(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 July 2009 (16.07.2009)

PCT

(10) International Publication Number
WO 2009/089093 A1

(51) International Patent Classification:
A61K 31/192 (2006.01) *A61P 5/14* (2006.01)
A61P 3/04 (2006.01) *A61P 5/06* (2006.01)
A61P 3/06 (2006.01) *A61P 19/10* (2006.01)
A61P 9/00 (2006.01) *A61P 25/24* (2006.01)
A61P 9/10 (2006.01)

(21) International Application Number:
PCT/US2009/030018

(22) International Filing Date: 2 January 2009 (02.01.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/019,086 4 January 2008 (04.01.2008) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,

[Continued on next page]

(54) Title: THYROID HORMONE RECEPTOR AGONISTS

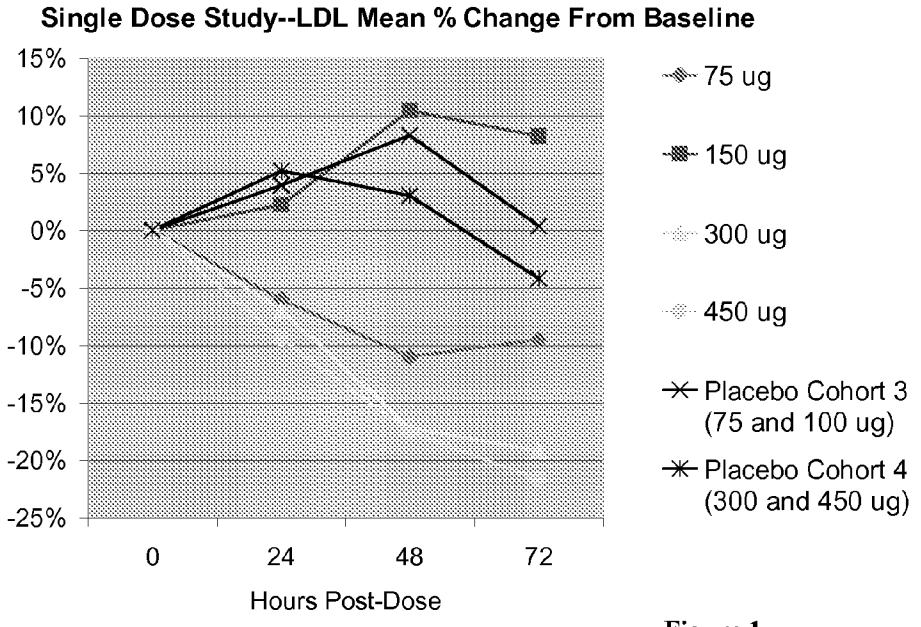


Figure 1

(57) Abstract: The present invention provides for dosage amounts and uses for 2-(4-(4-hydroxy-3- isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof agents in the treatment of disease states which are alleviated by treatment with a thyroid hormone receptor agonist. Also provided are unit dosage forms comprising 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenox)acetic acid.

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FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

13459-00215

THYROID HORMONE RECEPTOR AGONISTS

BACKGROUND

[0001] 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (GC-1) is a thyroid hormone receptor agonist (U.S. Patent No. 5,883,294; Trost et al. (2000) Endocrinology 141: 3057-3064; and Grover et al. (2004) Endocrinology 145: 1656-1661). 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid reduces serum levels of cholesterol in animals (Trost et al. (2000)). These effects are thought to result from stimulation of the thyroid hormone receptor TRß. However, compounds that are thyroid hormone receptor agonists can have undesirable effects, for example, if they exhibit cardiac stimulating effects such as elevation of heart rate through excessive activation of the thyroid hormone receptor TRα. The likelihood of thyroid hormone receptor agonists having effects on cardiac and other tissues other than the target tissue may be suggested by their impact on thyroid axis parameters such as the serum levels of TSH (thyroid stimulating hormone) and FT3 (free T3 (triiodothyronine)).

[0002] In animals, dose response studies have demonstrated that GC-1 decreases both TSH levels and cholesterol levels in parallel (Trost et al. (2000); and Brenta et al. (2007) Nature Clin. Practice: Endocrinol. and Metab. 3: 632-640). Accordingly, it is apparent that there exists a need to identify a dose of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid which will decrease LDL-cholesterol (low-density lipoprotein cholesterol) without significantly decreasing TSH levels.

SUMMARY

[0003] In one aspect, the present invention provides for methods of treating a human having a disease state which is alleviated by treatment with a thyroid hormone receptor agonist, which method comprises administering a therapeutically effective amount of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, to a human in need thereof in an amount of from about 10 µg to about 100 µg per day. In certain embodiments, the amount of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof is from about 30 µg to about 70 µg per day. In other embodiments, the amount of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof is from about 40 µg to about 60 µg per day. In still other embodiments, the amount of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof is from about 25 to about 45 µg/day. In other embodiments, the amount of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-

dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof is from about 55 to about 75 µg per day. In yet other embodiments, the amount of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof is 10 µg, 30 µg, 70 µg, or 100 µg per day. In other embodiments, the amount of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof is 30 µg per day. In other embodiments, the amount of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof is 50 µg per day. In other embodiments, the amount of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof is 70 µg per day. The 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid may be present as a pharmaceutically acceptable salt. In certain embodiments, 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid is in the free acid form. In certain embodiments, the disease state is cardiovascular disease, atherosclerosis, hypercholesterolemia, Fredrickson Type IIa dyslipidemia, Fredrickson Type IIb dyslipidemia, Fredrickson Type III dyslipidemia, Fredrickson Type IV dyslipidemia, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia. In one embodiment, the disease state is obesity. In another embodiment, the disease state is hypothyroidism in the setting of cardiac arrhythmia, resistance to thyroid hormone, or hypothyroidism in the setting of osteoporosis. In yet another embodiment, the disease state is depression. In certain embodiments, the LDL-cholesterol levels are decreased by greater than about 15% after 14 days of dosing at an amount of 10 to 100 µg/day. In other embodiments, LDL-cholesterol levels are decreased by greater than about 22% after 14 days of dosing at an amount of 10 to 100 µg/day. In still other embodiments, LDL-cholesterol levels are decreased from about 22% to about 33% after 14 days of dosing at an amount of 10 to 100 µg/day. In another embodiment, TSH is above 0.35 µIU/ml after 14 days of dosing at an amount of 10 to 100 µg/day. In certain embodiments, TSH is above 1 µIU/ml after 14 days of dosing at an amount of 10 to 100 µg/day. In particular embodiments, the FT_3 level is above about 2.3 pg/ml after 14 days of dosing at an amount of 10 to 100 µg/day. In other embodiments, the FT_3 level is above about 2.45 pg/ml after 14 days of dosing at an amount of 10 to 100 µg/day. In other embodiments, the TT_3 level is above about 0.6 ng/ml after 14 days of dosing at an amount of 10 to 100 µg/day. In still other embodiments, the TT_3 level is above about 0.6 ng/ml and below about 1.81 ng/ml after 14 days of dosing at an amount of 10 to 100 µg/day. In certain embodiments, the dose per day is from about 30 µg to about 70 µg per day after 14 days of dosing at an amount of 10 to 100 µg/day. In certain embodiments, the dose per day is from about 40 µg to about 60 µg per day. In certain embodiments, the dose per day is from about 25 to about 45 µg/day. In

certain embodiments, the dose per day is from about 55 to about 75 µg per day. In certain embodiments, the C_{max} is less than about 10 ng/ml after 14 days of dosing. In certain embodiments, the C_{max} is from about 0.18 to about 2.32 ng/ml after 14 days of dosing. In certain embodiments, the C_{max} is from about 0.50 to about 2.32 ng/ml after 14 days of dosing. In certain embodiments, the $AUC_{(0\text{-}tau)}$ is less than about 10 ng*h/ml after 14 days of dosing. In certain embodiments, the $AUC_{(0\text{-}tau)}$ is from about 0.73 to about 7.07 ng*h/ml after 14 days of dosing. In certain embodiments, the $AUC_{(0\text{-}tau)}$ is from about 1.38 to about 7.07 ng*h/ml after 14 days of dosing.

[0004] In another aspect, the present invention provides for pharmaceutical compositions comprising from about 10 µg to about 100 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In certain embodiments, the pharmaceutical composition comprises from about 30 µg to about 70 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 40 µg to about 60 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 25 to about 45 µg. In certain embodiments, the pharmaceutical composition comprises from about 55 to about 75 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises 10 µg, 30 µg, 70 µg, or 100 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises 30 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises 50 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises 70 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid in the free acid form. In certain embodiments, the disease state is cardiovascular disease, atherosclerosis, hypercholesterolemia, Fredrickson Type IIa dyslipidemia, Fredrickson Type IIb dyslipidemia, Fredrickson Type III dyslipidemia, Fredrickson Type IV dyslipidemia, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia. In one embodiment, the disease state is obesity. In another embodiment, the disease state is hypothyroidism in

the setting of cardiac arrhythmia, resistance to thyroid hormone, or hypothyroidism in the setting of osteoporosis. In yet another embodiment, the disease state is depression.

[0005] In another aspect, the present invention provides for unit dosage forms for the treatment of human suffering from a disease state which is alleviated by treatment with a thyroid hormone receptor agonist comprising from about 10 µg to about 100 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier. In certain embodiments, the unit dosage form comprises from about 30 µg to about 70 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the unit dosage form comprises from about 40 µg to about 60 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the unit dosage form comprises from about 25 to about 45 µg. In certain embodiments, the unit dosage form comprises from about 55 to about 75 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the unit dosage form comprises 10 µg, 30 µg, 70 µg, or 100 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the unit dosage form comprises 30 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the unit dosage form comprises 50 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the unit dosage form comprises 70 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the unit dosage form comprises 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid in the free acid form. In certain embodiments, the disease state is cardiovascular disease, atherosclerosis, hypercholesterolemia, Fredrickson Type IIa dyslipidemia, Fredrickson Type IIb dyslipidemia, Fredrickson Type III dyslipidemia, Fredrickson Type IV dyslipidemia, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia. In one embodiment, the disease state is obesity. In another embodiment, the disease state is hypothyroidism in the setting of cardiac arrhythmia, resistance to thyroid hormone, or hypothyroidism in the setting of osteoporosis. In yet another embodiment, the disease state is depression.

In certain embodiments, the unit dosage form when administered to a human decreases LDL-cholesterol levels by greater than about 15% after 14 days of dosing at an amount of 10 to 100 µg/day. In certain embodiments, the unit dosage form when administered to a human decreases LDL-cholesterol levels by greater than about 22% after 14 days of dosing at an

amount of 10 to 100 µg/day. In certain embodiments, the unit dosage form when administered to a human decreases LDL-cholesterol levels by from about 22% to about 33% after 14 days of dosing at an amount of 10 to 100 µg/day. In certain embodiments, when the unit dosage form is administered to a human, TSH is above 0.35 µIU/ml after 14 days of dosing at an amount of 10 to 100 µg/day. In certain embodiments, when the unit dosage form is administered to a human, TSH is above 1 µIU/ml after 14 days of dosing at an amount of 10 to 100 µg/day. In certain embodiments, when the unit dosage form is administered to a human, the FT_3 level is above about 2.3 pg/ml after 14 days of dosing at an amount of 10 to 100 µg/day. In certain embodiments, when the unit dosage form is administered to a human, the FT_3 level is above about 2.45 pg/ml after 14 days of dosing at an amount of 10 to 100 µg/day. In certain embodiments, when the unit dosage form is administered to a human, the TT_3 level is above about 0.6 ng/ml after 14 days of dosing at an amount of 10 to 100 µg/day. In certain embodiments, when the unit dosage form is administered to a human, the TT_3 level is above about 0.6 ng/ml and below about 1.81 ng/ml after 14 days of dosing at an amount of 10 to 100 µg/day. In certain embodiments, the unit dosage form is administered to a human produces a C_{max} of less than about 10 ng/ml after 14 days of dosing. In certain embodiments, the unit dosage form when administered to a human produces a C_{max} of from about 0.18 to about 2.32 ng/ml after 14 days of dosing. In certain embodiments, the unit dosage form when administered to a human produces a C_{max} of from about 0.50 to about 2.32 ng/ml after 14 days of dosing. In certain embodiments, the unit dosage form when administered to a human produces an $AUC_{(0\text{-}tau)}$ of less than about 10 ng*h/ml after 14 days of dosing. In certain embodiments, the unit dosage form when administered to a human produces an $AUC_{(0\text{-}tau)}$ of from about 0.73 to about 7.07 ng*h/ml after 14 days of dosing. In certain embodiments, the unit dosage form when administered to a human produces an $AUC_{(0\text{-}tau)}$ of from about 1.38 to about 7.07 ng*h/ml after 14 days of dosing.

[0006] Further objects, features and advantages of this invention will become readily apparent to persons skilled in the art after a review of the following description, with reference to the drawings and claims that are appended to and form a part of this specification.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] FIG. 1 is a graph of the mean % change in LDL-c (low-density lipoprotein cholesterol) serum levels versus hours post-administration of single doses of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (75 µg, 150 µg, 300 µg, or 450 µg) or placebo to healthy subjects not enriched for having elevated LDL-c.

[0008] FIG. 2 is a graph of the mean TSH (thyroid stimulating hormone) serum levels (micro International Units (μIU)/ml) versus hours post-administration of single doses of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (75 μg, 150 μg, 300 μg, or 450 μg) or placebo. The normal range for TSH is 0.35 - 5.50 μIU/mL.

[0009] FIG. 3 is a graph of the individual TSH (thyroid stimulating hormone) serum levels (micro International Units (μIU)/ml) for the four subjects who received the 450 μg dose (Subjects 401, 403, 406, and 408) versus hours post-administration of single doses of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid. The normal range for TSH is 0.35 - 5.50 μIU/mL.

[0010] FIG. 4 is a graph of the mean FT_4 (free T_4 (thyroxine)) (ng/dl) serum levels versus hours post-administration of a single dose of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (75 μg, 150 μg, 300 μg, or 450 μg) or placebo. The normal range for FT_4 is 0.89 - 1.76 ng/dL.

[0011] FIG. 5 is a graph of the mean FT_3 (free T_3 (triiodothyronine)) (pg/ml) serum levels versus hours post-administration of a single dose of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (75 μg, 150 μg, 300 μg, or 450 μg) or placebo. The normal range for FT_3 is 2.30 - 4.20 pg/mL.

[0012] FIG. 6 is a graph of the mean % change in LDL-cholesterol ("LDL-c") serum levels from baseline versus Day -1 (1 day prior to dosing) and Days 2, 3, 7, 10, and 14 where 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (10 μg, 30 μg, 70 μg, or 100 μg) or placebo was administered daily for from Day 1 to Day 14 to healthy subjects who were not enriched for having elevated LDL-c. Subject 404 (70 μg dose group), who had a low baseline LDL-c level of 76 mg/dL, and subject 405 (70 μg dose group), who had only received one dose of study drug prior to discontinuing from the study, were omitted entirely from the LDL-c analyses. For other subjects, LOCF (last observation carried forward) analysis was employed, where the most recent previous values from post-baseline results taken within 2 days of having received study drug were used in place of any missing results (e.g., in case of early termination from the study). "PBO" in this and on the graphs and tables indicates the results are for the placebo-treated subjects.

[0013] FIG. 7 is a graph of the mean TSH (thyroid stimulating hormone) serum levels (micro International Units (μIU)/ml), LOCF, versus Day -1 (1 day prior to dosing) and Days 2, 3, 7, 10, and 14, where 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid(10 μg, 30 μg, 70 μg, or 100 μg) or placebo was administered daily from Day 1 to Day 14 to healthy subjects. Subject 405, who had only received one dose of study drug prior to discontinuing from the study, was omitted entirely from this analysis. The dashed line marked LLN represents the lower limit of normal of 0.35 μIU/mL.

[0014] For Figures 8-13 and 17, subject 405, who had received only one dose of study drug prior to discontinuing from the study, was omitted entirely from the analyses.

[0015] FIG. 8 is a graph of the mean FT_3 (free T_3 (triiodothyronine) (pg/ml) serum levels, LOCF, versus Day -1 (1 day prior to dosing) and the Days 2, 3, 7, 10, and 14 where 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (10 µg, 30 µg, 70 µg, or 100 µg) or placebo was administered daily from Day 1 to Day 14 to healthy subjects. The dashed lines marked LLN and ULN represent the lower limit of normal of 2.30 pg/ml and the upper limit of normal of 4.20 pg/ml, respectively.

[0016] FIG. 9 is a graph of the mean FT_4 (free T_4 (thyroxine)) (ng/dl) serum levels, LOCF, versus Day -1 (1 day prior to dosing) and the Days 2, 3, 7, 10, and 14 where 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (10 µg, 30 µg, 70 µg, or 100 µg) or placebo was administered daily from Day 1 to Day 14 to healthy subjects. The dashed lines marked LLN and ULN represent the lower limit of normal of 0.89 ng/dl and the upper limit of normal of 1.76 ng/dl, respectively.

[0017] FIG. 10 is a graph of the mean TT_3 (total T_3 (triiodothyronine) (ng/ml) serum levels, LOCF, versus Day -1 (1 day prior to dosing) and the Days 2, 3, 7, 10, and 14 where 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (10 µg, 30 µg, 70 µg, or 100 µg) or placebo was administered daily from Day 1 to Day 14 to healthy subjects. The dashed lines marked LLN and ULN represent the lower limit of normal of 0.6 ng/ml and the upper limit of normal of 1.81 ng/ml, respectively.

[0018] FIG. 11 is a graph of the TT_4 (total T_4 (thyroxine)) (µg/dl) serum levels, LOCF, versus Day -1 (1 day prior to dosing) and the Days 2, 3, 7, 10, and 14 where 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (10 µg, 30 µg, 70 µg, or 100 µg) or placebo was administered daily from Day 1 to Day 14 to healthy subjects. The dashed line marked LLN represents the lower limit of normal of 4.50 µg/dl.

[0019] FIG. 12 is a graph of the reverse triiodothyronine (rT3) (pg/ml) serum levels, LOCF, versus Day -1 (1 day prior to dosing) and the Days 2, 3, 7, 10, and 14 where 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (10 µg, 30 µg, 70 µg, or 100 µg) or placebo was administered daily from Day 1 to Day 14 to healthy subjects. The normal range is noted as 90-350 pg/ml.

[0020] FIG. 13 is a graph of the thyroxine-binding globulin (TBG) (µg/ml) serum levels, LOCF, versus Day -1 (1 day prior to dosing) and the Days 2, 3, 7, 10, and 14 where 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (10 µg, 30 µg, 70 µg, or 100 µg) or placebo was administered daily from Day 1 to Day 14 to healthy subjects. The normal range is noted as 13-39 µg/ml.

[0021] FIG. 14 is a graph of the mean % change in LDL-c serum levels from baseline, LOCF (square symbols) (left-hand y-axis), and TSH levels (micro International Units (μIU)/ml), LOCF, (diamond symbols) (right-hand y-axis) for the 10 μg dose from Figures 6 and 7, respectively, versus days of the study.

[0022] FIG. 15 is a graph of the mean % change in LDL-c serum levels from baseline, LOCF, (square symbols) (left-hand y-axis) and TSH levels (micro International Units (μIU)/ml), LOCF, (diamond symbols) (right-hand y-axis) for the 30 μg dose from Figures 6 and 7, respectively, versus days of the study.

[0023] FIG. 16 is a graph of the mean % change in LDL serum levels from baseline, LOCF, (square symbols) (left-hand y-axis) and TSH levels (micro International Units (μIU)/ml), LOCF, (diamond symbols) (right-hand y-axis) for the 70 μg dose from Figures 6 and 7, respectively, versus days of the study. Subject 404 was omitted from the LDL-c analysis for this graph.

[0024] FIG. 17 is a graph of the mean % change in LDL serum levels from baseline, LOCF, (square symbols) (left-hand y-axis) and TSH levels (micro International Units (μIU)/ml), LOCF, (diamond symbols) (right-hand y-axis) for the 100 μg dose from Figures 6 and 7, respectively, versus days of the study.

[0025] FIG. 18 is a graph of the mean TSH (thyroid stimulating hormone) serum levels (micro International Units (μIU)/ml) versus Screening, Day -1 (1 day prior to dosing) and Days 7, 10, 14 (last day of dosing), and 21 (one week after last dose), where simvastatin 10 mg daily was administered with either 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (50 μg) or placebo daily from Day 1 to Day 14 to healthy subjects who had baseline LDL levels of >=130 mg/dl. The lower limit of normal for TSH in this study was 0.350 μIU/mL and the upper limit of normal was 5.500 μIU/mL.

[0026] FIG. 19 is a graph of the mean FT_3 (free T_3 (triiodothyronine) (pg/ml) serum levels versus Screening, Day -1 (1 day prior to dosing) and Days 7, 10, 14 (last day of dosing), and 21 (one week after last dose), where simvastatin 10 mg daily was administered with either 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (50 μg) or placebo daily from Day 1 to Day 14 to healthy subjects who had baseline LDL levels of >=130 mg/dl. The lower limit of normal for FT_3 in this study was 1.80 pg/ml and the upper limit of normal was 4.20 pg/ml.

[0027] FIG. 20 is a graph of the mean FT_4 (free T_4 (thyroxine) (ng/dl) serum levels versus Screening, Day -1 (1 day prior to dosing) and Days 7, 10, 14 (last day of dosing), and 21 (one week after last dose), where simvastatin 10 mg daily was administered with either 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (50 μg) or placebo daily from Day 1 to Day 14 to healthy subjects who had baseline LDL levels of >=130 mg/dl. The

lower limit of normal for FT_4 in this study was 0.90 ng/dl and the upper limit of normal was 1.80 ng/dl.

[0028] FIG. 21 is a graph of the mean TBG (thyroxine binding globulin (ug/ml)) serum levels versus Screening, Day -1 (1 day prior to dosing) and Days 7, 14 (last day of dosing), and 21 (one week after last dose), where simvastatin 10 mg daily was administered with either 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (50 µg) or placebo daily from Day 1 to Day 14 to healthy subjects who had baseline LDL levels of >=130 mg/dl. The lower limit of normal for TBG in this study was 12 µg/ml and the upper limit of normal was 26 µg/ml.

[0029] FIG. 22 is a graph of the mean % change from baseline in LDL-cholesterol ("LDL-c") (measured by a direct method, thus "LDL-Direct" in the graph) serum levels, LOCF, versus Baseline and Days 3, 7, 14, 21, and end-of-dosing, where 50 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid or placebo was administered daily for from Day 1 to Day 28 to healthy subjects who were enriched for having mildly elevated LDL-c of >= 110 mg/dL at baseline. Baseline values were calculated as a mean of LDL-Direct values measured on Days -2 (2 days prior to dosing), -1, and 1. End-of-dosing values were calculated as a mean of LDL-Direct values measured on Days 27, 28, and 29.

[0030] FIG. 23 is a graph of the mean TSH (thyroid stimulating hormone) serum levels (micro International Units (µIU)/ml), LOCF, versus Days -1 (one day prior to first dose), 7, 10, 14, 21, and 29 (one day after last dose), where 50 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid or placebo was administered daily for from Day 1 to Day 28 to healthy subjects who were enriched for having mildly elevated LDL-c of >= 110 mg/dl at baseline. The lower and upper limits of normal for TSH in this study were 0.350 and 5.500 µIU/ml, respectively. The horizontal dashed lines on the graph represent the upper and lower limits of normal for TSH.

[0031] FIG. 24 is a graph of the mean FT_3 (free triiodothyronine) serum levels (pg/ml), LOCF, versus Days -1 (one day prior to first dose), 7, 10, 14, 21, and 29 (one day after last dose), where 50 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid or placebo was administered daily for from Day 1 to Day 28 to healthy subjects who were enriched for having mildly elevated LDL-c of >= 110 mg/dl at baseline. The lower and upper limits of normal for FT_3 in this study were 1.8 and 4.2 pg/ml, respectively.

[0032] FIG. 25 is a graph of the mean FT_4 (free thyroxine) serum levels (ng/dl), LOCF, versus Days -1 (one day prior to first dose), 7, 10, 14, 21, and 29 (one day after last dose), where 50 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid or placebo was administered daily for from Day 1 to Day 28 to healthy subjects who were

enriched for having mildly elevated LDL-c of >= 110 mg/dl at baseline. The lower and upper limits of normal for FT_4 in this study were 0.90 and 1.80 ng/dl, respectively. The horizontal dashed lines on the graph represent the upper and lower limits of normal for FT_4.

[0033] FIG. 26 is a graph of the mean TT_3 (total triiodothyronine) serum levels (ng/ml), LOCF, versus Days -1 (one day prior to first dose), 7, 14, 21, and 29 (one day after last dose), where 50 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid or placebo was administered daily for from Day 1 to Day 28 to healthy subjects who were enriched for having mildly elevated LDL-c of >= 110 mg/dl at baseline. The lower and upper limits of normal for TT_3 in this study were 0.6 and 1.8 ng/ml, respectively. The horizontal dashed lines on the graph represent the upper and lower limits of normal for TT_3.

[0034] FIG. 27 is a graph of the mean TT_4 (total thyroxine) serum levels (µg/dl), LOCF, versus Days -1 (one day prior to first dose), 7, 14, 21, and 29 (one day after last dose), where 50 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid or placebo was administered daily for from Day 1 to Day 28 to healthy subjects who were enriched for having mildly elevated LDL-c of >= 110 mg/dl at baseline. The lower and upper limits of normal for TT_4 in this study were 4.5 and 10.9 µg/dl, respectively. The horizontal dashed lines on the graph represent the upper and lower limits of normal for TT_4.

DEFINITIONS

[0035] The term “treatment” includes the acute, chronic, or prophylactic diminishment or alleviation of at least one symptom or characteristic associated with or caused by the disease being treated. For example, treatment can include diminishment of one or several symptoms of a disease, inhibition of the pathological progression of a disease, or complete eradication of a disease.

[0036] The phrase “therapeutically effective amount” means an amount of a compound, or a pharmaceutically acceptable salt thereof, sufficient to inhibit, halt, or allow an improvement in the disease being treated when administered alone or in conjunction with another pharmaceutical agent or treatment in a particular subject or subject population. For example in a human a therapeutically effective amount can be determined experimentally in a laboratory or clinical setting, for the particular disease and subject being treated.

[0037] "Pharmaceutically acceptable salt" means those salts which retain the biological effectiveness and properties of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, and which are not biologically or otherwise undesirable. Such salts may be prepared from inorganic and organic bases. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, substituted amines including naturally-occurring

substituted amines, and cyclic amines, including isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, and N-ethylpiperidine. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example carboxylic acid amides, including carboxamides, lower alkyl carboxamides, di(lower alkyl) carboxamides, and the like.

DETAILED DESCRIPTION

[0038] The current invention concerns the discovery that 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, is useful for lowering serum LDL-cholesterol levels when administered at dosages of about 10 µg to about 100 µg/day. In certain embodiments, a dosage of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid lowers LDL-cholesterol levels without significantly lowering TSH (thyroid stimulating hormone) serum levels.

PHARMACEUTICAL COMPOSITIONS AND METHODS OF USE

[0039] This invention also provides for pharmaceutical compositions comprising a therapeutically effective amount of from about 10 µg to about 100 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier. The phrase “pharmaceutical composition” refers to a composition suitable for administration in medical use.

[0040] Generally, 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, will be administered as a formulation in association with one or more pharmaceutically acceptable carriers. The term “carrier” is used herein to describe any ingredient other than 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. The choice of carrier will to a large extent depend on factors such as the particular mode of administration, the effect of the carrier on solubility and stability and the nature of the dosage form.

[0041] 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, can be formulated as a pharmaceutical composition in the form of a syrup, an elixir, a suspension, a powder, a granule, a tablet, a capsule, a lozenge, a troche, an aqueous solution, a cream, an ointment, a lotion, a gel, a transdermal patch, an emulsion, etc. Preferably, 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, will cause a decrease in symptoms or a disease indicia associated with a disease state which is

alleviated by treatment with a thyroid hormone receptor agonist as measured quantitatively or qualitatively.

[0042] For preparing pharmaceutical compositions from 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0043] In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0044] Suitable carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0045] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0046] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0047] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. For example, 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, can be dissolved in 4% ethanol (in water). Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0048] Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0049] In certain embodiments, 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, is in unit dosage form, for example, a tablet or a capsule so that the patient may self-administer a single dose. The term "unit dosage form" refers to physically discrete units, such as tablets and capsules, suitable as unitary dosages, particularly as unitary daily dosages, for human subjects, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a pharmaceutically acceptable carrier. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0050] In general, unit dose forms contain from about 10 to about 100 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. Preferred unit dose forms contain from about 30 to about 70 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. Unit dosage forms may also comprise from about 40 to about 60 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. Other dosage forms comprise from about 25 to about 45 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. Another dosage form comprises from about 55 to about 75 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. Particular unit dosage forms within the range of the invention may comprise 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof. In certain embodiments, the present invention provides for unit dosage forms comprising 40, 45, 50, or 55 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid.

[0051] Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there are a wide variety of suitable formulations of pharmaceutical compositions of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a

pharmaceutically acceptable salt thereof. (see, e.g., *Remington: The Science and Practice of Pharmacy*, 20th ed., Gennaro et al. Eds., Lippincott Williams and Wilkins, 2000).

[0052] 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, alone or in combination with other suitable components, can be made into aerosol formulations (i.e., they can be "nebulized") to be administered via inhalation. Aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane nitrogen, and the like.

[0053] Formulations suitable for parenteral administration, such as, for example, by intravenous, intramuscular, intradermal, and subcutaneous routes, include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and nonaqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. In the practice of the present invention, compositions comprising 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, can be administered, for example, by intravenous infusion, orally, topically, intraperitoneally, intravesically or intrathecally. The formulations of compounds can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials. Injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0054] For administration, 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, can be administered at a rate determined by factors that can include the pharmacokinetic profile of the compound, contraindicated drugs, and the side effects of the compound at various concentrations, as applied to the mass and overall health of the subject. Administration can be accomplished via single or divided doses.

[0055] Examples of capsule formulations includes the following:

Capsule Formulation No. 1	
Ingredient	Amount
2-(4-(4-Hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid	100 µg
Dextrates NF Hydrated	122.40
Methocel E5 Prem LV	1.25 mg
Purified Water	(removed)
Magnesium Stearate	1.25 mg
	125 mg

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Capsule Formulation No. 2	
Ingredient	Amount
2-(4-(4-Hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid	100 µg
Dextrates NF Hydrated	157.9 mg
Methocel E5 Prem LV	0.40 mg
Purified Water	(removed)
Magnesium Stearate	1.6 mg
	160 mg

The active ingredient 2-(4-(4-Hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid is dispersed in water containing 2 % of Methocel E5. The water dispersion is sprayed into a fluidized bed containing dextrates as excipient. The granules are dried in the fluidized bed. The dried granules and magnesium stearate are mixed. The final blend is encapsulated in size 3 hard gelatin capsules.

[0056] An example of a tablet includes the following:

Tablet Formulation	
Ingredient	Amount
2-(4-(4-Hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid	60 µg
Lactose	120.04 mg
Cornstarch (for mix)	10 mg
Cornstarch (for paste)	8 mg
Magnesium Stearate (1%)	2 mg
	150 mg

2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, can be mixed with the lactose and cornstarch (for mix) and blended to uniformity to a powder. The cornstarch (for paste) is suspended water and heated with stirring to form a paste. The paste is added to the mixed powder, and the mixture is granulated. The wet granules are passed through a No. 8 hard screen and dried at 50°C. The mixture is lubricated with 1% magnesium stearate and compressed into a tablet.

[0057] 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, and pharmaceutical compositions comprising 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, can be administered to treat a subject suffering from a disease state which is alleviated by treatment with a thyroid hormone receptor agonist.

[0058] The phrase "disease state which is alleviated by treatment with a thyroid hormone receptor agonist" as used herein is intended to cover all disease states which are generally acknowledged in the art to be usefully treated with a thyroid hormone receptor agonist. Such disease states include, but are not limited to depression, hypothyroidism in the setting of cardiac arrhythmia, resistance to thyroid hormone, hypothyroidism in the setting of osteoporosis, cardiovascular disorders, atherosclerosis, peripheral vascular disease, hyperlipidemia, dyslipidemia, hyperbetalipoproteinemia, hypercholesterolemia,

hypertriglyceridemia, familial-hypercholesterolemia, angioplastic restenosis, hypertension, obesity, and vascular complications of diabetes. Examples of dyslipidemias include, but are not limited to, Fredrickson Type IIa dyslipidemia, Fredrickson Type IIb dyslipidemia, Fredrickson Type III dyslipidemia, and Fredrickson Type IV dyslipidemia.

[0059] In therapeutic applications, the 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, can be prepared and administered in a wide variety of oral and parenteral dosage forms. The term "administering" refers to the method of contacting a compound with a subject. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, parentally, or intraperitoneally. Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally, topically and via implantation. In certain embodiments, the compounds of the present invention are delivered orally. The compounds can also be delivered rectally, bucally, intravaginally, ocularly, or by inhalation. In a preferred embodiment, 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, is administered orally.

[0060] The 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, utilized in the pharmaceutical method of the invention are typically administered at a dosage of from about 0.1 μg/kg to about 1 μg/kg daily. In certain embodiments, the daily dose range is from about 0.3 μg/kg to about 1 μg/kg daily.

[0061] Generally, the active ingredient, 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, may be administered from 1 to 4 times a day. The dosage range for the invention is from about 10 to about 100 μg/day, or from about 30 to about 70 μg/day, or from about 40 to about 60 μg/day, or from about 25 to about 45 μg/day or from about 55 to about 75 μg/day. Particular dosages within the range of the invention are 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, and 100 μg/day. In certain embodiments, the present invention provides for dosages of 50 or 55 μg/day.

[0062] The dose will be determined by the efficacy of the particular compound employed and the condition of the subject, the severity of the disease being treated, as well as the body weight or surface area of the subject to be treated. The size of the dose also will be determined by the existence, nature and extent of any adverse side-effects that accompany the administration of a particular compound in a particular subject. In determining the effective amount of the compound to be administered in the treatment or

prophylaxis of the disease being treated, the physician can evaluate factors such as the circulating plasma levels of the compound, compound toxicities, levels of TSH and/or endogenous thyroid hormones, serum LDL-c levels, and/or the progression of the disease, etc. In addition, compounds of the present invention can be administered at a rate determined by factors that can include the pharmacokinetic profile of the compound, contraindicated drugs and the side-effects of the compound at various concentrations, as applied to the mass and overall health of the subject. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

[0063] 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, can also be co-administered with one or more compounds that are useful for the treatment of hypercholesterolemia, hypertriglyceridemia, atherosclerotic cardiovascular disease, heart disease, stroke, etc. such as aspirin; streptokinase; tissue plasminiogen activator; urokinase; anticoagulants; antiplatelet drugs (e.g., PLAVIX® (clopidogrel bisulfate), prasugrel, etc.); a statin (e.g., LIPITOR® (atorvastatin calcium), ZOCOR® (simvastatin), CRESTOR® (rosuvastatin); niacin, including long-acting forms such as NIASPAN® (niacin extended release tablets); a cholesterol uptake inhibitor such as ZETIA® (ezetimibe); a combination of a cholesterol uptake inhibitor with a statin such as VYTORIN® (ezetimibe and simvastatin); medications for controlling hypertension such as a beta blocker (e.g, Atenolol); an ACE inhibitor (e.g., Accupril® (quinapril hydrochloride), lisinopril, etc.); calcium channel blockers such as NORVASC® (amlodipine besylate); and angiotensin-2 receptor antagonists.

[0064] The compounds of the invention can also be co-administered with compounds that are useful for the treatment of obesity, such as XENICAL® (orlistat), phenteramine, ACOMPLIA® (rimonabant), and MERIDIA® (silbutramine hydrochloride monohydrate).

[0065] The compounds of the invention can also be co-administered with one or more compounds that are useful for the treatment of depression including, but not limited to, norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), NK-1 receptor antagonists, monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists, and atypical antidepressants. Suitable norepinephrine reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Suitable tertiary amine tricyclics and secondary amine tricyclics include amitriptyline, clomipramine, doxepin, imipramine, trimipramine, dothiepin, butripyline, iprindole, lofepramine, nortriptyline, protriptyline, amoxapine, desipramine and maprotiline. Suitable selective serotonin reuptake inhibitors include fluoxetine, fluvoxamine,

paroxetine, citalopram, and sertraline. Examples of monoamine oxidase inhibitors include isocarboxazid, phenelzine, and tranylcyclopramine. Suitable reversible inhibitors of monoamine oxidase include moclobemide. Suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include venlafaxine and duloxetine. Suitable atypical anti-depressants include bupropion, lithium, nefazodone, trazodone and viloxazine.

EXAMPLES

EXAMPLE 1 – Single rising dose study

[0066] A randomized, double-blind, placebo controlled, cross-over, single rising dose study of the study drug 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid was conducted in a population of healthy male volunteers that was not enriched for having elevated LDL cholesterol. 2-(4-(4-Hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid (5 mg) (in powder form) was dissolved in 2 mL EtOH (ethanol) and then diluted with 48 ml H_2O to make a stock solution. Aliquots of the stock solution were mixed with 4% EtOH (in H_2O) to achieve the appropriate concentration to deliver the desired dose of the drug. The placebo was 4% EtOH (in H_2O).

[0067] The subjects received a single oral liquid dose of either placebo or 1, 5, 25, 50, 75, 150, 300 and 450 μg 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid only one time with 8 oz. of water beginning at time zero There were 32 subjects/4 cohorts/8 subjects per group (4 active/4 placebo). The subjects fasted for 10 hours prior to dosing (water was permitted). Subjects fasted 4 hours post-dose on Day 1. Subjects were given a glass of water 2 hours post-dose and a standardized meal approximately 4 hours post-dose. Subjects received a standardized dinner at approximately 1900 hours on the day of dosing. The study subjects were housed at a clinical research center for 48 hours following dosing of the study drug.

[0068] Blood samples were taken from the subjects at 0, 24, 48, 72 and 168 hours post-dosing. Serum was prepared from those samples and used to determine the mean % change in LDL-cholesterol, mean free T_3 (("FT_3") (free triiodothyronine)), mean free T_4 (("FT_4" (free thyroxine)), and mean TSH (thyroid-stimulating hormone) levels. These values are graphed in Figures 1-5 and are also shown below in table format with the standard deviation from the mean ("S.D.").

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LDL (mg/dL)

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid single dose				PBO	
	Cohort 3		Cohort 4		Cohort 3	Cohort 4
	75 µg	150 µg	300 µg	450 µg		
Baseline* (S.D.)	121.3 (25.63)	95.8 (45.73)	120.3 (48.40)	109.8 (26.39)	107.1 (40.22)	105.9 (24.81)
24 hours (S.D.)	114.0 (25.53)	100.8 (55.30)	112.8 (51.15)	99.5 (25.28)	113.0 (49.91)	112.1 (30.90)
48 hours (S.D.)	108.0 (25.15)	108.0 (57.90)	98.0 (34.91)	91.5 (28.86)	116.3 (45.14)	109.6 (31.24)
72 hours (S.D.)	111.0 (31.89)	106.3 (57.86)	95.5 (33.60)	86.3 (26.27)	107.5 (41.22)	101.1 (25.90)

* Baseline is defined as the last non-missing scheduled pre-dose value relative to the treatment within a cohort.

LDL absolute change of the mean from baseline

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid single dose				PBO	
	Cohort 3		Cohort 4		Cohort 3	Cohort 4
	75 µg	150 µg	300 µg	450 µg		
24 hours (S.D.)	-7.3 (4.19)	5.0 (10.71)	-7.5 (11.00)	-10.3 (4.99)	5.9 (15.03)	6.3 (9.42)
48 hours (S.D.)	-13.3 (9.71)	12.3 (12.55)	-22.3 (13.72)	-18.3 (7.50)	9.1 (11.29)	3.8 (12.27)
72 hours (S.D.)	-10.3 (6.65)	10.5 (13.30)	-24.8 (15.37)	-23.5 (11.90)	0.4 (11.82)	-4.8 (12.37)

* Baseline is defined as the last non-missing scheduled pre-dose value relative to the treatment within a cohort.

LDL mean % change from baseline

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid single dose				PBO	
	Cohort 3		Cohort 4		Cohort 3	Cohort 4
	75 µg	150 µg	300 µg	450 µg		
24 hours (S.D.)	-6.1 (3.66)	2.3 (10.01)	-6.9 (7.69)	-9.5 (4.26)	4.0 (9.18)	5.2 (7.67)
48 hours (S.D.)	-11.0 (8.13)	10.5 (6.78)	-17.2 (5.10)	-17.5 (7.17)	8.3 (8.34)	3.0 (9.84)
72 hours (S.D.)	-9.5 (7.03)	8.2 (9.59)	-19.2 (6.69)	-21.7 (9.76)	0.4 (10.11)	-4.2 (10.89)

* Baseline is defined as the last non-missing scheduled pre-dose value relative to the treatment within a cohort.

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TSH (0.35-5.50 µIU/mL)

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid single dose				PBO	
	Cohort 3		Cohort 4		Cohort 3	Cohort 4
	75 µg	150 µg	300 µg	450 µg		
Baseline* (S.D.)	2.160 (1.0496)	1.908 (0.7042)	2.010 (0.4393)	1.508 (0.4634)	2.083 (1.2834)	1.559 (0.5310)
24 hours (S.D.)	1.600 (0.6420)	1.155 (0.5767)	0.718 (0.2477)	0.393 (0.1592)	1.849 (1.2552)	1.861 (0.4297)
48 hours (S.D.)	2.658 (1.2440)	2.045 (0.6863)	1.298 (0.9503)	0.523 (0.4405)	2.523 (1.5276)	2.399 (0.4538)
72 hours (S.D.)	2.555 (1.0188)	2.135 (0.3679)	1.735 (0.5747)	0.953 (0.5508)	2.515 (1.1127)	2.278 (0.3782)

* Baseline is defined as the last non-missing scheduled pre-dose value relative to the treatment within a cohort.

FT4 (0.89-1.76 ng/dL)

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid single dose				PBO	
	Cohort 3		Cohort 4		Cohort 3	Cohort 4
	75 µg	150 µg	300 µg	450 µg		
Baseline* (S.D.)	1.170 (0.1236)	1.365 (0.0794)	1.240 (0.1657)	1.255 (0.1162)	1.255 (0.1668)	1.231 (0.1464)
24 hours (S.D.)	1.133 (0.1565)	1.220 (0.1010)	1.188 (0.1087)	1.203 (0.1461)	1.214 (0.1473)	1.139 (0.1314)
48 hours (S.D.)	1.125 (0.1650)	1.073 (0.1050)	1.118 (0.1040)	1.118 (0.1040)	1.239 (0.0925)	1.199 (0.1765)
72 hours (S.D.)	1.293 (0.1962)	1.140 (0.0594)	1.178 (0.1403)	1.110 (0.1265)	1.234 (0.1730)	1.304 (0.1645)

* Baseline is defined as the last non-missing scheduled pre-dose value relative to the treatment within a cohort.

FT3 (2.30-4.20 pg/mL)

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid single dose				PBO	
	Cohort 3		Cohort 4		Cohort 3	Cohort 4
	75 µg	150 µg	300 µg	450 µg		
Baseline* (S.D.)	3.580 (0.2535)	3.335 (0.1559)	3.580 (0.4278)	3.528 (0.2428)	3.529 (0.2264)	3.404 (0.2502)
24 hours (S.D.)	3.020 (0.2015)	2.928 (0.0670)	2.845 (0.1162)	2.923 (0.1554)	3.198 (0.2600)	3.110 (0.1382)
48 hours (S.D.)	2.993 (0.2555)	3.025 (0.1190)	2.805 (0.2261)	2.930 (0.1490)	3.190 (0.1574)	3.336 (0.1565)
72 hours (S.D.)	3.523 (0.4814)	3.480 (0.3178)	3.205 (0.4194)	3.368 (0.2027)	3.499 (0.2823)	3.824 (0.2331)

* Baseline is defined as the last non-missing scheduled pre-dose value relative to the treatment within a cohort.

Pharmacokinetic parameters:

[0069] Plasma sampling for pharmacokinetic analysis was performed on Day 1 (pre-dose, 0.50, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 18 hours post-dose), Day 2 (24 hours post-dose), Day 3 (48 hours post-dose), Day 4 (72 hours post-dose) Day 8 (pre-dose, 0.50, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 18 hours post-dose), Day 9 (24 hours post-dose), Day 10 (48 hours post-dose), and Day 11 (72 hours post-dose). About four ml of venous blood was drawn into a blood collection tube containing K_2EDTA (dipotassium

ethylenediaminetetraacetic acid) and mixed by gentle inversion. The specimens were then centrifuged immediately. Aliquots of the plasma were transferred to new vials and stored at -70°C. The concentration of the drug was determined using an HPLC/MS assay.

[0070] The term C_{max} refers to the maximum drug concentration observed after the single dose administration.

[0071] The term AUC refers to the area under the serum concentration of drug (y-axis) versus time (x-axis) curve at a particular interval of time. The $AUC_{(0-t)}$ values were calculated from the time zero to the time of the last quantifiable concentration (t) with the non-compartmental method using the trapezoidal rule.

The C_{max} and $AUC_{(0-t)}$ values are reported below:

	C_{max} (ng/mL)	C_{max} S.D.	$AUC_{(0-t)}$ (ng*h/mL)	$AUC_{(0-t)}$ S.D.
5 µg	0.077	0.052	0.083	0.071
25 µg	0.45	0.28	0.98	0.87
50 µg	1.02	0.14	2.88	1.35
75 µg	2.03	0.69	5.66	3.79
150 µg	2.69	0.57	8.08	1.48
300 µg	5.80	2.64	21.7	8.98
450 µg	8.21	0.88	30.1	9.01

EXAMPLE 2

[0072] A randomized, double-blind, placebo controlled, multiple-dose safety and tolerance study of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid was conducted in a population of healthy male volunteers that was not enriched for having elevated LDL cholesterol.

[0073] 2-(4-(4-Hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid drug substance (in powder form) was dissolved in 2 mL EtOH and then diluted with 48 mL H_2O to make a stock solution. Aliquots of the stock solution were mixed with 4% EtOH (in H_2O) to achieve the appropriate concentration to deliver the desired dose of the drug in a 1-2 mL total volume. The subjects received study drug in the morning in this form daily for 14 days as described below.

Description of study:

[0074] All of the subjects, 24 healthy male volunteers had a screening visit within 6 weeks prior to the Baseline visit. The subjects were instructed in following the NCEP Adult Treatment Panel III (ATP III) Therapeutic Lifestyle Changes (TLC) diet approximately one week prior to dosing, and were expected to follow this diet starting at least 7 days prior to

dosing (Day -7). The diet was maintained during the subjects' stay in the research clinic from 2 days prior to dosing (Day -2) through Day 17 of the study. The TLC Diet in ATP III is as follows:

TLC Diet in ATP III	
Nutrient	Recommended Intake as Percent of Total Calories
Total Fat	25-35% - the 25-35% fat recommendation allows for increased intake of unsaturated fat in place of carbohydrates in people with metabolic syndrome or diabetes
Saturated Fat	Less than 7%
Polyunsaturated Fat	Up to 10 %
Monounsaturated Fat	Up to 20%
Carbohydrates	50-60% of total calories - carbohydrate should come mainly from foods rich in complex carbohydrates. These include grains, (especially whole grains), fruits and vegetables.
Protein	Approximately 15 %
Cholesterol	Less than 200 mg per day
Total calories	Balance energy intake and expenditure to maintain desirable body weight and prevent weight gain

[0075] The subjects received single oral liquid doses of either placebo or 10, 30, 70, or 100 μg 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid once daily with 8 oz. of water for two weeks beginning on Day 1 through Day 14 (i.e., drug or placebo was administered on Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14). The subjects fasted for 10 hours prior to dosing (water was permitted). Subjects fasted 4 hours post-dose on Days 1 and 14.

[0076] The subjects were confined in the clinic from 2 days prior to the start of the study ("Day -2") to Day 17 for monitoring of potential study drug effects. The subjects were released from the clinic on Day 17.

[0077] Blood samples were taken from the subjects 1 Day prior to dosing (Day -1), and on Days 2, 3, 7, 10, 14, and 17. Serum was prepared from those samples and used to determine the mean % change in LDL-cholesterol, mean TSH (thyroid-stimulating hormone), mean free T_3 (("FT_3") (free triiodothyronine)), mean free T_4 (("FT_4" (free thyroxine)), mean total T3, mean total T4, mean reverse triiodothyronine (rT3), and mean thyroxine-binding globulin (TBG). Serum levels of these parameters for the subjects were determined from the serum samples on Days -1, 2, 3, 7, 10, 14, and 17. These values are graphed in Figures 6-13 and are also shown below in table format with the standard deviation from the mean ("S.D.").

LDL-cholesterol at Day 14*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid daily dose				PBO
	10 µg	30 µg	70 µg**	100 µg	
Mean % Change from Baseline	-10.8	-22.2	-33.1	-40.7	-4.7
S.D.	6.62	15.92	7.48	2.19	17.88

* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

** Subject 404, who had a low baseline LDL-c level of 76 mg/dL, and subject 405, who had only one dose of study drug prior to discontinuing from the study, were omitted entirely from these analyses.

TSH at Day 14*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid daily dose				PBO
	10 µg	30 µg	70 µg**	100 µg	
TSH (µIU/mL) (0.35 - 5.50)	2.315	2.243	1.843	0.890	2.918
S.D.	0.8821	0.7757	1.2579	0.8379	0.7190

* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

** Subject 405, who had only one dose of study drug prior to discontinuing from the study, was omitted entirely from these analyses. Including this subject results in a mean 70 µg cohort TSH value at Day 14 of 1.523 µIU/mL with a S.D. of 1.2110 µIU/mL.

Free T_3 at Day 14*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid daily dose				PBO
	10 µg	30 µg	70 µg**	100 µg	
FT_3 (pg/mL) (2.30 - 4.20)	3.155	3.378	2.983	3.023	3.344
S.D.	0.3911	0.1767	0.4104	0.3781	0.2826

* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

** Subject 405, who had only one dose of study drug prior to discontinuing from the study, was omitted entirely from these analyses. Including this subject results in a mean 70 µg cohort FT_3 value at Day 14 of 2.900 pg/mL with a S.D. of 0.3743 pg/mL.

Free T_4 at Day 14*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid daily dose				PBO
	10 µg	30 µg	70 µg**	100 µg	
FT_4 (ng/dL) (0.89 - 1.76)	1.135	1.038	0.900	0.808	1.246
S.D.	0.0823	0.0096	0.1587	0.0802	0.1597

* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

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** Subject 405, who had only one dose of study drug prior to discontinuing from the study, was omitted entirely from these analyses. Including this subject results in a mean 70 µg cohort FT_4 value at Day 14 of 0.950 ng/dL with a S.D. of 0.1637 ng/dL.

Total T_3 at Day 14*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid daily dose				PBO
	10 µg	30 µg	70 µg**	100 µg	
TT_3 (ng/mL) (0.60 - 1.81)	1.160	1.378	1.007	1.058	1.295
S.D.	0. 0938	0.2317	0.2818	0.1638	0.1869

* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

** Subject 405, who had only one dose of study drug prior to discontinuing from the study, was omitted entirely from these analyses. Including this subject results in a mean 70 µg cohort TT_3 value at Day 14 of 0.973 ng/mL with a S.D. of 0.2401 ng/mL.

Total T_4 at Day 14*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid daily dose				PBO
	10 µg	30 µg	70 µg**	100 µg	
TT_4 (µg/dL) (4.5 - 10.90)	6.50	7.10	4.13	4.18	7.70
S.D.	0. 942	0.535	1.626	0.550	1.217

* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

** Subject 405, who had only one dose of study drug prior to discontinuing from the study, was omitted entirely from these analyses. Including this subject results in a mean 70 µg cohort TT_4 value at Day 14 of 4.75 µg/dL with a S.D. of 1.812 µg/dL.

Reverse T_3 at Day 14*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid daily dose				PBO
	10 µg	30 µg	70 µg**	100 µg	
rT3 (pg/mL) (90 - 350)	230.8	145.0	124.3	114.0	209.0
S.D.	12.95	23.83	34.12	32.09	39.74

* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

** Subject 405, who had only one dose of study drug prior to discontinuing from the study, was omitted entirely from these analyses. Including this subject results in a mean 70 µg cohort rT_3 value at Day 14 of 211.8 pg/mL with a S.D. of 177.04 pg/mL.

TBG at Day 14*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid daily dose				PBO
	10 µg	30 µg	70 µg**	100 µg	
TBG (µg/mL) (13 - 39)	14.5	20.8	15.3	13.3	19.5
S.D.	1.73	4.03	2.31	2.22	3.34

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* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

** Subject 405, who had only one dose of study drug prior to discontinuing from the study, was omitted entirely from these analyses. Including this subject results in a mean 70 µg cohort TBG value at Day 14 of 15.5 µg/mL with a S.D. of 1.91 µg/mL.

Pharmacokinetic parameters:

[0078] Plasma sampling for pharmacokinetic determinations was performed on Day 1 (pre-dose, 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, and 24 hours post-dose), and Day 14 (pre-dose, 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, and 24 hours post-dose). About four ml of venous blood was drawn into a blood collection tube containing K_2EDTA (dipotassium ethylenediaminetetraacetic acid) and mixed by gentle inversion. Specimens were centrifuged immediately at 3000 r.p.m. for 10 minutes. Aliquots of the plasma were transferred to new vials and stored at -70ºC. The concentration of the drug was determined using an HPLC/MS assay. The C_{max} and $AUC_{(0\text{-}tau)}$,values for Days 1 and 14 are reported below. The value n below represents the number of subjects.

[0079] The term C_{max} refers to the maximum drug concentration observed in a dosing interval. Here, the dosing interval was 24 hours.

[0080] The term AUC refers to the area under the serum concentration of drug (y-axis) versus time (x-axis) curve at a particular interval of time. The $AUC_{(0\text{-}tau)}$ is the AUC over a dosing interval and was calculated with the non-compartmental method using the trapezoidal rule.

Mean C_{max} (ng/ml) values on Day 1

Dose (µg)	n	C_{max} (ng/ml)	S.D. from mean
10	4	0.147	0.044
30	4	0.653	0.386
70	4	1.78	1.091
100	4	1.74	0.443

Mean C_{max} (ng/ml) values on Day 14

Dose (µg)	n	C_{max} (ng/ml)	S.D. from mean
10	3	0.180	0.014
30	3	0.504	0.413
70	2	2.32	1.68
100	2	1.53	0.05

Mean $AUC_{(0\text{-}tau)}$ (hr*ng/mL)values on Day 1

Dose (µg)	n	$AUC_{(0\text{-}tau)}$ (hr*ng/mL)	S.D. from mean
10	4	0.328	0.298
30	4	1.33	1.03
70	4	5.06	3.03
100	4	5.05	0.82

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Mean $AUC_{(0\text{-}tau)}$ (hr*ng/mL) values on Day 14

Dose (µg)	n	$AUC_{(0\text{-}tau)}$ (hr*ng/mL)	S.D. from mean
10	3	0.731	0.167
30	3	1.38	0.88
70	2	7.07	4.12
100	2	6.15	1.87

EXAMPLE 3

[0081] A randomized, double-blind, active controlled, multiple-dose safety and tolerance study of daily doses of simvastatin administered with and without daily doses of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid was conducted in a population of healthy male volunteers that was enriched for having elevated LDL cholesterol of >= 130 mg/dL.

[0082] 2-(4-(4-Hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid drug substance (in powder form) was dissolved in 2 mL EtOH and then diluted with 48 mL H_2O to make a stock solution. Aliquots of the stock solution were mixed with 4% EtOH (in H_2O) to achieve the appropriate concentration to deliver the desired dose of the drug in a 1 mL total volume. The subjects received sobetirome in the morning in this form daily for 14 days as described below.

Description of study:

[0083] All of the subjects, 15 healthy male volunteers had a screening visit within 6 weeks prior to the Baseline visit. The subjects were instructed in following the NCEP Adult Treatment Panel III (ATP III) Therapeutic Lifestyle Changes (TLC) diet approximately one week prior to dosing, and were expected to follow this diet starting at least 7 days prior to dosing (Day -7). The diet was maintained during the subjects' stay in the research clinic from 2 days prior to dosing (Day -2) through Day 15 of the study. The TLC Diet in ATP III is as follows:

TLC Diet in ATP III	
Nutrient	Recommended Intake as Percent of Total Calories
Total Fat	25-35% - the 25-35% fat recommendation allows for increased intake of unsaturated fat in place of carbohydrates in people with metabolic syndrome or diabetes
Saturated Fat	Less than 7%
Polyunsaturated Fat	Up to 10 %
Monounsaturated Fat	Up to 20%
Carbohydrates	50-60% of total calories - carbohydrate should come mainly from foods rich in complex carbohydrates. These include grains, (especially whole grains), fruits and vegetables.
Protein	Approximately 15 %

Cholesterol	Less than 200 mg per day
Total calories	Balance energy intake and expenditure to maintain desirable body weight and prevent weight gain

[0084] All subjects received single doses of simvastatin 10 mg once per day in the morning. Also, the subjects received single oral liquid doses of either placebo or 50 μg 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid once daily with 8 oz. of water for two weeks beginning on Day 1 through Day 14 (i.e., drug or placebo was administered on Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14). The subjects fasted for 10 hours prior to dosing (water was permitted). Subjects fasted for 1 hour post-dose on Days 1, 7, and 14.

[0085] The subjects were confined in the clinic from 2 days prior to the start of the study ("Day minus 2") to Day 15 for monitoring of potential study drug effects. The subjects were released from the clinic on Day 15.

[0086] Blood samples were taken from the subjects 2 and 1 days prior to dosing (Days -2 and -1), and on Days 1, 3, 7, 13, 14, and 15. Serum was prepared from those samples and used to determine the mean % change in LDL-cholesterol, mean TSH (thyroid-stimulating hormone), mean free T_3 ("FT_3") (free triiodothyronine)), mean free T_4 ("FT_4" (free thyroxine)), mean total T3, mean total T4, mean reverse triiodothyronine (rT3), and/or mean thyroxine-binding globulin (TBG). Serum levels of these parameters for the subjects were determined from the serum samples on Days -2, -1, 1, 3, 7, 13, 14, and/or 15. The mean TSH, FT3, FT4, and TBG thyroid parameter values are graphed in Figures 18-21 and are also shown below in table format.

TSH at Day 14

	Simvastatin 10 mg daily dose plus 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid 50 μg daily dose	**Simvastatin 10 mg daily dose plus PBO**
TSH (μIU/mL) (0.35 - 5.50)	2.05	1.86

Free T_3 at Day 14

	Simvastatin 10 mg daily dose plus 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid 50 μg daily dose	**Simvastatin 10 mg daily dose plus PBO**
FT_3 (pg/mL) (1.80 - 4.20)	**2.51**	**2.38**

Free T_4 at Day 14

	Simvastatin 10 mg daily dose plus 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-	**Simvastatin 10 mg daily**

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	dimethylphenoxy)acetic acid 50 µg daily dose	dose plus PBO
FT_4 (ng/dL) (0.90 – 1.80)	**0.945**	**1.11**

TBG at Day 14

	Simvastatin 10 mg daily dose plus 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid 50 µg daily dose	Simvastatin 10 mg daily dose plus PBO
TBG (µg/mL) (13 - 39)	**19**	**18.3**

Pharmacokinetic parameters:

[0087] Plasma sampling for pharmacokinetic determinations was performed on Day 1 (pre-dose, 0.50, 1, 2, and 3 hours post-dose), Day 7 (pre-dose, 0.50, 1, 2, and 3 hours post-dose), and Day 14 (pre-dose, 0.50, 1, 2, and 3 hours post-dose). About four ml of venous blood was drawn into a blood collection tube containing K_2EDTA (dipotassium ethylenediaminetetraacetic acid) and mixed by gentle inversion. Specimens were centrifuged immediately at 3000 r.p.m. for 10 minutes. Aliquots of the plasma were transferred to new vials and stored at -70ºC. The concentration of the drug was determined using an HPLC/MS assay. The C_{max} and values for Days 1, 7, and 14 from this limited PK sampling are reported below. The value n below represents the number of subjects.

[0088] The term C_{max} refers to the maximum drug concentration observed in a dosing interval. Here, the dosing interval was 24 hours.

Mean C_{max} (ng/ml) values on Day 1

Dose (µg)	n	C_{max} (ng/ml)	S.D. from mean
50	8	0.781	0.328

Mean C_{max} (ng/ml) values on Day 7

Dose (µg)	n	C_{max} (ng/ml)	S.D. from mean
50	8	0.955	0.283

Mean C_{max} (ng/ml) values on Day 14

Dose (µg)	n	C_{max} (ng/ml)	S.D. from mean
50	8	0.770	0.267

EXAMPLE 4

[0089] A randomized, double-blind, active controlled, multiple-dose safety and tolerance study of daily doses of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-

dimethylphenoxy)acetic acid was conducted in a population of healthy male volunteers that was enriched for having a mildly elevated LDL cholesterol of >= 110 mg/dL.

[0090] 2-(4-(4-Hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid drug substance (in powder form) was dissolved in 2 mL EtOH and then diluted with 48 mL H_2O to make a stock solution. Aliquots of the stock solution were mixed with 4% EtOH (in H_2O) to achieve the appropriate concentration to deliver the desired dose of the drug in a 1 mL total volume. The subjects received sobetirome in the morning in this form daily for 28 days as described below.

Description of study:

[0091] All of the subjects, 18 healthy male volunteers had a screening visit within 6 weeks prior to the Baseline visit. The subjects were instructed in following the NCEP Adult Treatment Panel III (ATP III) Therapeutic Lifestyle Changes (TLC) diet approximately one week prior to dosing, and were expected to follow this diet starting at least 7 days prior to dosing (Day -7). The diet was maintained during the subjects' stay in the research clinic from 2 days prior to dosing (Day -2) through Day 31 of the study. The TLC Diet in ATP III is as follows:

TLC Diet in ATP III	
Nutrient	Recommended Intake as Percent of Total Calories
Total Fat	25-35% - the 25-35% fat recommendation allows for increased intake of unsaturated fat in place of carbohydrates in people with metabolic syndrome or diabetes
Saturated Fat	Less than 7%
Polyunsaturated Fat	Up to 10 %
Monounsaturated Fat	Up to 20%
Carbohydrates	50-60% of total calories - carbohydrate should come mainly from foods rich in complex carbohydrates. These include grains, (especially whole grains), fruits and vegetables.
Protein	Approximately 15 %
Cholesterol	Less than 200 mg per day
Total calories	Balance energy intake and expenditure to maintain desirable body weight and prevent weight gain

[0092] The subjects received single oral liquid doses of either placebo or 50 μg 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid once daily with 8 oz. of water for two weeks beginning on Day 1 through Day 28 (i.e., drug or placebo was administered on Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, and 28). The subjects fasted for 10 hours prior to dosing (water was permitted). Subjects fasted for 1 hour post-dose on Days 1 and 28.

[0093] The subjects were confined in the clinic from 2 days prior to the start of the study ("Day minus 2") to Day 31 for monitoring of potential study drug effects. The subjects were released from the clinic on Day 31.

[0094] Blood samples were taken from the subjects 2 and 1 days prior to dosing (Days -2 and -1), and on Days 1, 3, 7, 10, 14, 21, 27, 28, and 29. Serum was prepared from those samples and used to determine the mean % change in LDL-cholesterol, mean TSH (thyroid-stimulating hormone), mean free T_3 (("FT_3") (free triiodothyronine)), mean free T_4 (("FT_4" (free thyroxine)), mean total T3, mean total T4, mean reverse triiodothyronine (rT3), and/or mean thyroxine-binding globulin (TBG). Serum levels of these parameters for the subjects were determined from the serum samples on Days -2, -1, 1, 3, 7, 10, 14, 21, 27, 28, and/or 29. The mean % change from baseline in LDL-cholesterol and the mean TSH, FT3, FT4, TT3, and TT4 thyroid parameter values are graphed in Figures 22-27 and are also shown below in table format.

LDL-cholesterol mean % change from baseline*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid 50 µg daily dose	**PBO**
Day 14	-24.5	0.98
Week 4**	-28.6	-0.10

* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

** Week 4 values are the mean of values from Days 27, 28, and 29.

TSH (normal range, 0.35-5.50 µIU/mL) absolute values*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid 50 µg daily dose	**PBO**
Day 14	1.625	2.305
Day 29	1.509	2.128

* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

Free T_3 (normal range, 1.80-4.20 pg/mL) absolute values*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid 50 µg daily dose	**PBO**
Day 14	**2.72**	**2.77**
Day 29	**2.46**	**2.73**

* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

Free T_4 (normal range, 0.90-1.80 ng/dL) absolute values*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid 50 µg daily dose	PBO
Day 14	**0.828**	**1.08**
Day 29	**0.840**	**1.19**

* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

Total T_3 (normal range, 0.60-1.8 ng/mL) absolute values*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid 50 µg daily dose	PBO
Day 14	1.13	1.24
Day 29	0.956	1.18

* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

Total T_4 (normal range, 4.5-10.9 µg/dL) absolute values*

	2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid 50 µg daily dose	PBO
Day 14	4.59	7.13
Day 29	4.06	7.18

* LOCF (last observation carried forward) values from post-baseline results were used to summarize any missing results for early termination subjects

[0095] As a person skilled in the art will readily appreciate, the above description is meant as an illustration of implementation of the principles this invention. This description is not intended to limit the scope or application of this invention in that the invention is susceptible to modification, variation and change, without departing from spirit of this invention, as defined in the following claims.

13459-00215

CLAIMS

What is claimed is:

1. A method of treating a human having a disease state which is alleviated by treatment with a thyroid hormone receptor agonist, which method comprises administering a therapeutically effective amount of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, to a human in need thereof in an amount of from about 10 µg to about 100 µg per day.

2. The method of claim 1, wherein said amount is from about 30 µg to about 70 µg per day.

3. The method of claim 1, wherein said amount is from about 40 µg to about 60 µg per day.

4. The method of claim 1, wherein said amount is from about 25 to about 45 µg/day.

5. The method of claim 1, wherein said amount is from about 55 to about 75 µg per day.

6. The method of claim 1, wherein said amount is 10 µg, 30 µg, 50 µg, 70 µg, or 100 µg per day.

7. The method of claim 1, wherein said amount is 30 µg per day.

8. The method of claim 1, wherein said amount is 50 µg per day.

9. The method of claim 1, wherein said amount is 70 µg per day.

10. The method of any of claims 2-6, wherein 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid is in the free acid form.

11. The method of claim 10, wherein the disease state is cardiovascular disease, atherosclerosis, hypercholesterolemia, Fredrickson Type IIa dyslipidemia, Fredrickson Type IIb dyslipidemia, Fredrickson Type III dyslipidemia, Fredrickson Type IV dyslipidemia, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia.

12. The method of claim 10, wherein the disease state is obesity.

13. The method of claim 10, wherein the disease state is hypothyroidism in the setting of cardiac arrhythmia, resistance to thyroid hormone, or hypothyroidism in the setting of osteoporosis.

14. The method of claim 10, wherein the disease state is depression.

15. The method of claim 10, wherein LDL-cholesterol levels are decreased by greater than about 15% after 14 days of dosing at an amount of 10 to 100 µg/day.

16. The method of claim 10, wherein LDL-cholesterol levels are decreased by greater than about 22% after 14 days of dosing at an amount of 10 to 100 µg/day.

17. The method of claim 10, wherein LDL-cholesterol levels are decreased from about 22% to about 33% after 14 days of dosing at an amount of 10 to 100 µg/day.

18. The method of claim 10, wherein TSH is above 0.35 µIU/ml after 14 days of dosing at an amount of 10 to 100 µg/day.

19. The method of claim 10, wherein TSH is above 1 µIU/ml after 14 days of dosing at an amount of 10 to 100 µg/day.

20. The method of claim 19, wherein the FT_3 level is above about 2.3 pg/ml after 14 days of dosing at an amount of 10 to 100 µg/day.

21. The method of claim 19, wherein the FT_3 level is above about 2.45 pg/ml after 14 days of dosing at an amount of 10 to 100 µg/day.

22. The method of claim 19, wherein the TT_3 level is above about 0.6 ng/ml after 14 days of dosing at an amount of 10 to 100 µg/day.

23. The method of claim 19, wherein the TT_3 level is above about 0.6 ng/ml and below about 1.81 ng/ml after 14 days of dosing at an amount of 10 to 100 µg/day.

24. The method of claim 19, wherein said amount is from about 30 µg to about 70 µg per day.

25. The method of claim 19, wherein said amount is from about 40 µg to about 60 µg per day.

26. The method of claim 19, wherein said amount is from about 25 to about 45 µg/day.

27. The method of claim 19, wherein said amount is from about 55 to about 75 µg per day.

28. The method of claim 19, wherein said amount is 10 µg, 30 µg, 70 µg, or 100 µg per day.

29. The method of claim 19, wherein said amount is 30 µg per day.

30. The method of claim 19, wherein said amount is 50 µg per day.

31. The method of claim 19, wherein said amount is 70 µg per day.

32. The method of claim 1, wherein the C_{max} is less than about 10 ng/ml after 14 days of dosing.

33. The method of claim 1, wherein the C_{max} is from about 0.18 to about 2.32 ng/ml after 14 days of dosing.

34. The method of claim 1, wherein the C_{max} is from about 0.50 to about 2.32 ng/ml after 14 days of dosing.

35. The method of claim 1, wherein the $AUC_{(0\text{-}tau)}$ is less than about 10 ng*h/ml after 14 days of dosing.

36. The method of claim 1, wherein the $AUC_{(0\text{-}tau)}$ is from about 0.73 to about 7.07 ng*h/ml after 14 days of dosing.

37. The method of claim 1, wherein the $AUC_{(0\text{-}tau)}$ is from about 1.38 to about 7.07 ng*h/ml after 14 days of dosing.

38. A pharmaceutical composition comprising from about 10 µg to about 100 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

39. The pharmaceutical composition of claim 38, comprising from about 30 µg to about 70 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

40. The pharmaceutical composition of claim 38, comprising from about 40 µg to about 60 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

41. The pharmaceutical composition of claim 38, comprising from about 25 to about 45 µg.

42. The pharmaceutical composition of claim 38, comprising from about 55 to about 75 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

43. The pharmaceutical composition of claim 38, comprising 10 µg, 30 µg, 70 µg, or 100 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

44. The pharmaceutical composition of claim 38, comprising 30 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

45. The pharmaceutical composition of claim 38, comprising 50 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

46. The pharmaceutical composition of claim 38, comprising 70 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

47. The pharmaceutical composition of any of claims 39-43, wherein 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid is in the free acid form.

48. The pharmaceutical composition of claim 47, wherein the disease state is cardiovascular disease, atherosclerosis, hypercholesterolemia, Fredrickson Type IIa dyslipidemia, Fredrickson Type IIb dyslipidemia, Fredrickson Type III dyslipidemia,

Fredrickson Type IV dyslipidemia, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia.

49. The pharmaceutical composition of claim 47, wherein the disease state is obesity.

50. The pharmaceutical composition of claim 47, wherein the disease state is hypothyroidism in the setting of cardiac arrhythmia, resistance to thyroid hormone, or hypothyroidism in the setting of osteoporosis.

51. The pharmaceutical composition of claim 47, wherein the disease state is depression.

52. The pharmaceutical composition of claim 48, comprising 30 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

53. The pharmaceutical composition of claim 48, comprising 50 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

54. The pharmaceutical composition of claim 48, comprising 70 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

55. A unit dosage form for the treatment of human suffering from a disease state which is alleviated by treatment with a thyroid hormone receptor agonist comprising from about 10 μg to about 100 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

56. The unit dosage form of claim 55, comprising from about 30 μg to about 70 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

57. The unit dosage form of claim 55, comprising from about 40 μg to about 60 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

58. The unit dosage form of claim 55, comprising from about 25 to about 45 μg/day.

59. The unit dosage form of claim 55, comprising from about 55 to about 75 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

60. The unit dosage form of claim 55, comprising 10 µg, 30 µg, 70 µg, or 100 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

61. The unit dosage form of claim 55, comprising 30 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

62. The unit dosage form of claim 55, comprising 50 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

63. The unit dosage form of claim 55, comprising 70 µg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

64. The unit dosage form of any of claims 56-60, wherein 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid is in the free acid form.

65. The unit dosage form of claim 64, wherein the disease state is cardiovascular disease, atherosclerosis, hypercholesterolemia, Fredrickson Type IIa dyslipidemia, Fredrickson Type IIb dyslipidemia, Fredrickson Type III dyslipidemia, Fredrickson Type IV dyslipidemia, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia.

66. The unit dosage form of claim 56, wherein the disease state is obesity.

67. The unit dosage form of claim 56, wherein the disease state is hypothyroidism in the setting of cardiac arrhythmia, resistance to thyroid hormone, or hypothyroidism in the setting of osteoporosis.

68. The unit dosage form of claim 56, wherein the disease state is depression.

69. The unit dosage form of claim 68, wherein when administered to a human, the unit dosage decreases LDL-cholesterol levels by greater than about 15% after 14 days of dosing at an amount of 10 to 100 µg/day.

70. The unit dosage form of claim 68, wherein when administered to a human, the unit dosage decreases LDL-cholesterol levels by greater than about 22% after 14 days of dosing at an amount of 10 to 100 µg/day.

71. The unit dosage form of claim 68, wherein when administered to a human, the unit dosage decreases LDL-cholesterol levels by from about 22% to about 33% after 14 days of dosing at an amount of 10 to 100 µg/day.

72. The unit dosage form of claim 69, wherein when administered to a human, TSH is above 0.35 µIU/ml after 14 days of dosing at an amount of 10 to 100 µg/day.

73. The unit dosage form of claim 69, wherein when administered to a human, TSH is above 1 μIU/ml after 14 days of dosing at an amount of 10 to 100 μg/day.

74. The unit dosage form of claim 73, wherein when administered to a human, the FT_3 level is above about 2.3 pg/ml after 14 days of dosing at an amount of 10 to 100 μg/day.

75. The unit dosage form of claim 73, wherein when administered to a human, the FT_3 level is above about 2.45 pg/ml after 14 days of dosing at an amount of 10 to 100 μg/day.

76. The unit dosage form of claim 73, wherein when administered to a human, the TT_3 level is above about 0.6 ng/ml after 14 days of dosing at an amount of 10 to 100 μg/day.

77. The unit dosage form of claim 73, wherein when administered to a human, the TT_3 level is above about 0.6 ng/ml and below about 1.81 ng/ml after 14 days of dosing at an amount of 10 to 100 μg/day.

78. The unit dosage form of claim 73, comprising from about 30 μg to about 70 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

79. The unit dosage form of claim 73, comprising from about 40 μg to about 60 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

80. The unit dosage form of claim 73, comprising from about 25 to about 45 μg.

81. The unit dosage form of claim 73, comprising from about 55 to about 75 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

82. The unit dosage form of claim 73, comprising 10 μg, 30 μg, 50 μg, 70 μg, or 100 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

83. The unit dosage form of claim 73, comprising 30 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

84. The unit dosage form of claim 73, comprising 50 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

85. The unit dosage form of claim 73, comprising 70 μg of 2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetic acid, or a pharmaceutically acceptable salt thereof.

86. The unit dosage form of claim 55, wherein when administered to a human, the unit dosage produces a C_{max} of less than about 10 ng/ml after 14 days of dosing.

87. The unit dosage form of claim 55, wherein when administered to a human, the unit dosage produces a C_{max} of from about 0.18 to about 2.32 ng/ml after 14 days of dosing.

88. The unit dosage form of claim 55, wherein when administered to a human, the unit dosage produces a C_{max} of from about 0.50 to about 2.32 ng/ml after 14 days of dosing.

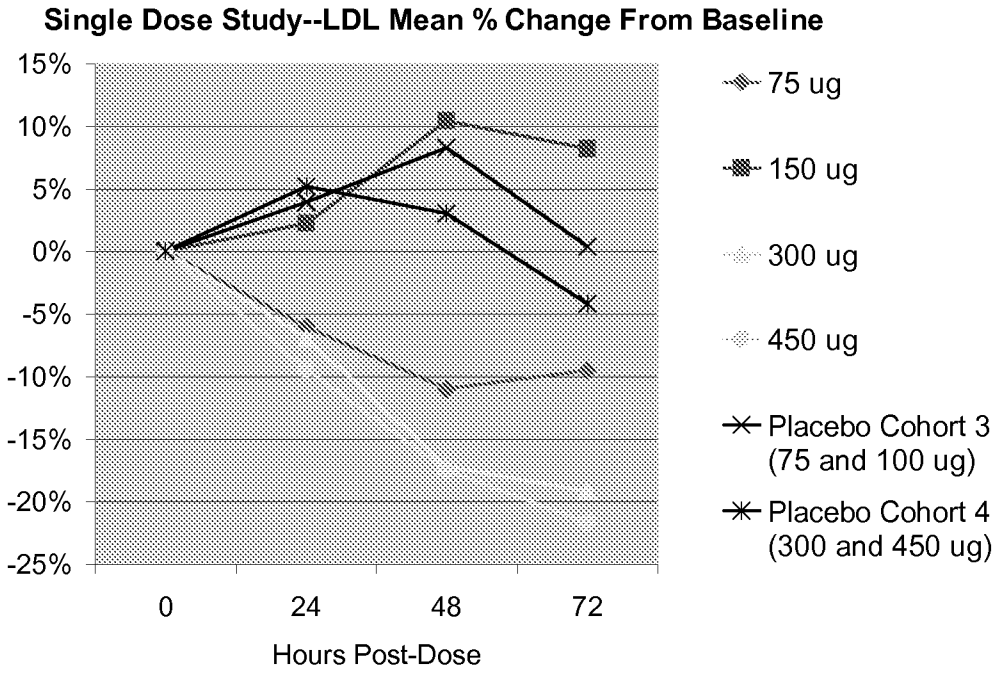
89. The unit dosage form of claim 55, wherein when administered to a human, the unit dosage produces an $AUC_{(0\text{-}tau)}$ of less than about 10 ng*h/ml after 14 days of dosing.

90. The unit dosage form of claim 55, wherein when administered to a human, the unit dosage produces an $AUC_{(0\text{-}tau)}$ of from about 0.73 to about 7.07 ng*h/ml after 14 days of dosing.

91. The unit dosage form of claim 55, wherein when administered to a human, the unit dosage produces an $AUC_{(0\text{-}tau)}$ of from about 1.38 to about 7.07 ng*h/ml after 14 days of dosing.

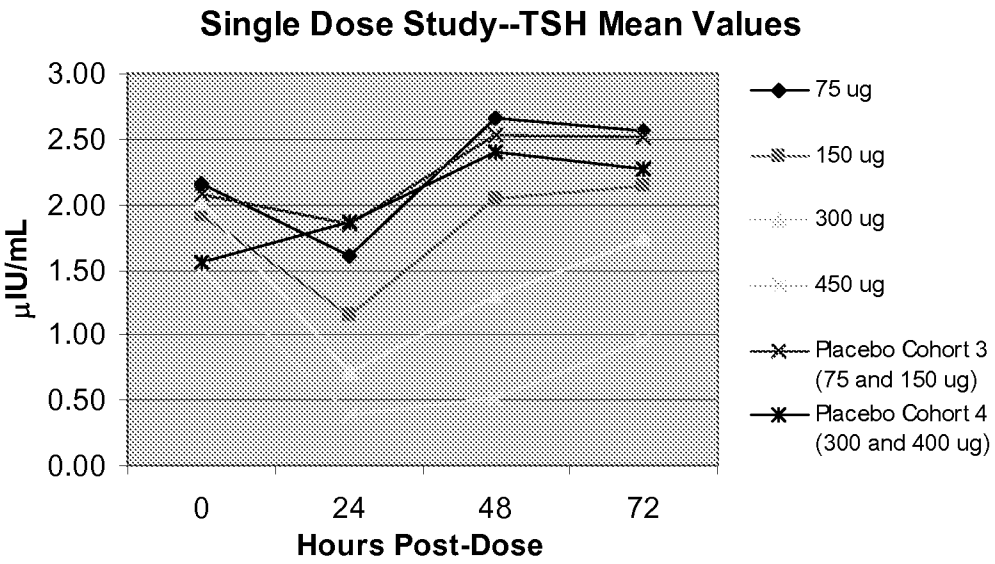
13459-00215

Figure 1



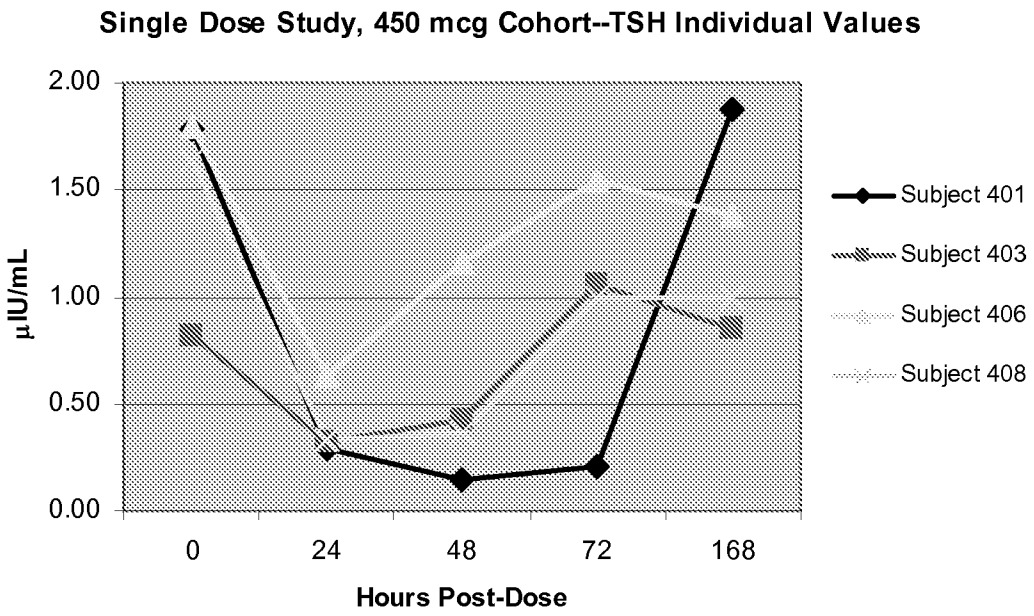
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Figure 2



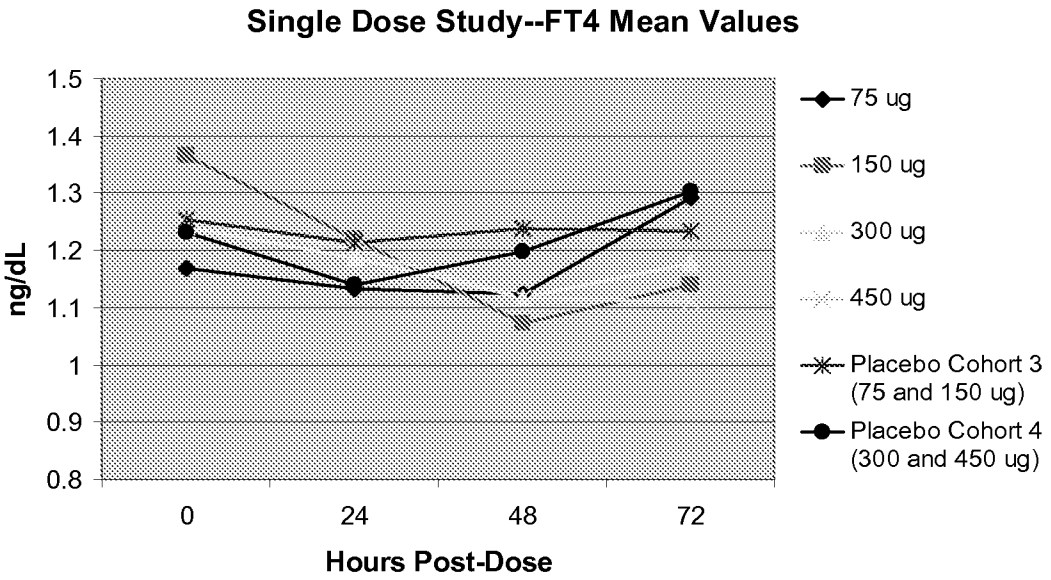
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Figure 3



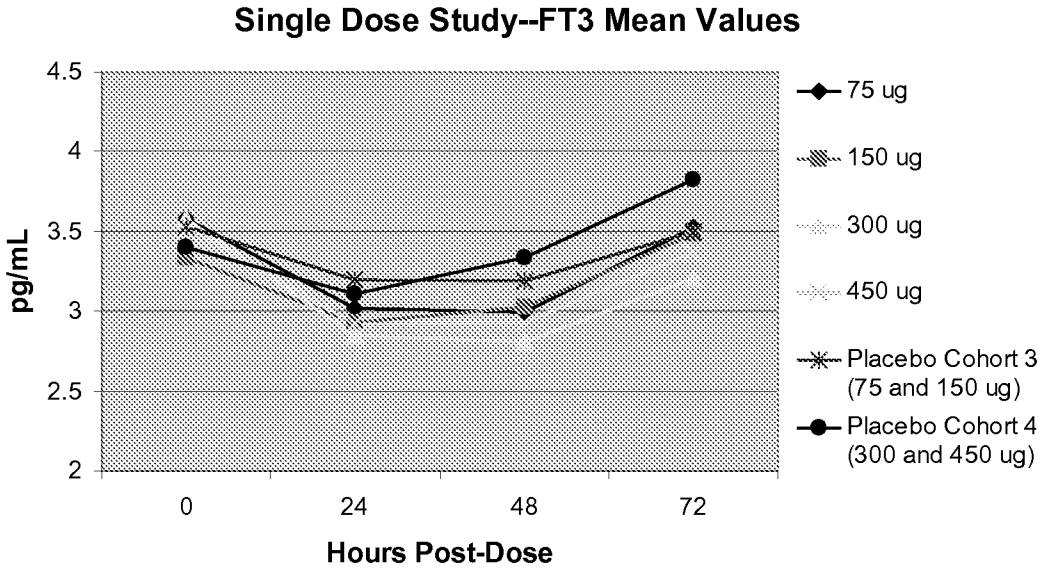
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Figure 4



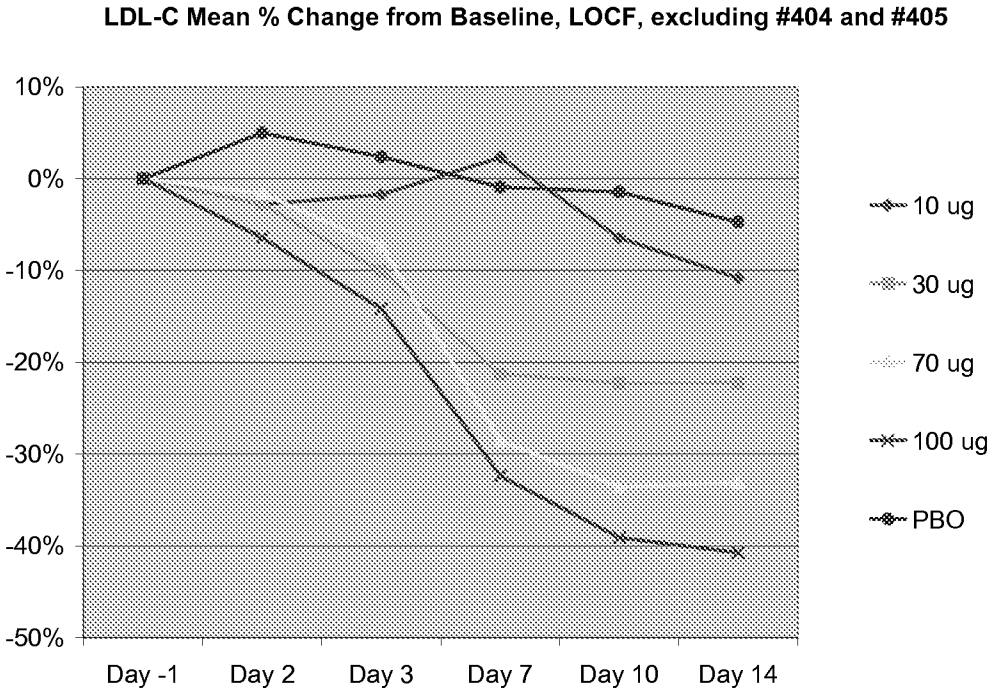
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Figure 5



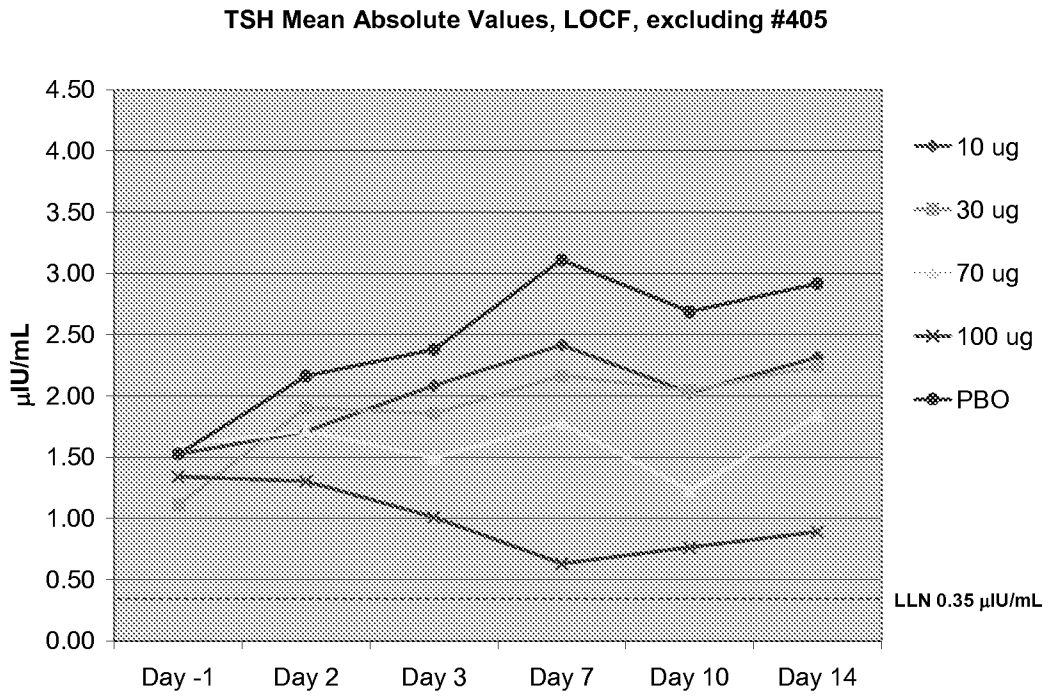
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Figure 6



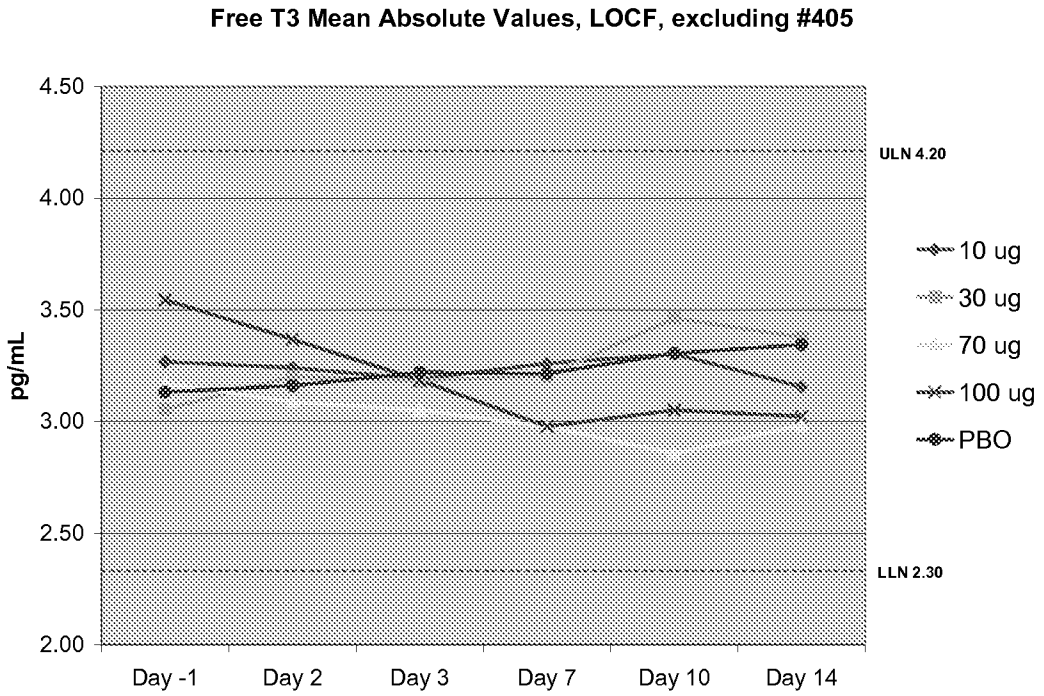
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Figure 7



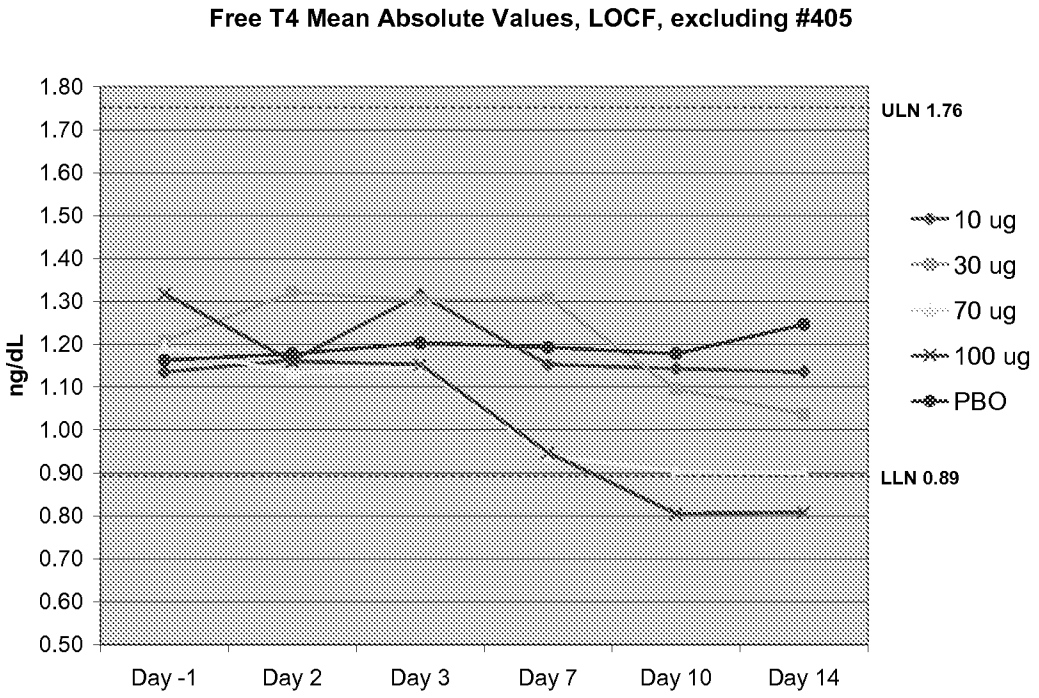
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Figure 8



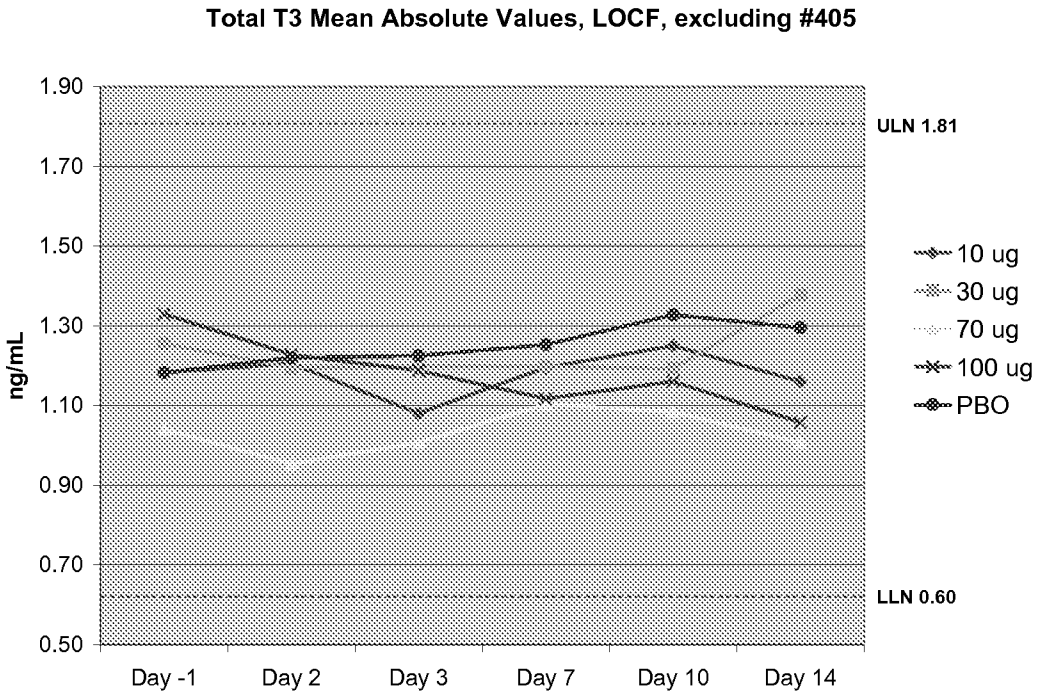
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Figure 9



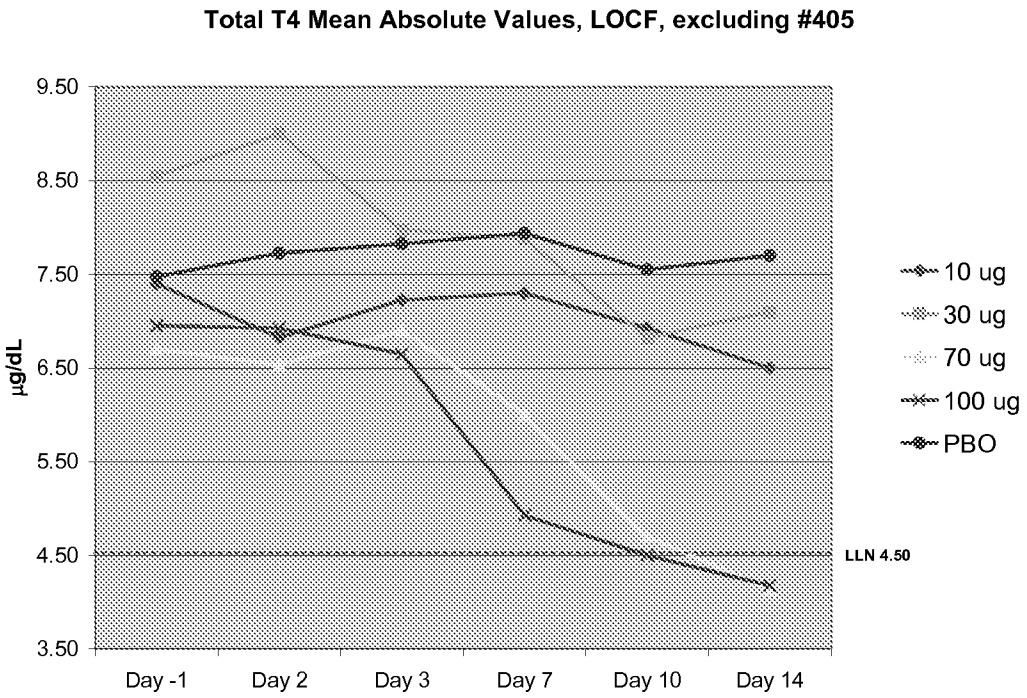
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Figure 10



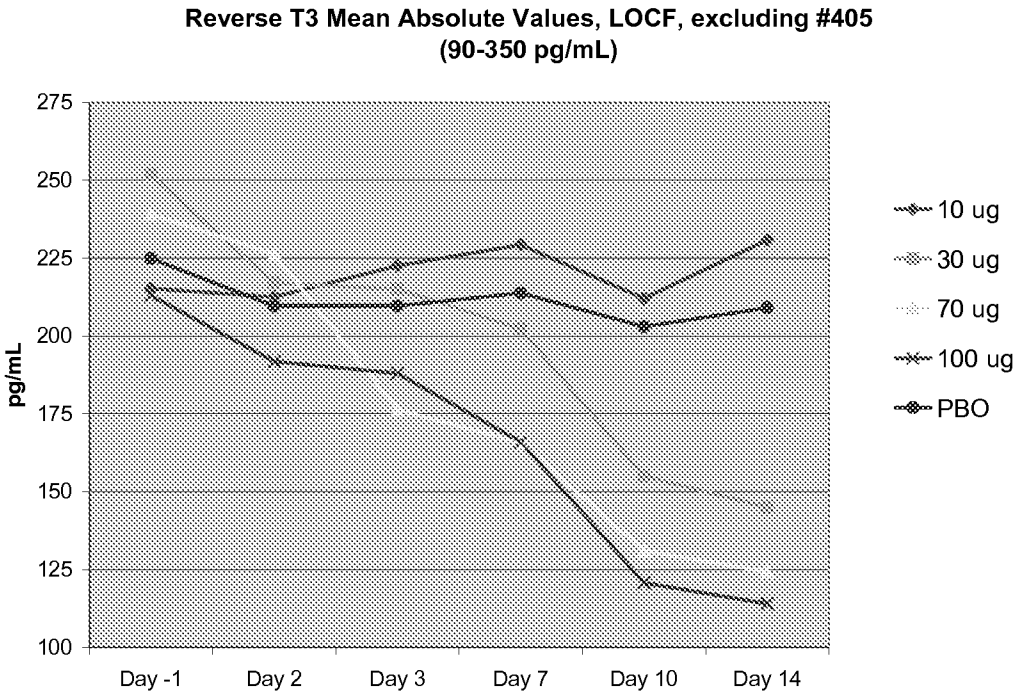
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Figure 11



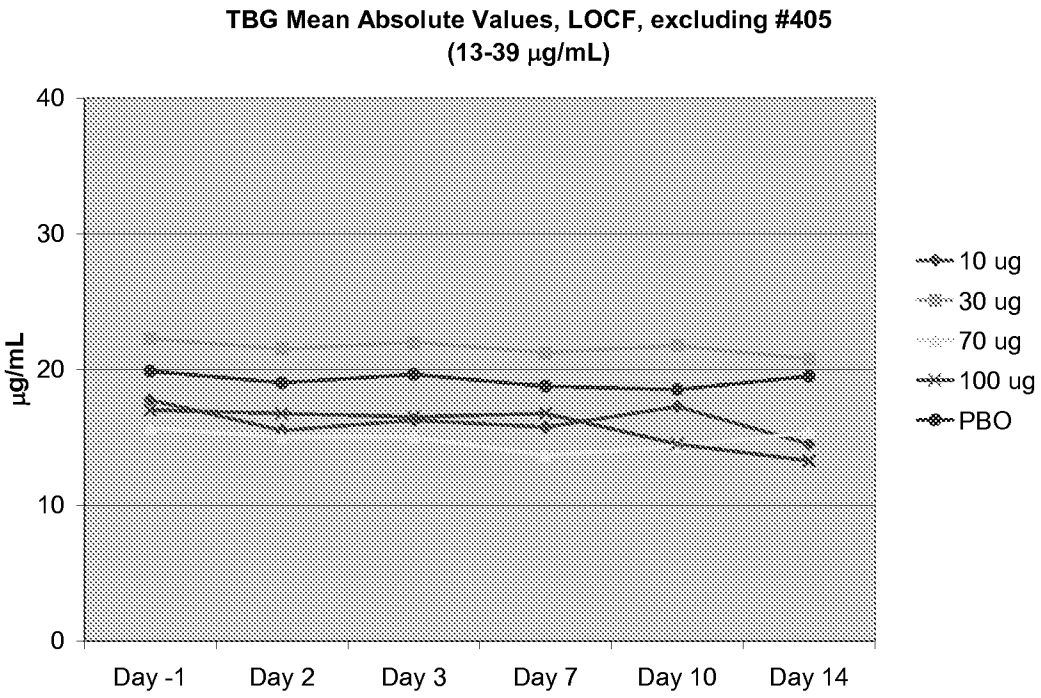
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Figure 12



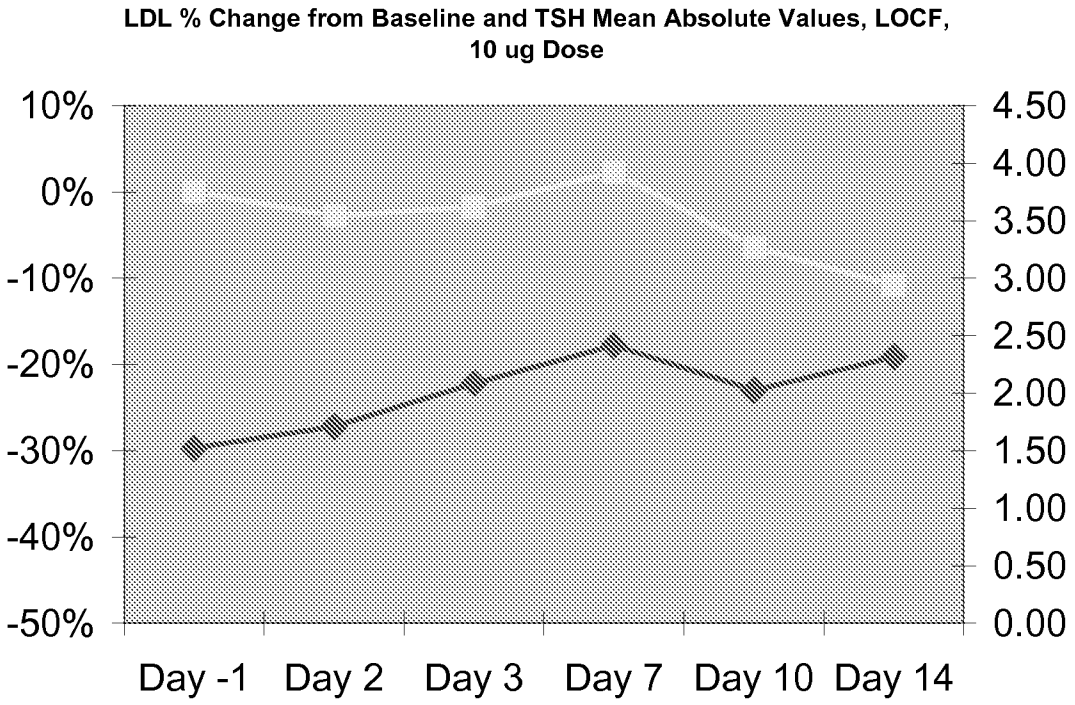
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Figure 13



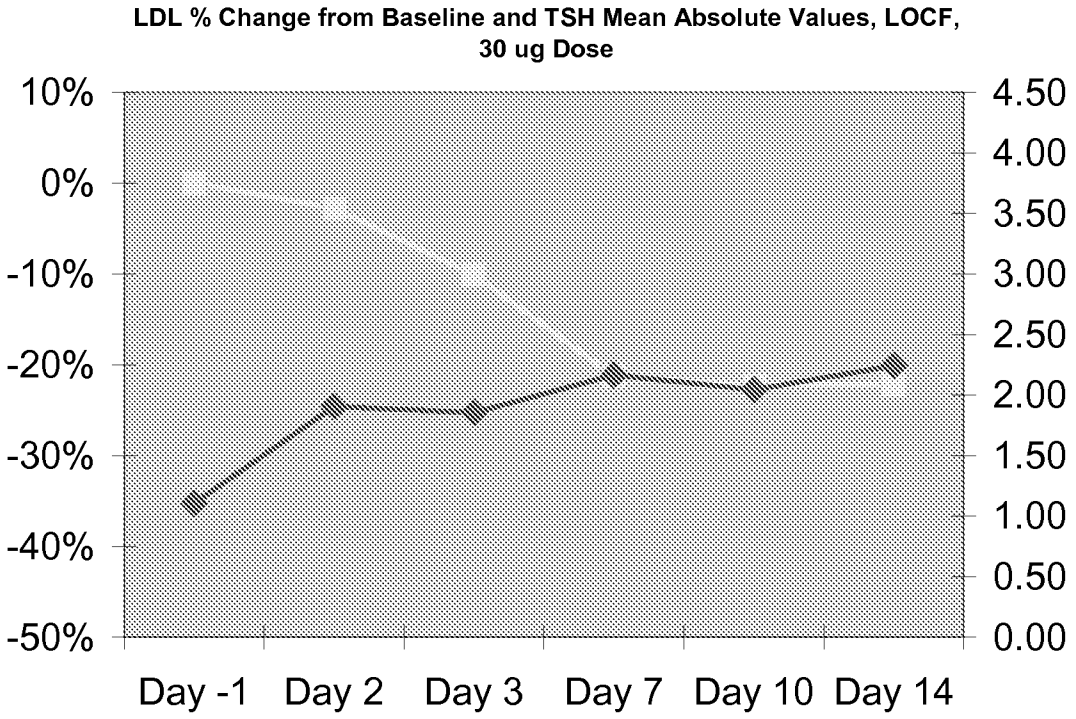
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Figure 14



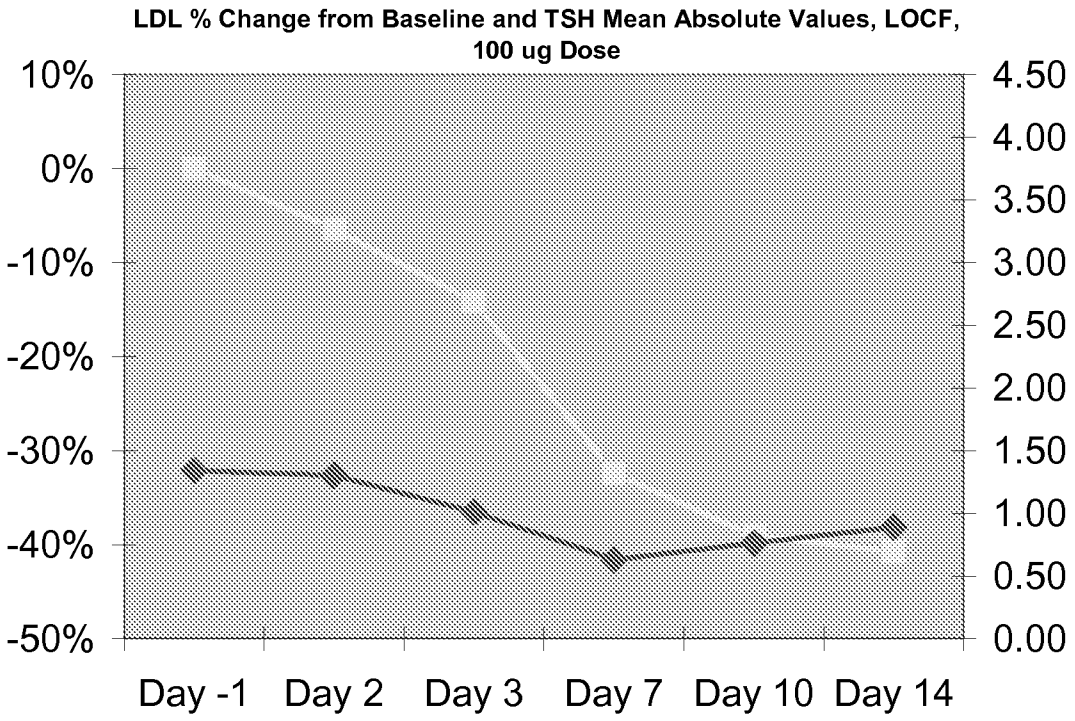
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Figure 15



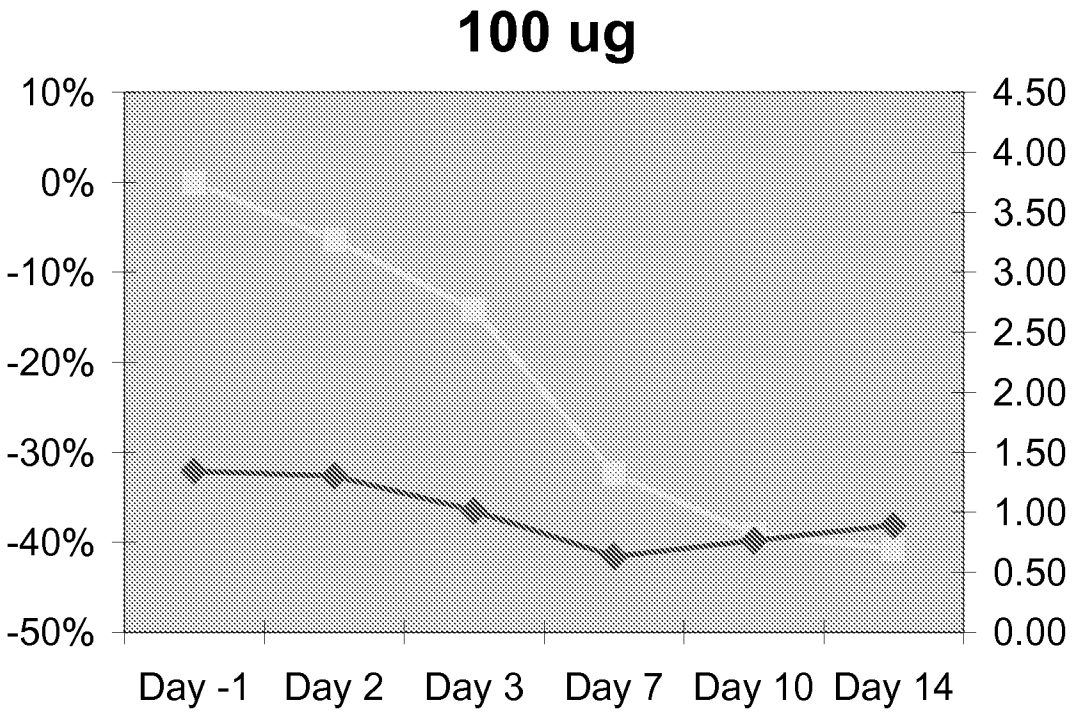
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Figure 16



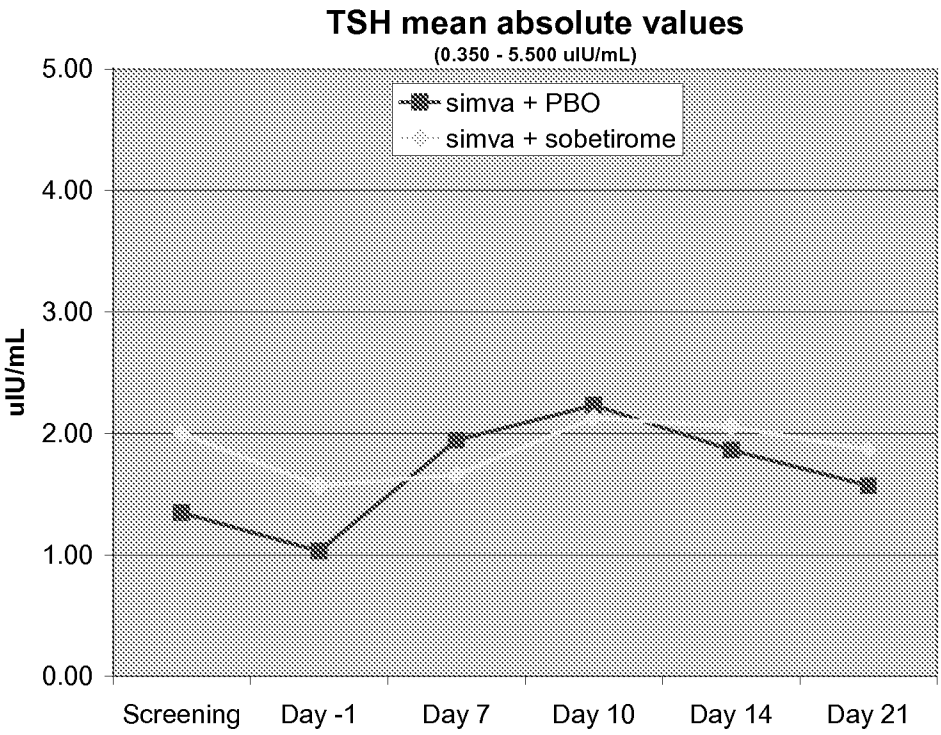
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Figure 17



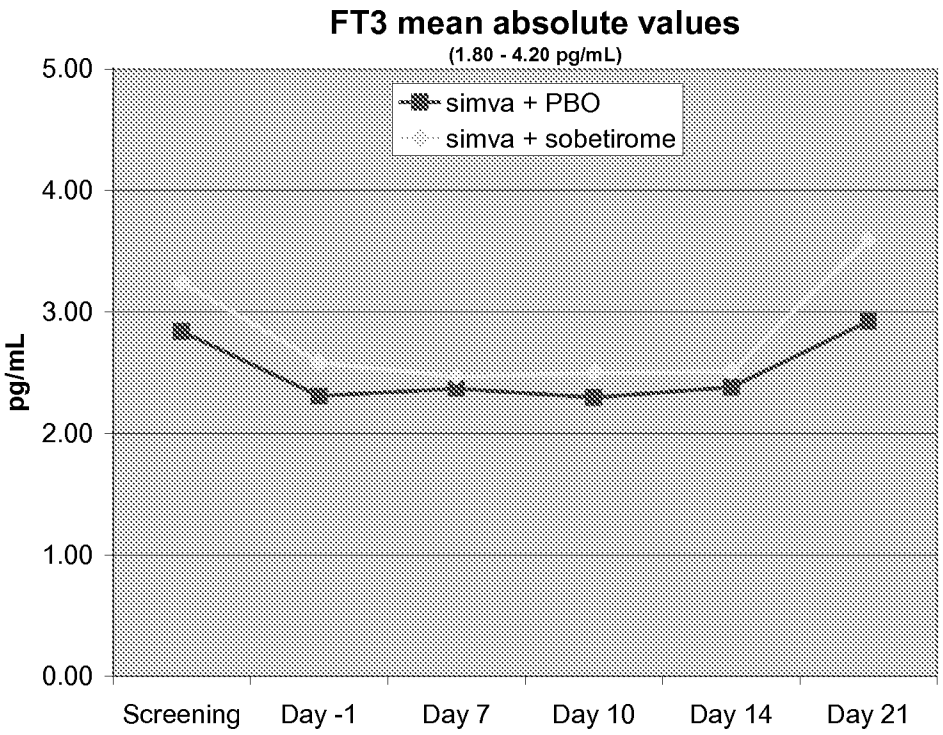
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Figure 18



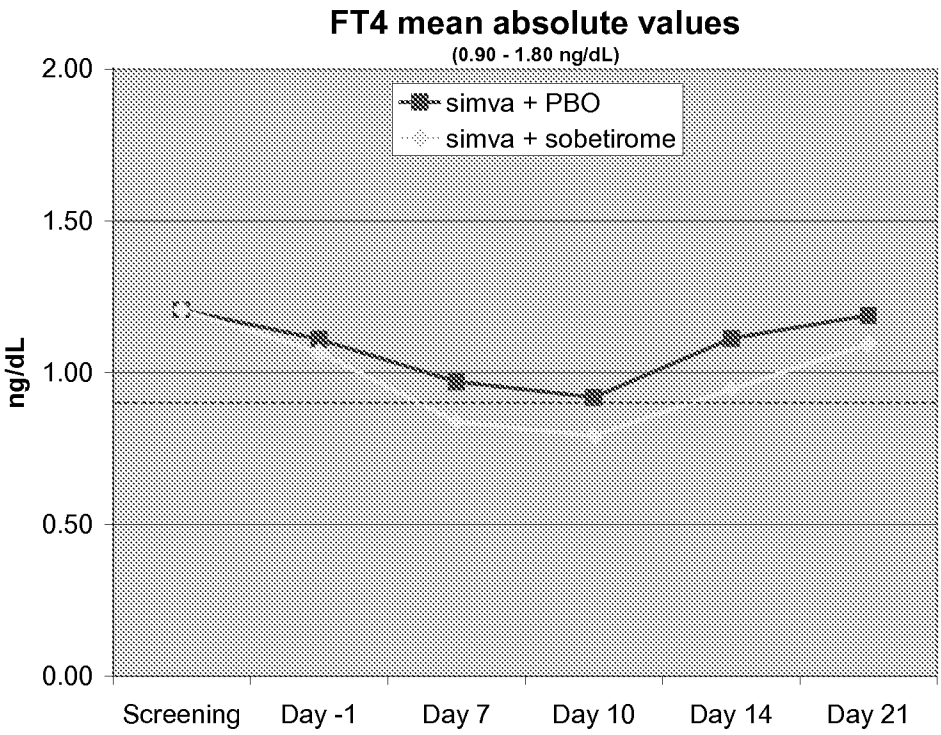
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Figure 19



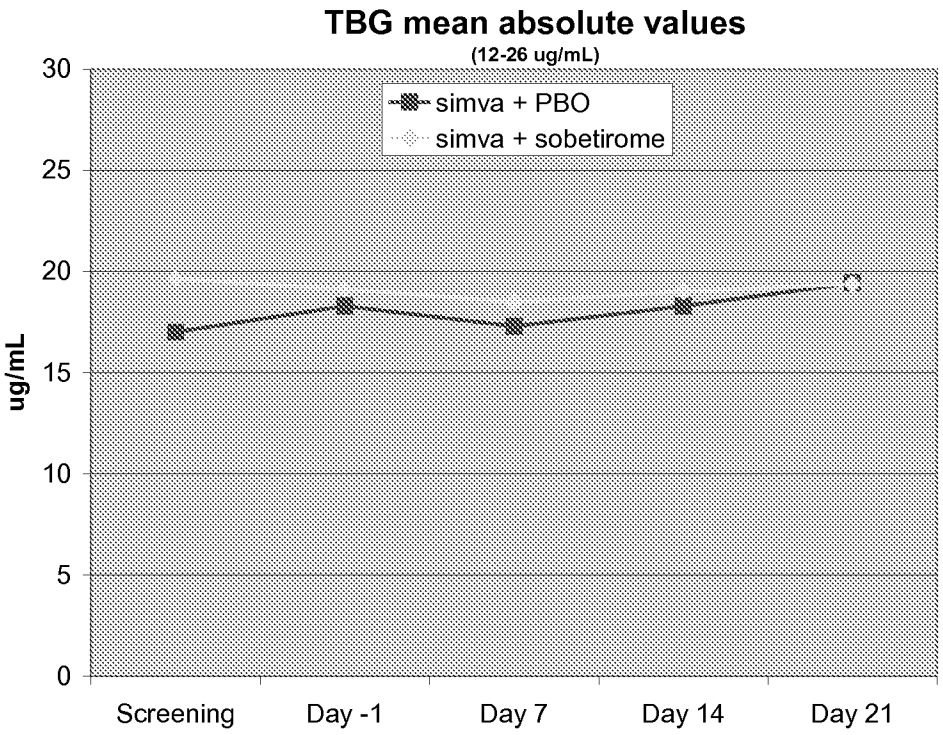
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Figure 20



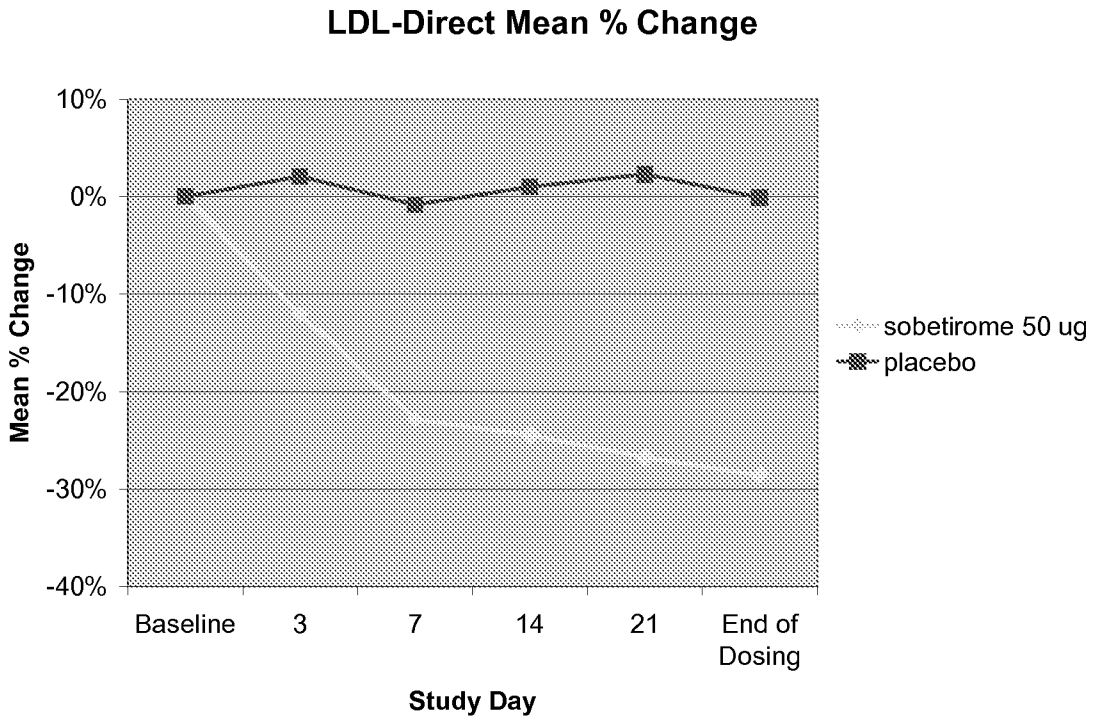
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Figure 21



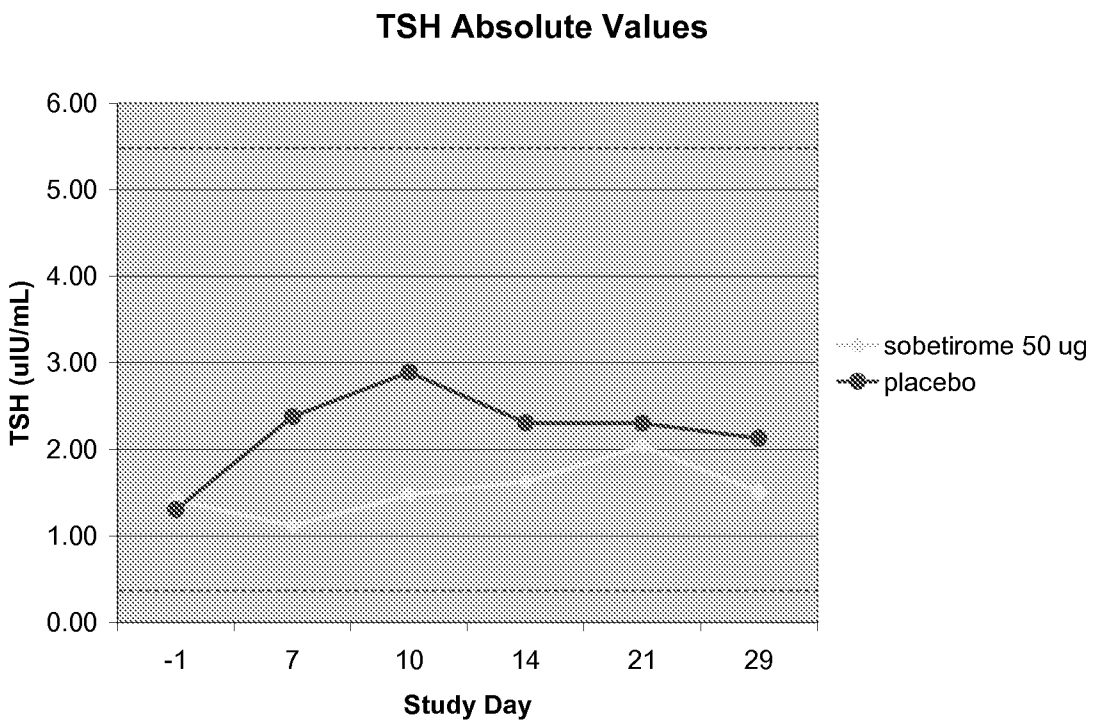
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Figure 22



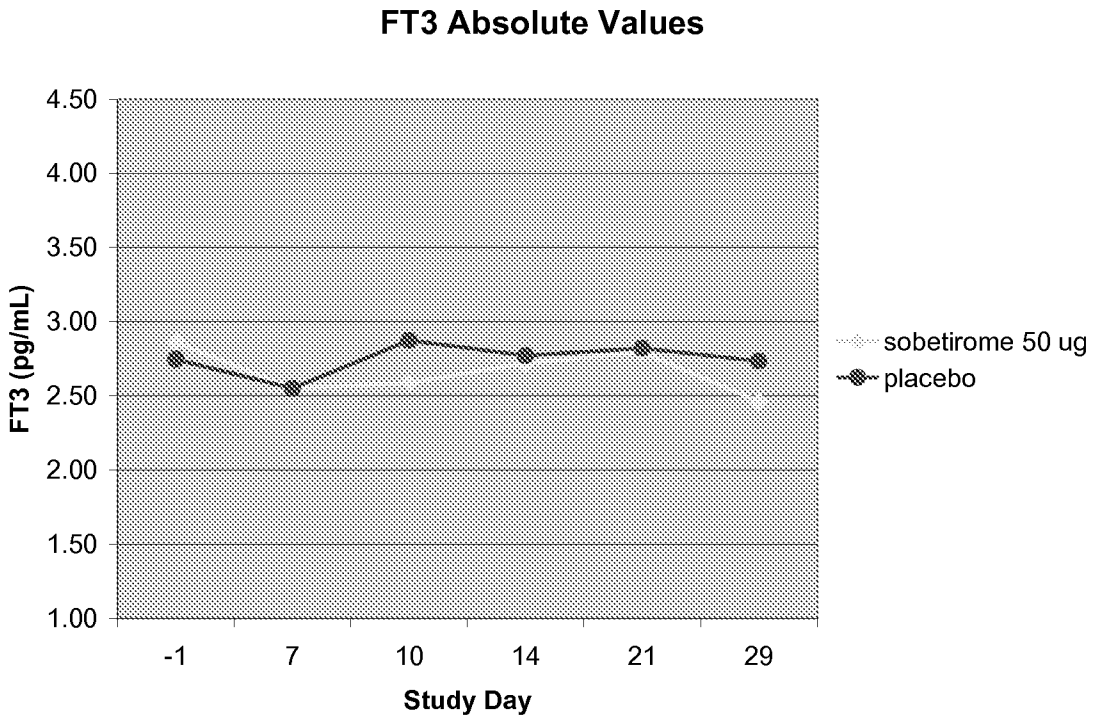
13459-00215

Figure 23



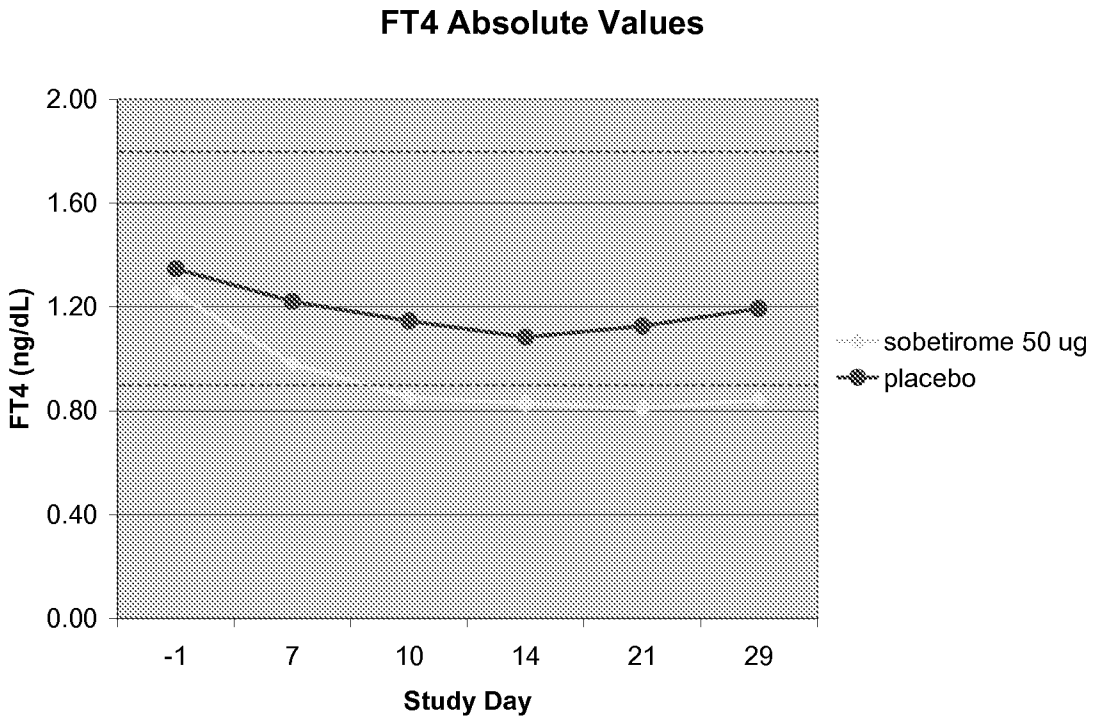
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Figure 24



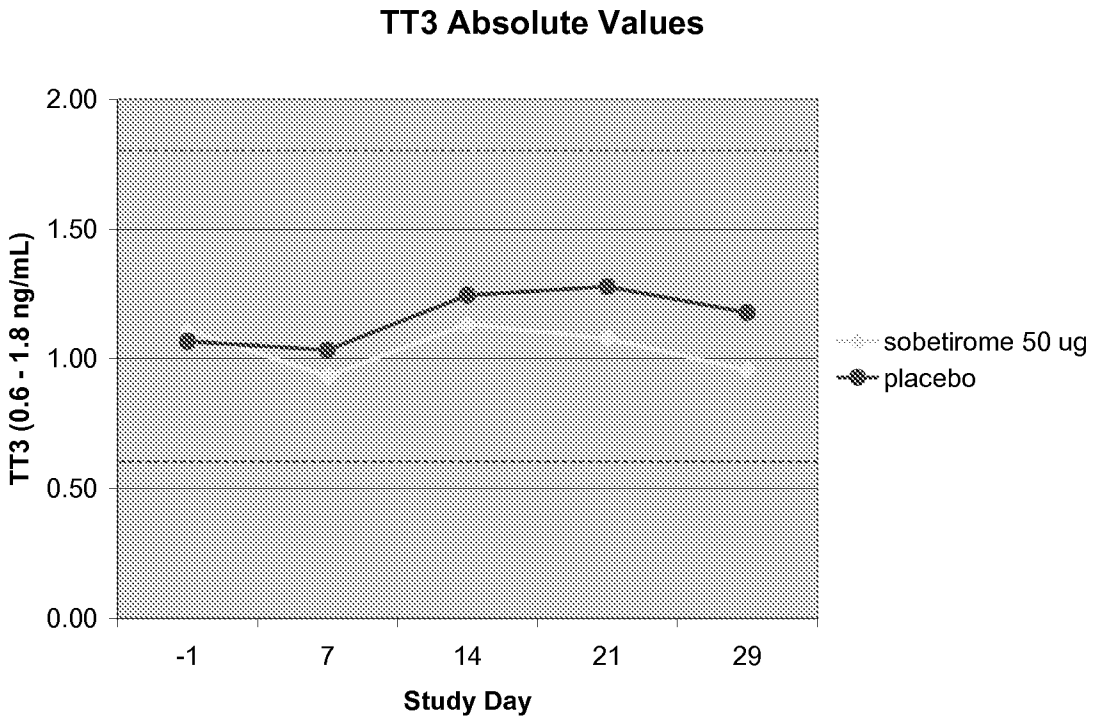
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Figure 25



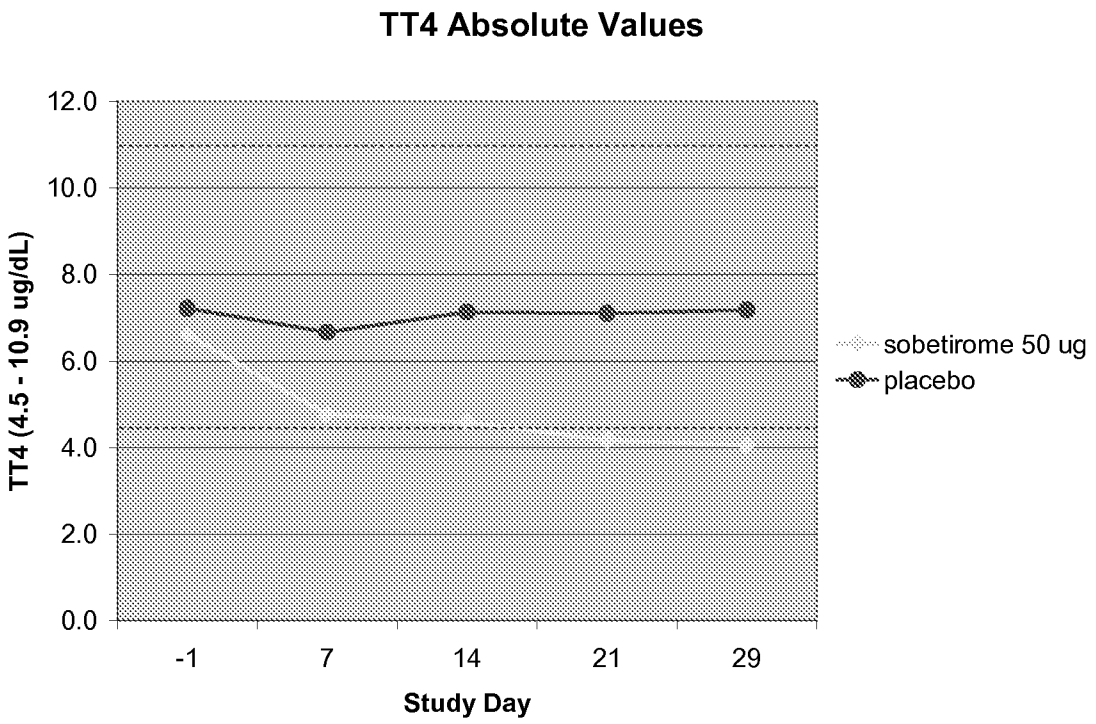
13459-00215

Figure 26



13459-00215

Figure 27



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/030018

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/192 A61P3/04 A61P3/06 A61P9/00 A61P9/10
A61P5/14 A61P5/06 A61P19/10 A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/57919 A (UNIV CALIFORNIA [US]) 23 December 1998 (1998-12-23)	1-3,5,6, 8-25,27, 28, 30-40, 42,43, 45-51, 53-57, 59,60, 62-79, 81,82, 84-91
Y	page 2, lines 14-26 - page 3, lines 1-10 page 29 - page 32; examples 15-20 page 41; claim 6 page 5, line 21 - line 23 page 41 - page 42; claims 11-17 -/--	4,7,26, 29,44, 52,58, 61,80,83

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 April 2009	08/05/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Opravz, Petra

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	page 9, lines 31,32	
X	TROST S U ET AL: "The thyroid hormone receptor-beta-selective agonist GC-1 differentially affects plasma lipids and cardiac activity." ENDOCRINOLOGY SEP 2000, vol. 141, no. 9, September 2000 (2000-09), pages 3057-3064, XP002521413 ISSN: 0013-7227	38-43, 45, 47-50,53
Y	page 3062, left-hand column abstract page 3058; figure 1 page 3061; figures 4,5 page 3062; figure 6 page 3058, right-hand column	4,7,26, 29,44, 52,58, 61,80,83
X	GROVER GARY J ET AL: "Effects of the thyroid hormone receptor agonist GC-1 on metabolic rate and cholesterol in rats and primates: selective actions relative to 3,5,3'-triiodo-L-thyronine." ENDOCRINOLOGY APR 2004, vol. 145, no. 4, April 2004 (2004-04), pages 1656-1661, XP002521414 ISSN: 0013-7227	38-43, 47-50
Y	abstract page 1657; figure 1 page 1658; figure 3 page 1657, left-hand column, paragraph 1 page 1658 page 1661	4,7,26, 29,44, 52,58, 61,80,83
X	JOHANSSON LISEN ET AL: "Selective thyroid receptor modulation by GC-1 reduces serum lipids and stimulates steps of reverse cholesterol transport in euthyroid mice." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 19 JUL 2005, vol. 102, no. 29, 19 July 2005 (2005-07-19), pages 10297-10302, XP002521415 ISSN: 0027-8424 abstract page 10297, left-hand column page 10298, right-hand column page 10299	38

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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