CLAIMS

1. ~~A method of treating an estrogen-dependent disease in a human patient in need thereof, the method comprising periodically administering to the patient a therapeutically effective amount~~Use of a gonadotropin-releasing hormone (GnRH) antagonist in the manufacture of a medicament for use in ~~over the course of~~ a method of ~~treating~~ment an estrogen-dependent disease in a human patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of the GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

2. The ~~method~~ use of claim 1, wherein the estrogen-dependent disease is uterine fibroids or endometriosis.

~~3. A method of reducing the volume of menstrual blood loss in a human patient diagnosed as having uterine fibroids, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.~~

~~4. A method of inducing amenorrhea in a human patient diagnosed as having uterine fibroids, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.~~

~~5. A method of reducing the volume of one or more uterine fibroids in a human patient diagnosed as having uterine fibroids, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.~~

~~6. A method of preserving or increasing hemoglobin in a human patient diagnosed as having uterine fibroids, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.~~

~~7. The method of claim 1, wherein the estrogen-dependent disease is endometriosis.~~

~~8. A method of reducing the volume of one or more endometriosis nodes in a human patient diagnosed as having endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.~~

~~9. A method of reducing pelvic pain in a human patient diagnosed as having endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.~~

~~10. A method of reducing dysmenorrhea in a human patient diagnosed as having endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.~~

11. A method of reducing dyspareunia in a human patient diagnosed as having endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

12. A method of reducing dyschezia in a human patient diagnosed as having endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

13. A method of reducing uterine bleeding in a human patient diagnosed as having endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

14. A method of inducing amenorrhea in a human patient diagnosed as having endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

15. The method of claim 1, wherein the estrogen-dependent disease is adenomyosis.

16. A method of reducing uterine volume in a human patient diagnosed as having adenomyosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

17. A method of reducing the thickness of the anterior and/or posterior region of the uterine myometrium in a human patient diagnosed as having adenomyosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

18. A method of reducing pelvic pain in a human patient diagnosed as having adenomyosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

19. A method of reducing dysmenorrhea in a human patient diagnosed as having adenomyosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

20. A method of reducing dyspareunia in a human patient diagnosed as having adenomyosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

21. A method of reducing dyschezia in a human patient diagnosed as having adenomyosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

22. A method of reducing uterine tenderness in a human patient diagnosed as having adenomyosis, the method comprising periodically administering to the patient a therapeutically effective

amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

23. A method of reducing uterine bleeding in a human patient diagnosed as having adenomyosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

24. A method of inducing amenorrhea in a human patient diagnosed as having adenomyosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

25. The method of claim 1, wherein the estrogen-dependent disease is rectovaginal endometriosis.

26. A method of reducing the volume of one or more rectovaginal endometriosis nodes in a human patient diagnosed as having rectovaginal endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

27. A method of reducing the volume of one or more type III rectovaginal endometriosis nodes in a human patient diagnosed as having rectovaginal endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

28. A method of reducing pelvic pain in a human patient diagnosed as having rectovaginal endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

29. A method of reducing dysmenorrhea in a human patient diagnosed as having rectovaginal endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

30. A method of reducing dyspareunia in a human patient diagnosed as having rectovaginal endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

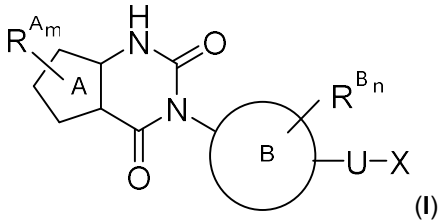
31. A method of reducing dyschezia in a human patient diagnosed as having rectovaginal endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.

32. A method of reducing uterine bleeding in a human patient diagnosed as having rectovaginal endometriosis, the method comprising periodically administering to the patient a therapeutically effective

~~amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.~~

~~33. A method of inducing amenorrhea in a human patient diagnosed as having rectovaginal endometriosis, the method comprising periodically administering to the patient a therapeutically effective amount of a GnRH antagonist over the course of a treatment period having a duration of at least 52 weeks.~~

~~34.~~3. The ~~method~~ use of ~~any one of~~ claims ~~1~~ 1 or 2~~-33~~, wherein the GnRH antagonist is a compound represented by formula (**I**)



(**I**)

wherein ring A is a thiophene ring;

each R^A is independently a halogen atom, a cyano group, a nitro group, an optionally substituted lower alkyl group, an optionally substituted lower alkenyl group, an optionally substituted lower alkynyl group, a hydroxyiminomethyl group, an optionally substituted sulfonyl group, an optionally substituted sulfinyl group, a tetrazolyl group, OW^1, SW^1, COW^1, $COOW^1$, $NHCOW^1$, $NHCONW^2W^3$, NW^2W^3, $CONW^2W^3$, or $SO_2NW^2W^3$, wherein W^1 to W^3 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^2 and W^3 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group;

m is an integer from 0 to 3;

ring B is an aryl group or a monocyclic heteroaryl group;

each R^B is independently a halogen atom, a cyano group, an optionally substituted lower alkyl group, OW^4, COW^4, $COOW^4$, or $CONW^5W^6$, wherein W^4 to W^6 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^5 and W^6 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group;

n is an integer from 0 to 2;

U is a single bond;

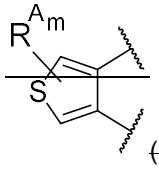
X is a group represented by —S—L—Y, —O—L—Y, —CO—L—Y, or —SO_2—L—Y, wherein L is an optionally substituted lower alkylene group;

Y is a group represented by Z or —NW^7W^8, wherein W^7 and W^8 independently are a hydrogen atom, an optionally substituted lower alkyl group, or Z with the proviso that W^7 and W^8 are not simultaneously hydrogen atoms, or W^7 and W^8 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group; and

Z is an optionally fused and optionally substituted cycloalkyl group, an optionally fused and optionally substituted heterocycloalkyl group, an optionally fused and optionally substituted aryl group, or an optionally fused and optionally substituted heteroaryl group;

or a pharmaceutically acceptable salt thereof.

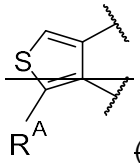
35. The method of claim 34, wherein the ring A is a thiophene ring represented by formula (**IIa**)



(**IIa**).

36. The method of claim 34 or 35, wherein m is 1.

37. The method of claim 36, wherein the ring A is an optionally substituted thiophene ring represented by formula (**IIb**)



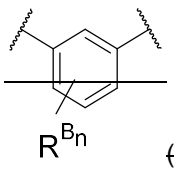
(**IIb**).

38. The method of any one of claims 34-37, wherein each R^A is independently a halogen atom, an optionally substituted lower alkyl group, $COOW^1$, or $CONW^2W^3$, wherein W^1 to W^3 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^2 and W^3 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group.

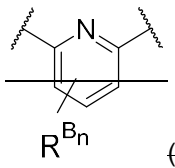
39. The method of claim 38, wherein each R^A is COOH or pharmaceutically acceptable salt thereof.

40. The method of any one of claims 34-39, wherein the ring B is an optionally substituted benzene ring, pyridine ring, or thiophene ring.

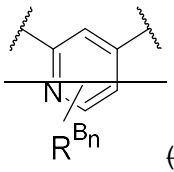
41. The method of claim 40, wherein the ring B is represented by a formula selected from the group consisting of:



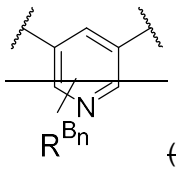
(**IIIa**);



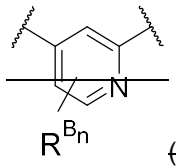
(**IIIb**);



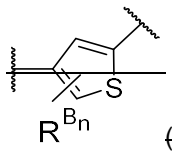
(**IIIc**);



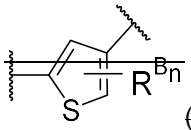
~~(IIId);~~



~~(IIIe);~~



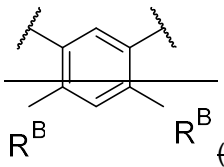
~~(IIIf); and~~



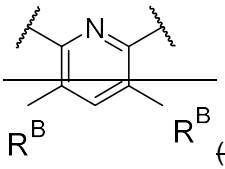
~~(IIIg).~~

~~42. The method of any one of claims 34-41, wherein n is 2.~~

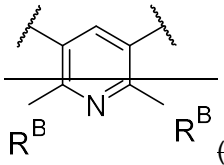
~~43. The method of claim 42, wherein the ring B is represented by a formula selected from the group consisting of:~~



~~(IVa);~~



~~(IVb); and~~



~~(IVc).~~

~~44. The method of any one of claims 34-43, wherein each R^B is independently a halogen atom, an optionally substituted lower alkyl group, or OW^4, wherein each W^4 is independently a hydrogen atom or an optionally substituted lower alkyl group.~~

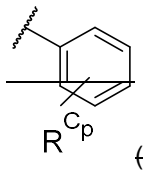
~~45. The method of claim 44, wherein each R^B is independently a fluorine atom, chlorine atom, bromine atom, methyl group, or methoxy group.~~

~~46. The method of any one of claims 34-45, wherein U is a single bond.~~

~~47. The method of any one of claims 34-46, wherein X is a group represented by —O—L—Y.~~

~~48. The method of any one of claims 34-47, wherein L is a methylene group.~~

~~49. The method of any one of claims 34-48, wherein Y is an optionally substituted benzene ring represented by formula (**V**)~~

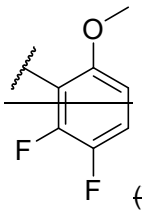


~~(**V**)~~

~~wherein each R^C is independently a halogen atom, an optionally substituted lower alkyl group, or OW^9, wherein each W^9 is independently a hydrogen atom or an optionally substituted lower alkyl group; and~~

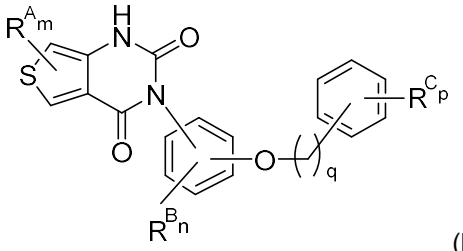
~~p is an integer from 0 to 3.~~

~~50. The method of claim 49, wherein Y is a substituted benzene ring represented by formula (**Va**)~~



~~(**Va**).~~

~~51.~~4. The ~~method~~ use of claim 34, wherein the compound is represented by formula (**Ia**)



(**Ia**)

wherein each R^A is independently a halogen atom, a cyano group, a nitro group, an optionally substituted lower alkyl group, an optionally substituted lower alkenyl group, an optionally substituted lower alkynyl group, a hydroxyiminomethyl group, an optionally substituted sulfonyl group, an optionally substituted sulfinyl group, a tetrazolyl group, OW^1, SW^1, COW^1, $COOW^1$, $NHCOW^1$, $NHCONW^2W^3$, NW^2W^3, $CONW^2W^3$, or $SO_2NW^2W^3$, wherein W^1 to W^3 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^2 and W^3 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group;

m is an integer from 0 to 3;

each R^B is independently a halogen atom, a cyano group, an optionally substituted lower alkyl

group, OW^4, COW^4, $COOW^4$, or $CONW^5W^6$, wherein W^4 to W^6 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^5 and W^6 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group;

n is an integer from 0 to 2;

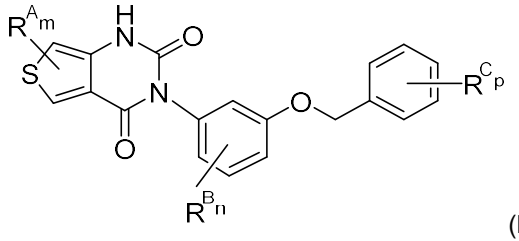
q is an integer from 0 to 3;

each R^C is independently a halogen atom, an optionally substituted lower alkyl group, or OW^9, wherein each W^9 is independently a hydrogen atom or an optionally substituted lower alkyl group; and

p is an integer from 0 to 3;

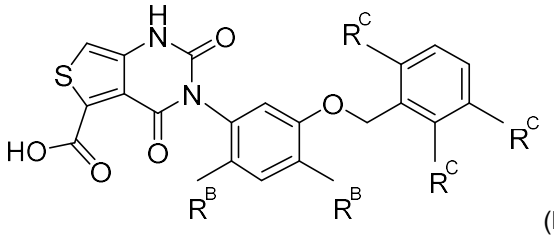
or a pharmaceutically acceptable salt thereof.

~~52.~~5. The ~~method~~ use of claim 4~~35~~, wherein the compound is represented by formula (**Ib**)



(**Ib**).

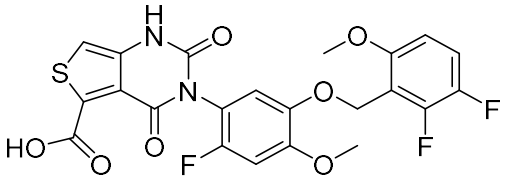
~~53.~~6. The ~~method~~ use of claim 5~~36~~, wherein the compound is represented by formula (**Ic**)



(**Ic**)

or a pharmaceutically acceptable salt thereof.

~~54.~~7. The ~~method~~ use of claim ~~any one of claims 34-53~~6, wherein the compound is represented by formula (**VI**)



(**VI**)

or a pharmaceutically acceptable salt thereof.

~~55.~~8. The ~~method~~ use of claim ~~54~~7, wherein the compound is the choline salt of the compound represented by formula (**VI**).

~~56. The method of claim 55, wherein the compound is in a crystalline state.~~

57. The method of claim 56, wherein the compound exhibits characteristic X-ray powder diffraction (XRPD) peaks at about 7.1° 2θ, about 11.5° 2θ, about 19.4° 2θ, about 21.5° 2θ, about 22.0° 2θ, about 22.6° 2θ, about 23.5° 2θ, and about 26.2° 2θ.

58. The method of claim 56 or 57, wherein the compound exhibits ^{13}C solid-state nuclear magnetic resonance (NMR) peaks centered at about 55.5 ppm, about 57.1 ppm, about 58.7 ppm, about 69.8 ppm, about 98.1 ppm, about 110.3 ppm, about 111.6 ppm, about 113.7 ppm, about 118.0 ppm, about 145.3 ppm, about 149.8 ppm, and about 155.8 ppm.

59. The method of any one of claims 56-58, wherein the compound exhibits ^{19}F solid-state NMR peaks centered at about -151.8 ppm, -145.2 ppm, and -131.6 ppm.

60. The method of any one of claims 34-59, wherein the compound is orally administered to the patient.

61. The method of any one of claims 34-60, wherein the compound is administered to the patient one or more times per day, week, or month during the treatment period.

62. The method of claim 61, wherein the compound is administered to the patient one or more times daily during the treatment period.

63. The method of claim 62, wherein the compound is administered to the patient once daily during the treatment period.

64. The method of any one of claims 61-63, wherein the compound is administered to the patient in an amount of from about 25 mg per day to about 400 mg per day during the treatment period.

65. The method of claim 64, wherein the compound is administered to the patient in an amount of from about 35 mg to about 65 mg per day during the treatment period.

66. The method of claim 65, wherein the compound is administered to the patient in an amount of about 50 mg per day during the treatment period.

67. The method of claim 64, wherein the compound is administered to the patient in an amount of from about 60 mg per day to about 90 mg per day during the treatment period.

68. The method of claim 67, wherein the compound is administered to the patient in an amount of about 75 mg per day during the treatment period.

69. The method of claim 64, wherein the compound is administered to the patient in an amount of from about 85 mg to about 115 mg per day during the treatment period.

70. The method of claim 69, wherein the compound is administered to the patient in an amount of about 100 mg per day during the treatment period.

71. The method of claim 64, wherein the compound is administered to the patient in an amount of from about 185 mg to about 215 mg per day during the treatment period.

72. The method of claim 71, wherein the compound is administered to the patient in an amount of about 200 mg per day during the treatment period.

73. The method of any one of claims 1-33, wherein the GnRH antagonist is elagolix, relugolix, opigolix (ASP1707), BAY-784, or SK-2706.

74. The method of claim 73, wherein the GnRH antagonist is elagolix.

75. The method of claim 74, wherein the GnRH antagonist is orally administered to the patient.

76. The method of claim 74 or 75, wherein the GnRH antagonist is administered to the patient one or more times per day, week, or month during the treatment period.

77. The method of claim 76, wherein the GnRH antagonist is administered to the patient one or more times daily during the treatment period.

78. The method of claim 77, wherein the GnRH antagonist is administered to the patient once daily during the treatment period.

79. The method of any one of claims 74-78, wherein the GnRH antagonist is administered to the patient in an amount of from about 100 mg to about 600 mg per day during the treatment period.

80. The method of claim 79, wherein the GnRH antagonist is administered to the patient in an amount of about 150 mg per day during the treatment period.

81. The method of claim 79, wherein the GnRH antagonist is administered to the patient in an amount of about 300 mg per day during the treatment period.

82. The method of claim 79, wherein the GnRH antagonist is administered to the patient in an amount of about 400 mg per day during the treatment period, optionally wherein the GnRH antagonist is administered to the patient in two daily doses of 200 mg per dose during the treatment period.

83. The method of claim 79, wherein the GnRH antagonist is administered to the patient in an amount of about 600 mg per day during the treatment period, optionally wherein the GnRH antagonist is administered to the patient in two daily doses of 300 mg per dose during the treatment period.

84. The method of claim 73, wherein the GnRH antagonist is relugolix.

85. The method of claim 84, wherein the GnRH antagonist is orally administered to the patient.

86. The method of claim 84 or 85, wherein the GnRH antagonist is administered to the patient one or more times per day, week, or month during the treatment period.

87. The method of claim 86, wherein the GnRH antagonist is administered to the patient one or more times daily during the treatment period.

88. The method of claim 87, wherein the GnRH antagonist is administered to the patient once daily during the treatment period.

~~89. The method of any one of claims 84-88, wherein the GnRH antagonist is administered to the patient in an amount of from about 10 mg to about 60 mg per day during the treatment period.~~

~~90. The method of claim 89, wherein the GnRH antagonist is administered to the patient in an amount of from about 20 mg to about 50 mg per day during the treatment period.~~

~~91. The method of claim 90, wherein the GnRH antagonist is administered to the patient in an amount of about 40 mg per day during the treatment period.~~

~~92. The method of any one of claims 1-91, wherein the treatment period has a duration of at least 13 months.~~

~~93. The method of claim 92, wherein the treatment period has a duration of at least 14 months.~~

~~94. The method of claim 93, wherein the treatment period has a duration of at least 15 months.~~

~~95. The method of claim 94, wherein the treatment period has a duration of at least 16 months.~~

~~96. The method of claim 95, wherein the treatment period has a duration of at least 17 months.~~

~~97. The method of claim 96, wherein the treatment period has a duration of at least 18 months.~~

~~98. The method of claim 97, wherein the treatment period has a duration of at least 19 months.~~

~~99. The method of claim 98, wherein the treatment period has a duration of at least 20 months.~~

~~100. The method of claim 99, wherein the treatment period has a duration of at least 21 months.~~

~~101. The method of claim 100, wherein the treatment period has a duration of at least 22 months.~~

~~102. The method of claim 101, wherein the treatment period has a duration of at least 23 months.~~

~~103. The method of claim 102, wherein the treatment period has a duration of at least 24 months.~~

~~104. The method of any one of claims 1-91, wherein the treatment period has a duration of from about 12 months to about 60 months.~~

~~105. The method of claim 104, wherein the treatment period has a duration of from about 12 months to about 48 months.~~

~~106. The method of claim 105, wherein the treatment period has a duration of from about 12 months to about 36 months.~~

~~107. The method of claim 106, wherein the treatment period has a duration of from about 12 months to about 24 months.~~

~~108. The method of any one of claims 1-91, wherein the treatment period has a duration of about 12 months.~~

~~109. The method of any one of claims 1-91, wherein the treatment period has a duration of about 18 months.~~

~~110. The method of any one of claims 1-91, wherein the treatment period has a duration of about 24 months.~~

~~111. The method of any one of claims 1-91, wherein the treatment period has a duration of about 30 months.~~

~~112. The method of any one of claims 1-91, wherein the treatment period has a duration of about 36 months.~~

~~113. The method of any one of claims 1-91, wherein the treatment period has a duration of about 42 months.~~

~~114. The method of any one of claims 1-91, wherein the treatment period has a duration of about 48 months.~~

~~115. The method of any one of claims 1-91, wherein the treatment period has a duration of about 54 months.~~

~~116. The method of any one of claims 1-91, wherein the treatment period has a duration of about 60 months.~~

~~117. The method of any one of claims 1-116, wherein add-back therapy is periodically administered to the patient during the treatment period.~~

~~118. The method of claim 117, wherein the add-back therapy is administered to the patient one or more times daily during the treatment period.~~

~~119. The method of claim 118, wherein the add-back therapy is administered to the patient once daily, concurrently with the GnRH antagonist, during the treatment period.~~

~~120. The method of claim 118, wherein the add-back therapy is administered to the patient once daily, prior to administration of the GnRH antagonist, during the treatment period.~~

~~121. The method of claim 118, wherein the add-back therapy is administered to the patient once daily, following administration of the GnRH antagonist, during the treatment period.~~

~~122. The method of claim 121, wherein the add-back therapy is administered to the patient in the form of a pharmaceutical composition comprising the GnRH antagonist.~~

~~123. The method of any one of claims 117-122, wherein the add-back therapy comprises an estrogen.~~

~~124. The method of claim 123, wherein the estrogen is selected from the group consisting of β17-estradiol, ethinyl estradiol, and conjugated estrogens.~~

~~125. The method of claim 124, wherein the estrogen is β17-estradiol.~~

126. The method of claim 125, wherein the β17-estradiol is administered to the patient in an amount of about 1.0 mg/day during the treatment period.

127. The method of claim 125, wherein the β17-estradiol is administered to the patient in an amount of about 0.5 mg/day during the treatment period.

128. The method of claim 124, wherein the estrogen is ethinyl estradiol.

129. The method of claim 128, wherein the ethinyl estradiol is administered to the patient in an amount of about 5.0 µg/day during the treatment period.

130. The method of claim 128, wherein the ethinyl estradiol is administered to the patient in an amount of about 2.5 µg/day during the treatment period.

131. The method of claim 124, wherein the estrogen is a conjugated estrogen.

132. The method of claim 131, wherein the conjugated estrogen is administered to the patient in an amount of about 0.625 mg/day during the treatment period.

133. The method of claim 131, wherein the conjugated estrogen is administered to the patient in an amount of about 0.45 mg/day during the treatment period.

134. The method of claim 131, wherein the conjugated estrogen is administered to the patient in an amount of about 0.3 mg/day during the treatment period.

135. The method of any one of claims 117-134, wherein the add-back therapy comprises a progestin.

136. The method of claim 135, wherein the progestin is selected from the group consisting of norethindrone or an ester thereof, progesterone, norgestimate, medroxyprogesterone, and drospirenone.

137. The method of claim 136, wherein the progestin is norethindrone or norethindrone acetate.

138. The method of claim 137, wherein the norethindrone or norethindrone acetate is administered to the patient in an amount of about 1.0 mg/day during the treatment period.

139. The method of claim 137, wherein the norethindrone or norethindrone acetate is administered to the patient in an amount of about 0.5 mg/day during the treatment period.

140. The method of claim 137, wherein the norethindrone or norethindrone acetate is administered to the patient in an amount of about 0.1 mg/day during the treatment period.

141. The method of claim 136, wherein the progestin is progesterone.

142. The method of claim 141, wherein the progesterone is administered to the patient in an amount of about 200 mg/day during the treatment period.

143. The method of claim 141, wherein the progesterone is administered to the patient in an amount of about 100 mg/day during the treatment period.

144. The method of claim 136, wherein the progestin is norgestimate.

145. The method of claim 144, wherein the norgestimate is administered to the patient in an amount of about 0.09 mg/day during the treatment period.

146. The method of claim 136, wherein the progestin is medroxyprogesterone.

147. The method of claim 146, wherein the medroxyprogesterone is administered to the patient in an amount of about 5 mg/day during the treatment period.

148. The method of claim 146, wherein the medroxyprogesterone is administered to the patient in an amount of about 2.5 mg/day during the treatment period.

149. The method of claim 146, wherein the medroxyprogesterone is administered to the patient in an amount of about 1.5 mg/day during the treatment period.

150. The method of claim 136, wherein the progestin is drospirenone.

151. The method of claim 150, wherein the drospirenone is administered to the patient in an amount of about 0.5 mg/day during the treatment period.

152. The method of claim 150, wherein the drospirenone is administered to the patient in an amount of about 0.25 mg/day during the treatment period.

153. The method of any one of claims 117-152, wherein the add-back therapy comprises about 1.0 mg of β17-estradiol and about 0.5 mg of norethindrone acetate.

154. The method of any one of claims 117-152, wherein the add-back therapy comprises about 0.5 mg of β17-estradiol and about 0.1 mg of norethindrone acetate.

155. The method of any one of claims 1-154, wherein the patient is a pre-menopausal female of from about 18 to about 48 years of age.

156. The method of any one of claims 1-155, wherein the patient has been determined to exhibit a serum concentration of follicle-stimulating hormone (FSH) of about 20 IU/L or less prior to administration of the GnRH antagonist to the patient.

157. The method of any one of claims 1-156, wherein the patient has been determined to exhibit a rectal (type II) and/or vaginal (type III) endometriosis node of at least 2 cm prior to administration of the GnRH antagonist to the patient.

158. The method of claim 157, wherein the length of the type II and/or type III endometriosis node is assessed by way of magnetic resonance imaging (MRI).

159. The method of any one of claims 1-158, wherein the patient has been determined to exhibit a junctional-zone width of about 12 mm or more prior to administration of the GnRH antagonist to the patient.

160. The method of claim 159, wherein the junctional-zone width is assessed by way of MRI.

161. The method of any one of claims 1-160, wherein the patient exhibits a reduction in serum concentration of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and/or β17-estradiol (E2) following administration of the GnRH antagonist to the patient.

162. The method of claim 161, wherein the patient exhibits the reduction in serum concentration of LH, FSH, and/or E2 within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

163. The method of any one of claims 1, 2, 5-12, 15-22, 25-31, and 34-162, wherein the patient exhibits a reduction in uterine bleeding following administration of the GnRH antagonist to the patient.

164. The method of any one of claims and 3, 13, 23, 32, and 163, wherein the patient exhibits the reduction in uterine bleeding within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

165. The method of any one of claims 3, 13, 23, 32, 163, and 164, wherein the reduction in uterine bleeding is assessed by way of an alkaline hematin method.

166. The method of any one of claims 1-3, 5-13, 15-23, 25-32, and 34-165, wherein the patient exhibits amenorrhea following administration of the GnRH antagonist to the patient.

167. The method of any one of claims 4, 14, 24, 33, and 166, wherein the patient exhibits the amenorrhea within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

168. The method of any one of claims 1-7, 9-25, and 28-167, wherein the patient exhibits a reduction in the volume of one or more rectovaginal endometriosis nodes following administration of the GnRH antagonist to the patient.

169. The method of any one of claims 8, 26, 27, and 168, wherein the patient exhibits the reduction in volume of the one or more rectovaginal endometriosis nodes within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

170. The method of any one of claims 8, 26, 27, 168, and 169, wherein the reduction in volume of the one or more rectovaginal endometriosis nodes is assessed by way of MRI or TVUS.

171. The method of any one of claims 1-170, wherein the patient exhibits a reduction in bowel involvement of one or more type III endometriosis nodes following administration of the GnRH antagonist to the patient.

172. The method of claim 171, wherein the patient exhibits the reduction in bowel involvement of the one or more type III endometriosis nodes within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

173. The method of any one of claims 1-8, 10-17, 19-27, and 29-172, wherein the patient exhibits a reduction in pelvic pain following administration of the GnRH antagonist to the patient.

174. The method of any one of claims 9, 18, 28, and 173, wherein the patient exhibits the reduction in pelvic pain within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

175. The method of any one of claims 9, 18, 28, 173, and 174, wherein the reduction in pelvic pain is assessed by way of a modified Biberoglu & Behrman (mB&B) score, Numerical Rating Scale (NRS) score, or Verbal Rating Scale (VRS) score.

176. The method of any one of claims 1-9, 11-18, 20-28, and 39-175, wherein the patient exhibits a reduction in dysmenorrhea following administration of the GnRH antagonist to the patient.

177. The method of any one of claims 10, 19, 29, and 176, wherein the patient exhibits the reduction in dysmenorrhea within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

178. The method of any one of claims 10, 19, 29, 176, and 177, wherein the reduction in dysmenorrhea is assessed by way of an mB&B score, NRS score, or VRS score.

179. The method of any one of claims 1-10, 12-19, 21-29, and 31-178, wherein the patient exhibits a reduction in dyspareunia following administration of the GnRH antagonist to the patient.

180. The method of any one of claims 11, 20, 30, and 179, wherein the patient exhibits the reduction in dyspareunia within from about one day to about 36 weeks commencement of the onset of administration of the GnRH antagonist to the patient.

181. The method of any one of claims 11, 20, 30, 179, and 180, wherein the reduction in dyspareunia is assessed by way of an mB&B score, NRS score, or VRS score.

182. The method of any one of claims 1-11, 13-20, 22-30, and 32-181, wherein the patient exhibits a reduction in dyschezia following administration of the GnRH antagonist to the patient.

183. The method of any one of claims 12, 21, 31, and 182, wherein the patient exhibits the reduction in dyschezia within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

184. The method of any one of claims 12, 21, 31, 182, and 183, wherein the reduction in dyschezia is assessed by way of an mB&B score, NRS score, or VRS score.

185. The method of any one of claims 1-15 and 17-184, wherein the patient exhibits a reduction in uterine volume following administration of the GnRH antagonist to the patient.

186. The method of any one of claims 16 and 185, wherein the patient exhibits the reduction in uterine volume within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

187. The method of any one of claims 16, 185, and 186, wherein the reduction in uterine volume is assessed by way of MRI or transvaginal ultrasound (TVUS).

188. The method of any one of claims 1-16 and 18-187, wherein the patient exhibits a reduction in the thickness of the anterior and/or posterior region of the uterine myometrium following administration of the GnRH antagonist to the patient.

189. The method of any one of claims 17 and 188, wherein the patient exhibits the reduction in thickness of the anterior and/or posterior region of the uterine myometrium within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

190. The method of any one of claims 1-21 and 23-189, wherein the patient exhibits a reduction in uterine tenderness following administration of the GnRH antagonist to the patient.

191. The method of any one of claims 22 and 190, wherein the patient exhibits the reduction in uterine tenderness within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

192. The method of any one of claims 1-191, wherein the patient exhibits a reduction in the diameter of a junctional zone of adenomyosis following administration of the GnRH antagonist to the patient.

193. The method of claim 192, wherein the patient exhibits the reduction in the diameter of the junctional zone of adenomyosis within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

194. The method of any one of claims 1-193, wherein the patient exhibits an improvement in Endometriosis Health Profile questionnaire (EHP-30) score following administration of the GnRH antagonist to the patient.

195. The method of claim 194, wherein the patient exhibits the improvement in the EHP-30 score within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

196. The method of any one of claims 1-195, wherein the patient exhibits a positive Patient Global Impression of Change (PGIC) score core following administration of the GnRH antagonist to the patient.

197. The method of claim 196, wherein the patient exhibits the positive PGIC score within from about one day to about 36 weeks of the onset of administration of the GnRH antagonist to the patient.

198. The method of any one of claims 1-197, the method further comprising monitoring the patient's bone mineral density (BMD) at the end of the treatment period.

199. The method of claim 198, the method further comprising determining that the patient does not exhibit a reduction in BMD of greater than 5% at the end of the treatment period relative to a measurement of the patient's BMD obtained prior to, or during, the treatment period.

200. The method of any one of claims 1-199, wherein the patient does not exhibit a reduction in BMD of greater than 5% at the end of the treatment period relative to a measurement of the patient's BMD obtained prior to, or during, the treatment period.

201. The method of claim 200, wherein the patient does not exhibit a reduction in BMD of greater than 4% at the end of the treatment period relative to a measurement of the patient's BMD obtained prior to, or during, the treatment period.

202. The method of claim 201, wherein the patient does not exhibit a reduction in BMD of greater than 3% at the end of the treatment period relative to a measurement of the patient's BMD obtained prior to, or during, the treatment period.

203. The method of claim 202, wherein the patient does not exhibit a reduction in BMD of greater than 2% at the end of the treatment period relative to a measurement of the patient's BMD obtained prior to, or during, the treatment period.

204. The method of claim 203, wherein the patient does not exhibit a reduction in BMD of greater than 1% at the end of the treatment period relative to a measurement of the patient's BMD obtained prior to, or during, the treatment period.

205. The method of any one of claims 198-204, wherein the BMD is assessed by dual energy X-ray absorptiometry.

206. The method of claim 205, wherein the BMD is assessed in the spine or femur of the patient.

207. The method of any one of claims 198-204, wherein the BMD is assessed by comparing the concentration of bone specific alkaline phosphatase (BAP) in a sample isolated from the patient following the administration of the GnRH antagonist to the concentration of BAP in a sample isolated from the patient prior to the administration of the GnRH antagonist.

208. The method of any one of claims 198-204, wherein the BMD is assessed by comparing the concentration of deoxypyridinoline (DPD) in a sample isolated from the patient following the administration of the GnRH antagonist to the concentration of DPD in a sample isolated from the patient prior to the administration of the GnRH antagonist.

209. The method of any one of claims 198-204, wherein the BMD is assessed by comparing the concentration of type I collagen C-terminal telopeptide (CTX) in a sample isolated from the patient following the administration of the GnRH antagonist to the concentration of CTX in a sample isolated from the patient prior to the administration of the GnRH antagonist.

210. The method of any one of claims 198-204, wherein the BMD is assessed by comparing the concentration of procollagen 1 N-terminal peptide (P1NP) in a sample isolated from the patient following the administration of the GnRH antagonist to the concentration of P1NP in a sample isolated from the patient prior to the administration of the GnRH antagonist.

211. The method of any one of claims 1-210, wherein the patient does not exhibit an increase in total cholesterol level of greater than 10% after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period relative to a measurement of the patient's total cholesterol level obtained prior to the treatment period.

~~212. The method of any one of claims 1-211, wherein the patient does not exhibit an increase in low-density lipoprotein-cholesterol level of greater than 10% after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period relative to a measurement of the patient's low-density lipoprotein-cholesterol level obtained prior to the treatment period.~~

~~213. The method of any one of claims 1-212, wherein the patient does not exhibit an increase in their ratio of low-density lipoprotein-cholesterol to high-density lipoprotein-cholesterol of greater than 10% after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period relative to a measurement of the patient's ratio of low-density lipoprotein-cholesterol to high-density lipoprotein-cholesterol obtained prior to the treatment period.~~

~~214. The method of any one of claims 1-213, wherein the patient does not exhibit an increase in low-density lipoprotein-cholesterol level to a level greater than 160 mg/dl after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period.~~

~~215. The method of any one of claims 1-214, wherein the patient does not exhibit an increase in low-density lipoprotein-cholesterol level from a level less than 160 mg/dl (e.g., from a level less than 130 mg/dl) to a level greater than 190 mg/dl after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period.~~

~~216. The method of any one of claims 1-215, wherein the patient does not exhibit an increase in serum triglyceride level of greater than 30% after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period relative to a measurement of the patient's serum triglyceride level obtained prior to the treatment period.~~

~~217. The method of any one of claims 1-216, wherein the patient does not exhibit an increase in serum triglyceride level to a level greater than 200 mg/dl after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period.~~

~~218. The method of any one of claims 1-217, wherein the patient does not exhibit an increase in serum triglyceride level from a level less than 300 mg/dl to a level greater than 500 mg/dl after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period.~~

~~219.~~9. The ~~method~~ use of any one of claims 1-~~218~~, the method comprising:

a) monitoring the patient's total cholesterol level after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period;

b) determining that the patient does not exhibit an increase in total cholesterol level of greater than 10% relative to a measurement of the patient's total cholesterol level obtained prior to the treatment period; and

c) continuing to administer the GnRH antagonist to the patient for the remainder of the treatment period.

~~220.~~10. The ~~method~~ use of any one of claims 1-~~219~~, the method comprising:

a) monitoring the patient's low-density lipoprotein-cholesterol level after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period;

b) determining that the patient does not exhibit an increase in low-density lipoprotein-cholesterol level of greater than 10% relative to a measurement of the patient's low-density lipoprotein-cholesterol level obtained prior to the treatment period; and

c) continuing to administer the GnRH antagonist to the patient for the remainder of the treatment period.

~~221.~~11. The ~~method~~ use of any one of claims 1-~~220~~10, the method comprising:

a) monitoring the patient's ratio of low-density lipoprotein-cholesterol to high-density lipoprotein-cholesterol after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period;

b) determining that the patient does not exhibit an increase in their ratio of low-density lipoprotein-cholesterol to high-density lipoprotein-cholesterol of greater than 10% relative to a measurement of the patient's ratio of low-density lipoprotein-cholesterol to high-density lipoprotein-cholesterol obtained prior to the treatment period; and

c) continuing to administer the GnRH antagonist to the patient for the remainder of the treatment period.

~~222.~~12. The ~~method~~ use of any one of claims 1-~~221~~11, the method comprising:

a) monitoring the patient's low-density lipoprotein-cholesterol level after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period;

b) determining that the patient does not exhibit an increase in low-density lipoprotein-cholesterol level to a level greater than 160 mg/dl; and

c) continuing to administer the GnRH antagonist to the patient for the remainder of the treatment period.

~~223.~~13. The ~~method~~ use of any one of claims 1-~~222~~12, the method comprising:

a) monitoring the patient's low-density lipoprotein-cholesterol level after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period;

b) determining that the patient does not exhibit an increase in low-density lipoprotein-cholesterol level from a level less than 160 mg/dl (e.g., from a level less than 130 mg/dl) to a level greater than 190 mg/dl; and

c) continuing to administer the GnRH antagonist to the patient for the remainder of the treatment period.

~~224.~~14. The ~~method~~ use of any one of claims 1-~~223~~13, the method comprising:

a) monitoring the patient's serum triglyceride level after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period;

b) determining that the patient does not exhibit an increase in serum triglyceride level of greater than 30% relative to a measurement of the patient's serum triglyceride level obtained prior to the treatment period; and

c) continuing to administer the GnRH antagonist to the patient for the remainder of the treatment period.

~~225.~~15. The ~~method~~ use of any one of claims 1-~~224~~14, the method comprising:

a) monitoring the patient's serum triglyceride level after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period;

b) determining that the patient does not exhibit an increase in serum triglyceride level to a level greater than 200 mg/dl; and

c) continuing to administer the GnRH antagonist to the patient for the remainder of the treatment period.

~~226.~~16. The ~~method~~ use of any one of claims 1-~~224~~14, the method comprising:

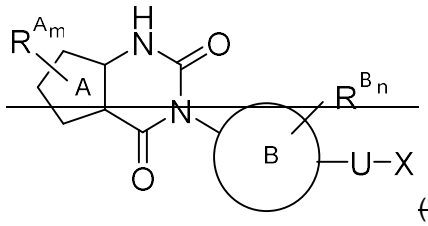
a) monitoring the patient's serum triglyceride level after from about 6 weeks to about 52 weeks of being administered the GnRH antagonist during the treatment period;

b) determining that the patient does not exhibit an increase in serum triglyceride level from a level less than 300 mg/dl to a level greater than 500 mg/dl; and

c) continuing to administer the GnRH antagonist to the patient for the remainder of the treatment period.

~~227. A kit comprising a GnRH antagonist and a package insert instructing a user of the kit to administer the GnRH antagonist to a human patient in accordance with the method of any one of claims 1-226.~~

~~228. The kit of claim 227, wherein the GnRH antagonist is a compound represented by formula (I)~~



~~(I)~~

~~wherein ring A is a thiophene ring;~~

~~each R^A is independently a halogen atom, a cyano group, a nitro group, an optionally substituted lower alkyl group, an optionally substituted lower alkenyl group, an optionally substituted lower alkynyl group, a hydroxyiminomethyl group, an optionally substituted sulfonyl group, an optionally substituted sulfinyl group, a tetrazolyl group, OW^1, SW^1, COW^1, $COOW^1$, $NHCOW^1$, $NHCONW^2W^3$, NW^2W^3, $CONW^2W^3$, or $SO_2NW^2W^3$, wherein W^1 to W^3 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^2 and W^3 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group;~~

~~m is an integer from 0 to 3;~~

~~ring B is an aryl group or a monocyclic heteroaryl group;~~

~~each R^B is independently a halogen atom, a cyano group, an optionally substituted lower alkyl group, OW^4, COW^4, $COOW^4$, or $CONW^5W^6$, wherein W^4 to W^6 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^5 and W^6 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group;~~

~~n is an integer from 0 to 2;~~

~~U is a single bond;~~

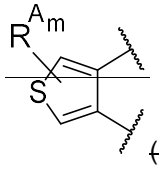
X is a group represented by —S—L—Y, —O—L—Y, —CO—L—Y, or —SO_2—L—Y, wherein L is an optionally substituted lower alkylene group;

Y is a group represented by Z or —NW^7W^8, wherein W^7 and W^8 independently are a hydrogen atom, an optionally substituted lower alkyl group, or Z with the proviso that W^7 and W^8 are not simultaneously hydrogen atoms, or W^7 and W^8 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group; and

Z is an optionally fused and optionally substituted cycloalkyl group, an optionally fused and optionally substituted heterocycloalkyl group, an optionally fused and optionally substituted aryl group, or an optionally fused and optionally substituted heteroaryl group;

or a pharmaceutically acceptable salt thereof.

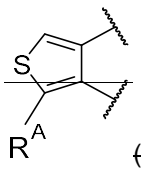
229. The kit of claim 228, wherein the ring A is a thiophene ring represented by formula (**IIa**)



(**IIa**).

230. The kit of claim 228 or 229, wherein m is 1.

231. The kit of claim 230, wherein the ring A is an optionally substituted thiophene ring represented by formula (**IIb**)



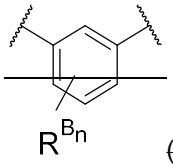
(**IIb**).

232. The kit of any one of claims 228-231, wherein each R^A is independently a halogen atom, an optionally substituted lower alkyl group, $COOW^1$, or $CONW^2W^3$, wherein W^1 to W^3 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^2 and W^3 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group.

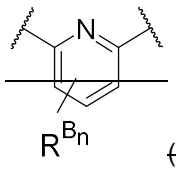
233. The kit of claim 232, wherein each R^A is COOH or pharmaceutically acceptable salt thereof.

234. The kit of any one of claims 228-233, wherein the ring B is an optionally substituted benzene ring, pyridine ring, or thiophene ring.

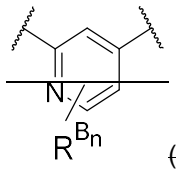
235. The kit of claim 234, wherein the ring B is represented by a formula selected from the group consisting of:



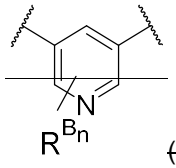
(**IIIa**);



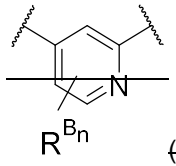
(~~IIIb~~);



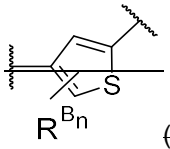
(~~IIIc~~);



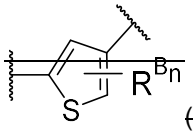
(~~IIId~~);



(~~IIIe~~);



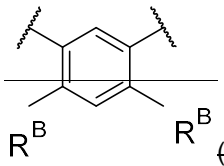
(~~IIIf~~); and



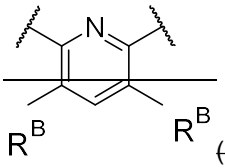
(~~IIIg~~).

~~236. The kit of any one of claims 228-235, wherein n is 2.~~

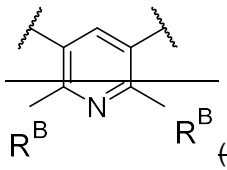
~~237. The kit of claim 236, wherein ring B is represented by a formula selected from the group consisting of:~~



(~~IVa~~);



(~~IVb~~); and



(**IVc**).

238. The kit of any one of claims 228-237, wherein each R^B is independently a halogen atom, an optionally substituted lower alkyl group, or OW^4, wherein each W^4 is independently a hydrogen atom or an optionally substituted lower alkyl group.

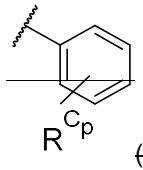
239. The kit of claim 238, wherein each R^B is independently a fluorine atom, chlorine atom, bromine atom, methyl group, or methoxy group.

240. The kit of any one of claims 228-239, wherein U is a single bond.

241. The kit of any one of claims 228-240, wherein X is a group represented by —O—L—Y.

242. The kit of any one of claims 228-241, wherein L is a methylene group.

243. The kit of any one of claims 228-242, wherein Y is an optionally substituted benzene ring represented by formula (**V**)

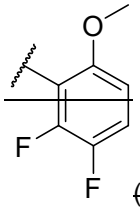


(**V**)

wherein each R^C is independently a halogen atom, an optionally substituted lower alkyl group, or OW^9, wherein each W^9 is independently a hydrogen atom or an optionally substituted lower alkyl group; and

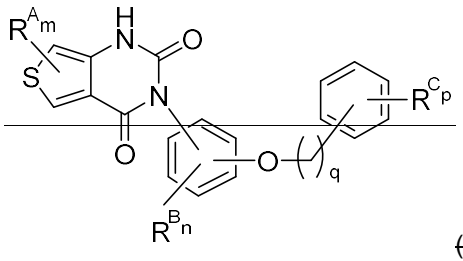
p is an integer from 0 to 3.

244. The kit of claim 243, wherein Y is a substituted benzene ring represented by formula (**Va**)



(**Va**).

245. The kit of claim 228, wherein the compound is represented by formula (**Ia**)



~~(Ia)~~

~~wherein each R^A is independently a halogen atom, a cyano group, a nitro group, an optionally substituted lower alkyl group, an optionally substituted lower alkenyl group, an optionally substituted lower alkynyl group, a hydroxyiminomethyl group, an optionally substituted sulfonyl group, an optionally substituted sulfinyl group, a tetrazolyl group, OW^1, SW^1, COW^1, $COOW^1$, $NHCOW^1$, $NHCONW^2W^3$, NW^2W^3, $CONW^2W^3$, or $SO_2NW^2W^3$, wherein W^1 to W^3 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^2 and W^3 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group;~~

~~m is an integer from 0 to 3;~~

~~each R^B is independently a halogen atom, a cyano group, an optionally substituted lower alkyl group, OW^4, COW^4, $COOW^4$, or $CONW^5W^6$, wherein W^4 to W^6 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^5 and W^6 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group;~~

~~n is an integer from 0 to 2;~~

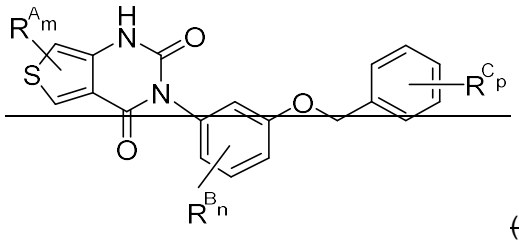
~~q is an integer from 0 to 3;~~

~~each R^C is independently a halogen atom, an optionally substituted lower alkyl group, or OW^9, wherein each W^9 is independently a hydrogen atom or an optionally substituted lower alkyl group; and~~

~~p is an integer from 0 to 3;~~

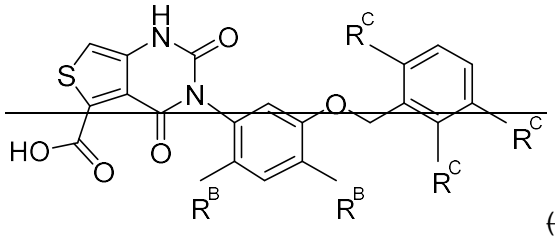
~~or a pharmaceutically acceptable salt thereof.~~

~~246. The kit of claim 245, wherein the compound is represented by formula (**Ib**)~~



~~(Ib).~~

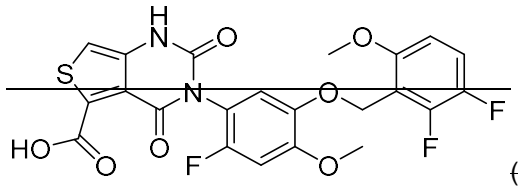
~~247. The kit of claim 246, wherein the compound is represented by formula (**Ic**)~~



~~(Ic)~~

~~or a pharmaceutically acceptable salt thereof.~~

~~248. The kit of any one of claims 228-247, wherein the compound is represented by formula (VI)~~



(~~VI~~)

~~or a pharmaceutically acceptable salt thereof.~~

~~249. The kit of claim 248, wherein the compound is the choline salt of the compound represented by formula (VI).~~

~~250. The kit of claim 227, wherein the GnRH antagonist is elagolix, relugolix, opigolix (ASP1707), BAY-784, or SK-2706.~~

~~251.~~17. ~~A method~~Use of a GnRH antagonist in the manufacture of a medicament for use in a method of treating an estrogen-dependent disease or alleviating one or more symptoms of an estrogen-dependent disease in a human patient in need thereof, the method comprising:

a) periodically administering to the patient a therapeutically effective amount of a GnRH antagonist during a treatment period,

b) determining that the patient does not exhibit a significant increase in total cholesterol level relative to a measurement of the patient's total cholesterol level obtained prior to the treatment period, optionally wherein the determining occurs from about 6 weeks to about 52 weeks after the onset of the treatment period, and

c) continuing to periodically administer the GnRH antagonist to the patient for the remainder of the treatment period.

~~252.~~18. ~~A~~ Use of a GnRH antagonist in the manufacture of a medicament for use in a method of treating an estrogen-dependent disease or alleviating one or more symptoms of an estrogen-dependent disease in a human patient in need thereof, the method comprising:

a) periodically administering to the patient a therapeutically effective amount of a GnRH antagonist during a treatment period,

b) determining that the patient does not exhibit a significant increase in low-density lipoprotein-cholesterol level relative to a measurement of the patient's low-density lipoprotein-cholesterol level obtained prior to the treatment period, optionally wherein the determining occurs from about 6 weeks to about 52 weeks after the onset of the treatment period, and

c) continuing to periodically administer the GnRH antagonist to the patient for the remainder of the treatment period.

~~253.~~19. Use of a GnRH antagonist in the manufacture of a medicament for use in a~~A~~ method of treating an estrogen-dependent disease or alleviating one or more symptoms of an estrogen-dependent disease in a human patient in need thereof, the method comprising:

a) periodically administering to the patient a therapeutically effective amount of a GnRH antagonist during a treatment period,

b) determining that the patient does not exhibit a significant increase in their ratio of ratio of low-density lipoprotein-cholesterol to high-density lipoprotein-cholesterol relative to a measurement of the patient's ratio of low-density lipoprotein-cholesterol to high-density lipoprotein-cholesterol obtained prior to the treatment period, optionally wherein the determining occurs from about 6 weeks to about 52 weeks after the onset of the treatment period, and

c) continuing to periodically administer the GnRH antagonist to the patient for the remainder of the treatment period.

~~254. A method of treating an estrogen-dependent disease or alleviating one or more symptoms of an estrogen-dependent disease in a human patient in need thereof, the method comprising:~~

~~a) periodically administering to the patient a therapeutically effective amount of a GnRH antagonist during a treatment period,~~

~~b) determining that the patient does not exhibit an increase in low-density lipoprotein-cholesterol level to a level greater than 160 mg/dl, optionally wherein the determining occurs from about 6 weeks to about 52 weeks after the onset of the treatment period, and~~

~~c) continuing to periodically administer the GnRH antagonist to the patient for the remainder of the treatment period.~~

~~255. A method of treating an estrogen-dependent disease or alleviating one or more symptoms of an estrogen-dependent disease in a human patient in need thereof, the method comprising:~~

~~a) periodically administering to the patient a therapeutically effective amount of a GnRH antagonist during a treatment period,~~

~~b) determining that the patient does not exhibit an increase in low-density lipoprotein-cholesterol level from a level less than 160 mg/dl (e.g., from a level less than 130 mg/dl) to a level greater than 190 mg/dl, optionally wherein the determining occurs from about 6 weeks to about 52 weeks after the onset of the treatment period, and~~

~~c) continuing to periodically administer the GnRH antagonist to the patient for the remainder of the treatment period.~~

~~256. A method of treating an estrogen-dependent disease or alleviating one or more symptoms of an estrogen-dependent disease in a human patient in need thereof, the method comprising:~~

~~a) periodically administering to the patient a therapeutically effective amount of a GnRH antagonist during a treatment period,~~

~~b) determining that the patient does not exhibit an increase in serum triglyceride level of greater than 30% relative to a measurement of the patient's serum triglyceride level obtained prior to the treatment period, optionally wherein the determining occurs from about 6 weeks to about 52 weeks after the onset of the treatment period, and~~

~~c) continuing to periodically administer the GnRH antagonist to the patient for the remainder of the treatment period.~~

~~257. A method of treating an estrogen-dependent disease or alleviating one or more symptoms of an estrogen-dependent disease in a human patient in need thereof, the method comprising:~~

~~a) periodically administering to the patient a therapeutically effective amount of a GnRH antagonist during a treatment period,~~

~~b) determining that the patient does not exhibit an increase in serum triglyceride level to a level greater than 200 mg/dl, optionally wherein the determining occurs from about 6 weeks to about 52 weeks after the onset of the treatment period, and~~

~~c) continuing to periodically administer the GnRH antagonist to the patient for the remainder of the treatment period.~~

~~258. A method of treating an estrogen-dependent disease in a human patient in need thereof, the method comprising:~~

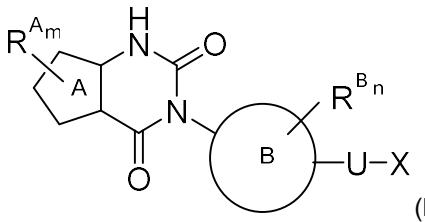
~~a) periodically administering to the patient a therapeutically effective amount of a GnRH antagonist during a treatment period,~~

~~b) determining that the patient does not exhibit an increase in serum triglyceride level from a level less than 300 mg/dl to a level greater than 500 mg/dl, optionally wherein the determining occurs from about 6 weeks to about 52 weeks after the onset of the treatment period, and~~

~~c) continuing to periodically administer the GnRH antagonist to the patient for the remainder of the treatment period.~~

~~259.~~20. The ~~method~~ use of any one of claims ~~251-258~~17-19, wherein the estrogen-dependent disease is uterine fibroids, or endometriosis, ~~adenomyosis, or rectovaginal endometriosis~~.

~~260.~~21. The ~~method~~ use of any one of claims ~~251-259~~17-20, wherein the GnRH antagonist is a compound represented by formula (**I**)



(**I**)

wherein ring A is a thiophene ring;

each R^A is independently a halogen atom, a cyano group, a nitro group, an optionally substituted lower alkyl group, an optionally substituted lower alkenyl group, an optionally substituted lower alkynyl group, a hydroxyiminomethyl group, an optionally substituted sulfonyl group, an optionally substituted sulfinyl group, a tetrazolyl group, OW^1, SW^1, COW^1, $COOW^1$, $NHCOW^1$, $NHCONW^2W^3$, NW^2W^3, $CONW^2W^3$, or $SO_2NW^2W^3$, wherein W^1 to W^3 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^2 and W^3 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group;

m is an integer from 0 to 3;

ring B is an aryl group or a monocyclic heteroaryl group;

each R^B is independently a halogen atom, a cyano group, an optionally substituted lower alkyl group, OW^4, COW^4, $COOW^4$, or $CONW^5W^6$, wherein W^4 to W^6 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^5 and W^6 may bind together with the neighboring nitrogen

atom to form an optionally substituted cyclic amino group;

n is an integer from 0 to 2;

U is a single bond;

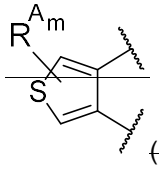
X is a group represented by —S—L—Y, —O—L—Y, —CO—L—Y, or —SO_2—L—Y, wherein L is an optionally substituted lower alkylene group;

Y is a group represented by Z or —NW^7W^8, wherein W^7 and W^8 independently are a hydrogen atom, an optionally substituted lower alkyl group, or Z with the proviso that W^7 and W^8 are not simultaneously hydrogen atoms, or W^7 and W^8 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group; and

Z is an optionally fused and optionally substituted cycloalkyl group, an optionally fused and optionally substituted heterocycloalkyl group, an optionally fused and optionally substituted aryl group, or an optionally fused and optionally substituted heteroaryl group;

or a pharmaceutically acceptable salt thereof.

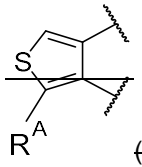
~~261. The method of claim 260, wherein the ring A is a thiophene ring represented by formula (**IIa**)~~



~~(**IIa**).~~

~~262. The method of claim 260 or 261, wherein m is 1.~~

~~263. The method of claim 262, wherein the ring A is an optionally substituted thiophene ring represented by formula (**IIb**)~~



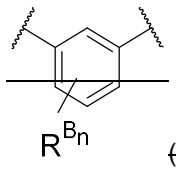
~~(**IIb**).~~

~~264. The method of any one of claims 260-263, wherein each R^A is independently a halogen atom, an optionally substituted lower alkyl group, $COOW^1$, or $CONW^2W^3$, wherein W^1 to W^3 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^2 and W^3 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group.~~

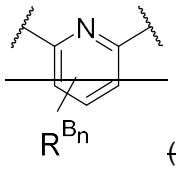
~~265. The method of claim 264, wherein each R^A is COOH or pharmaceutically acceptable salt thereof.~~

~~266. The method of any one of claims 260-265, wherein the ring B is an optionally substituted benzene ring, pyridine ring, or thiophene ring.~~

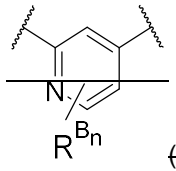
~~267. The method of claim 266, wherein the ring B is represented by a formula selected from the group consisting of:~~



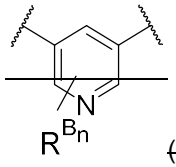
(**IIIa**);



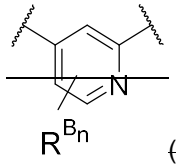
(**IIIb**);



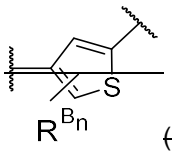
(**IIIc**);



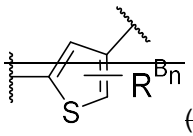
(**IIId**);



(**IIIe**);



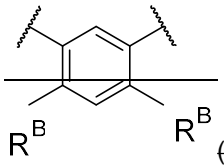
(**IIIf**); and



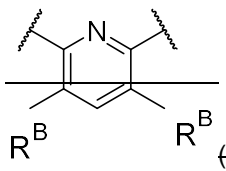
(**IIIg**).

268. The method of any one of claims 260-267, wherein n is 2.

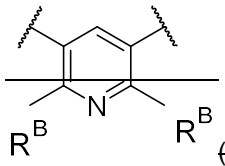
269. The method of claim 268, wherein the ring B is represented by a formula selected from the group consisting of:



(**IVa**);



~~(**IVb**); and~~



~~(**IVc**).~~

~~270. The method of any one of claims 260-269, wherein each R^B is independently a halogen atom, an optionally substituted lower alkyl group, or OW^4, wherein each W^4 is independently a hydrogen atom or an optionally substituted lower alkyl group.~~

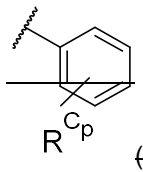
~~271. The method of claim 270, wherein each R^B is independently a fluorine atom, chlorine atom, bromine atom, methyl group, or methoxy group.~~

~~272. The method of any one of claims 260-271, wherein U is a single bond.~~

~~273. The method of any one of claims 260-272, wherein X is a group represented by —O—L—Y.~~

~~274. The method of any one of claims 260-273, wherein L is a methylene group.~~

~~275. The method of any one of claims 260-274, wherein Y is an optionally substituted benzene ring represented by formula (**V**)~~

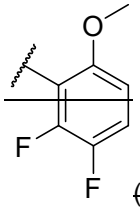


~~(**V**)~~

~~wherein each R^C is independently a halogen atom, an optionally substituted lower alkyl group, or OW^9, wherein each W^9 is independently a hydrogen atom or an optionally substituted lower alkyl group; and~~

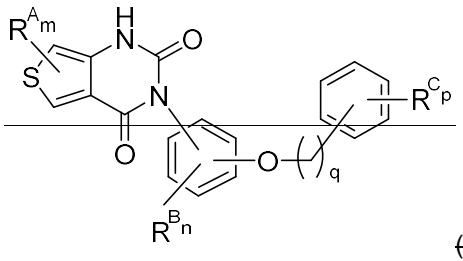
~~p is an integer from 0 to 3.~~

~~276. The method of claim 275, wherein Y is a substituted benzene ring represented by formula (**Va**)~~



~~(**Va**).~~

~~277. The method of claim 260, wherein the compound is represented by formula (**Ia**)~~



~~(Ia)~~

~~wherein each R^A is independently a halogen atom, a cyano group, a nitro group, an optionally substituted lower alkyl group, an optionally substituted lower alkenyl group, an optionally substituted lower alkynyl group, a hydroxyiminomethyl group, an optionally substituted sulfonyl group, an optionally substituted sulfinyl group, a tetrazolyl group, OW^1, SW^1, COW^1, $COOW^1$, $NHCOW^1$, $NHCONW^2W^3$, NW^2W^3, $CONW^2W^3$, or $SO_2NW^2W^3$, wherein W^1 to W^3 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^2 and W^3 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group;~~

~~m is an integer from 0 to 3;~~

~~each R^B is independently a halogen atom, a cyano group, an optionally substituted lower alkyl group, OW^4, COW^4, $COOW^4$, or $CONW^5W^6$, wherein W^4 to W^6 independently are a hydrogen atom or an optionally substituted lower alkyl group, or W^5 and W^6 may bind together with the neighboring nitrogen atom to form an optionally substituted cyclic amino group;~~

~~n is an integer from 0 to 2;~~

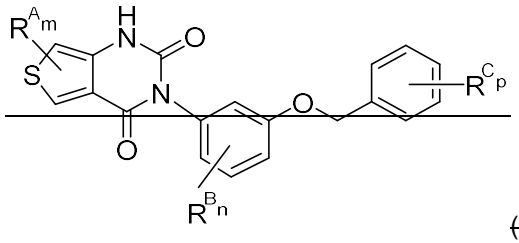
~~q is an integer from 0 to 3;~~

~~each R^C is independently a halogen atom, an optionally substituted lower alkyl group, or OW^9, wherein each W^9 is independently a hydrogen atom or an optionally substituted lower alkyl group; and~~

~~p is an integer from 0 to 3;~~

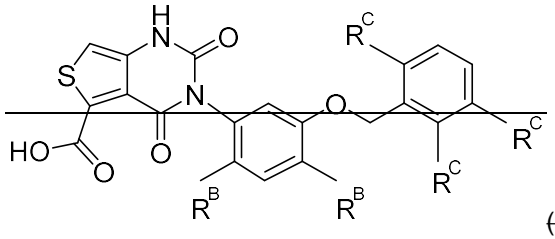
~~or a pharmaceutically acceptable salt thereof.~~

~~278. The method of claim 277, wherein the compound is represented by formula (**Ib**)~~



~~(Ib)~~.

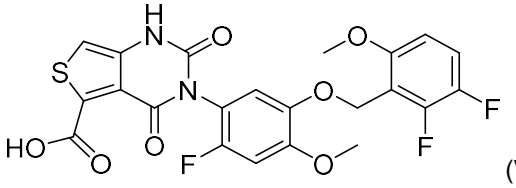
~~279. The method of claim 278, wherein the compound is represented by formula (**Ic**)~~



~~(Ic)~~

~~or a pharmaceutically acceptable salt thereof.~~

~~280.~~22. The ~~method~~ use of claim ~~any one of claims 260-279~~21, wherein the compound is represented by formula (**VI**)



(**VI**)

or a pharmaceutically acceptable salt thereof.

~~281.~~23. The ~~method~~ use of claim ~~280~~22, wherein the compound is the choline salt of the compound represented by formula (**VI**).

~~282. The method of claim 281, wherein the compound is in a crystalline state.~~

~~283. The method of claim 282, wherein the compound exhibits characteristic X-ray powder diffraction (XRPD) peaks at about 7.1° 2θ, about 11.5° 2θ, about 19.4° 2θ, about 21.5° 2θ, about 22.0° 2θ, about 22.6° 2θ, about 23.5° 2θ, and about 26.2° 2θ.~~

~~284. The method of claim 282 or 283, wherein the compound exhibits ^{13}C solid-state nuclear magnetic resonance (NMR) peaks centered at about 55.5 ppm, about 57.1 ppm, about 58.7 ppm, about 69.8 ppm, about 98.1 ppm, about 110.3 ppm, about 111.6 ppm, about 113.7 ppm, about 118.0 ppm, about 145.3 ppm, about 149.8 ppm, and about 155.8 ppm.~~

~~285. The method of any one of claims 282-284, wherein the compound exhibits ^{19}F solid-state NMR peaks centered at about -151.8 ppm, -145.2 ppm, and -131.6 ppm.~~

~~286. The method of any one of claims 260-285, wherein the compound is orally administered to the patient.~~

~~287. The method of any one of claims 260-286, wherein the compound is administered to the patient one or more times per day, week, or month during the treatment period.~~

~~288. The method of claim 287, wherein the compound is administered to the patient one or more times daily during the treatment period.~~

~~289. The method of claim 288, wherein the compound is administered to the patient once daily during the treatment period.~~

~~290. The method of any one of claims 287-289, wherein the compound is administered to the patient in an amount of from about 25 mg per day to about 400 mg per day during the treatment period.~~

~~291. The method of claim 290, wherein the compound is administered to the patient in an amount of from about 35 mg to about 65 mg per day during the treatment period.~~

~~292. The method of claim 291, wherein the compound is administered to the patient in an amount of about 50 mg per day during the treatment period.~~

~~293. The method of claim 290, wherein the compound is administered to the patient in an amount of from about 60 mg per day to about 90 mg per day during the treatment period.~~

~~294. The method of claim 293, wherein the compound is administered to the patient in an amount of about 75 mg per day during the treatment period.~~

~~295. The method of claim 290, wherein the compound is administered to the patient in an amount of from about 85 mg to about 115 mg per day during the treatment period.~~

~~296. The method of claim 295, wherein the compound is administered to the patient in an amount of about 100 mg per day during the treatment period.~~

~~297. The method of claim 290, wherein the compound is administered to the patient in an amount of from about 185 mg to about 215 mg per day during the treatment period.~~

~~298. The method of claim 297, wherein the compound is administered to the patient in an amount of about 200 mg per day during the treatment period.~~

~~299. The method of any one of claims 251-298, wherein the determining occurs from about 6 weeks to about 52 weeks after the onset of the treatment period.~~

~~300. The method of any one of claims 251-298, wherein the determining occurs from about 6 weeks to about 48 weeks after the onset of the treatment period.~~

~~301. The method of any one of claims 251-298, wherein the determining occurs from about 6 weeks to about 44 weeks after the onset of the treatment period.~~

~~302. The method of any one of claims 251-298, wherein the determining occurs from about 6 weeks to about 42 weeks after the onset of the treatment period.~~

~~303. The method of any one of claims 251-298, wherein the determining occurs from about 6 weeks to about 38 weeks after the onset of the treatment period.~~

~~304. The method of any one of claims 251-298, wherein the determining occurs from about 6 weeks to about 36 weeks after the onset of the treatment period.~~

~~305. The method of any one of claims 251-298, wherein the determining occurs from about 6 weeks to about 32 weeks after the onset of the treatment period.~~

~~306. The method of any one of claims 251-298, wherein the determining occurs from about 6 weeks to about 28 weeks after the onset of the treatment period.~~

~~307. The method of any one of claims 251-298, wherein the determining occurs from about 6 weeks to about 24 weeks after the onset of the treatment period.~~

308. The method of any one of claims 251-298, wherein the determining occurs from about 6 weeks to about 18 weeks after the onset of the treatment period.

309. The method of any one of claims 251-298, wherein the determining occurs from about 6 weeks to about 16 weeks after the onset of the treatment period.

310. The method of any one of claims 251-298, wherein the determining occurs from about 6 weeks to about 12 weeks after the onset of the treatment period.

311. The method of any one of claims 251-298, wherein the determining occurs from about 12 weeks to about 36 weeks after the onset of the treatment period.

312. The method of any one of claims 251-298, wherein the determining occurs from about 16 weeks to about 32 weeks after the onset of the treatment period.

313. The method of any one of claims 251-298, wherein the determining occurs from about 20 weeks to about 28 weeks after the onset of the treatment period.

314. The method of any one of claims 251-298, wherein the determining occurs from about 21 weeks to about 27 weeks after the onset of the treatment period.

315. The method of any one of claims 251-298, wherein the determining occurs from about 22 weeks to about 26 weeks after the onset of the treatment period.

316. The method of any one of claims 251-298, wherein the determining occurs from about 23 weeks to about 25 weeks after the onset of the treatment period.

317. The method of any one of claims 251-298, wherein the determining occurs about 6 weeks after the onset of the treatment period.

318. The method of any one of claims 251-298, wherein the determining occurs about 8 weeks after the onset of the treatment period.

319. The method of any one of claims 251-298, wherein the determining occurs about 10 weeks after the onset of the treatment period.

320. The method of any one of claims 251-298, wherein the determining occurs about 12 weeks after the onset of the treatment period.

321. The method of any one of claims 251-298, wherein the determining occurs about 14 weeks after the onset of the treatment period.

322. The method of any one of claims 251-298, wherein the determining occurs about 16 weeks after the onset of the treatment period.

323. The method of any one of claims 251-298, wherein the determining occurs about 18 weeks after the onset of the treatment period.

~~324. The method of any one of claims 251-298, wherein the determining occurs about 20 weeks after the onset of the treatment period.~~

~~325. The method of any one of claims 251-298, wherein the determining occurs about 22 weeks after the onset of the treatment period.~~

~~326. The method of any one of claims 251-298, wherein the determining occurs about 24 weeks after the onset of the treatment period.~~

~~327. The method of any one of claims 251-298, wherein the determining occurs about 26 weeks after the onset of the treatment period.~~

~~328. The method of any one of claims 251-298, wherein the determining occurs about 28 weeks after the onset of the treatment period.~~

~~329. The method of any one of claims 251-298, wherein the determining occurs about 30 weeks after the onset of the treatment period.~~

~~330. The method of any one of claims 251-298, wherein the determining occurs about 32 weeks after the onset of the treatment period.~~

~~331. The method of any one of claims 251-298, wherein the determining occurs about 34 weeks after the onset of the treatment period.~~

~~332. The method of any one of claims 251-298, wherein the determining occurs about 36 weeks after the onset of the treatment period.~~

~~333. The method of any one of claims 251-298, wherein the determining occurs about 38 weeks after the onset of the treatment period.~~

~~334. The method of any one of claims 251-298, wherein the determining occurs about 40 weeks after the onset of the treatment period.~~

~~335. The method of any one of claims 251-298, wherein the determining occurs about 42 weeks after the onset of the treatment period.~~

~~336. The method of any one of claims 251-298, wherein the determining occurs about 44 weeks after the onset of the treatment period.~~

~~337. The method of any one of claims 251-298, wherein the determining occurs about 46 weeks after the onset of the treatment period.~~

~~338. The method of any one of claims 251-298, wherein the determining occurs about 48 weeks after the onset of the treatment period.~~

~~339. The method of any one of claims 251-298, wherein the determining occurs about 50 weeks after the onset of the treatment period.~~

~~340. The method of any one of claims 251-298, wherein the determining occurs about 52 weeks after the onset of the treatment period.~~