY MEDICATION AND HAVE AT LEAST ONE POST-RANDOMIZATION PAIN INTENSITY (PI) ASSESSMENT.

[0276] Causes of early termination from study drug BID during the open-label titration period are shown in Table 5. Out of the 146 subjects that terminated during the open label titration period 124 terminated due to adverse events. This constituted 22.2% of the total population of 558 subjects that enrolled in open-label period.

TABLE 5

TERMINATION FROM STUDY DRUG DURING THE OPEN-LABEL TITRATION PERIOD ANALYSIS POPULATION: OPEN-LABEL SAFETY POPULATION

	OXY BID (N = 146)
DID THE PATIENT TERMINATE STUDY DRUG EARLY?	
NO	0 (0.0%)
YES	146 (26.2%)
INADEQUATE PAIN RELIEF	4 (0.7%)
ADVERSE EVENT	124 (22.2%)
PROTOCOL VIOLATION	10 (1.8%)
INAPPROPRIATE ENROLLMENT	5
NEED FOR PROHIBITED MEDICATION	0
OTHER	5
PATIENT REQUEST UNRELATED TO STUDY	5 (0.9%)
OTHER	3 (0.5%)

NOTE:
OPEN-LABEL SAFETY POPULATION - ALL PATIENTS WHO TAKE AT LEAST ONE DOSE OF STUDY MEDICATION IN OPEN-LABEL PERIOD.
NOTE:
THIS TABLE IS FOR OPEN-LABEL SAFETY PERIOD - ONLY PATIENTS WHO EARLY TERMINATED DURING OPEN-LABEL TITRATION.

[0277] The types of adverse events and their incidences reported by the subjects that terminated during the open-label titration period are shown in Table 6. The most frequent of these adverse events (AEs) were those commonly associated with opioid medications: dizziness, constipation, dry mouth, nausea, vomiting, somnolence, and pruritis.

TABLE 6

ADVERSE EVENTS CAUSING DISCONTINUATION OF STUDY MEDICATION DURING THE OPEN-LABEL TITRATION PERIOD [1] ANALYSIS POPULATION: OPEN-LABEL SAFETY POPULATION

SYSTEM ORGAN CLASS PREFERRED TERM	NUMBER (%) OF PATIENTS REPORTING EVENTS OXY BID (N = 558)
GASTROINTESTINAL DISORDERS	65 (11.6%)
ABDOMINAL PAIN UPPER	3 (0.5%)
CONSTIPATION	13 (2.3%)
DIARRHOEA	2 (0.4%)

TABLE 6-continued

ADVERSE EVENTS CAUSING DISCONTINUATION OF STUDY MEDICATION DURING THE OPEN-LABEL TITRATION PERIOD [1] ANALYSIS POPULATION: OPEN-LABEL SAFETY POPULATION

SYSTEM ORGAN CLASS PREFERRED TERM	NUMBER (%) OF PATIENTS REPORTING EVENTS OXY BID (N = 558)
DRY MOUTH	1 (0.2%)
NAUSEA	45 (8.1%)
STOMACH DISCOMFORT	2 (0.4%)
VOMITING	10 (1.8%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	14 (2.5%)
ASTHENIA	1 (0.2%)
CHEST PAIN	1 (0.2%)
FATIGUE	9 (1.6%)
IRRITABILITY	1 (0.2%)
OEDEMA	1 (0.2%)
OEDEMA PERIPHERAL	1 (0.2%)
PAIN	1 (0.2%)
PYREXIA	1 (0.2%)
INFECTIONS AND INFESTATIONS	1 (0.2%)
SINUSITIS	1 (0.2%)
INVESTIGATIONS	1 (0.2%)
HEPATIC ENZYME INCREASED	1 (0.2%)
METABOLISM AND NUTRITION DISORDERS	1 (0.2%)
ANOREXIA	1 (0.2%)
MUSCULOSKELLETAL AND CONNECTIVE TISSUE DISORDERS	3 (0.5%)
ARTHRIALGIA	1 (0.2%)
MYALGIA	1 (0.2%)
PAIN IN EXTREMITY	1 (0.2%)
NERVOUS SYSTEM DISORDER	68 (12.2%)
DISTURBANCE IN ATTENTION	2 (0.4%)
DIZZINESS	24 (4.3%)
DYSARTHRIA	4 (0.7%)
HEADACHE	8 (1.4%)
LETHARGY	3 (0.5%)
MEMORY IMPAIRMENT	1 (0.2%)
SCIATICA	1 (0.2%)
SEDATION	1 (0.2%)
SOMNOLENCE	41 (7.3%)
PSYCHIATRIC DISORDERS	21 (3.8%)
ABNORMAL DREAMS	1 (0.2%)
AGITATION	1 (0.2%)
ANXIETY	1 (0.2%)
CONFUSIONAL STATE	11 (2.0%)
DEPRESSION	1 (0.2%)
DISORIENTATION	1 (0.2%)
EUPHORIC MOOD	1 (0.2%)
HALLUCINATION	1 (0.2%)
HALLUCINATION, AUDITORY	1 (0.2%)
HALLUCINATION, VISUAL	1 (0.2%)
INSOMNIA	1 (0.2%)
LIBIDO DECREASED	1 (0.2%)
MENTAL STATUS CHANGES	3 (0.5%)
MOOD SWINGS	1 (0.2%)
PERSONALITY CHANGE	1 (0.2%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.2%)
ERECTILE DYSFUNCTION	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (0.5%)
COUGH	2 (0.4%)
DYSPNOEA	1 (0.2%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	19 (3.4%)
HYPERHIDROSIS	4 (0.7%)
PRURITUS	14 (2.5%)
RASH	2 (0.4%)
SWELLING FACE	1 (0.2%)
VASCULAR DISORDERS	3 (0.5%)
HOT FLUSH	1 (0.2%)

TABLE 6-continued

ADVERSE EVENTS CAUSING DISCONTINUATION OF STUDY MEDICATION DURING THE OPEN-LABEL TITRATION PERIOD [1]
ANALYSIS POPULATION: OPEN-LABEL SAFETY POPULATION

SYSTEM ORGAN CLASS PREFERRED TERM	NUMBER (%) OF PATIENTS REPORTING EVENTS OXY BID (N = 558)
HYPOTENSION	1 (0.2%)
ORTHOSTATIC HYPOTENSION	1 (0.2%)

NOTE:

OPEN-LABEL SAFETY POPULATION - ALL PATIENTS WHO TAKE AT LEAST ONE DOSE OF STUDY MEDICATION IN OPEN-LABEL PERIOD.

[1] ADVERSE EVENT START DATE IS BETWEEN THE FIRST DOSE DATE OF STUDY MEDICATION IN THE OPEN-LABEL TITRATION PERIOD THROUGH THE LAST DOSE DATE OF STUDY MEDIATION IN THE OPEN-LABEL TITRATION PERIOD.

[0278] The characteristics of the 412 subjects enrolled in the twelve week double-blind treatment period are shown in Table 7. Thus, 412 subjects that tolerated study drug administered during the open-label titration period continued in the double-blind treatment period.

TABLE 7

PATIENT CHARACTERISTICS
12-WEEK DOUBLE-BLIND PERIOD
ANALYSIS POPULATION: DOUBLE-BLIND SAFETY POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 205)	TOTAL (N = 412)
AGE (YEARS)			
MEAN (SD)	58.5 (8.44)	58.0 (7.86)	58.2 (8.15)
MEDIAN	58.5	57.5	57.7
MIN, MAX	40.4, 75.7	40.4, 75.0	40.4, 75.7
N	207	205	412
<=60	119 (57.5%)	119 (58.0%)	238 (57.8%)
>60	88 (42.5%)	86 (42.0%)	174 (42.2%)
SEX			
FEMALE	141 (68.1%)	147 (71.7%)	288 (69.9%)
MALE	66 (31.9%)	58 (28.3%)	124 (30.1%)
TOTAL	207 (100.0%)	205 (100.0%)	412 (100.0%)
ETHNICITY			
HISPANIC OR LATINO	17 (8.2%)	4 (2.0%)	21 (5.1%)
NOT HISPANIC OR LATINO	187 (91.3%)	200 (97.6%)	389 (94.4%)
RACE			
AMERICAN INDIAN OR ALASKA NATIVE	2 (1.0%)	3 (1.5%)	5 (1.2%)
ASIAN	0 (0.0%)	0 (0.0%)	0 (0.0%)
BLACK OR AFRICAN AMERICAN	33 (15.9%)	36 (17.6%)	69 (16.7%)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0 (0.0%)	0 (0.0%)	0 (0.0%)
WHITE	171 (82.6%)	167 (81.5%)	338 (82.0%)
HEIGHT (CM)			
MEAN (SD)	168.0 (9.98)	166.6 (10.14)	167.3 (10.07)
MEDIAN	165.1	165.1	165.1
MIN, MAX	147.3, 193.0	137.2, 208.3	137.2, 208.3
N	207	204	411

TABLE 7-continued

PATIENT CHARACTERISTICS
12-WEEK DOUBLE-BLIND PERIOD
ANALYSIS POPULATION: DOUBLE-BLIND SAFETY POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 205)	TOTAL (N = 412)
WEIGHT (KG)			
MEAN (SD)	96.7 (19.77)	94.4 (20.05)	95.6 (19.92)
MEDIAN	97.6	96.2	97.2
MIN, MAX	50.4, 136.2	50.8, 136.2	50.4, 136.2
N	207	205	412
TARGET JOINT			
HIP	43 (20.8%)	46 (22.4%)	89 (21.6%)
KNEE	164 (79.2%)	159 (77.6%)	323 (78.4%)
WASHOUT PERIOD ACET-AMINOPHEN USAGE			
YES	201 (97.1%)	196 (95.6%)	397 (96.4%)
NO	6 (2.9%)	9 (4.4%)	15 (3.6%)
SCREENING CLINIC PI			
MEAN (SD)	7.0 (1.38)	7.1 (1.48)	7.0 (1.43)
MEDIAN	7.0	7.0	7.0
MIN, MAX	5.0, 10.0	4.0, 10.0	4.0, 10.0
N	207	205	412
BASELINE PI			
MEAN (SD)	7.6 (1.36)	7.6 (1.35)	7.6 (1.35)
MEDIAN	7.5	7.5	7.5
MIN, MAX	5.0, 10.0	5.0, 10.0	5.0, 10.0
N	207	205	412
<7.5	90 (43.5%)	89 (43.4%)	179 (43.4%)
>=7.5	117 (56.5%)	116 (56.6%)	233 (56.6%)
PRE-RANDOM-IZATION PI			
MEAN (SD)	5.4 (2.11)	5.2 (2.19)	5.3 (2.15)
MEDIAN	5.5	5.5	5.5
MIN, MAX	0.0, 10.0	0.0, 10.0	0.0, 10.0
N	207	205	412
<5	72 (34.8%)	73 (35.6%)	145 (35.2%)
=5	135 (65.2%)	132 (64.4%)	267 (64.8%)

[0279] All subjects begin dosing at 20 mg study drug BID (or placebo BID). Subjects in the placebo group were titrated down over the first two weeks of the double-blind treatment period to prevent the emergence of opioid withdrawal symptoms (15 mg BID for the first 3 days of Week 1, 10 mg BID for the remainder of Week 1, and 5 mg BID for Week 2). Subjects returned to the clinic at the end of each week (±1 day) for the first four weeks and then every two weeks (14-16 days) for the remainder of the double-blind fixed-dose treatment period.

[0280] During the 12-week treatment period, subjects recorded their PI every 24 hours in their daily diary immediately before their bedtime dose. In addition, subjects recorded adverse events and date/time of taking the study medication in the daily diary. At each study center visit, the investigator collected additional data, including quality of analgesia, pain control, the SF-12 Health Survey, the WOMAC Osteoarthritis Index and a global assessment of study medication. Unscheduled study center visits were allowed throughout the study for treatment of adverse events. Adverse events, opioid toxicity

assessments, drug accountability, concomitant medication and vital signs were performed at each scheduled study center visit.

[0281] Subjects were allowed to increase their dose of study drug during study center visits at the end of Weeks 1, 2, and 3 of the double-blind treatment period if the following criteria are met: (1) the subject tolerated the study drug (no unacceptable adverse events); the subject's Pain Intensity (PI) score was >2; and (3) both the Investigator and the subject agreed that dose should be increased. Subjects may choose not to increase dose of study drug if they had a PI>2 that they found acceptable. Subjects may also decrease their dose of study medication during the first four weeks of the double-blind treatment period if they had unacceptable adverse events. At the end of Week 4 the final dosage of study drug was fixed for the remainder of the double-blind fixed-dose treatment period.

[0282] The following titration schedule outlines the allowed dose increments for subjects requiring dose adjustments of study drug. The maximum allowed dose for study drug is 40 mg BID (total daily dose 80 mg). Subjects were not allowed to skip a dose increment if a dose was titrated up or down. Titrating up more than one dose increment may lead to study drug-related adverse events, and titrating down more than one dose increment may lead to inadequate analgesia. Subjects were dispensed one or two blister packets of study drug at each study center visit.

Study Drug 5 mg BID
Study Drug 10 mg BID
Study Drug 15 mg BID
Study Drug 20 mg BID
Study Drug 30 mg BID
Study Drug 40 mg BID

[0283] At the conclusion of the 12-week double-blind treatment period, subjects were gradually tapered off of study drug over a period of 0 to 15 days, depending on the final fixed dose, to prevent the emergence of opioid withdrawal symptoms as follows:

Final Fixed Dose	Days 0-3 Taper Period	Days 4-6 Taper Period	Days 7-9 Taper Period	Days 10-12 Taper Period	Days 13-15 Taper Period
40 mg BID	30 mg	20 mg	15 mg	10 mg	5 mg
30 mg BID	20 mg	15 mg	10 mg	5 mg	—
15 or 20	10 mg	5 mg	—	—	—
5 or 10 mg	No taper required				

[0284] Also at the conclusion of the clinical trial, subjects were educated about the possibility of study drug withdrawal symptoms. Any subject experiencing symptoms of study drug withdrawal could return to the study center for an additional visit for treatment. Subjects were required to return to the study center for a post-treatment follow-up visit approximately one week (±two days) after the final dose of study drug.

[0285] Safety of the study drug was evaluated by vital signs (blood pressure, heart rate, respiratory rate and temperature), physical examinations, electrocardiograms (EKGs), clinical laboratory tests, adverse event monitoring, and opioid toxicity assessments. Subjects could return to the study center in-between scheduled visits for treatment of study drug-related adverse events and investigators were encouraged to treat opioid-related adverse events (e.g., constipation, nausea, vomiting, dizziness, and pruritis) as soon as they occurred to avoid unnecessary dropouts from the study.

[0286] Inclusion criteria were as follows:

[0287] (1) Males and females who are 40 and 75 years of age;

[0288] (2) Subject had moderate to severe pain in one or more hip or knee joint(s) for at least three months prior to the Screening Visit due to osteoarthritis as demonstrated by clinical and radiographic evidence according to the American College of Rheumatology (ACR) criteria for the diagnosis of osteoarthritis of the hip or knee;

[0289] (3) Subject had moderate to severe pain in the hip or knee joint(s) while taking ≥4 days/week every week for the past four weeks prior to the Screening Visit one or more of the following types of oral analgesic medication(s): NSAIDs, COX-2 inhibitors, tramadol, opioids;

[0290] (4) Subject had received: no opioids within 72 hours of the Screening Visit and either: no opioids or an average daily opioid dose equivalent of oxycodone ≤20 mg or tramadol ≤200 mg within one week prior to the Screening Visit; or a daily opioid dose equivalent of oxycodone (>20 mg and ≤80 mg) or tramadol >200 mg within one week prior to the Screening Visit and had undergone an opioid taper prior to study entry;

[0291] (5) Subject had a pain intensity score of ≥5 on an 11-point numerical scale at the Screening Visit;

[0292] (6) Subject had a mean daily diary overall pain intensity of ≥5 on an 11-point numerical scale during the last two days of the washout period (Baseline PI; calculated by IVRS);

[0293] (7) Subject completed daily telephone diary pain intensity assessments for ≥75% days (calculated by IVRS) during the washout period and during the open-label titration period;

[0294] (8) Subject completed the open-label titration period and was able to tolerate study drug at 20 mg BID;

[0295] (9) Subject agreed to refrain from taking any pain medications other than study drug during the study period. [Aspirin (up to 325 mg/day) was permitted for cardiovascular prophylaxis if at a stable dose one month prior to the Screening Visit. Acetaminophen was allowed during the washout period only];

[0296] (10) Subject must be ambulatory;

[0297] (11) Females who were postmenopausal, physically incapable of childbearing, or practicing an acceptable method of birth control. Acceptable methods of birth control include surgical sterilization, hormonal contraceptives, or double-barrier methods (condom or diaphragm with a spermicidal agent or intrauterine device [IUD]). If practicing an acceptable method of birth control, a negative urine pregnancy test result has been obtained prior to starting the open-label titration period; and

[0298] (12) Subject was able to understand and cooperate with study procedures, has access to a touch-tone telephone at home, and has signed a written informed consent form prior to any study procedures.

[0299] Exclusion criteria for subjects were as follows:

[0300] (1) Subject had a positive urine drug screen at the Baseline Visit;

[0301] (2) Subject had received a daily opioid dose equivalent of oxycodone >80 mg for 4 or more days/week during the week prior to the initial Screening Visit;

[0302] (3) Subject had pain in the hip(s) or knee(s) caused by conditions other than osteoarthritis, e.g., malignancy, gout, inflammatory disease such as rheumatoid arthritis, fibromyalgia, recent trauma within the past six months, or infection;

[0303] (4) Subject had a history of Paget's disease, or autoimmune diseases associated with arthritis (e.g. rheumatoid arthritis, lupus, Sjogren's are exclusionary diagnoses);

[0304] (5) Subject had major surgery within three months prior to the Screening Visit or had surgery planned during the proposed study period;

[0305] (6) Subject had received oral, intra-articular, or parenteral corticosteroid therapy within one month prior to the Screening Visit;

[0306] (7) Subject had received an intra-articular injection of hyaluronic acid in the hip or knee within six months prior to the Screening Visit;

[0307] (8) Subject weighed more than 300 lbs or less than 100 lbs;

[0308] (9) Subject was pregnant or breast-feeding;

[0309] (10) Subject had received an epidural or intrathecal infusion of any analgesic medication(s) within one month prior to the Screening Visit;

[0310] (11) Subject had severe impairment of pulmonary function, hypercarbia, hypoxia, cor pulmonale, sleep apnea syndrome, severe/uncontrolled asthma, chronic obstructive pulmonary disease, or a history of respiratory depression;

[0311] (12) Subject had a history of gastric bypass surgery; any gastric or small intestine surgery leading to malabsorption; or any disease that causes clinical malabsorption;

[0312] (13) Subject had unstable cardiac disease (e.g. inadequately controlled hypertension, congestive heart failure, a history of myocardial infarction within the previous year); or subject has any health condition(s) that pose a significant health risk in the event of opioid withdrawal;

[0313] (14) Subject had started, stopped, or changed the dose of the following medications within four weeks prior to the Screening Visit: monoamine oxidase inhibitors, tricyclic antidepressants, serotonin reuptake inhibitors or other antidepressants; gabapentin, pregabalin, and glucosamine/chondroitin;

[0314] (15) Subject had started or stopped physical therapy, transcutaneous electrical nerve stimulation, chiropractic, osteopathic, acupuncture, or other complementary treatment within four weeks prior to the Screening Visit or is expected to undergo any changes in these therapies during the study;

[0315] (16) Subject had received high doses of sedatives, hypnotics or tranquilizers that may, in the opinion of the investigator, increase the risk of opioid toxicity;

[0316] (17) Subject had received phenothiazines or other agents that compromise vasomotor tone. (Promethazine is allowed);

[0317] (18) Subject had a history of alcohol or drug abuse within the past 5 years;

[0318] (19) Subject had a medical illness/condition, psychiatric illness, and/or abnormal diagnostic finding that would interfere with the completion of the study, confound the results of the study, or pose risk to the subject;

[0319] (20) Subject had a history of leukemia, lymphoma, myeloproliferative disease, multiple myeloma, or metastatic cancer; subject has a history of prostate, breast, thyroid or lung cancer within five years of study entry; or subject had a history of any other localized malignancy within two years of study entry. (Subjects with treated localized prostate, breast, thyroid or lung cancer without recurrence for five years, any other treated localized malignancy without recurrence for 2 years, or a history of curative treatment of basal or squamous cell carcinoma of the skin were not excluded.);

[0320] (21) Subject had a history of an allergic reaction or hypersensitivity to any of the study medications or structurally similar compounds: oxycodone, morphine, hydromorphone, hydrocodone, levorphanol, pentazocine, codeine, etc. or acetaminophen;

[0321] (22) Subject had AST, ALT, or alkaline phosphatase >2 times the upper limit of normal; hematocrit <30%; creatinine ≥1.8; or ESR >20 from the Screening Visit;

[0322] (23) Subject had previously received the study drug;

[0323] (24) Subject had participated in another investigational drug trial or therapeutic trial within 30 days of the Screening Visit;

[0324] (25) Subject had taken analgesic medication (other than acetaminophen) during the washout period prior to enrollment; or subject had taken any analgesic medication (other than study drug) during the open-label titration period prior to randomization.

[0325] The physical descriptions of the study drugs used for this clinical trial study were as follows. The study drugs were available in capsules containing study drug or placebo. The study drug capsules were available in 5 mg, 10 mg, 15 mg 20 mg, 30 mg and 40 mg. Dosage strengths came in four different sized capsules. The 5 mg dosage strength came in Size 4 (small) capsules, the 10 mg dosage strength came in Size 2 (medium) capsules, the 15 and 20 mg dosage strengths came in Size 1 (large) capsules, and the 30 and 40 mg dosage strengths came in Size 00 (extra large) capsules. Placebo capsules were indistinguishable from the study drug capsules. For the 4- to 10-day washout period, a container of acetaminophen (500 mg caplets) was dispensed at the Screening Visit in a sufficient quantity for dosing up to six caplets per day. The investigational drug supplies were in capsule dosage forms containing study drug BID or placebo BID. All of the capsule dosage forms were indistinguishable from one another to facilitate blinding.

[0326] One or two containers of acetaminophen (APAP) were dispensed at the Screening Visit for the 4- to 10-day washout period. A commercially available source of acetaminophen tablets (500 mg) was supplied. A single panel label was applied to commercially sourced plastic bottles of acetaminophen to obscure the original dosing instructions.

[0327] Throughout the study, investigational drug supplies (study drug) were dispensed in child-resistant blister cards. Each blister card contained a one-week (Days 1-7) supply of study drug as well as extra study drug (Days 8-10) to allow for flexibility in planning return clinic visits. Blister cards for the double-blind taper period contained a 6- to 15-day supply of study drug, depending on the subject's final fixed dose. The extra study drug had to remain intact within its original packaging so that it could be returned at each clinic visit.

[0328] During the open-label titration period, capsules were arranged on each blister card by day and contained two capsules per day. For the first week, the blister card contained 20 capsules (Days 1-10) consisting of Size 4 and Size 2 capsules; the first three days were 5 mg capsules and the remaining days were 10 mg capsules. The Week 2 blister card

contained Size 1 capsules; the first three days were 15 mg capsules and the remaining days were 20 mg capsules.

[0329] During the first two weeks of the double-blind treatment period, the blister card contained 40 capsules. Capsules were arranged on each blister card by day (Days 1-10) and contained four capsules per day. All subjects were instructed to take two capsules with breakfast and two capsules with dinner for the first two weeks of the double-blind treatment period. The purpose of this change in the number of capsules was to allow placebo subjects to be titrated off of PTI-821 to prevent opioid withdrawal while still maintaining the double-blind.

[0330] During the remainder of the double-blind treatment period up until the end of the fixed-dose treatment period, the blister cards contained 20 capsules. Capsules were arranged on each blister card by days (Days 1-10) and contained two capsules per day. Subjects were instructed to take one capsule of study drug BID for the remainder of the study.

[0331] At the conclusion of the 12-week fixed dose portion of the double-blind treatment period, subjects who had been on study drug for at least four weeks (including the open-label titration period) were tapered off of study drug over a period of 0-15 days, depending on the final fixed dose. Tapering was performed in a blinded fashion. Subjects taking 40 mg BID required a 15 day taper, subjects taking 30 mg BID required a 12 day taper, subjects taking 15 or 20 mg BID required a 6 day taper, and subjects taking 10 or 5 mg BID did not require a taper. Each blister card contained 12, 24, or 30 capsules. Capsules were arranged on each blister card by days and contained two capsules per day. Subjects were instructed to take one capsule of study drug BID until there are no capsules remaining in the blister card.

[0332] The label on each blister card contained a unique kit number that was assigned to patients at weekly or biweekly intervals. An Interactive Voice Response System (IVRS) provided assignment of kit numbers.

[0333] One blister card was dispensed for each week of the open-label titration period and for the first four weeks of the double-blind fixed-dose treatment period. Two blister cards were dispensed at the biweekly visits for the remainder of the 12-week double-blind fixed-dose treatment period. If the subject required a taper, one blister card was dispensed at the end of treatment visit.

[0334] Each blister card had a label consisting of two parts. One part remained attached to the kit and the other was a tear-off label, which was adhered onto the appropriate Case Report Form (CRF). The information included on the label was in accordance with local requirements. All blister cards, empty or containing unused capsules, were saved for final disposition by the sponsor or designee.

[0335] The study procedures were as follows. Prior to any study-related activities, written informed consent was signed and dated by the subject. Clinical examinations were performed that comprised the standard-of-care evaluations routinely performed as part of ongoing care for subjects with moderate to severe chronic pain due to osteoarthritis of the hip or knee. Pain assessments were performed by assessing: (1) Pain Intensity, (2) Quality of Analgesia, (3) Pain Control, and (4) Global Assessment of Study Medication.

[0336] Pain Intensity was assessed by prompting the subject with the question, "How would you rate your overall pain intensity at this time?", and the PI score was recorded in the clinic. Pain Intensity was also assessed by prompting the subject with the question, "How would you rate your overall pain intensity during the past 24 hours?", and a daily PI diary score was recorded by the subject at bedtime. For both Pain Intensity prompts, the response is scored on an 11-point numerical scale (0=no pain and 10=severe pain).

[0337] Quality of Analgesia was assessed weekly at clinic visits. The subject was prompted with the question, "How would you rate the quality of your pain relief at this time?", and responses were selected from poor, fair, good, very good, and excellent.

[0338] Pain Control was also assessed weekly at clinic visits. The subject was prompted with the question, "During the past week, how would you describe your pain control during the course of each day?" Responses were selected from: Pain was controlled for (1) a few hours or less each day; (2) several hours each day; (3) most of each day; and (4) throughout each day.

[0339] Global Assessment of Study Medication was also assessed weekly at clinic visits. The subject was prompted with the question, "How would you rate the study medication you received this past week? (Please consider the quality of your pain relief, your side effects, your activity level, your mood and sense of well-being, etc. in this evaluation.)". Responses were selected from poor, fair, good, very good, and excellent.

[0340] Additionally, functional assessments were conducted with the SF-12 Health Survey (see Table 1) and the WOMAC Osteoarthritis Index (see Table 2).

[0341] Safety procedures include taking vital signs (blood pressure, respiratory rate, heart rate and temperature), physical examinations, EKGs, clinical laboratory tests, adverse events, opioid toxicity assessments and the assessment of opiate withdrawal symptoms. The opioid toxicity assessment included: (a) CNS review by assessing for (1) confusion, altered mental state, (2) excessive drowsiness, lethargy, stupor, (3) slurred speech (new onset), (4) respiratory, (5) hypoventilation, shortness of breath, apnea, (6) hypoxia, hypercarbia; and (b) cardiac review by assessing for bradycardia, hypotension, and shock. Subjects experiencing opioid toxicity, as determined by the Investigator, were early terminated from the study and had to stop taking study drug. If subjects were terminated from the study, the Early Drug Termination assessments and the Post-Treatment Follow-Up Visit were completed. Subjects who were early terminated because of opioid toxicity did not have to undergo a taper; study drug must be stopped immediately in order to allow the blood levels of study drug to decline. Sites monitored subjects who early terminated due to opioid toxicity closely, with a minimum of daily telephone calls until resolution of symptoms. If symptoms of opioid withdrawal occurred, the subject could return to the study center for treatment.

[0342] Opioid toxicity assessments were performed at clinic visits to evaluate dose escalation and to evaluate whether it was safe for the patient to continue on the study medication. Opioid toxicity is distinct from opioid-related adverse events in that it signifies an unacceptable safety risk to the patient to remain on study medication (e.g. risk of overdose from respiratory depression). Opioid toxicity assessments had to be conducted by an MD or DO Principal Investigator/Sub-Investigator. The assessments included a review of the following:

Opioid Toxicity Assessment

Organ System	Signs/Symptoms
Central Nervous System*	Confusion, altered mental status Excessive drowsiness, lethargy, stupor Slurred speech (new onset)
Respiratory	Apnea Decreased respiratory rate (<8/minute) or cyanosis
Cardiac	Bradycardia, hypotension, or shock

[0343] Alterations in mental status had to be present in order to make the diagnosis of opioid toxicity. Subjects experiencing opioid toxicity, as determined by the Investigator, had to be early terminated from the study and had to stop taking study drug. If subjects had to be terminated from the study, the Early Drug Termination assessments and the Post-Treatment Follow-Up Visit were completed. Subjects who were early terminated because of opioid toxicity did not undergo a taper; study drug had to be stopped immediately in order to allow the blood levels of study drug to decline. Study centers monitored patients who early terminated due to opioid toxicity closely, with a minimum of daily telephone calls until resolution of symptoms. If symptoms of opioid withdrawal occurred, the patient could return to the study center for treatment.

[0344] Additionally, adverse events were monitored throughout the course of the study. An adverse event (AE) is any undesirable event that occurs to a participant during the course of a clinical study, whether or not that event is considered study drug-related. Examples include:

[0345] (1) Any treatment-emergent signs and symptoms (e.g., events that are marked by a change from the subject's baseline/entry status such as an increase in severity or frequency of pre-existing abnormality or disorder);

[0346] (2) All reactions from the study drug, an overdose, abuse of drug, withdrawal phenomena, sensitivity or toxicity to the study drug;

[0347] (3) Apparently unrelated illnesses;

[0348] (4) Injury or accidents (Note: if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as two separate medical events, for example, for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately); and/or

[0349] (5) Extensions or exacerbations of symptoms, subjective subject-reported events, new clinically significant abnormalities in clinical laboratory, physiological testing or physical examination.

[0350] All adverse events, whether or not related to the study drug, were fully and completely documented on the adverse event page of the case report form (CRF) and in the subject's clinical chart. In the event that a subject was withdrawn from the study because of an adverse event, it had to be recorded on the CRF. However, the withdrawn subject had to be followed and treated by the Investigator until the abnormal parameter or symptom had resolved or stabilized.

[0351] The Investigator had to report all directly observed adverse events and all spontaneously reported adverse events. At each visit the Investigator asked the subject a non-specific question (e.g., "Have you noticed anything different since your last visit?") to assess whether any adverse events have been experienced since the last report or visit. Adverse events (AEs) were identified and documented on the adverse event CRF in appropriate medical terminology. The severity and the relationship to the study drug was determined and reported on the CRF.

[0352] In addition to reporting the medication on the Concomitant Medication CRF, the investigator or designee needed to question whether an adverse event had occurred when intermittent or as needed ("prn") use of any medication (and specifically any newly prescribed medication) were taken during treatment period for conditions worsened from or not present before enrollment into study. This may indicate the occurrence of an adverse event that may also needed to be recorded on the adverse event CRF.

[0353] The severity of each adverse event was characterized and then classified into one of three clearly defined categories as follows:

[0354] (1) Mild—the adverse event does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance,

[0355] (2) Moderate—the adverse event produces some impairment of functioning, but is not hazardous to health. It is uncomfortable or an embarrassment, or

[0356] (3) Severe—the adverse event produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

[0357] These three categories were based on the Investigator's clinical judgment, which in turn depended on consideration of various factors such as the subject's report, the physician's observations and the physician's prior experience. The severity of the adverse event was recorded in the appropriate section of the adverse event CRF.

[0358] The relationship of each adverse event to the study drug was classified into one of three defined categories as follows:

[0359] (1) Unlikely—a causal relationship between the adverse event and the study drug is unlikely,

[0360] (2) Possible—a causal relationship between the adverse event and the study drug is possible, or

[0361] (3) Probable—a causal relationship between the adverse event and the study drug is probable. For example, the adverse event is a common adverse event known to occur with the pharmacological class the study drug belongs to; or the adverse event abated on study drug discontinuation and reappeared upon rechallenge with the study drug.

[0362] These three categories are based on the Investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's report, the timing of the adverse event in relationship to study drug administration/discontinuation, the physician's observations and the physician's prior experience. The relationship of the adverse event to the study drug is recorded in the appropriate section of the adverse event CRF.

[0363] Any adverse event that suggests a significant hazard, contraindication, side effect or precaution is defined as a Serious Adverse Event (SAE). An SAE includes (but is not limited to) an experience occurring at any dose that results in any of the following outcomes:

[0364] (1) Death;

[0365] (2) A life-threatening event (i.e., the subject is at immediate risk of death from the reaction as it occurs). "Life-threatening" does not include an event that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of

hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal;

[0366] Subject hospitalization (hospital admission, not an emergency room visit) or prolongation of existing hospitalization;

[0367] (4) A persistent or significant disability/incapacity (i.e., a substantial disruption of the subject's ability to carry out normal life functions); and/or

[0368] (5) A congenital anomaly/birth defect.

[0369] In addition, medical and scientific judgment must be exercised in deciding whether other situations are to be considered an SAE (e.g., important medical events that may not be immediately life-threatening or result in death, but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above). Examples of such medical events include: allergic bronchospasm requiring intensive treatment in an emergency room or at home, or blood dyscrasias or new-onset seizures that do not result in subject hospitalization.

[0370] An unexpected adverse event is one for which the specificity or severity is not consistent with the current Investigator's Brochure. For example, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure only listed elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure only listed cerebral vascular accidents.

[0371] The reporting of SAEs by the Sponsor to Regulatory Authorities (e.g., Food and Drug Administration (FDA)) is a regulatory requirement. Each Regulatory Agency has established a timetable for reporting SAEs based upon established criteria. Likewise, it is the responsibility of the Principal Investigator to report SAEs to their ECs/IRBs immediately.

[0372] All SAEs must be reported immediately (within 24 hours of learning of the event) by telephone to the Sponsor or Contract Research Organization (CRO) designee. Any additional information, if collected, can be reported to the Sponsor (or CRO designee) as a follow-up to the initial report.

[0373] In the case of a death or other SAE that has occurred within 30 days after receiving study drug, the Principal Investigator must also report such an event within 24 hours of being notified.

[0374] In the event of any SAE (other than death), the subject is instructed to contact the study physician (Principal Investigator or designee) using the phone number provided in the Informed Consent Form. All subjects that experience a SAE are seen by a Principal Investigator or designee as soon as feasible following the report of an SAE.

[0375] At the first visit, pre-enrollment screening is performed. The following assessments are conducted at Visit I (Screening Visit):

[0376] (1) Obtain written informed consent from the subject;

[0377] (2) Screen subject's PI (must be ≥5 to continue the screening process);

[0378] (3) Review inclusion and exclusion criteria;

[0379] (4) Obtain subject's detailed medical history including concomitant medications taken one month prior to the Screening Visit;

[0380] (5) Complete subject's physical examination including height, weight and vital signs;

[0381] (6) Perform an EKG (QTc interval);

[0382] (7) Obtain blood samples for clinical laboratory tests;

[0383] (8) Obtain urine sample for urinalysis;

[0384] (9) Perform urine pregnancy test for all women of childbearing potential;

[0385] (10) Obtain an X-ray of the subject's hip/knee. All subjects must have radiographic evidence of osteoarthritis of the hip or knee according to ACR diagnostic criteria. Subjects who do not have an X-ray report that documents radiographic evidence of osteoarthritis of the hip or knee within the past two years must have an X-ray performed prior to the next (Baseline) visit;

[0386] (11) Contact IVRS to obtain a subject identification number and to register the subject for the daily touch-tone phone diary;

[0387] (12) Review each section of the diary with the subject and provide written instructions for use of the diary; and

[0388] (13) IVRS provides an acetaminophen bottle number and dispense acetaminophen to the subject.

[0389] At the conclusion of the visit the subject is given an appointment card for the next study visit.

[0390] The study nurse thoroughly reviewed each section of the diary with the subject. The subject is advised to telephone IVRS prior to bedtime each day of the washout period to record their overall PI over the past 24 hours.

[0391] At a second visit, four to ten days after the Screening Visit, the subjects return to the study center for completion of the pre-dose assessments (Baseline/Open-Label Titration Visit). This visit includes the following:

[0392] (1) Screen the subject's urine sample using a rapid drug screen kit;

[0393] (2) Contact IVRS to review the subject's daily diary PI scores from the washout period to verify that: the mean daily overall PI score collected in the diary over the last two days of the washout period is ≥5 (on a scale of 0 to 10) while off all analgesic medications (except acetaminophen), and that the subject completed daily diary PI assessments ≥75% of the days during the washout period;

[0394] (3) Collect the bottle of acetaminophen and perform accountability; and,

[0395] (4) Review inclusion and exclusion criteria to verify that the subject has radiographic evidence of OA of hip or knee within the past two years (Inclusion #2) according to ACR diagnostic criteria and that the clinical laboratory test results from the Screening Visit are without significant clinical abnormalities (Exclusion #22) (e.g., the urine pregnancy test is negative (if required; Inclusion #11).

[0396] If subjects fail to meet inclusion/exclusion criteria, they are considered screening failures. Subjects meeting all study entry criteria continue in the screening process and receive the following assessments:

[0397] (1) Obtain subject's interim medical history (to identify any changes from the Screening Visit);

[0398] (2) Obtain the subject's vital signs; and

[0399] (3) Review and record the subject's concomitant medications.

[0400] Subjects who have no clinically significant changes in interim medical history and vital signs that would prohibit them from entering the study and who have not taken any prohibited medications (or stopped, started, or changed the dose of restricted medications) can enter the open-label titration period. The following assessments will be performed:

[0401] (1) WOMAC Osteoarthritis Index (select target joint to be assessed throughout the study; Appendix 1). The subject

must select a target joint which is defined as the hip or knee joint with osteoarthritis causing the subject the most pain. The subject must refer to the same joint throughout the study when completing the WOMAC; and

[0402] (2) SF-12 Health Survey.

[0403] Once these assessments and procedures are completed, subjects are enrolled in the open-label titration period. IVRS is telephoned to obtain a blister card for the subject for Week 1 of the open-label titration period and one blister card of study medication is dispensed to the subject with 3 days of 5 mg BID and 7 days of 10 mg BID. The blister card of study drug has a two-part clinical label. The tear-off portion of the label is removed and attached to the CRF.

[0404] An appointment card is provided to the subject before he/she leaves the clinic for the next visit. The subject is instructed to take one capsule of study drug with breakfast and one capsule of study drug with dinner. The subjects are further instructed that they must administer doses with meals at least eight hours apart and the subjects are informed that taking the study drug on an empty stomach may lead to insufficient pain relief.

[0405] The touch-tone daily diary is used to record overall PI in the past 24 hours immediately prior to bedtime.

[0406] At a third visit (End of Week 1 of the Open-Label Titration Period), subjects return to the study center for completion of the pre-dose assessments (Baseline/Open-Label Titration Visit). This visit includes the following assessments:

[0407] (1) Perform opioid toxicity assessments (must be performed by MD or DO Principal Investigator/Sub-Investigator);

[0408] (2) Contact IVRS to review diary (overall daily PI and subject compliance);

[0409] (3) Record new/changed adverse events and concomitant medications. Subjects may experience opioid-related adverse events during the titration period. Subjects are to be instructed that mild opioid-related AEs (feeling drowsy, nausea, vomiting, pruritis, dizziness) often go away within 24-48 hours of dose titration, with the exception of constipation. Subjects may return for additional visits to receive treatment of opioid-related AEs. Investigators are encouraged to treat opioid-related adverse events as soon as they occur to avoid subject discomfort/early termination;

[0410] (4) Collect study medication from previous week and account for used/unused supplies;

[0411] (5) Obtain the subject's vital signs;

[0412] (6) Telephone IVRS in order to assign subjects one blister card for the remaining week of the open-label titration period; and

[0413] (7) Dispense the blister card of study medication to the subject with 3 days of 15 mg BID and 7 days of 20 mg BID. The blister card of study drug has a two-part clinical label. Remove the tear-off portion of the label and attach it to the CRF;

[0414] An appointment card is provided to the subject before he/she leaves the clinic for the next visit. The subject is instructed to take one capsule of study drug with breakfast and one capsule of study drug with dinner. The subjects are further instructed that they must administer doses with meals at least eight hours apart and the subjects are informed that taking the study drug on an empty stomach may lead to insufficient pain relief.

[0415] The touch-tone daily diary is used to record overall PI in the past 24 hours immediately prior to bedtime.

[0416] At a fourth visit (End of the Open-Label Titration Period/Randomization Visit or Early Drug Termination from Open-Label Titration Period Visit), subjects return to the study center at the end of the week (7-8 days after the last visit). In addition, any subject who early terminates from the open-label titration period and took at least one dose of study medication must return for follow-up safety assessments. The following assessments are performed:

[0417] (1) Opioid toxicity assessments (must be performed by MD or DO Principal Investigator/Sub-Investigator);

[0418] (2) Contact IVRS to review diary (overall daily PI and subject compliance);

[0419] (3) Verify that the subject completed daily diary assessments ≥75% of the days during the open-label titration period (Inclusion #7);

[0420] (4) Record new/changed adverse events and concomitant medications;

[0421] (5) Verify that subject is able to tolerate AEs (if any) associated with administration of study drug 20 mg (Inclusion #8);

[0422] (6) Verify that the subject did not take any prohibited analgesics during the open-label titration period (Exclusion #25); and the subject did not start, stop or change the dose of any of the medications listed in Exclusion #14;

[0423] (7) Collect study medication from previous week and account for used/unused supplies;

[0424] (8) Obtain vital signs;

[0425] (9) Obtain blood samples for clinical laboratory tests; and

[0426] (10) Obtain urine sample for urinalysis.

[0427] Subjects who continue to meet all inclusion/exclusion criteria are randomized. Subjects who have early terminated from the open-label titration period require no further assessments at this visit, but must return for the Post-Treatment Follow-Up Visit.

[0428] The following assessments are performed on continuing subjects:

[0429] (1) WOMAC Osteoarthritis Index (target joint assessed throughout study); and

[0430] (2) SF-12 Health Survey.

[0431] Once these assessments and procedures are completed, subjects will be randomly assigned to one of the two treatment groups. The following procedures were taken:

[0432] (1) Telephone IVRS to assign subjects a randomization number and a blister card for Week 1 of the double-blind treatment period; and

[0433] (2) Dispense a blister card of study medication to the subject. The blister card will contain four capsules of study drug per day. The blister card of study drug has a two-part clinical label. Remove the tear-off portion of the label and attach it to the CRF;

[0434] An appointment card is provided to the subject before he/she leaves the clinic for the next visit. The subject is instructed to take one capsule of study drug with breakfast and one capsule of study drug with dinner. The subjects are further instructed that they must administer doses with meals at least eight hours apart and the subjects are informed that taking the study drug on an empty stomach may lead to insufficient pain relief.

[0435] The touch-tone daily diary is used to record overall PI in the past 24 hours immediately prior to bedtime. The touch-tone diary is used to record the following information: (1) overall PI in the past 24 hours (daily); (2) quality of analgesia (weekly), and (3) global assessment of study medi-

cation (weekly). The weekly assessment sections (quality of analgesia and global assessment of study medication) of the touch-tone phone diary are thoroughly reviewed with the subject.

[0436] At a fifth visit (End of Week 1 of the Double-Blind Treatment Period (Titration), subjects return to the study center at the end of Week 1 (±one day). The following assessments are performed:

[0437] (1) Opioid toxicity assessments (must be performed by MD or DO Principal Investigator/Sub-Investigator);

[0438] (2) Contact IVRS to review diary (overall daily PI and subject compliance);

[0439] (3) Record new/changed adverse events and concomitant medications;

[0440] (4) Collect study medication from previous visit and account for used/unused supplies; (5) Obtain vital signs;

[0441] (6) Determine if a dose increment or dose decrease is required. Dose and adverse events will be evaluated. The dose may be increased to the next dose level (30 mg BID) if the clinic PI is >2, the subject is not experiencing any intolerable adverse events, and the subject and Investigator agree that the dose should be increased. Subjects may choose not to increase dose of study drug if they have a PI>2 that they find acceptable. If a subject reports experiencing any opioid-related adverse events, the Investigator should offer treatment if not resolved (see Appendix F). If the subject or Investigator finds the adverse events unacceptable, the dose will be decreased to the previous level (15 mg BID);

[0442] (7) Telephone IVRS in order to assign subjects one blister card; dispense one blister card to the subject. Each blister card has a two-part clinical label. Remove the tear-off portion of the label and attach it to the CRF; and

[0443] (9) Review the instructions on the blister card with the subject.

[0444] An appointment card is provided to the subject before he/she leaves the clinic for the next visit. The subject is instructed to take one capsule of study drug with breakfast and one capsule of study drug with dinner. The subjects are further instructed that they must administer doses with meals at least eight hours apart and the subjects are informed that taking the study drug on an empty stomach may lead to insufficient pain relief.

[0445] The touch-tone daily diary is used to record overall PI in the past 24 hours immediately prior to bedtime. The touch-tone diary is used to record the following information: (1) overall PI in the past 24 hours (daily); (2) quality of analgesia (weekly); and (3) global assessment of study medication (weekly).

[0446] At visits 6 to 8 (End of Weeks 2, 3, and 4 of the Double-Blind Treatment Period (Titration)), subjects return to the study center at the end of Weeks 2, 3 and 4 (±one day). The following assessments are performed at each visit:

[0447] (1) Perform opioid toxicity assessments (must be performed by MD or DO Principal Investigator/Sub-Investigator);

[0448] (2) Contact IVRS to review diary (overall daily PI and subject compliance);

[0449] (3) Record new/changed adverse events and concomitant medications;

[0450] (4) Collect study medication from previous visit and account for used/unused supplies;

[0451] (5) Check vital signs;

[0452] (6) Determine if dose adjustment is required (increase allowed only at End of Weeks 1, 2 or 3; decrease allowed at End of Weeks 1, 2, 3 or 4). Dose and adverse events will be evaluated at each visit. The dose may be increased to the next dose level at the End of Weeks 1, 2, or 3 if the clinic PI is >2, the subject is not experiencing any intolerable adverse events, and the subject and Investigator agree that the dose should be increased. Subjects may choose not to increase dose of study drug if they have a PI>2 that they find acceptable. If a subject reports experiencing any opioid-related adverse events, the Investigator should offer treatment if not resolved. If the subject or Investigator finds the adverse events unacceptable, the dose will be decreased to the previous level. The dose may be decreased at the End of Weeks 1, 2, 3, or 4. Subjects are required to remain on the dose of study drug administered at the End of Week 4 for the remainder of the study;

[0453] (7) Telephone IVRS in order to assign subjects one or two (End of Week 4) blister cards; and

[0454] (8) Dispense one or two (End of Week 4) blister cards to the subject. Each blister card has a two-part clinical label. Remove the tear-off portion of the label and attach it to the CRF.

[0455] An appointment card is provided to the subject before he/she leaves the clinic for the next visit. The subject is instructed to take one capsule of study drug with breakfast and one capsule of study drug with dinner. The subjects are further instructed that they must administer doses with meals at least eight hours apart and the subjects are informed that taking the study drug on an empty stomach may lead to insufficient pain relief.

[0456] The touch-tone daily diary is used to record overall PI in the past 24 hours immediately prior to bedtime. The touch-tone diary is used to record the following information: (1) overall PI in the past 24 hours (daily); (2) quality of analgesia (weekly); and (3) global assessment of study medication (weekly).

[0457] At visits 9 to 11 (End of Weeks 6, 8, and 10 of the Double-Blind Treatment Period (Fixed Dose)), subjects will return to the study center every two weeks (14-16 days after the last visit) for the remainder of the study. Subjects are required to remain on the dose of study drug administered at the End of Week 4. The following assessments are performed at each visit:

[0458] (1) Perform opioid toxicity assessments (must be performed by MD or DO Principal Investigator/Sub-Investigator);

[0459] (2) Contact IVRS to review diary (overall daily PI and subject compliance);

[0460] (3) Record new/changed adverse events and concomitant medications;

[0461] (4) Collect study medication from previous visit and account for used/unused supplies;

[0462] (5) Check vital signs. If a subject reports experiencing any opioid-related adverse events, the Investigator should offer treatment;

[0463] (6) Telephone IVRS in order to assign subjects two blister cards; and

[0464] (7) Dispense two blister cards to the subject. Each blister card has a two-part clinical label. Remove the tear-off portion of the label and attach it to the CRF.

[0465] An appointment card is provided to the subject before he/she leaves the clinic for the next visit. The subject is instructed to take one capsule of study drug with breakfast and one capsule of study drug with dinner. The subjects are further instructed that they must administer doses with meals

at least eight hours apart and the subjects are informed that taking the study drug on an empty stomach may lead to insufficient pain relief.

[0466] The touch-tone daily diary is used to record overall PI in the past 24 hours immediately prior to bedtime. The touch-tone diary is used to record the following information: (1) overall PI in the past 24 hours (daily); (2) quality of analgesia (weekly); and (3) global assessment of study medication (weekly).

[0467] At visit 12 (End of Week 12 of Double-Blind Treatment Period/Early Drug Termination), subjects return to the study center at either the end of Week 12 (14-16 days after the last visit) or after early drug termination for the following assessments:

[0468] (1) perform opioid toxicity assessments (must be performed by MD or DO Principal Investigator/Sub-Investigator);

[0469] (2) contact IVRS to review daily diary (overall daily PI and subject compliance);

[0470] (3) record new/changed adverse events and concomitant medications;

[0471] (4) collect study medication and account for used/unused supplies;

[0472] (5) complete physical examination and vital signs;

[0473] (6) perform EKG (QTc interval);

[0474] (7) obtain blood samples for clinical laboratory tests;

[0475] (8) obtain urine sample for urinalysis;

[0476] (9) WOMAC osteoarthritis index (target joint assessed throughout the study); and

[0477] (10) SF-12 Health Survey.

[0478] Subjects may require a taper to prevent opioid withdrawal depending on the duration of treatment with study drug and the final dose of study drug administered during the fixed dose treatment period. Subjects taking 5 or 10 mg BID do not require a taper and are to return to the clinic in approximately one week for a post-treatment follow-up visit. Subjects who early terminate from the study require a taper if they have been on study drug for greater than four weeks (including the open-label titration period) and were on a dose >10 mg of study drug BID at the time of early termination. For subjects requiring a taper, the following procedures are performed:

[0479] (1) Telephone IVRS in order to assign subjects a blister card; and

[0480] (2) Dispense 1 blister card to the subject. The tear-off portion of the clinical label on the blister card is removed and attached to the CRF. Subjects are given the following blister cards depending on their final fixed dose: Final fixed dose of 40 mg BID, blister card with 15 days of study drug, Final fixed dose of 30 mg BID: blister card with 12 days of study drug, Final fixed dose of 15 or 20 mg BID: blister card with 6 days of study drug, or a Final fixed dose of 5 or 10 mg BID: no taper required.

[0481] An appointment card is provided to the subject before he/she leaves the clinic for the next visit to occur one week after the subject's final dose of study medication (up to 22 days). The subject is instructed to take one capsule of study drug with breakfast and one capsule of study drug with dinner. The subjects are further instructed that they must administer doses with meals at least eight hours apart and the subjects are informed that taking the study drug on an empty stomach may lead to insufficient pain relief.

[0482] Subjects are educated about the possibility of opioid withdrawal after study drug discontinuation. Subjects are instructed to refrain from taking any opioid-containing medications (including tramadol or combination medications such as Vicodin) during the double-blind taper period and subjects are instructed to contact the study center immediately if severe/intolerable symptoms of opioid withdrawal are experienced. If required, subjects may take non-opioid analgesics.

[0483] If a subject experiences intolerable pain during the double-blind taper period in spite of maximal non-opioid analgesic therapy, the Investigator may early terminate the subject from the study and refer for appropriate pain management.

[0484] Subjects may telephone sites to request additional visits if they experience opioid-related AEs. Subjects are to be instructed that, with the exception of constipation, mild opioid-related AEs (feeling drowsy, nausea, vomiting, pruritis, dizziness) often go away within 24-48 hours. Subjects may return for additional visits to receive treatment of opioid-related AEs. Investigators are encouraged to treat opioid-related adverse events as soon as they occur to avoid subject discomfort/early termination. The following assessments are performed:

[0485] (1) Perform opioid toxicity assessment;

[0486] Record new/changed adverse events and concomitant medications;

[0487] Obtain vital signs; and

[0488] Treat opioid-related AEs (if applicable).

[0489] If the subject is experiencing opioid toxicity, the subject must be early terminated from the trial. If the subject is not experiencing opioid toxicity but is experiencing significant opioid-related adverse events, the Investigator is to offer treatment for the following opioid-related AEs: nausea, vomiting, pruritic, dizziness, or constipation. Unscheduled visits for treatment of opioid-related adverse events are allowed throughout the study.

[0490] At visit 13 (Post-Treatment Follow-up), subjects return to the study center approximately one week (±two days) after the last dose of study medication for a post-treatment follow-up visit. At this visit, the following assessments are completed:

[0491] (1) Collect study medication and account for used/unused supplies for subjects requiring a taper; and

[0492] (2) Record new/changed adverse events and concomitant medications.

[0493] Subjects could choose to discontinue study drug or study participation at any time, for any reason, specified or unspecified, and without prejudice. If a subject chooses to discontinue study drug early during the open-label titration period, the investigator must request that the subject return to the clinic within 24 hours of stopping the study medication and complete the assessments for early drug termination from the open-label titration period. If a subject chooses to discontinue study drug early during the double-blind treatment period, the investigator must request that the subject return to the clinic within 24 hours of stopping the study medication and complete the End of Week 12/Early Drug Termination assessments. In addition, if the subject has been on study drug for greater than four weeks (including the open-label titration period), the subject is to be tapered off of study drug according to the subject's current dose at the time of discontinuation. Subjects who are early terminated from the study because of opioid toxicity should not undergo a taper and must stop taking study drug immediately.

[0494] Subjects must be educated about the possibility of withdrawal after study drug discontinuation. Instruct the subject to contact the study center immediately if severe/intolerable symptoms of opioid withdrawal are experienced. The investigator must also request that the subject complete the Post-Treatment Follow-Up Visit and the double-blind taper period (if applicable) for safety reasons.

[0495] The SF-12 evaluations, recorded at baseline and at the end of each week, were scored as described in Ware et al., "SF-12: How to score the SF-12 physical and mental health summary scales." QualityMetric Inc., Lincoln, R.I., and the Health Assessment Lab, Boston, Mass. (3d Ed. 1998), which is incorporated by reference herein. The summarization and analysis of the WOMAC Osteoarthritis Index were specified in the Statistical Analysis Plan per the WOMAC User Guide, which is obtainable at the WOMAC organization website www.womac.org/contact/index.cfm and incorporated by reference herein.

[0496] Adverse events reported were mapped to preferred terms and organ systems using the MedDRA mapping system. Adverse events were associated with weeks according to their onset date. The number and percentage of subjects reporting each event are summarized by treatment group and week.

[0497] Treatment groups are examined for differences in the incidence and severity of selected opioid-associated adverse events, including constipation, dizziness, somnolence, headache, pruritus, nausea, vomiting, urinary retention, and bradypnoea. The homogeneity of response between males and females is investigated descriptively.

[0498] All subjects that take at least one dose of study medication following randomization and complete at least one post-randomization pain intensity assessment are evaluable for efficacy analyses. All subjects who take at least one dose of oral study medication are evaluable for safety analyses.

[0499] The primary efficacy analysis population is the intent-to-treat (ITT) population. The ITT population consists of all randomized subjects who are administered any study medication, have at least one post-randomization PI assessment and are used for efficacy analyses. All subjects who take at least one dose of study medication are used for safety analyses.

[0500] Demographic variables and subject characteristics are summarized descriptively by treatment group. Demographic variables include age, weight, height, gender, and race/ethnicity. Baseline characteristics include target joint, mean daily overall PI collected through the IVRS over the last two days of the washout and open-label titration periods, screening clinic PI, washout period acetaminophen usage, and baseline and pre-randomization values of efficacy and quality of life variables. Baseline and post-baseline patient characteristics include study drug administration, prior and concomitant medications, final study drug dose, and opioid use within one month prior to study.

[0501] The following endpoints are summarized and analyzed for efficacy analysis:

[0502] Daily diary PI score are analyzed as weekly values as follows: For each week, the PI recorded during all days of the week are averaged. Baseline PI is defined as the average PI recorded during the two days immediately prior to the Baseline visit. Pre-randomization PI is defined as the average PI recorded during the two days immediately prior to randomization at the end of the open-label titration period;

[0503] (2) Quality of analgesia is assessed and analyzed weekly;

[0504] (3) Global assessment of study medication is assessed and analyzed weekly;

[0505] (4) WOMAC Osteoarthritis Index is assessed and analyzed at baseline, pre-randomization and at the end of treatment; calculated per the WOMAC User Guide; and

[0506] (5) SF-12 is assessed and analyzed at baseline, pre-randomization and at the end of treatment, scored as described in the documentation.

[0507] The following endpoints are summarized and analyzed for safety analysis:

[0508] (1) Adverse events reported on case report forms are mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary;

[0509] (2) The number and percent of subjects reporting each event are summarized during the open-label titration period and by treatment group during the double-blind treatment period. Incidence of adverse events by maximum reported severity are also tabulated. Serious adverse events and adverse events leading to discontinuation are displayed;

[0510] (3) Vital signs are summarized descriptively based on actual value, change from baseline, and change from randomization. QTc interval is summarized descriptively based on actual value and change from baseline;

[0511] (4) Laboratory data are summarized descriptively based on actual value, change from baseline and in terms of the normal range. Physical examination results are summarized by number and percentage of patients with abnormalities in each body system examined.

[0512] For primary analysis of data, the primary efficacy endpoint is the percent change from baseline in pain intensity at the conclusion of the study. The primary efficacy variable is the area under the curve (AUC) for the change in PI from randomization to the end of the Week 12 fixed dose portion of the double-blind treatment period. AUC is determined by linear trapezoidal method. The primary efficacy analysis compares the mean AUC for the study drug treatment group versus the placebo group, using treatment as a factor and pre-randomization PI score as a covariate in an ANCOVA model. Missing data is not imputed. For randomized patients who drop out, whether for adverse events or lack of adequate pain relief or use of rescue medication, only data prior to withdrawal is used. Implicitly AUC assigns zero differences from baseline after withdrawals. The double-blind taper period is not included in the AUC calculation.

[0513] For secondary analysis of data, quality of analgesia, global assessment of study medication, WOMAC Osteoarthritis Index, and the SF-12 Health Survey are analyzed. The weekly averaged PI scores are analyzed at the end of each week of titration and at the end of each week of the double-blind fixed dose period. The change and percent change from baseline and from randomization is compared across treatment groups using the same ANCOVA as the primary analysis. In addition, this data is presented by target joint, sex and age.

[0514] The quality of analgesia and global assessment of study medication are analyzed as categorical variables using a stratified Cochran-Mantel-HaenszelT (CMH) test with baseline and pre-randomization PI to define the strata. The comparisons across treatment groups are presented overall, and by target joint, sex and age.

[0515] The WOMAC Osteoarthritis Index (pain subscale, stiffness subscale, physical function subscale, total score) and SF-12 are analyzed at the end of treatment in terms of change and percent change from randomization. The change and percent change from randomization is compared across treatment groups using the same ANCOVA as the primary analysis. The change and percent change from baseline is also analyzed. In addition, the comparison is made by target joint, sex and age.

[0516] AUC is calculated for the change from baseline PI including the two-week open-label titration period for each treatment group using treatment as a factor and baseline PI score as a covariate in an ANCOVA model. AUC is determined by linear trapezoidal method. Comparative analysis will follow the ANCOVA model as the primary analysis.

[0517] For the purpose of sample size and power calculations, placebo subjects who complete the study period are assumed to have at least a mean decrease in change from baseline P1 of up to 25%. The majority of withdrawals in enrichment designs occur during the open-label titration phase. The assumed withdrawal rate after randomization is 25%.

[0518] To design a study with greater than 90% power, with a common standard deviation of 30%, a mean difference of 10% in average AUC in PI requires a sample size of 200 patients per treatment group (400 total) using a 0.05 two-sided significance level.

[0519] Unless otherwise indicated, all testing of statistical hypotheses is two-sided, and a difference resulting in a p-value of less than or equal to 0.05 is considered statistically significant.

[0520] Causes of early termination from study drug during the double-blind treatment period are shown in Table 8. The majority of subjects who terminated from the trial (10.6% of subjects taking placebo BID and 21.0% of subjects taking study drug BID) experienced an adverse event. Out of the 145 subjects that terminated during the double-blind period 65 (15.8%) terminated due to adverse events. This constituted (10.6%) of the subjects administered placebo BID and (21. 0%) of subjects administered study drug BID.

TABLE 8

TERMINATION FROM STUDY DRUG DURING THE 12-WEEK DOUBLE-BLIND PERIOD ANALYSIS POPULATION: DOUBLE-BLIND SAFETY POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 205)	TOTAL (N = 412)
DID THE PATIENT TERMINATE STUDY DRUG EARLY?			
NO	132 (63.8%)	131 (63.9%)	263 (63.8%)
YES	75 (36.2%)	70 (34.1%)	145 (35.2%)
INADEQUATE PAIN RELIEF	38 (18.4%)	12 (5.9%)	50 (12.1%)
ADVERSE EVENT	22 (10.6%)	43 (21.0%)	65 (15.8%)
PROTOCOL VIOLATION	6 (2.9%)	7 (3.4%)	13 (3.2%)
INAPPROPRIATE ENROLLMENT	1	1	2
NEED FOR PROHIBITED MEDICATION	2	2	4
OTHER	3	4	7
PATIENT REQUEST UNRELATED TO STUDY	4 (1.9%)	8 (3.9%)	12 (2.9%)
OTHER	5 (2.4%)	0 (0.0%)	5 (1.2%)

NOTE:

DOUBLE-BLIND SAFETY POPULATION - ALL PATIENTS WHO TAKE AT LEAST ONE DOSE OF STUDY MEDICATION IN DOUBLE-BLIND PERIOD.

[0521] The most frequent adverse events (AEs) reported were those commonly associated with opioid medications: dizziness, constipation, dry mouth, nausea, vomiting, somnolence, and pruritis. Table 9 shows the AEs that caused termination from the clinical trial from randomization through the post-treatment follow-up visit.

TABLE 9

ADVERSE EVENTS CAUSING DISCONTINUATION OF STUDY MEDIATION FROM RANDOMIZATION THROUGH THE POST-TREATMENT FOLLOW-UP VISIT [1] ANALYSIS POPULATION: DOUBLE-BLIND SAFETY POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 205)	TOTAL (N = 412)
CARDIAC DISORDERS	0 (0.0%)	1 (0.5%)	1 (0.2%)
PALPITATIONS	0 (0.0%)	1 (0.5%)	1 (0.2%)
GASTROINTESTINAL DISORDERS	7 (3.4%)	16 (7.8%)	23 (5.6%)
ABDOMINAL PAIN	1 (0.5%)	1 (0.5%)	2 (0.5%)
CONSTIPATION	1 (0.5%)	2 (1.0%)	3 (0.7%)
DIARRHEA	0 (0.0%)	1 (0.5%)	1 (0.2%)
DRY MOUTH	0 (0.0%)	1 (0.5%)	1 (0.2%)
FAECALOMA	0 (0.0%)	1 (0.5%)	1 (0.2%)
NAUSEA	5 (2.4%)	9 (4.4%)	14 (3.4%)
VOMITING	2 (1.0%)	4 (2.0%)	6 (1.5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (1.4%)	2 (1.0%)	5 (1.2%)
ASTHENIA	1 (0.5%)	0 (0.0%)	1 (0.2%)
CHEST PAIN	0 (0.0%)	1 (0.5%)	1 (0.2%)
CHILLS	0 (0.0%)	1 (0.5%)	1 (0.2%)
FATIGUE	1 (0.5%)	0 (0.0%)	1 (0.2%)
OEDEMA	1 (0.5%)	0 (0.0%)	1 (0.2%)
PYREXIA	0 (0.0%)	1 (0.5%)	1 (0.2%)

TABLE 9-continued

ADVERSE EVENTS CAUSING DISCONTINUATION OF STUDY MEDIATION FROM RANDOMIZATION THROUGH THE POST-TREATMENT FOLLOW-UP VISIT [1]
ANALYSIS POPULATION: DOUBLE-BLIND SAFETY POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 205)	TOTAL (N = 412)
HEPATOBILIARY DISORDERS	1 (0.5%)	0 (0.0%)	1 (0.2%)
CHOLELITHIASIS	1 (0.5%)	0 (0.0%)	1 (0.2%)
INFECTIONS AND INFESTATIONS	0 (0.0%)	1 (0.5%)	1 (0.2%)
BRONCHITIS	0 (0.0%)	1 (0.5%)	1 (0.2%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.5%)	0 (0.0%)	1 (0.2%)
INCISION SITE COMPLICATION	1 (0.5%)	0 (0.0%)	1 (0.2%)
INVESTIGATIONS	1 (0.5%)	0 (0.0%)	1 (0.2%)
ASPARTATE AMINOTRANSFERASE INCREASED	1 (0.5%)	0 (0.0%)	1 (0.2%)
METABOLISM AND NUTRITION DISORDERS	1 (0.5%)	2 (1.0%)	3 (0.7%)
ANOREXIA	0 (0.0%)	2 (1.0%)	2 (0.5%)
GOUT	1 (0.5%)	0 (0.0%)	1 (0.2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (1.0%)	1 (0.5%)	3 (0.7%)
ARHRALGIA	1 (0.5%)	1 (0.5%)	2 (0.5%)
BACK PAIN	1 (0.5%)	0 (0.0%)	1 (0.2%)
OSTEOARTHRITIS	1 (0.5%)	0 (0.0%)	1 (0.2%)
PAIN IN EXTREMITY	1 (0.5%)	0 (0.0%)	1 (0.2%)
NERVOUS SYSTEM DISORDERS	6 (2.9%)	11 (5.4%)	17 (4.1%)
DIZZINESS	3 (1.4%)	3 (1.5%)	6 (1.5%)
DYSARTHRIA	0 (0.0%)	1 (0.5%)	1 (0.2%)
DYSGEUSIA	0 (0.0%)	1 (0.5%)	1 (0.2%)
LETHARGY	1 (0.5%)	0 (0.0%)	1 (0.2%)
PARAESTHESIA	0 (0.0%)	1 (0.5%)	1 (0.2%)
SOMNOLENCE	1 (0.5%)	6 (2.9%)	7 (1.7%)
STUPOR	0 (0.0%)	1 (0.5%)	1 (0.2%)
TRANSIENT ISCHAEMIC ATTACK	0 (0.0%)	1 (0.5%)	1 (0.2%)
TREMOR	1 (0.5%)	0 (0.0%)	1 (0.2%)
PSYCHIATRIC DISORDERS	4 (1.9%)	8 (3.9%)	12 (2.9%)
AGITATION	1 (0.5%)	0 (0.0%)	1 (0.2%)
ANXIETY	0 (0.0%)	1 (0.5%)	1 (0.2%)
CONFUSIONAL STATE	1 (0.5%)	4 (2.0%)	5 (1.2%)
DEPRESSION	0 (0.0%)	2 (1.0%)	2 (0.5%)
INSOMNIA	1 (0.5%)	0 (0.0%)	1 (0.2%)
MENTAL STATUS CHANGES	0 (0.0%)	2 (1.0%)	2 (0.5%)
MOOD SWINGS	0 (0.0%)	1 (0.5%)	1 (0.2%)
PERSONALITY CHANGE	1 (0.5%)	0 (0.0%)	1 (0.2%)
SUICIDE ATTEMPT	0 (0.0%)	1 (0.5%)	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0%)	2 (1.0%)	2 (0.5%)
DYSPNOEA	0 (0.0%)	1 (0.5%)	1 (0.2%)
HAEMOPTYSIS	0 (0.0%)	1 (0.5%)	1 (0.2%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (1.0%)	2 (1.0%)	4 (1.0%)
HYPERHIDROSIS	0 (0.0%)	1 (0.5%)	1 (0.2%)
PRURITUS	2 (1.0%)	1 (0.5%)	3 (0.7%)

NOTE:

DOUBLE-BLIND SAFETY POPULATION - ALL PATIENTS WHO TAKE AT LEAST ONE DOSE OF STUDY MEDICATION IN DOUBLE-BLIND PERIOD.

[1] ADVERSE EVENT START DATE IS BETWEEN THE FIRST DOSE OF STUDY MEDICATION IN THE DOUBLE-BLIND PERIOD THROUGH THE DATE OF POST-TREATMENT FOLLOW-UP/STUDY TERMINATION, INCLUSIVE.

[0522] The primary efficacy endpoint for the clinical trial was a decrease in pain intensity (AUC) between study drug BID and placebo BID during the twelve week double-blind treatment period. Subjects that received study drug BID demonstrated a statistically significant decrease in their pain intensity-AUC as compared to the subjects that received placebo BID and thus the study met its prospectively defined primary endpoint with a p=0.007 as shown in Table 10.

TABLE 10

PAIN INTENSITY - AUC
12 WEEK DOUBLE-BLIND PERIOD
ANALYSIS POPULATION: INTENT TO TREAT POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
AREA UNDER CURVE (AUC)			
MEAN (SD)	−30.4 (140.38)	−54.9 (122.44)	−42.5 (132.21)
MEDIAN	−1.5	−27.1	−9.8
MINIMUM, MAXIMUM	−501.8, 370.7	−683.3, 382.8	−683.3, 382.8
N	205	201	406
MODEL P-VALUES			
TREATMENT [1]	0.007		
PRE-RANDOMIZATION PI [1]	<0.001		

NOTE:

INTENT TO TREAT POPULATION - ALL RANDOMIZED PATIENTS WHO TAKE ANY STUDY MEDICATION AND HAVE AT LEAST ONE POST-RANDOMIZATION PI ASSESSMENT.

NOTE:

THE AREA UNDER THE CURVE (AUC) IS CALCULATED BY THE LINEAR TRAPEZOIDAL METHOD USING CHANGE FROM PRE-RANDOMIZATION PAIN INTENSITY SCORES.

[1] P-VALUES FROM ANCOVA MODEL INCLUDING TREATMENT AS THE MAIN EFFECT AND PRE-RANDOMIZATION PAIN INTENSITY AS A COVARIATE.

[0523] A secondary efficacy endpoint for this study was change in pain intensity from baseline at each of the twelve weeks of the double-blind treatment period. In general, the group that received the study drug BID had consistently lower pain intensity scores at each week during the twelve week double-blind treatment period as compared to the group that received placebo BID (see, e.g., at week twelve p=0.024). Table 11 shows the pain intensity scores at each of the twelve weeks during the double-blind treatment period for the treated group and the placebo group.

TABLE 11

PAIN INTENSITY - BY WEEK
OPEN-LABEL TITRATION AND 12-WEEK DOUBLE-BLIND PERIODS LAST OBSERVATION CARRIED FORWARD IMPUTATION ANALYSIS POPULATION: INTENT TO TREAT POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
PRE-RANDOMIZATION			
MEAN (SD)	5.4 (2.11)	5.2 (2.19)	5.3 (2.15)
MEDIAN	5.5	5.0	5.5
MINIMUM, MAXIMUM	0.0, 10.0	0.0, 10.0	0.0, 10.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	0.259		
DOUBLE-BLIND WEEK 1			
MEAN (SD)	5.7 (2.00)	5.2 (2.00)	5.4 (2.01)
MEDIAN	6.0	5.1	5.5
MINIMUM, MAXIMUM	0.0, 10.0	0.0, 10.0	0.0, 10.0
N	207	202	409

TABLE 11-continued

PAIN INTENSITY - BY WEEK
OPEN-LABEL TITRATION AND 12-WEEK DOUBLE-BLIND PERIODS LAST OBSERVATION CARRIED FORWARD IMPUTATION ANALYSIS POPULATION: INTENT TO TREAT POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
MODEL P-VALUES			
TREATMENT [1]	0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 1			
MEAN (SD)	0.2 (1.14)	−0.0 (1.09)	0.1 (1.13)
MEDIAN	0.1	0.0	0.0
MINIMUM, MAXIMUM	−3.5, 4.4	−4.6, 5.4	−4.6, 5.4
N	207	202	409
MODEL P-VALUES			
TREATMENT [1]	0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
DOUBLE-BLIND WEEK 2			
MEAN (SD)	5.6 (2.05)	4.9 (2.07)	5.2 (2.09)
MEDIAN	5.7	4.9	5.2
MINIMUM, MAXIMUM	0.0, 10.0	0.0, 9.9	0.0, 10.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 2			
MEAN (SD)	0.1 (1.62)	−0.3 (1.61)	−0.1 (1.63)
MEDIAN	0.0	−0.3	−0.1
MINIMUM, MAXIMUM	−4.8, 4.3	−6.9, 6.7	−6.9, 6.7
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
DOUBLE-BLIND WEEK 3			
MEAN (SD)	5.5 (2.13)	4.6 (2.07)	5.1 (2.15)
MEDIAN	5.3	4.6	5.0
MINIMUM, MAXIMUM	0.0, 10.0	0.0, 10.0	0.0, 10.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 3			
MEAN (SD)	0.1 (1.94)	−0.6 (1.81)	−0.2 (1.90)
MEDIAN	0.0	−0.6	−0.2
MINIMUM, MAXIMUM	−6.0, 5.3	−9.5, 7.3	−9.5, 7.3
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION [1]	<0.001		

TABLE 11-continued

PAIN INTENSITY - BY WEEK
OPEN-LABEL TITRATION AND 12-WEEK DOUBLE-BLIND PERIODS LAST OBSERVATION CARRIED FORWARD IMPUTATION ANALYSIS POPULATION: INTENT TO TREAT POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
DOUBLE-BLIND WEEK 4			
MEAN (SD)	5.4 (2.17)	4.4 (2.07)	4.9 (2.17)
MEDIAN	5.3	4.4	4.9
MINIMUM, MAXIMUM	0.0, 10.0	0.0, 10.0	0.0, 10.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 4			
MEAN (SD)	−0.0 (2.09)	−0.8 (1.78)	−0.4 (1.97)
MEDIAN	0.0	−0.9	−0.3
MINIMUM, MAXIMUM	−6.8, 5.0	−9.5, 4.0	−9.5, 5.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
DOUBLE-BLIND WEEK 5			
MEAN (SD)	5.3 (2.22)	4.4 (2.08)	4.8 (2.20)
MEDIAN	5.2	4.3	4.8
MINIMUM, MAXIMUM	0.0, 10.0	0.0, 10.0	0.0, 10.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 5			
MEAN (SD)	−0.1 (2.19)	−0.8 (1.79)	−0.5 (2.03)
MEDIAN	0.0	−0.7	−0.4
MINIMUM, MAXIMUM	−6.5, 5.0	−9.5, 4.0	−9.5, 5.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
DOUBLE-BLIND WEEK 6			
MEAN (SD)	5.3 (2.32)	4.3 (2.03)	4.8 (2.22)
MEDIAN	5.1	4.2	4.7
MINIMUM, MAXIMUM	0.0, 10.0	0.0, 10.0	0.0, 10.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 6			
MEAN (SD)	−0.2 (2.23)	−0.9 (1.86)	−0.5 (2.08)
MEDIAN	0.0	−0.9	−0.4
MINIMUM, MAXIMUM	−6.8, 5.2	−8.8, 4.8	−8.8, 5.2
N	207	203	410

TABLE 11-continued

PAIN INTENSITY - BY WEEK
OPEN-LABEL TITRATION AND 12-WEEK DOUBLE-BLIND PERIODS LAST OBSERVATION CARRIED FORWARD IMPUTATION ANALYSIS POPULATION: INTENT TO TREAT POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
DOUBLE-BLIND WEEK 7			
MEAN (SD)	5.2 (2.33)	4.3 (2.13)	4.8 (2.27)
MEDIAN	5.0	4.2	4.7
MINIMUM, MAXIMUM	0.0, 10.0	0.0, 10.0	0.0, 10.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATOIN TO DOUBLE-BLIND WEEK 7			
MEAN (SD)	−0.2 (2.30)	−0.9 (1.91)	−0.6 (2.13)
MEDIAN	−0.1	−0.8	−0.5
MINIMUM, MAXIMUM	−6.9, 5.9	−9.5, 6.3	−9.5, 6.3
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
DOUBLE-BLIND WEEK 6			
MEAN (SD)	5.2 (2.33)	4.4 (2.14)	4.8 (2.26)
MEDIAN	5.1	4.4	4.8
MINIMUM, MAXIMUM	0.0, 10.0	0.0, 10.0	0.0, 10.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	0.002		
PRE-RANDOMIZATION PI [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 8			
MEAN (SD)	−0.3 (2.34)	−0.8 (2.01)	−0.5 (2.19)
MEDIAN	−0.2	−0.8	−0.5
MINIMUM, MAXIMUM	−7.1, 5.0	−9.5, 9.0	−9.5, 9.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	0.002		
PRE-RANDOMIZATION PI [1]	<0.001		
DOUBLE-BLIND WEEK 9			
MEAN (SD)	5.1 (2.33)	4.4 (2.15)	4.8 (2.27)
MEDIAN	5.0	4.4	4.8
MINIMUM, MAXIMUM	0.0, 10.0	0.0, 10.0	0.0, 10.0
N	207	203	410

TABLE 11-continued

PAIN INTENSITY - BY WEEK
OPEN-LABEL TITRATION AND 12-WEEK DOUBLE-BLIND PERIODS LAST OBSERVATION CARRIED FORWARD IMPUTATION ANALYSIS POPULATION: INTENT TO TREAT POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
MODEL P-VALUES			
TREATMENT [1]	0.002		
PRE-RANDOMIZATION PI [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 9			
MEAN (SD)	−0.3 (2.43)	−0.8 (1.95)	−0.5 (2.21)
MEDIAN	−0.2	−0.7	−0.5
MINIMUM, MAXIMUM	−8.2, 5.0	−9.5, 4.7	−9.5, 5.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	0.002		
PRE-RANDOMIZATION PI [1]	<0.001		
DOUBLE-BLIND WEEK 10			
MEAN (SD)	5.2 (2.37)	4.4 (2.16)	4.8 (2.30)
MEDIAN	5.0	4.3	4.8
MINIMUM, MAXIMUM	0.0, 10.0	0.0, 10.0	0.0, 10.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 10			
MEAN (SD)	−0.3 (2.45)	−0.8 (2.06)	−0.5 (2.28)
MEDIAN	0.0	−0.7	−0.3
MINIMUM, MAXIMUM	−9.0, 5.0	−9.5, 7.8	−9.5, 7.8
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	<0.001		
PRE-RANDOMIZATION PI [1]	<0.001		
DOUBLE-BLIND WEEK 11			
MEAN (SD)	5.1 (2.39)	4.4 (2.15)	4.8 (2.30)
MEDIAN	5.0	4.2	4.7
MINIMUM, MAXIMUM	0.0, 10.0	0.0, 10.0	0.0, 10.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	0.002		
PRE-RANDOMIZATION PI [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 11			
MEAN (SD)	−0.3 (2.50)	−0.8 (2.02)	−0.6 (2.28)
MEDIAN	0.0	−0.8	−0.5

TABLE 11-continued

PAIN INTENSITY - BY WEEK
OPEN-LABEL TITRATION AND 12-WEEK DOUBLE-BLIND PERIODS LAST OBSERVATION CARRIED FORWARD IMPUTATION ANALYSIS POPULATION: INTENT TO TREAT POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
MINIMUM, MAXIMUM	−9.0, 4.7	−8.9, 7.0	−9.0, 7.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	0.002		
PRE-RANDOMIZATION PI [1]	<0.001		
DOUBLE-BLIND WEEK 12			
MEAN (SD)	5.1 (2.41)	4.5 (2.15)	4.8 (2.30)
MEDIAN	5.0	4.3	4.8
MINIMUM, MAXIMUM	0.0, 10.0	0.0, 10.0	0.0, 10.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	0.024		
PRE-RANDOMIZATION PI [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATOIN TO DOUBLE-BLIND WEEK 12			
MEAN (SD)	−0.3 (2.48)	−0.7 (2.05)	−0.5 (2.28)
MEDIAN	0.0	−0.6	−0.2
MINIMUM, MAXIMUM	−9.0, 5.0	−8.5, 6.0	−9.0, 6.0
N	207	203	410
MODEL P-VALUES			
TREATMENT [1]	0.024		
PRE-RANDOMIZATION PI [1]	<0.001		

[1] P-VALUES FROM ANCOVA MODEL INCLUDING TREATMENT AS THE MAIN EFFECT

[0524] Another secondary efficacy endpoint for this study was global assessment. For global assessment, the group that received study drug BID showed a consistently better global assessment at each week during the twelve week double-blind treatment period as compared to the group that received placebo BID (see, e.g., at week twelve p=0.007). Table 12 shows the results of the global assessment during the double-blind treatment period.

TABLE 12

GLOBAL ASSESSMENT - BY WEEK
12-WEEK DOUBLE-BLIND PERIOD
LAST OBSERVATION CARRIED FORWARD IMPUTATION
ANALYSIS POPULATION: INTENT TO TREAT POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
THE DOUBLE-BLIND WEEK 1			
EXCELLENT (4)	5 (2.4%)	6 (3.0%)	11 (2.7%)
VERY GOOD (3)	6 (2.9%)	14 (6.9%)	20 (4.9%)
GOOD (2)	62 (30.0%)	70 (34.5%)	132 (32.2%)
FAIR (1)	75 (36.2%)	66 (32.5%)	141 (34.4%)
POOR (0)	29 (14.0%)	25 (12.3%)	54 (13.2%)
OVERALL P-VALUE [1]	0.115		
THE DOUBLE-BLIND WEEK 2			
EXCELLENT (4)	1 (0.5%)	5 (2.5%)	6 (1.5%)
VERY GOOD (3)	16 (7.7%)	17 (8.4%)	33 (8.0%)
GOOD (2)	58 (28.0%)	79 (38.9%)	137 (33.4%)
FAIR (1)	65 (31.4%)	66 (32.5%)	131 (32.0%)
POOR (0)	39 (18.8%)	23 (11.3%)	62 (15.1%)
OVERALL P-VALUE [1]	0.012		
THE DOUBLE-BLIND WEEK 3			
EXCELLENT (4)	1 (0.5%)	9 (4.4%)	10 (2.4%)
VERY GOOD (3)	16 (7.7%)	25 (12.3%)	41 (10.0%)
GOOD (2)	52 (25.1%)	70 (34.5%)	122 (29.8%)
FAIR (1)	67 (32.4%)	62 (30.5%)	129 (31.5%)
POOR (0)	45 (21.7%)	25 (12.3%)	70 (17.1%)
OVERALL P-VALUE [1]	<0.001		
THE DOUBLE-BLIND WEEK 4			
EXCELLENT (4)	4 (1.9%)	5 (2.5%)	9 (2.2%)
VERY GOOD (3)	22 (10.6%)	30 (14.8%)	52 (12.7%)
GOOD (2)	49 (23.7%)	79 (38.9%)	128 (31.2%)
FAIR (1)	55 (26.6%)	53 (26.1%)	108 (26.3%)
POOR (0)	53 (25.6%)	24 (11.8%)	77 (18.8%)
OVERALL P-VALUE [1]	<0.001		
THE DOUBLE-BLIND WEEK 5			
EXCELLENT (4)	3 (1.4%)	5 (2.5%)	8 (2.0%)
VERY GOOD (3)	13 (6.3%)	33 (16.3%)	46 (11.2%)
GOOD (2)	55 (26.6%)	70 (34.5%)	125 (30.5%)
FAIR (1)	63 (30.4%)	62 (30.5%)	125 (30.5%)
POOR (0)	49 (23.7%)	22 (10.8%)	71 (17.3%)
OVERALL P-VALUE [1]	<0.001		
THE DOUBLE-BLIND WEEK 6			
EXCELLENT (4)	5 (2.4%)	2 (1.0%)	7 (1.7%)
VERY GOOD (3)	18 (8.7%)	24 (11.8%)	42 (10.2%)
GOOD (2)	51 (24.6%)	80 (39.4%)	131 (32.0%)
FAIR (1)	57 (27.5%)	67 (33.0%)	124 (30.2%)
POOR (0)	52 (25.1%)	19 (9.4%)	71 (17.3%)
OVERALL P-VALUE [1]	0.002		
THE DOUBLE-BLIND WEEK 7			
EXCELLENT (4)	3 (1.4%)	6 (3.0%)	9 (2.2%)
VERY GOOD (3)	22 (10.6%)	27 (13.3%)	49 (12.0%)
GOOD (2)	51 (24.6%)	74 (36.5%)	125 (30.5%)
FAIR (1)	53 (25.6%)	57 (28.1%)	110 (26.8%)
POOR (0)	54 (26.1%)	28 (13.8%)	82 (20.0%)
OVERALL P-VALUE [1]	0.002		
THE DOUBLE-BLIND WEEK 8			
EXCELLENT (4)	4 (1.9%)	9 (4.4%)	13 (3.2%)
VERY GOOD (3)	19 (9.2%)	24 (11.8%)	43 (10.5%)
GOOD (2)	59 (28.5%)	75 (36.9%)	134 (32.7%)
FAIR (1)	46 (22.2%)	55 (27.1%)	101 (24.6%)
POOR (0)	55 (26.6%)	29 (14.3%)	84 (20.5%)
OVERALL P-VALUE [1]	0.003		
THE DOUBLE-BLIND WEEK 9			
EXCELLENT (4)	4 (1.9%)	4 (2.0%)	8 (2.0%)
VERY GOOD (3)	19 (9.2%)	25 (12.3%)	44 (10.7%)
GOOD (2)	52 (25.1%)	71 (35.0%)	123 (30.0%)

TABLE 12-continued

GLOBAL ASSESSMENT - BY WEEK
12-WEEK DOUBLE-BLIND PERIOD
LAST OBSERVATION CARRIED FORWARD IMPUTATION
ANALYSIS POPULATION: INTENT TO TREAT POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
FAIR (1)	53 (25.6%)	62 (30.5%)	115 (28.0%)
POOR (0)	55 (26.6%)	30 (14.8%)	85 (20.7%)
OVERALL P-VALUE [1]	0.009		
THE DOUBLE-BLIND WEEK 10			
EXCELLENT (4)	7 (3.4%)	6 (3.0%)	13 (3.2%)
VERY GOOD (3)	15 (7.2%)	29 (14.3%)	44 (10.7%)
GOOD (2)	52 (25.1%)	72 (35.5%)	124 (30.2%)
FAIR (1)	52 (25.1%)	54 (26.6%)	106 (25.9%)
POOR (0)	57 (27.5%)	31 (15.3%)	88 (21.5%)
OVERALL P-VALUE [1]	0.001		
THE DOUBLE-BLIND WEEK 11			
EXCELLENT (4)	5 (2.4%)	5 (2.5%)	10 (2.4%)
VERY GOOD (3)	19 (9.2%)	23 (11.3%)	42 (10.2%)
GOOD (2)	49 (23.7%)	73 (36.0%)	122 (29.8%)
FAIR (1)	57 (27.5%)	59 (29.1%)	116 (28.3%)
POOR (0)	53 (25.6%)	32 (15.8%)	85 (20.7%)
OVERALL P-VALUE [1]	0.015		
THE DOUBLE-BLIND WEEK 12			
EXCELLENT (4)	6 (2.9%)	7 (3.4%)	13 (3.2%)
VERY GOOD (3)	19 (9.2%)	25 (12.3%)	44 (10.7%)
GOOD (2)	49 (23.7%)	67 (33.0%)	116 (28.3%)
FAIR (1)	52 (25.1%)	63 (31.0%)	115 (28.0%)
POOR (0)	57 (27.5%)	30 (14.8%)	87 (21.2%)
OVERALL P-VALUE [1]	0.007		

[1] COCHRAN-MANTEL-HAENSZEL (ROW MEAN SCORES) TEST ACROSS TREATMENT GROUPS USING EQUALLY SPACED SCORES ADJUSTING FOR BASELINE PI (≥7.5 AND <7.5) AND PRE-RANDOMIZATION PI (≥5 AND <5).

[0525] Another secondary efficacy endpoint for this study was quality of analgesia. For quality of analgesia, the group that received study drug BID showed a consistent and greater improvement in the quality of analgesia at each week during the twelve week double-blind treatment period as compared to the group that received the placebo BID (see, e.g., at week twelve p=0.004). Table 13 shows the quality of analgesia at each of the twelve weeks during the double-blind treatment period.

TABLE 13

QUALITY OF ANALGESIA - BY WEEK
12-WEEK DOUBLE-BLIND PERIOD
LAST OBSERVATION CARRIED FORWARD IMPUTATION
ANALYSIS POPULATION: INTENT TO TREAT POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
THE DOUBLE-BLIND WEEK 1			
EXCELLENT	5 (2.4%)	4 (2.0%)	9 (2.2%)
VERY GOOD	12 (5.8%)	23 (11.3%)	35 (8.5%)
GOOD	55 (26.6%)	67 (33.0%)	122 (29.8%)
FAIR	71 (34.3%)	64 (31.5%)	135 (32.9%)
POOR	39 (18.8%)	30 (14.8%)	69 (16.8%)
OVERALL P-VALUE [1]	0.072		
THE DOUBLE-BLIND WEEK 2			
EXCELLENT	3 (1.4%)	5 (2.5%)	8 (2.0%)
VERY GOOD	15 (7.2%)	28 (13.8%)	43 (10.5%)
GOOD	61 (29.5%)	69 (34.0%)	130 (31.7%)

TABLE 13-continued

QUALITY OF ANALGESIA - BY WEEK
12-WEEK DOUBLE-BLIND PERIOD
LAST OBSERVATION CARRIED FORWARD IMPUTATION
ANALYSIS POPULATION: INTENT TO TREAT POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
FAIR	59 (28.5%)	61 (30.0%)	120 (29.3%)
POOR	45 (21.7%)	27 (13.3%)	72 (17.6%)
OVERALL P-VALUE [1]	0.007		
THE DOUBLE-BLIND WEEK 3			
EXCELLENT	4 (1.9%)	4 (2.0%)	8 (2.0%)
VERY GOOD	20 (9.7%)	32 (15.8%)	52 (12.7%)
GOOD	53 (25.6%)	80 (39.4%)	133 (32.4%)
FAIR	55 (26.6%)	51 (25.1%)	106 (25.9%)
POOR	51 (24.6%)	24 (11.8%)	75 (18.3%)
OVERALL P-VALUE [1]	<0.001		
THE DOUBLE-BLIND WEEK 4			
EXCELLENT	4 (1.9%)	8 (3.9%)	12 (2.9%)
VERY GOOD	20 (9.7%)	35 (17.2%)	55 (13.4%)
GOOD	51 (24.6%)	73 (36.0%)	124 (30.2%)
FAIR	56 (27.1%)	49 (24.1%)	105 (25.6%)
POOR	52 (25.1%)	26 (12.8%)	78 (19.0%)
OVERALL P-VALUE [1]	<0.001		
THE DOUBLE-BLIND WEEK 5			
EXCELLENT	5 (2.4%)	5 (2.5%)	10 (2.4%)
VERY GOOD	19 (9.2%)	36 (17.7%)	55 (13.4%)
GOOD	41 (19.8%)	62 (30.5%)	103 (25.1%)
FAIR	63 (30.4%)	62 (30.5%)	125 (30.5%)
POOR	55 (26.6%)	27 (13.3%)	82 (20.0%)
OVERALL P-VALUE [1]	<0.001		
THE DOUBLE-BLIND WEEK 6			
EXCELLENT	5 (2.4%)	4 (2.0%)	9 (2.2%)
VERY GOOD	15 (7.2%)	32 (15.8%)	47 (11.5%)
GOOD	53 (25.6%)	71 (35.0%)	124 (30.2%)
FAIR	49 (23.7%)	52 (25.6%)	101 (24.6%)
POOR	61 (29.5%)	33 (16.3%)	94 (22.9%)
OVERALL P-VALUE [1]	<0.001		
THE DOUBLE-BLIND WEEK 7			
EXCELLENT	5 (2.4%)	5 (2.5%)	10 (2.4%)
VERY GOOD	20 (9.7%)	32 (15.8%)	52 (12.7%)
GOOD	57 (27.5%)	64 (31.5%)	121 (29.5%)
FAIR	47 (22.7%)	57 (28.1%)	104 (25.4%)
POOR	54 (26.1%)	34 (16.7%)	88 (21.5%)
OVERALL P-VALUE [1]	0.033		
THE DOUBLE-BLIND WEEK 8			
EXCELLENT	7 (3.4%)	7 (3.4%)	14 (3.4%)
VERY GOOD	17 (8.2%)	31 (15.3%)	48 (11.7%)
GOOD	52 (25.1%)	64 (31.5%)	116 (28.3%)
FAIR	50 (24.2%)	57 (28.1%)	107 (26.1%)
POOR	57 (27.5%)	33 (16.3%)	90 (22.0%)
OVERALL P-VALUE [1]	0.007		
THE DOUBLE-BLIND WEEK 9			
EXCELLENT	6 (2.9%)	4 (2.0%)	10 (2.4%)
VERY GOOD	20 (9.7%)	32 (15.8%)	52 (12.7%)
GOOD	48 (23.2%)	59 (29.1%)	107 (26.1%)
FAIR	46 (22.2%)	63 (31.0%)	109 (26.6%)
POOR	63 (30.4%)	34 (16.7%)	97 (23.7%)
OVERALL P-VALUE [1]	0.013		
THE DOUBLE-BLIND WEEK 10			
EXCELLENT	8 (3.9%)	4 (2.0%)	12 (2.9%)
VERY GOOD	15 (7.2%)	34 (16.7%)	49 (12.0%)
GOOD	55 (26.6%)	64 (31.5%)	119 (29.0%)

TABLE 13-continued

QUALITY OF ANALGESIA - BY WEEK
12-WEEK DOUBLE-BLIND PERIOD
LAST OBSERVATION CARRIED FORWARD IMPUTATION
ANALYSIS POPULATION: INTENT TO TREAT POPULATION

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
FAIR	43 (20.8%)	66 (32.5%)	109 (26.6%)
POOR	62 (30.0%)	24 (11.8%)	86 (21.0%)
OVERALL P-VALUE [1]	0.001		
THE DOUBLE-BLIND WEEK 11			
EXCELLENT	6 (2.9%)	6 (3.0%)	12 (2.9%)
VERY GOOD	23 (11.1%)	30 (14.8%)	53 (12.9%)
GOOD	49 (23.7%)	65 (32.0%)	114 (27.8%)
FAIR	44 (21.3%)	58 (28.6%)	102 (24.9%)
POOR	61 (29.5%)	33 (16.3%)	94 (22.9%)
OVERALL P-VALUE [1]	0.015		
THE DOUBLE-BLIND WEEK 12			
EXCELLENT	5 (2.4%)	9 (4.4%)	14 (3.4%)
VERY GOOD	25 (12.1%)	25 (12.3%)	50 (12.2%)
GOOD	45 (21.7%)	67 (33.0%)	112 (27.3%)
FAIR	45 (21.7%)	61 (30.0%)	106 (25.9%)
POOR	63 (30.4%)	30 (14.8%)	93 (22.7%)
OVERALL P-VALUE [1]	0.004		

[1] COCHRAN-MANTEL-HAENSZEL (ROW MEAN SCORES) TEST ACROSS TREATMENT GROUPS USING EQUALLY SPACED SCORES ADJUSTING FOR BASELINE PI (≥7.5 AND <7.5) AND PRE-RANDOMIZATION PI (≥5 AND <5).

[0526] Another secondary efficacy endpoint for this study was SF-12. For SF-12, the group that received study drug BID had a higher value for the physical component score of the SF-12 (see, e.g., at week twelve p=0.003) and for the mental component score of the SF-12 (see, e.g., at week twelve p=0.055) as compared to the group administered placebo BID, wherein higher values correspond to better health or functioning. Table 14 shows the SF-12 results at each of the twelve weeks during the double-blind treatment period.

TABLE 14

SF-12 HEALTH SURVEY - CHANGE AND PERCENT CHANGE FROM PRE-RANDOMIZATION
12-WEEK DOUBLE-BLIND PERIOD
OBSERVED CASES
ANALYSIS POPULATION: INTENT TO TREAT POPULATION
NORM-BASED STANDARDIZED MENTAL COMPONENT SUMMARY (MCS)

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
PRE-RANDOMIZATION			
MEAN (SD)	52.2 (10.35)	53.8 (10.48)	53.0 (10.43)
MEDIAN	54.0	56.1	55.2
MIN, MAX	26.3, 72.9	18.6, 72.3	18.6, 72.9
N	206	198	404
MODEL P-VALUES			
TREATMENT [1]	0.128		
DOUBLE-BLIND WEEK 12/ET			
MEAN (SD)	52.2 (11.42)	50.6 (12.22)	51.4 (11.84)
MEDIAN	54.7	53.9	54.3
MIN, MAX	16.0, 73.8	16.9, 71.0	16.0, 73.8
N	167	164	331
MODEL P-VALUES			
TREATMENT [1]	0.055		
PRE-RANDOMIZATION SCORE [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 12/ET			
MEAN (SD)	−0.5 (10.49)	−3.4 (12.40)	−1.9 (11.55)
MEDIAN	−0.1	−1.8	−0.8

TABLE 14-continued

SF-12 HEALTH SURVEY - CHANGE AND PERCENT CHANGE FROM PRE-RANDOMIZATION
12-WEEK DOUBLE-BLIND PERIOD
OBSERVED CASES
ANALYSIS POPULATION: INTENT TO TREAT POPULATION
NORM-BASED STANDARDIZED MENTAL COMPONENT SUMMARY (MCS)

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
MIN, MAX	−33.8, 30.7	−36.9, 28.4	−36.9, 30.7
N	167	162	329
MODEL P-VALUES			
TREATMENT [1]	0.055		
PRE-RANDOMIZATION SCORE [1]	<0.001		
PRE-RANDOMIZATION			
MEAN (SD)	35.2 (8.75)	34.8 (8.48)	35.0 (8.61)
MEDIAN	35.2	34.8	350
MIN, MAX	12.0, 56.7	7.2, 56.5	7.2, 56.7
N	206	198	404
MODEL P-VALUES			
TREATMENT [1]	0.585		
DOUBLE-BLIND WEEK 12/ET			
MEAN (SD)	34.9 (9.36)	37.3 (9.31)	36.1 (9.40)
MEDIAN	34.2	37.1	35.9
MIN, MAX	13.4, 67.9	9.7, 60.2	9.7, 67.9
N	167	164	331
MODEL P-VALUES			
TREATMENT [1]	0.003		
PRE-RANDOMIZATION SCORE [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 12/ET			
MEAN (SD)	−0.4 (7.93)	2.2 (7.98)	0.9 (8.04)
MEDIAN	−0.6	2.0	0.7
MIN, MAX	−23.7, 29.2	−20.8, 23.6	−23.7, 29.2
N	167	162	329
MODEL P-VALUES			
TREATMENT [1]	0.003		
PRE-RANDOMIZATION SCORE [1]	<0.001		

NOTE:

INTENT TO TREAT POPULATION - ALL RANDOMIZED PATIENTS WHO TAKE ANY STUDY MEDICATION AND HAVE AT LEAST ONE POST-RANDOMIZATION PI ASSESSMENT.

NOTE:

LOWER VALUES CORRESPOND TO BETTER HEALTH OR FUNCTIONING.

[1] P-VALUES FROM ANOVA MODEL INCLUDING TREATMENT AS THE MAIN EFFECT.

[0527] Another secondary efficacy endpoint for this study was a functional assessment using WOMAC, including its three subscales for pain, stiffness and physical function. For the stiffness (Tables 15C-D) and physical function (Tables 15E-F) subscales of the WOMAC, although the values were lower in the group administered study drug BID as compared to the group administered placebo BID, as expected, the differences were not significant (stiffness subscale p=0.366 at week twelve and physical function subscale p=0.221 at week twelve). For the pain subscale of the WOMAC, the values (% change from baseline to week twelve) were significantly lower in the group administered study drug BID as compared to the group administered placebo BID (p=0.023 at week twelve), wherein lower values correspond to better health or functioning (Tables 15A-B). Total scores are shown in Tables 15G-H.

TABLE 15A

WOMAC OSTEOARTHRITIS INDEX
CHANGE AND PERCENT CHANGE FROM PRE-RANDOMIZATION
12-WEEK DOUBLE-BLIND PERIOD
OBSERVED CASES
ANALYSIS POPULATION: INTENT TO TREAT POPULATION
PAIN SUBSCALE

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
PRE-RANDOMIZATION			
MEAN (SD)	230.1 (117.83)	229.0 (125.07)	229.6 (121.27)
MEDIAN	234.5	232.0	234.0
MIN, MAX	3.0, 494.0	0.0, 497.0	0.0, 497.0
N	206	197	403
MODEL P-VALUES			
TREATMENT [1]	0.928		

NOTE:
LOWER VALUES CORRESPOND TO BETTER HEALTH OR FUNCTIONING.
[1] P-VALUES FROM ANCOVA MODEL INCLUDING TREATMENT AS THE MAIN EFFECT.

TABLE 15B

WOMAC OSTEOARTHRITIS INDEX
CHANGE AND PERCENT CHANGE FROM PRE-RANDOMIZATION
12-WEEK DOUBLE-BLIND PERIOD
OBSERVED CASES
ANALYSIS POPULATION: INTENT TO TREAT POPULATION
PAIN SUBSCALE

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
DOUBLE-BLIND WEEK 12/ET			
MEAN (SD)	232.7 (126.08)	199.7 (122.09)	216.4 (125.04)
MEDIAN	258.0	195.0	214.0
MIN, MAX	3.0, 488.0	12.0, 486.0	3.0, 488.0
N	168	163	331
MODEL P-VALUES			
TREATMENT [1]	0.023		
PRE-RANDOMIZATION SCORE [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 12/ET			
MEAN (SD)	−2.3 (118.49)	−22.5 (117.61)	−12.2 (118.32)
MEDIAN	−2.0	−8.0	−5.5
MIN, MAX	−296.0, 377.0	−437.0, 305.0	−437.0, 377.0
N	168	162	330
MODEL P-VALUES			
TREATMENT [1]	0.023		
PRE-RANDOMIZATION SCORE [1]	<0.001		

NOTE:
LOWER VALUES CORRESPOND TO BETTER HEALTH OR FUNCTIONING.
[1] P-VALUES FROM ANCOVA MODEL INCLUDING TREATMENT AS THE MAIN EFFECT.

TABLE 15C

WOMAC OSTEOARTHRITIS INDEX
CHANGE AND PERCENT CHANGE FROM PRE-RANDOMIZATION
12-WEEK DOUBLE-BLIND PERIOD
OBSERVED CASES
ANALYSIS POPULATION: INTENT TO TREAT POPULATION
STIFFNESS SUBSCALE

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
PRE-RANDOMIZATION			
MEAN (SD)	111.7(51.46)	106.3(51.95)	109.0(51.71)
MEDIAN	122.0	113.0	118.0
MIN, MAX	5.0, 197.0	0.0, 198.0	0.0, 198.0
N	206	197	403
MODEL P-VALUES			
TREATMENT [1]	0.295		

NOTE:
LOWER VALUES CORRESPOND TO BETTER HEALTH OR FUNCTIONING.
[1] P-VALUES FROM ANCOVA MODEL INCLUDING TREATMENT AS THE MAIN EFFECT.

TABLE 15E

WOMAC OSTEOARTHRITIS INDEX
CHANGE AND PERCENT CHANGE FROM PRE-RANDOMIZATION
12-WEEK DOUBLE-BLIND PERIOD
OBSERVED CASES
ANALYSIS POPULATION: INTENT TO TREAT POPULATION
PHYSICAL FUNCTION SUBSCALE

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
PRE-RANDOMIZATION			
MEAN (SD)	853.0(399.35)	834.5(403.94)	844.0(401.20)
MEDIAN	906.5	877.5	895.0
MIN, MAX	10.0, 1606.0	0.0, 1654.0	0.0, 1654.0
N	206	196	402
MODEL P-VALUES			
TREATMENT [1]	0.644		

NOTE:
LOWER VALUES CORRESPOND TO BETTER HEALTH OR FUNCTIONING.
[1] P-VALUES FROM ANCOVA MODEL INCLUDING TREATMENT AS THE MAIN EFFECT.

TABLE 15D

WOMAC OSTEOARTHRITIS INDEX
CHANGE AND PERCENT CHANGE FROM PRE-RANDOMIZATION
12-WEEK DOUBLE-BLIND PERIOD
OBSERVED CASES
ANALYSIS POPULATION: INTENT TO TREAT POPULATION
STIFFNESS SUBSCALE

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
DOUBLE-BLIND WEEK 12/ET			
MEAN (SD)	107.7(54.58)	97.6(55.16)	102.7(55.02)
MEDIAN	119.0	101.0	110.0
MIN, MAX	2.0, 195.0	4.0, 195.0	2.0, 195.0
N	168	163	331
MODEL P-VALUES			
TREATMENT [1]	0.366		
PRE-RANDOMIZATION SCORE [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 12/ET			
MEAN (SD)	−5.8(49.64)	−5.8(54.44)	−5.8(51.97)
MEDIAN	−8.5	0.5	−3.5
MIN, MAX	−128.0, 133.0	−174.0, 147.0	−174.0, 147.0
N	168	162	330
MODEL P-VALUES			
TREATMENT [1]	0.366		
PRE-RANDOMIZATION SCORE [1]	<0.001		

NOTE:
LOWER VALUES CORRESPOND TO BETTER HEALTH OR FUNCTIONING.
[1] P-VALUES FROM ANCOVA MODEL INCLUDING TREATMENT AS THE MAIN EFFECT.

TABLE 15F

WOMAC OSTEOARTHRITIS INDEX
CHANGE AND PERCENT CHANGE FROM PRE-RANDOMIZATION
12-WEEK DOUBLE-BLIND PERIOD
OBSERVED CASES
ANALYSIS POPULATION: INTENT TO TREAT POPULATION
PHYSICAL FUNCTION SUBSCALE

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
DOUBLE-BLIND WEEK 12/ET			
MEAN (SD)	819.5(439.81)	738.3(425.43)	779.6(434.06)
MEDIAN	841.5	753.5	800.0
MIN, MAX	7.0, 1616.0	33.0, 1647.0	7.0, 1647.0
N	168	162	330
MODEL P-VALUES			
TREATMENT [1]	0.221		
PRE-RANDOMIZATION SCORE [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-CLIND WEEK 12/ET			
MEAN (SD)	−41.2(406.39)	−68.3(382.61)	−54.4(394.60)
MEDIAN	−26.5	−38.0	−31.5
MIN, MAX	−1008.0, 1122.0	−1347.0, 868.0	−1347.0, 1122.0
N	168	160	328
MODEL P-VALUES			
TREATMENT [1]	0.221		
PRE-RANDOMIZATION SCORE [1]	<0.001		

NOTE:
LOWER VALUES CORRESPOND TO BETTER HEALTH OR FUNCTIONING.
[1] P-VALUES FROM ANCOVA MODEL INCLUDING TREATMENT AS THE MAIN EFFECT.

TABLE 15G

WOMAC OSTEOARTHRITIS INDEX
CHANGE AND PERCENT CHANGE FROM PRE-RANDOMIZATION
12-WEEK DOUBLE-BLIND PERIOD
OBSERVED CASES
ANALYSIS POPULATION: INTENT TO TREAT POPULATION
TOTAL SCORE

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
PRE-RANDOMIZATION			
MEAN (SD)	1194.8(553.78)	1170.2(566.69)	1182.8(559.55)
MEDIAN	1255.5	1211.5	1240.0

TABLE 15G-continued

WOMAC OSTEOARTHRITIS INDEX
CHANGE AND PERCENT CHANGE FROM PRE-RANDOMIZATION
12-WEEK DOUBLE-BLIND PERIOD
OBSERVED CASES
ANALYSIS POPULATION: INTENT TO TREAT POPULATION
TOTAL SCORE

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
MIN, MAX	33.0, 2342.0	0.0, 2341.0	0.0, 2342.0
N	206	196	402
MODEL P-VALUES			
TREATMENT [1]	0.660		

NOTE:
LOWER VALUES CORRESPOND TO BETTER HEALTH OR FUNCTIONING.
[1] P-VALUES FROM ANCOVA MODEL INCLUDING TREATMENT AS THE MAIN EFFECT.

TABLE 15H

WOMAC OSTEOARTHRITIS INDEX
CHANGE AND PERCENT CHANGE FROM PRE-RANDOMIZATION
12-WEEK DOUBLE-BLIND PERIOD
OBSERVED CASES
ANALYSIS POPULATION: INTENT TO TREAT POPULATION
TOTAL SCORE

	PLACEBO BID (N = 207)	OXY BID (N = 203)	TOTAL (N = 410)
DOUBLE-BLIND WEEK 12/ET			
MEAN (SD)	1159.9(605.96)	1035.3(586.35)	1098.8(598.77)
MEDIAN	1191.0	1042.5	1144.0
MIN, MAX	12.0, 2260.0	49.0, 2317.0	12.0, 2317.0
N	168	162	330
MODEL P-VALUES			
TREATMENT [1]	0.147		
PRE-RANDOMIZATION SCORE [1]	<0.001		
CHANGE FROM PRE-RANDOMIZATION TO DOUBLE-BLIND WEEK 12/ET			
MEAN (SD)	−492(552.69)	−97.9(532.83)	−73.0(542.81)
MEDIAN	−17.5	−56.0	−24.0
MIN, MAX	−1327.0, 1624.0	−1924.0, 1108.0	−1924.0, 1624.0
N	168	160	328
MODEL P-VALUES			
TREATMENT [1]	0.147		
PRE-RANDOMIZATION SCORE [1]	0.001		

NOTE:
LOWER VALUES CORRESPOND TO BETTER HEALTH OR FUNCTIONING.
[1] P-VALUES FROM ANCOVA MODEL INCLUDING TREATMENT AS THE MAIN EFFECT.

[0528] No drug related safety issues were noted in this study.

Example 2

Preparation of Opioid Formulations

[0529] Exemplary opioid dosage forms comprising oxycodone are prepared as described herein. For clinical studies as described in Example 1, capsules having different amounts of oxycodone are produced.

[0530] Capsule formulations containing oxycodone at various dose levels (5.0, 10.0, 20.0, 30.0 and 40.0 mg/capsule) and matching placebo capsules are prepared.

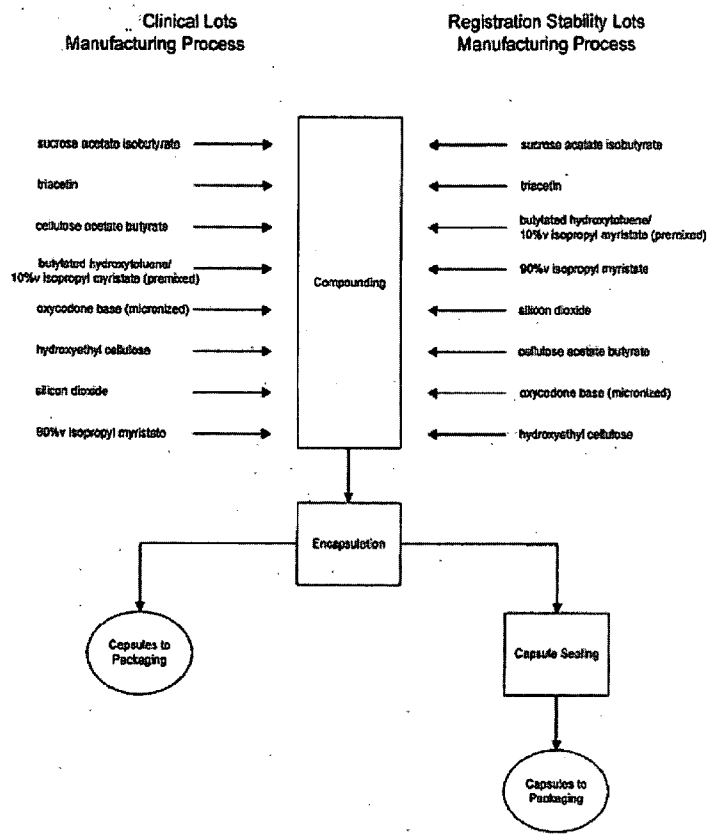
[0531] The components, pharmaceutical grade, and function of each component used to make oxycodone capsules are provided in Table 16 below.

TABLE 16

Components for Oxycodone Capsules

Component	Function
Oxycodone base (micronized)	Active pharmaceutical ingredient
Sucrose acetate isobutyrate	Liquid carrier material
Triacetin, USP	Solvent
Isopropyl myristate, NF	Rheology modifier
Cellulose acetate butyrate, NF/EP, ethanol washed (grade 381-20 BP)	Network former
Hydroxyethyl cellulose, NF	Hydrophilic agent
Colloidal silicon dioxide, NF	Viscosity enhancing agent
Butylated hydroxytoluene, NF	Antioxidant
Hard gelatin capsule	Dosage form

[0532] The following steps were used to prepare capsules comprising oxycodone. These steps as well as in-process controls (IPC) are summarized in the flowchart below.



[454] The following raw materials were used to create the formulations: Oxycodone base, micronized; Isopropyl Myristate, NF ("IPM"); Colloidal silicon dioxide (CABOSIL™, Cabot Corp) (SiO_2"); Butylated hydroxyl toluene, NF ("BHT"); Hydroxyethyl cellulose, NF ("HEC"); Sucrose Acetate Isobutyrate (Eastman), ("SAIB"); Triacetin USP ("TA"); Cellulose Acetate Butyrate, grade 381-20 BP, ethanol washed (Eastman) ("CAB"); Sodium Lauryl Sulfate NF ("SDS"); and Labrafil M2125 CS ("LAB").

[455] Two different processes were developed for opioid dosage forms as shown in the flowchart above. In process one, compounding was carried out at a 45 kg scale. In

[0533] The following raw materials were used to create the formulations: Oxycodone base, micronized; Isopropyl Myristate, NF ("IPM"); Colloidal silicon dioxide (CABOSIL™, Cabot Corp) (SiO_2"); Butylated hydroxyl toluene, NF ("BHT"); Hydroxyethyl cellulose, NF ("HEC"); Sucrose Acetate Isobutyrate (Eastman), ("SAIB"); Triacetin USP ("TA"); Cellulose Acetate Butyrate, grade 381-20 BP, ethanol washed (Eastman) ("CAB"); Sodium Lauryl Sulfate NF ("SDS"); and Labrafil M2125 CS ("LAB").

[0534] Two different processes were developed for opioid dosage forms as shown in the flowchart above. In process one, compounding was carried out at a 45 kg scale. In process two, compounding was carried out at 150 kg scale. The same materials were used in both processes but there were some differences. One difference was the order in which ingredients were added during the manufacture in order to enhance mixing and efficiency during the compounding process. For example, in process two, IPM and SiO_2 were added earlier in the process and CAB was added later in the process to lower fluid viscosity during the first part of the compounding process. Another difference in the oral dosage forms used in some of the clinical studies was that the capsules filled from process one were not sealed, while capsules filled from process two were sealed using a liquid encapsulation microspray sealing (LEMS) process from Capsugel.

[0535] Table 17 shows a manufacturing process and equipment comparison.

TABLE 17

Manufacturing Process and Equipment Comparison
Process and Equipment Information

Process Description	Process 1	Process 2
API Milling (micronization)	8-20 kg scale Spiral Jet Mill Hosokawa Alpine model 50AS	28-36 Kg scale Spiral Jet Mill Hosokawa Alpine Model 50AS
Compounding	45 kg scale Multishaft mixer including low shear anchor agitator high speed disperser high shear rotor-stator Charles Ross mixer model VMC 10	150 kg scale Multishaft mixer including low shear anchor agitator high speed disperser high shear rotor-stator Charles Ross mixer model PVM 40
Encapsulation	Hard gelatin capsule filling machine Shionogi encapsulator model F-40	Hard gelatin capsule filling machine Zanasi encapsulator model 40E
Capsule Sealing	None- capsules were not sealed	Capsules sealed with LEMS technology Capsugel sealing machine model LEMS30

[0536] Compounding for process one was carried out using a Ross VMC-10 Mixer with SLIM. Accordingly, all references to a specific rpm numeric throughout this compounding process correspond to this model. In a first step, sucrose acetate isobutyrate (SAIB) was preheated to 50-65° C. and then added into a compounding vessel with an anchor speed of at 20-40 rpm. The temperature of the product was maintained at 50-60° C. In a second step, triacetin was added into the compounding vessel and mixed at anchor speed of 20-40 rpm and a disperser speed of 700-2000 rpm. The vessel contents were mixed to achieve a uniform solution of SAIB in triacetin. Again, the product temperature was maintained at 50-60° C. In a third step, pre-sieved, cellulose acetate butyrate (CAB) was inducted into the vessel using high shear dispersion during the addition to prevent formation of agglomerates. The vessel contents were mixed with an anchor speed of 20-50 rpm, a rotor stator speed of 700-4500 rpm and a disperser speed of 700-3500 rpm until the CAB was completely dissolved and a clear gel formed. After formation of the clear-gel the vessel contents were mixed for an additional thirty minutes with the same anchor, rotor stator and disperser speeds. In a fourth step, in a separate container, a solution was prepared containing butylated hydroxytoluene (BHT) and approximately 15% portion of isopropyl myristate (IPM). A 10% portion of the IPM may be set aside to be used as a rinse solvent later in the process. The remaining quantity of the IPM-BHT solution was subsequently added to the compounding vessel and mixed to achieve uniformity with an anchor speed of 20-50 rpm and disperser speed of 700-3500 rpm. After formation of a uniform mixture, the vessel contents were mixed for an additional five minutes with the same anchor and disperser speeds. During the additional mixing, the stator was jogged as necessary at 700-1200 rpm. Again, the product temperature was maintained at 50-60° C. In a fifth step, oxycodone was inducted into the compounding vessel and mixed to achieve uniformity with an anchor speed of 20-50 rpm, disperser speed of 700-3500 rpm and a rotor stator speed of 800-4500 rpm. The product temperature was maintained at 55-65° C. The vessel contents were mixed for a minimum of an additional two minutes with the same anchor, disperser and rotor stator speeds. In a sixth step, hydroxyethyl cellulose (HEC) was inducted into the vessel using high shear dispersion during the addition and mixed to achieve a uniform dispersion with an anchor speed of 20-50 rpm, disperser speed of 700-3500 rpm and a rotor stator speed of 800-4500 rpm. The vessel contents were mixed for an additional two minutes with the same anchor, disperser and rotor stator speeds. Again, the product temperature was maintained at 55-65° C. In a seventh step, colloidal silicon dioxide (SiO_2) was inducted with to the vessel using high shear dispersion during the addition and mixed with an anchor speed of 20-50 rpm, disperser speed of 700-3500 rpm and a rotor stator speed of 800-4500 rpm. The vessel contents were mixed for a minimum of an additional two minutes with the same anchor, disperser and rotor stator speeds. Again, the product temperature was maintained at 55-65° C. In an eighth step, IPM was inducted into the vessel and mixed with an anchor speed of 20-50 rpm, disperser speed of 700-2000 rpm and rotor stator speed of 1500-3000 rpm. The vessel contents were continuously mixed with anchor and maintained at 50-60° C. The final compounded mass was de-aerated by vacuum and flushed with nitrogen at 4-5 psig for at least five minutes. The compounded, controlled-release mass was filled into hard gelatin capsules and packaged into unit dose blisters or multidose plastic bottles with child-resistant closures for clinical supply.

[0537] Compounding for process two was carried out with a Ross PVM-40 Mixer with SLIM. Accordingly, all references to a specific rpm numeric throughout this compounding procedure correspond to this model. In a first step, sucrose acetate isobutyrate (SAIB) was preheated to 50-65° C. and added to a compounding vessel. In a second step, triacetin was added to the compounding vessel. In a third step, a butylated hydroxytoluene/isopropyl myristate solution was prepared by dispensing a portion of isopropyl myristate (bal-

ance of IPM is added in next step) into a separate stainless steel container. Butylated hydroxytoluene was added to the container and the solution was mixed for at least ten minutes until BHT was dissolved. The BHT hydroxytoluene/isopropyl myristate solution was then added to the compounding vessel. In a fourth step, isopropyl myristate was added to the compounding vessel and mixed to homogeneity with an anchor speed of 10-50 rpm and a disperser speed of 1-2550 rpm. The product temperature was maintained at 35-50° C. In a fifth step, colloidal silicon dioxide (SiO_2) was inducted into the compounding vessel and mixed to achieve uniform dispersion with an anchor speed of 10-50 rpm (e.g., 20 rpm), a disperser speed of 1-2550 rpm (e.g., 1000 rpm) and an rotor stator speed of 1-3600 rpm (e.g. 2500 rpm). Again the product temperature was maintained at 35-50° C. The vessel contents were mixed for an additional two to four minutes with the same anchor, disperser and rotor stator speeds. In a sixth step, cellulose acetate butyrate (CAB) was inducted into to the compounding vessel and mixed with an anchor speed of 10-50 rpm (e.g., 20 rpm), a disperser speed of 1-2550 rpm (e.g., 1500 rpm) and a rotor stator speed of 1-3600 rpm (e.g., 3000 rpm). The product temperature was maintained at 40-60° C. The vessel contents were mixed for an additional two to four minutes with the same anchor, disperser and rotor stator speeds. In a seventh step, oxycodone is inducted into the compounding vessel and mixed to achieve a uniform dispersion with an anchor speed of 10-50 rpm (e.g., 20 rpm), a disperser speed of 1-2550 rpm (e.g., 1500 rpm), and an speed of 1-3600 rpm (e.g., 3000 rpm). Again the product temperature was maintained at 40-60° C. The vessel contents were mixed for an additional two to four minutes with the same anchor, disperser and rotor stator speeds. In an eighth step, hydroxyethyl cellulose (HEC) was inducted into the compounding vessel and mixed with an anchor speed of 10-50 rpm (e.g., 20 rpm), a disperser speed of 1-2550 rpm (e.g., 1500 rpm), and a rotor stator speed of 1-3600 rpm (e.g., 3000 rpm). Again the product temperature was maintained at 40-60° C. The vessel contents were mixed for an additional two to four minutes with the same anchor, disperser and rotor stator speeds. The final compounded mass was de-aerated by vacuum at no less than 14 mm Hg for no less than two hours with anchor speed of 10-50 rpm (e.g., 20 rpm) and dispersion speed of 1-2250 rpm (e.g., 1250 rpm). The compounded, controlled-release mass was filled into hard gelatin capsules. Filled capsules were sealed using LEMS (liquid encapsulation microspray sealing) from Capsugel and packaged into unit dose blisters or multidose plastic bottles with child-resistant closures.

[0538] The compounded mass prepared by process 2 is encapsulated using a Zanasi Liqui-Fill Encapsulator and sealed using a LEMS30 Capsule Sealer. Initially, the compounded mass is transferred from the Ross PVM-40 Mixer to a Zanasi Hopper. The transfer lines are heated with a heated hose controller to a temperature of 55-65° C. Then, a Zansai Liqui-Fill Encapsulator is readied by adjusting the Stroke Scale until the proper fill weight is obtained and the temperature of the compounded mass for filling is maintained at 60-65° C. Depending on the size of the dosage form capsule, a variety of filling nozzles were designed with varying nozzle diameters (e.g., 1.2-2.0 mm) for use on the Encapsulator. For a 5 mg, 10 mg or 20 mg capsule dosage form, a 1.2 mm diameter nozzle is used. For a 30 mg or 40 mg capsule dosage form, a 1.5 mm diameter nozzle is used. Next, capsules are removed from the Zansai Liqui-Fill Encapsulator into a collection container and sealed using the LEMS30 Capsule Sealer.

[0539] In some cases, the oxycodone used in process one or process two was micronized. Micronization of the oxycodone was conducted using a Hosokawa Alpine Spiral Jet Mill. In operation, a feed material comprising a non-micronized opioid is injected into a flat cylindrical grinding chamber, the chamber having nozzles arranged tangentially on a peripheral wall, in the presence of a propellant air pressure and grinding air pressure appropriate for providing the desired flow dynamics within the chamber needed to effect collision of the opioid particles with each other. An appropriate speed and pressure of the propellant air pressure (such as an injector air pressure of 6.8 Bar) and the grinding air pressure (such as 6.2 Bar) is applied such that a particle on particle collision and interaction with the chamber wall results. The injector gas pressure was always approximately 0.3 to 0.7 Bar higher than grinding pressure to obtain constant flow of oxycodone into the spiral jet mill. A micronized particle thus occurs, providing an opioid preparation having a reduced particle size, the particle size being less than about 10μ. The larger particles are held in the mill by centrifugal (mass) force, while the fine, micronized particles leave the mill in an air stream and are collected (drag force). One set of processing parameters that may be used in the methods for preparing a micronized opioid preparation within a jet gas mill, includes, a batch size of 4 kg; injector clearance default of +3 mm; a feed rate of 40 to 50 g/min; a grinding gas pressure of 6.8 Bar and an injector gas pressure of 6.2 Bar.

[0540] Immediately following micronization, the micronized oxycodone is packaged in plastic bags with dessicant and then stored in plastic drums to preserve the integrity of the micronized particles. This is necessary to maintain stabilized micronized opioid particle preparations. The micronized opioids, particularly the salt forms such as oxycodone HCl or hydromorphone HCl, are hydroscopic. The immediate packaging with dessication is required to prevent agglomeration and/or fused particles. For example, the micronized oxydocone is placed into a labeled anti-static bag and secured with a cable or twist tie at the open end of the bag. The anti-static bag is placed into a poly bag with a layer of eight-unit, silica gel, printer, Natrasorb® S Tyvek® four-side seal bag desiccant separating the anti-static bag from the poly bag. The label on the anti-static bag is checked to ensure that it is visible through the poly bag and the poly bag is sealed at its open end. The poly bag is placed in a HDPE (high density polyethylene) drum with a layer of eight-unit, silica gel, printer, Natrasorb® S Tyvek® four-side seal bag desiccant separating the poly bag from the drum. A lid is placed on the open end of the drum and secured using a uniquely numbered security locking tag through a side lever-lock (SSL). Such dessicant packaged and stored micronized opioid preparations may be used in the manufacturing processes, including the compounding processes described herein.

[0541] All of the raw materials were used as obtained from the various manufacturers with the following exceptions. The active ingredient (Oxycodone) was subject to a jet milling process to micronize the solid material into a substantially homogenous particle size. After collection from the jet mill apparatus, the micronized oxycodone was passed through a 20-mesh stainless steel screen and weighed. The CAB raw material was washed using ethanol (EtOH) to remove possible contaminants.

[0542] The amounts of active ingredients and excipients in various capsules of different strengths are set forth in Tables 18 through 22.

[0543] Table 18 sets forth the composition of exemplary 5.0 mg strength capsules (capsules comprising 5.0 mg oxycodone).

TABLE 18

Component	Quantity per Capsule (mg) (Study Drug)	Quantity per Capsul (mg) (Placebo)
Oxycodone base (micronized)	5.0	0.0
Sucrose acetate isobutyrate	40.0	42.1
Triacetin, USP	26.6	28.1
Isopropyl myristate, NF	13.9	14.6
Cellulose acetate butyrate, NF/EP, ethanol washed (grade 381-20 BP)	4.6	4.9
Hydroxyethyl cellulose, NF	5.5	5.9
Colloidal silicon dioxide, NF	1.8	2.0
Butylated hydroxytoluene, NF	0.02	0.02
Total	97.5	97.5

[0544] Table 19 sets forth the composition of exemplary 10.0 mg strength capsules (capsules comprising 10.0 mg oxycodone).

TABLE 19

Component	Quantity per Capsule (mg) (Study Drug)	Quantity per Capsul (mg) (Placebo)
Oxycodone base (micronized)	10.0	0.0
Sucrose acetate isobutyrate	79.9	84.2
Triacetin, USP	53.3	56.1
Isopropyl myristate, NF	27.7	29.3
Cellulose acetate butyrate, NF/EP, ethanol washed (grade 381-20 BP)	9.2	9.8
Hydroxyethyl cellulose, NF	11.1	11.7
Colloidal silicon dioxide, NF	3.7	3.9
Butylated hydroxytoluene, NF	0.04	0.04
Total	195.0	195.0

[0545] Table 20 sets forth the composition of exemplary 20.0 mg strength capsules (capsules comprising 20.0 mg oxycodone).

TABLE 20

Component	Quantity per Capsule (mg) (Study Drug)	Quantity per Capsul (mg) (Placebo)
Oxycodone base (micronized)	20.0	0.0
Sucrose acetate isobutyrate	159.8	168.4
Triacetin, USP	106.5	112.3
Isopropyl myristate, NF	55.5	58.5
Cellulose acetate butyrate, NF/EP, ethanol washed (grade 381-20 BP)	18.5	19.5
Hydroxyethyl cellulose, NF	22.2	23.4
Colloidal silicon dioxide, NF	7.4	7.8
Butylated hydroxytoluene, NF	0.08	0.08
Total	390.0	390.0

[0546] Table 21 sets forth the composition of exemplary 30.0 mg strength capsules (capsules comprising 30.0 mg oxycodone).

TABLE 21

Component	Quantity per Capsule (mg) (Study Drug)	Quantity per Capsul (mg) (Placebo)
Oxycodone base (micronized)	30.0	0.0
Sucrose acetate isobutyrate	239.7	42.1
Triacetin, USP	159.8	28.1
Isopropyl myristate, NF	83.2	14.6
Cellulose acetate butyrate, NF/EP, ethanol washed (grade 381-20 BP)	27.8	4.9
Hydroxyethyl cellulose, NF	33.3	5.9
Colloidal silicon dioxide, NF	11.1	2.0
Butylated hydroxytoluene, NF	0.12	0.02
Total	585.0	

[0547] Table 22 sets forth the composition of exemplary 40.0 mg strength capsules (capsules comprising 40.0 mg oxycodone).

TABLE 22

Component	Quantity per Capsule (mg) (Study Drug)	Quantity per Capsul (mg) (Placebo)
Oxycodone base (micronized)	40.0	0.0
Sucrose acetate isobutyrate	319.6	336.9
Triacetin, USP	213.1	224.6
Isopropyl myristate, NF	111.0	117.0
Cellulose acetate butyrate, NF/EP, ethanol washed (grade 381-20 BP)	37.0	39.0
Hydroxyethyl cellulose, NF	44.4	46.8
Colloidal silicon dioxide, NF	14.8	15.6
Butylated hydroxytoluene, NF	0.16	0.16
Total	780.0	780.0

[0548] Clinical supplies of oxycodone capsules or placebo capsules were packaged in plastic film blister packs with foil backing. The blister packs were placed inside a foil/foil pouch with a silica gel desiccant to assure that products conform to specifications while in use.

[0549] While the invention will be described in connection with one or more embodiments, it will be understood that the invention is not limited to those embodiments. On the contrary, the invention includes all alternatives, modification, and equivalents as may be included within the spirit and scope of the appended claims.

What is claimed is:

1. A method for treating pain, said method comprising administering to a subject a pharmaceutical composition for oral administration which comprises:

(a) an opioid;

(b) sucrose acetate isobutyrate;

(c) triacetin;

(d) isopropyl myristate;

(e) cellulose acetate butyrate;

(f) hydroxyethyl cellulose;

(g) colloidal silicon dioxide; and

(h) butylated hydroxytoluene, wherein one or more symptoms or signs associated with the subject's pain is alleviated.

2. The method of claim **1**, wherein:

(i) the opioid is in the form of a free base or a salt, and/or

(ii) the opioid is micronized, and/or

(iii) the opioid is oxycodone, oxymorphone, hydrocodone or hydromorphone.

3. The method of claim **1**, wherein the pharmaceutical composition is administered no more than twice in a 24-hour period.

4. The method of claim **1**, wherein the pharmaceutical composition is encapsulated.

5. The method of claim **1**, wherein the pain is associated with cancer or the pain is chronic pain such as chronic pain that is associated with an arthritic condition.

6. A method for treating an arthritic condition, said method comprising administering to a subject a pharmaceutical composition for oral administration which comprises:

(a) an opioid;

(b) sucrose acetate isobutyrate;

(c) triacetin;

(d) isopropyl myristate;

(e) cellulose acetate butyrate;

(f) hydroxyethyl cellulose;

(g) colloidal silicon dioxide; and

(h) butylated hydroxytoluene, wherein one or more symptoms or signs associated with the subject's arthritic condition are alleviated.

7. The method of claim **6**, wherein:

(i) the opioid is in the form of a free base or a salt, and/or

(ii) the opioid is micronized, and/or

(iii) the opioid is oxycodone, oxymorphone, hydrocodone or hydromorphone.

8. The method of claim **6**, wherein the pharmaceutical composition is administered no more than twice in a 24-hour period.

9. The method of claim **6**, wherein the arthritic condition is associated with a joint, hip, knee, back, neck, or lower back of the subject.

10. A method for treating inflammation, said method comprising administering to a subject a pharmaceutical composition for oral administration which comprises:

(a) an opioid;

(b) sucrose acetate isobutyrate;

(c) triacetin;

(d) isopropyl myristate;

(e) cellulose acetate butyrate;

(f) hydroxyethyl cellulose;

(g) colloidal silicon dioxide; and

(h) butylated hydroxytoluene, wherein one or more symptoms or signs associated with the subject's inflammation are alleviated.

11. The method of claim **10**, wherein:

(i) the opioid is in the form of a free base or a salt, and/or

(ii) the opioid is micronized, and/or

(iii) the opioid is oxycodone, oxymorphone, hydrocodone or hydromorphone.

12. The method of claim **10**, wherein the pharmaceutical composition is administered no more than twice in a 24-hour period.

13. The method of claim **10**, wherein the inflammation is associated with an arthritic condition which preferably is associated with a joint, hip, knee, back, neck, or lower back of the subject.

14. A pharmaceutical composition for oral administration to a human subject, the pharmaceutical composition comprising: (a) an opioid; (b) sucrose acetate isobutyrate; (c) triacetin; (d) isopropyl myristate; (e) cellulose acetate butyrate; (f) hydroxyethyl cellulose; (g) colloidal silicon dioxide; and (h) butylated hydroxytoluene.

15. The composition of claim **14**, wherein:

(i) the opioid is in the form of a free base or a salt, and/or

(ii) the opioid is micronized, and/or

(iii) the opioid is oxycodone, oxymorphone, hydrocodone or hydromorphone.

16. The composition of claim **14**, wherein said composition is intended for administration to a subject no more than twice in a 24-hour period.

17. The composition of claim **14**, wherein said composition is encapsulated.

* * * * *