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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 January 2018 (11.01.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/009842 A1

(51) International Patent Classification:
A61K 31/41 (2006.01) *A61K 31/44* (2006.01)
A61K 31/4164 (2006.01) *G01N 33/53* (2006.01)

(21) International Application Number:
PCT/US2017/041162

(22) International Filing Date:
07 July 2017 (07.07.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/360,262 08 July 2016 (08.07.2016) 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, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) **Title:** METHODS FOR ROSUVASTATIN DOSING BY AUC

(57) **Abstract:** Methods for anti-dyslipidemia drug dosing by pharmacokinetic parameter determination. In one embodiment, the anti-dyslipidemia drug is rosuvastatin and the pharmacokinetic parameter is AUC. The methods are effective for treating dyslipidemia.

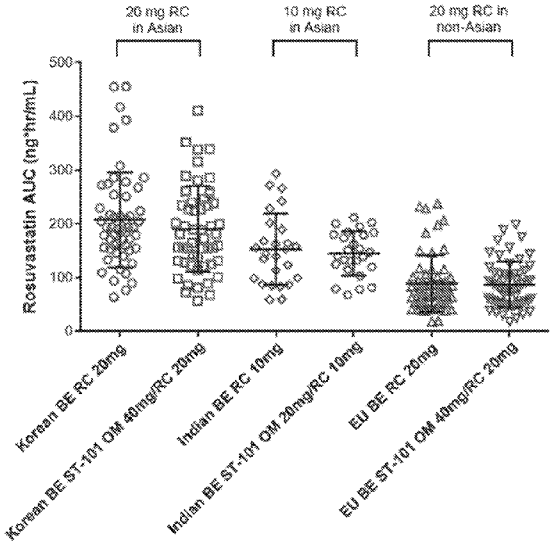

Fig. 1

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METHODS FOR ROSUVASTATIN DOSING BY AUC

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of US Application No. 62/360,262, filed July 8, 2016, expressly incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to method for dosing rosuvastatin by AUC and related methods for treating dyslipidemia.

BACKGROUND OF THE INVENTION

Dyslipidemia (hyperlipidemia) is a condition that is regarded as a risk factor that progress heart diseases and ultimately cause adverse cardiac symptoms. Individual therapeutic agents for individually treating dyslipidemia are well known.

HMG-CoA reductase inhibitors (e.g., statins) are potent therapeutic agents for the reduction of plasma cholesterol and therefore the reduction of risk for atherosclerosis/ cardiovascular events. However, statins are associated with myalgia and other side effects which limited its usage. Rosuvastatin, an HMG-CoA reductase inhibitor, is useful for the treatment of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis; and rosuvastatin's calcium salt is commercially available under the designation Crestor™.

There is high variability of the pharmacokinetics for statins when conventionally dosed at mg/day, which in turn results in highly variable outcomes. Additionally, there are statins, such as rosuvastatin, that suffer from race effect such that a lower dose of statin is required for Asian in order to achieve comparable efficacy as non-Asian. The primary responsible factor being higher drug exposure – as AUC – in Asian versus non-Asian including Caucasian populations.

Therefore, despite advances in the development of dyslipidemia treatments and related therapeutic drugs, their formulations, and methods for their administration, a need exists to further improve the clinical effectiveness of the administration of statins. The present invention seeks to fulfill this need and provides further related advantages.

SUMMARY OF THE INVENTION

Pharmacokinetic (PK) variability and differences can be mitigated with PK-guided rosuvastatin dosing (e.g., area-under-the-curve, AUC). Because lower rosuvastatin dose is recommended for Asian population, and that no target rosuvastatin

exposure level (e.g., target AUC level) has been suggested by the art, the inventor performed clinical PK studies to define the target AUC based on the median AUC of Caucasians treated at optimal dose of 20 mg/day. Furthermore, the inventor demonstrated that surprisingly, PK for the Asian population is not dose proportional and therefore PK-guided dosing will require determining the AUC; adjusting the rosuvastatin dose, confirming the rosuvastatin AUC, and re-dosing rosuvastatin. These steps are repeated (i.e., iterated) until the target rosuvastatin AUC is achieved.

In one aspect, the invention defines a target AUC for patients treated with rosuvastatin and provides a method for rosuvastatin dosing guided by AUC.

In accordance with the invention and as described herein, a target rosuvastatin AUC for patients treated with rosuvastatin was determined to be 80 ng*hr/mL ± 15% (i.e., from 68 to 92 ng*hr/mL).

In one embodiment, the method comprises:

(a) administering rosuvastatin at a first dose to a subject (i.e., patient) in need of therapy;

(b) determining the concentration of rosuvastatin the subject's blood at one or more time points after administration of rosuvastatin to provide a set of rosuvastatin concentration/time data points;

(c) transforming the set of rosuvastatin concentration/time data points to provide rosuvastatin area-under-the-curve (AUC); and

(d) administering rosuvastatin to the subject at subsequent doses (e.g., second and subsequent doses) to achieve a target rosuvastatin AUC of 80 ng*hr/mL.

In another aspect, the invention provides a method for anti-dyslipidemia drug dosing by one or more pharmacokinetic parameters. In one embodiment, the method comprises:

(a) administering an anti-dyslipidemia drug at a first dose to a subject in need of therapy;

(b) determining the concentration of the anti-dyslipidemia drug in the subject's blood at one or more time points after administration of the anti-dyslipidemia drug to provide a set of anti-dyslipidemia drug concentration/time data points;

(c) transforming the set of anti-dyslipidemia drug concentration/time data points to provide one or more pharmacokinetic parameters; and

(d) administering the anti-dyslipidemia drug to the subject at subsequent doses (e.g., second and subsequent doses) to achieve a target optimal value for the one or more pharmacokinetic parameters.

The one or more pharmacokinetic parameters can be one or more of concentration time course, peak concentration (C_{max}), and time after administration to peak concentration, terminal half-life, area-under-the-curve (AUC), bioavailability, absorption, distribution, metabolism, excretion, biotransformation, and combinations thereof. In one embodiment, the pharmacokinetic parameter is area-under-the-curve (AUC).

In certain embodiments, the target optimal value (rosuvastatin AUC) is ± 15% of the target optimal value. In other embodiments, the target optimal value (rosuvastatin AUC) is ± 20% of the target optimal value. In further embodiments, the target optimal value (rosuvastatin AUC) is ± 30% of the target optimal value.

In certain embodiments of the above methods, the second dose is the same or substantially the same as the first dose; in other embodiments, the second dose is greater than the first dose; and in further embodiments, the second dose is less than the first dose.

In certain embodiments, the above methods further including repeating steps (a)-(d) until dyslipidemia control is achieved.

In certain embodiments of the above methods, the subject is in need of treatment for dyslipidemia, and the method comprises administration of an anti-dyslipidemia drug.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings.

FIGURE 1 compares rosuvastatin AUC from three BE studies conducted in Asian and non-Asian populations.

FIGURE 2 compares mean single dose AUC of rosuvastatin at different dose strengths in Asian and non-Asian healthy subjects (AUC, area under the concentration-time curve; PK, pharmacokinetics; RC, rosuvastatin). The large solid circle indicates the rosuvastatin PK study in Korean subjects.

FIGURE 3 compares dose-normalized AUC of rosuvastatin at different dose strengths in Asian and non-Asian healthy subjects (AUC, area under the concentration-time curve; AUC/dose, dose-normalized area under the concentration-time curve; PK,

pharmacokinetics; RC, rosuvastatin). The large solid circle indicates the rosuvastatin PK study in Korean subjects.

FIGURES 4A and 4B compare dose-normalized AUC of rosuvastatin (4A) and body weight (4B) among non-Asian, Asian and Korean (ST-101) subjects (AUC, area under the concentration-time curve; AUC/dose, dose-normalized area under the concentration-time curve; PK, pharmacokinetics; RC, rosuvastatin). The large solid circles indicate the rosuvastatin PK study in Korean subjects.

FIGURE 5 compares plots of AUC/dose of rosuvastatin against body weight with regression lines for Asian and non-Asian groups (AUC/dose, dose-normalized area under the concentration-time curve; solid dot, PK study in non-Asian subjects; circle, PK study in Asian subjects; triangle, ST101 PK study in Korean subjects).

FIGURE 6 illustrates mean rate of LDL-C reduction from clinical studies at different dose of rosuvastatin calcium (LDL-C, low-density lipoprotein cholesterol; LS, least squares; solid dot, PD study in non-Asian subjects; circle, PD study in Asian subjects; shaded circle, PD study in Korean subjects; triangle, ST101 PD study in Korean subjects). The regression line indicates the correlation between LDL-C reduction and dose.

FIGURE 7 compares plots of LDL-C reduction rate against dose with regression lines for Asian and non-Asian groups (LDL-C, low-density lipoprotein cholesterol; LS, least squares; solid dot, PD study in non-Asian subjects; circle, PD study in Asian subjects; shaded circle, PD study in Korean subjects; red triangle, ST101 PD study in Korean subjects).

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the invention provides methods for treating dyslipidemia by administering rosuvastatin. In the method, a dosing regimen targeting specific rosuvastatin AUC is provided in which AUC determined from first dosing with rosuvastatin is used to adjust subsequent rosuvastatin dosing to achieve the targeted AUC. The targeted AUC dosing regimen for rosuvastatin was made taking into account the targeted AUC value derived from rosuvastatin pharmacokinetic studies.

In certain embodiments, the pharmacokinetic parameter used in the method is area-under-the-curve (AUC).

The methods of the invention are effective in treating dyslipidemia.

As noted above, the high PK variability and high drug exposure and dose non-proportionality of rosuvastatin require repeated drug monitoring following dosing to achieve the desired AUC (i.e., target AUC).

Pharmacokinetic Variability

Anti-dyslipidemia drug pharmacokinetic variability was determined for rosuvastatin, a representative anti-dyslipidemia drug.

Anti-Dyslipidemia Drug Dose Response Correlation

The high variability of PK and the resulting pharmacodynamics (PD) of rosuvastatin can result in weak correlation between dose and response. Furthermore, as described herein, differences between Asian and non-Asian subjects was observed.

Determination of First Pharmacokinetic Parameter and Prediction of Subsequent Pharmacokinetic Parameter

There is no known natural law to predict anti-dyslipidemia drug (e.g., rosuvastatin) pharmacokinetic parameters (e.g., AUC). The complexity of pharmacokinetics precludes any predictive methods for the accurate prediction of human rosuvastatin pharmacokinetics. The only means of predicting the pharmacokinetic parameters is to actually perform the pharmacokinetic study, which is shown herein to be predictive of subsequent pharmacokinetic parameter determination.

Anti-dyslipidemia Drug Dose Non-Proportionality in Asian Populations

A demonstration of anti-dyslipidemia drug dose proportionality allows for AUC dosing. However, as described herein, this was not observed for the Asian population.

Anti-dyslipidemia Drug Dosing by AUC

Given that subsequent pharmacokinetic parameters (e.g., AUC) can only be estimated by first pharmacokinetic parameter quantitation, the method of the invention provides a method that improves the delivery of anti-dyslipidemia drugs in general and rosuvastatin in particular.

In a representative method, rosuvastatin is administered to a subject to achieve a target AUC, which is defined as the median of conventional rosuvastatin PK (AUC) at conventional mg/day dosing (e.g., 80 ng*hr/mL ± 15%). If dosing is below or above the target AUC, dose adjustment is adjusted up (increased) or down (decreased), respectively.

The target AUC dosing can be varied to higher or lower target AUC when the patient is demonstrating resistance or sensitivity, respectively, to the anti-dyslipidemia drug. Regardless, once the targeted AUC for the patient has been defined, the target

AUC needed to be maintained despite changes in physical condition (weight) and physiological condition (kidney, liver functional status etc.). Variables such as weight and organ function factors are known to affect rosuvastatin pharmacokinetics. However, with frequent monitoring, it is possible to keep dosing at constant AUC by appropriate adjustment of dosing when changes are noted.

The methods of the invention effectively administer anti-dyslipidemia drugs (e.g., rosuvastatin) by pharmacokinetic parameter (e.g., AUC) dosing to avoid the problems associated with pharmacokinetic variability described above. Pharmacokinetic variability is avoided in the method by adjusting drug dose to achieve a targeted AUC.

Rosuvastatin Dosing by AUC

In one aspect, the invention provides a method for rosuvastatin dosing by AUC. In certain embodiments, the method comprises:

(a) administering rosuvastatin at a first dose (e.g., under a first regimen, such as once a day) to a subject in need of therapy;

(b) determining the concentration of rosuvastatin in the subject's blood at one or more time points (e.g., a series of time points, such as 0.5, 1, 2, 4, 8, 12, 16, hour) after rosuvastatin administration to provide a set of rosuvastatin concentration/time data points;

(c) transforming the set of rosuvastatin concentration/time data points to provide area-under-the-curve (AUC) (i.e., the AUC resulting from the first dose); and

(d) administering rosuvastatin at subsequent doses (e.g., a second dose and subsequent doses) to achieve a target rosuvastatin AUC (i.e., 80 ng*hr/mL ± 15%).

In certain embodiments, the target rosuvastatin AUC is ± 15% of the target. In other embodiments, the target rosuvastatin AUC is ± 20% of the target. In further embodiments, the target rosuvastatin AUC is ± 30% of the target.

Because of dose non-proportionality, determination of the AUC following the second dose (and subsequent does, as necessary) is required. Although the dose adjustment (e.g., reduction) can be estimated from a dose response curve, the dose adjustment cannot be accurately determined from the curve.

Area-under-the-curve (AUC) is a pharmacokinetic parameter that is used in the method of the invention to dose olmesartan. As used herein, the term "area under the curve (AUC)" is the area under the curve in a plot of concentration of drug in blood plasma as a function of time. Typically, the area is calculated starting at the time the drug

is administered and ending when the concentration in plasma is negligible. AUC represents the total drug exposure over time.

As used herein, the phrase "transforming the concentration/time data points" refers to the application of mathematical operations, formulas, theories, and/or principles (i.e., a formula for calculating AUC) to the concentrations/time data points of the individual subject to provide AUC.

The target rosuvastatin AUC was determined from statistical analysis of a subject population receiving rosuvastatin. The target AUC is the median AUC value determined from a population of subjects receiving rosuvastatin at a conventional dose (20 mg/day, daily administration) among non-Asian/Caucasian patients.

In the methods of the invention, the nature of the device or method for determining the concentrations/time data points for calculating AUC is not critical. Some methods and devices for determining therapeutic drug (e.g., rosuvastatin) concentrations are known in the art and can be used. In certain embodiments, a point-of-care device can be used to determine the concentrations and create the concentration/time data, transmit the data to a central location, and/or transmitting instructions to the patient to alter the administration.

In certain embodiments, the device and method for determining the concentrations/time data points for calculating AUC is an immunoassay assay device and method that utilizes one or more rosuvastatin antibodies (e.g., monoclonal antibodies) or functional fragments thereof. In certain of these embodiments, the device is a lateral flow device.

The method of the invention is therapeutically effective for delivery of rosuvastatin and therefore is effective for treating dyslipidemia.

The above method is also effective for treating subjects in need of combined hypertension and dyslipidemia therapy. In certain embodiments, the subject treatable by the method is a subject that is in need of treatment for hypertension and dyslipidemia. In certain embodiments of this method, olmesartan and an anti-dyslipidemia drug are individually administered. In other embodiments of this method, a single dosage form that comprises olmesartan and an anti-dyslipidemia drug (e.g., rosuvastatin or a salt thereof) is administered. In certain embodiments of this method, the single dosage form comprises olmesartan and rosuvastatin calcium.

Anti-dyslipidemia Drug Dosing by AUC

In another aspect, the invention provides a method for anti-dyslipidemia drug dosing by AUC. In certain embodiments, the method comprises:

(a) administering an anti-dyslipidemia drug at a first dose to a subject in need of therapy;

(b) determining the concentration of the anti-dyslipidemia drug the subject's blood at one or more time points after anti-dyslipidemia drug administration to provide a set of anti-dyslipidemia drug concentration/time data points;

(c) transforming the set of anti-dyslipidemia drug concentration/time data points to provide one or more pharmacokinetic parameters; and

(d) administering the anti-dyslipidemia drug at subsequent doses (e.g., a second dose and subsequent doses) to the subject to achieve a target optimal value for the one or more pharmacokinetic parameters.

As noted above, the target pharmacokinetic parameter is the pre-determined optimal value. In certain embodiments, the target pharmacokinetic parameter is the pre-determined optimal value ±15%. In other embodiments, the target pharmacokinetic parameter is the pre-determined optimal value ±20%. In further embodiments, the target pharmacokinetic parameter is the pre-determined optimal value ±30%.

In certain embodiments, the method further comprising repeating steps (a)-(d) until the target pharmacokinetic parameter value(s) is achieved.

Any suitable pharmacokinetic (PK) parameter or parameters can be used in accordance with this aspect of the invention, including without limiting concentration, concentration time course, peak concentration, and time after administration to peak concentration, terminal half-life, area-under-the-curve (AUC), bioavailability, absorption, distribution, metabolism, excretion, biotransformation, or a combination thereof.

As used herein, the phrase "transforming the concentration/time data points" refers to the application of mathematical operations, formulas, theories, and/or principles (e.g., a formula for calculating AUC) to the concentrations/time data points of the individual subject to provide the pharmacokinetic value (e.g., AUC).

The target pharmacokinetic value is pre-determined by statistical analysis from a population of subjects receiving the anti-dyslipidemia drug at its optimal dose. The term "optimal dose" refers to a dose (e.g., mg/day) associated with desirable drug efficacy at lower risk doses of a drug (e.g., the C_{max} range corresponding to patients experiencing high drug efficacy at a low dose) and is determined from a statistical analysis of a subject

population receiving doses of the anti-dyslipidemia drug for whom there was therapeutic improvement without significant adverse drug reactions or significant side effects. Significant adverse drug reactions refer to ADRs that the subject finds intolerable, impair physiologic functions, and put the subject at risk for immobility and/or death or combinations thereof. Significant side effects refer to side effects that the subject finds intolerable, impair physiologic functions, and put the patient at risk for immobility and/or death or combinations thereof.

As noted above, in the methods of the invention, the nature of the device or method for determining the concentrations/time data points for calculating the pharmacokinetic parameter is not critical. Methods and devices for determining therapeutic drug (e.g., anti-dyslipidemia drugs) concentrations are known in the art and can be used. In certain embodiments, a point-of-care device can be used.

In certain embodiments, the device and method for determining the concentrations/time data points for calculating the pharmacokinetic parameter is an immunoassay assay device and method that utilizes one or more dyslipidemia antibodies (e.g., monoclonal antibodies) or functional fragments thereof. In certain of these embodiments, the device is a lateral flow device.

The above method is also effective for treating subjects in need of combined hypertension and dyslipidemia therapy. In certain embodiments, the subject treatable by the method is a subject that is in need of treatment for hypertension and dyslipidemia. In certain embodiments of this method, an antihypertensive drug and an anti-dyslipidemia drug are individually administered. In other embodiments of this method, a single dosage form that comprises an antihypertensive drug and an anti-dyslipidemia drug (e.g., rosuvastatin or a salt thereof) is administered. In certain embodiments of this method, the single dosage form comprises olmesartan and rosuvastatin.

Hypertension and Dyslipidemia

An estimated 40 to 45 percent of hypertensive patients also suffer from dyslipidemia. Because it is considered advantageous to treat patients suffering from hypertension and dyslipidemia with a single therapeutic agent, combinations of therapeutic agents in single dose form have been developed for concomitantly treating both diseases. Combination formulations of antihypertensive and antihyperlipidemic agents are described in WO 95/26188, WO 97/37688, WO 99/11260, WO 00/45818,

WO 04/062729, and WO 06/040085. One such single dose form is Caduet™, which is a clinically useful combination formulation of atorvastatin and amlodipine.

Rosuvastatin, an HMG-CoA reductase inhibitor, is useful for the treatment of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis; and rosuvastatin's calcium salt is commercially available under the designation Crestor™. Olmesartan medoxomil is useful for the treatment of essential hypertension and is commercially available under the designation Benicar™. When a single matrix formulation of rosuvastatin and olmesartan medoxomil is administered, a drug-drug interaction (DDI) between rosuvastatin and olmesartan medoxomil occurs that results in delaying the *in vivo* release (i.e., dissolution) of rosuvastatin calcium to the gastrointestinal fluid and thus delaying the translocation thereof to the gastrointestinal membrane, inhibiting the absorption of rosuvastatin.

Olmesartan

Olmesartan medoxomil formulations should be designed so as to exhibit high dissolution rate of olmesartan medoxomil in an *in vitro* comparative dissolution test, in order to obtain a bioequivalent formulation to other single formulations containing olmesartan medoxomil. In order to obtain the high *in vitro* dissolution rate, olmesartan medoxomil tablet comprises a preferred disintegrant, which may be one or more selected from the group consisting of low substituted hydroxypropyl cellulose, carboxymethylcellulose calcium, croscarmellose sodium, crospovidone, sodium starch glycolate, and pregelatinized starch. In one embodiment, olmesartan medoxomil tablet comprises 7.5 or more % by weight of low substituted hydroxypropyl cellulose, 5 or more % by weight of carboxymethylcellulose calcium, 15 or more % by weight of croscarmellose sodium, 10 or more % by weight of crospovidone, 5 or more % by weight of sodium starch glycolate, or 5 or more % by weight of pregelatinized starch, based on the total weight of the tablet comprising olmesartan medoxomil. In another embodiment, the compartment comprising olmesartan medoxomil comprises 7.5 to 65 % by weight of low substituted hydroxypropyl cellulose, 5 to 60 % by weight of carboxymethylcellulose calcium, 15 to 30 % by weight of croscarmellose sodium, 10 to 40 % by weight of crospovidone, 5 to 40 % by weight of sodium starch glycolate, or 5 to 60 % by weight of pregelatinized starch, based on the total weight of the tablet comprising olmesartan medoxomil. In a further embodiment, the tablet comprising olmesartan medoxomil comprises 7.5 to 65 % by weight, preferably 10 to 60 % by weight, more preferably about

20 ± 1 % by weight of low substituted hydroxypropyl cellulose, based on the total weight of the tablet comprising olmesartan medoxomil.

Olmesartan/rosuvastatin FDC

An improved pharmaceutical composition that is a single dosage form of olmesartan medoxomil and rosuvastatin or its salts is described in WO 2013/147462. This single dosage form comprises separate compartments for each drug in which each drug is separately and independently formulated. When the single dosage form is administered the interaction to *in vivo* absorption is minimized and the combination formulation is bioequivalent to the single formulation of each of drugs.

In certain embodiments, the subject treatable by the methods of the invention is a subject that is in need of treatment for hypertension and dyslipidemia. In certain embodiments of this method, an antihypertensive drug and an anti-dyslipidemia drug are individually administered. In other embodiments of this method, a single dosage form that comprises an antihypertensive drug and an anti-dyslipidemia drug (e.g., rosuvastatin or a salt thereof) is administered. In certain embodiments of this method, the single dosage form comprises olmesartan and rosuvastatin.

A description of representative single dosage forms useful in the methods of the invention and methods for making the single dose forms are described in WO 2013/147462, expressly incorporated herein by reference in its entirety. Representative single dose forms useful in the method of the inventions and a method for making them are described below.

The pharmaceutical composition useful in the methods of the invention, which includes olmesartan medoxomil and rosuvastatin or its salt (e.g., rosuvastatin calcium), are formulated into a combination dosage form having separate compartments. That is, the pharmaceutical composition has a single dosage form comprising a compartment comprising olmesartan medoxomil; and a compartment comprising rosuvastatin or its salt, wherein the compartments are formulated in a separate form.

In the pharmaceutical composition, the active ingredients (i.e., olmesartan medoxomil and rosuvastatin or its salt) may be used in a therapeutically effect amount. For example, olmesartan medoxomil may be used in an amount of about 5 mg to about 80 mg, preferably about 10 mg to about 40 mg, in a unit formulation (i.e., unit dosage form).; and rosuvastatin or its salt may be used in an amount of about 2 mg to about 40 mg, preferably about 5 mg to about 20 mg, in a unit formulation (i.e., unit dosage

form). The salt of rosuvastatin may be a conventional pharmaceutically acceptable salt, such as calcium salt, hydrochloride, hydrobromide, sulfate, phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, besylate, and camsylate. Preferably, rosuvastatin calcium may be used in the present invention. The pharmaceutical composition may be administered once a day, but not limited thereto.

The pharmaceutical composition has a combination dosage form having separate compartments (i.e., a double-layered tablet form), comprising or consisting essentially of a layer comprising rosuvastatin or its salt and a layer comprising olmesartan medoxomil.

When the compartment comprising rosuvastatin or its salt includes a certain disintegrant (i.e., cellulose-type and/or povidone-type disintegrants), in a certain amount, rapid disintegration and high initial dissolution rate of rosuvastatin or its salt can be accomplished, thereby being able to obtain a combination formulation bioequivalent to the single formulation of rosuvastatin or its salt. The disintegrant may be one or more selected from the group consisting of povidone (for example, Kolidone™), crospovidone (for example, Polyplasdone™), low substituted hydroxypropyl cellulose, croscarmellose sodium, and carboxymethylcellulose calcium. Preferably, the disintegrant may be a mixture of crospovidone and croscarmellose sodium; or croscarmellose sodium. The disintegrant may be present in an amount ranging from 2 to 20 % by weight, preferably from 3 to 15 % by weight, based on the total weight of the compartment comprising rosuvastatin or its salt. When other disintegrants are used, the dissolution rate of rosuvastatin or its salt is decreased; and/or the amount used is increased, which may cause insufficient compression force during the compressing step, thereby leading to high friability of the resulting formulation (e.g., tablet). In addition, the use of other disintegrants brings about insufficient hardness, which may cause unwanted problems in packaging or delivery.

For olmesartan medoxomil, a combination formulation comprising rosuvastatin and olmesartan medoxomil should be designed so as to exhibit high dissolution rate of olmesartan medoxomil in an *in vitro* comparative dissolution test, in order to obtain a bioequivalent formulation to the single formulation containing olmesartan medoxomil. In order to obtain the high *in vitro* dissolution rate, the compartment comprising olmesartan medoxomil comprises a preferred disintegrant, which may be one or more selected from the group consisting of low substituted hydroxypropyl cellulose, carboxymethylcellulose calcium, croscarmellose sodium, crospovidone, sodium starch glycolate, and

pregelatinized starch. In an embodiment, the compartment comprising olmesartan medoxomil comprises 7.5 or more % by weight of low substituted hydroxypropyl cellulose, 5 or more % by weight of carboxymethylcellulose calcium, 15 or more % by weight of croscarmellose sodium, 10 or more % by weight of crospovidone, 5 or more % by weight of sodium starch glycolate, or 5 or more % by weight of pregelatinized starch, based on the total weight of the compartment comprising olmesartan medoxomil. In another embodiment, the compartment comprising olmesartan medoxomil comprises 7.5 to 65 % by weight of low substituted hydroxypropyl cellulose, 5 to 60 % by weight of carboxymethylcellulose calcium, 15 to 30 % by weight of croscarmellose sodium, 10 to 40 % by weight of crospovidone, 5 to 40 % by weight of sodium starch glycolate, or 5 to 60 % by weight of pregelatinized starch, based on the total weight of the compartment comprising olmesartan medoxomil. In a further embodiment, the compartment comprising olmesartan medoxomil comprises 7.5 to 65 % by weight, preferably 10 to 60 % by weight, more preferably about 20 ± 1 % by weight of low substituted hydroxypropyl cellulose, based on the total weight of the compartment comprising olmesartan medoxomil.

The pharmaceutical composition may further comprise one or more excipients conventionally used in the field of pharmaceutics, for example a diluent (or additive), a binder, a lubricant, in addition to said disintegrant. The pharmaceutical composition may be also coated with an appropriate coating agent, such as a film-coating agent.

The diluent (or additive) includes lactose (including its hydrate), dextrin, mannitol, sorbitol, starch, microcrystalline cellulose (for example, Celphere™), silicified microcrystalline cellulose (for example, Prosolv™), calcium hydrogen phosphate (including its hydrate), anhydrous calcium hydrogen phosphate, calcium carbonate, saccharides, and a mixture thereof. The binder includes polyvinylpyrrolidone, copovidone, gelatin, starch, sucrose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl alkylcellulose (for example, hydroxypropyl methylcellulose), and a mixture thereof. The lubricant includes stearic acid, stearates (for example, magnesium stearate), talc, corn starch, carnauba wax, light anhydrous silicic acid, magnesium silicate, synthetic aluminum silicate, hydrogenated oil, hydrogenated oil, titanium oxide, microcrystalline cellulose, macrogol 4000 or 6000, isopropyl myristate, calcium hydrogen phosphate, and a mixture thereof. The coating agent, for example a film-coating agent, includes a conventional polymer such as

Opadry™. The film-coating agent may be used in a minimum amount for providing an appropriate size of the formulation, but not limited thereto.

The pharmaceutical composition having a double-layered tablet form may be prepared by preparing granules containing rosuvastatin and granules containing olmesartan medoxomil, respectively; and then compressing the mixture thereof with a double-layer tablet-press machine. If necessary, the resulting double-layered tablet may be coated with a film-coating agent such as Opadry™. The granules containing rosuvastatin and the granules containing olmesartan medoxomil may be prepared according to dry granulation methods or wet granulation methods. For example, the granules containing rosuvastatin may be prepared according to a dry granulation method. That is, the granules containing rosuvastatin may be prepared by mixing rosuvastatin calcium, an additive (diluent), a disintegrant, and a lubricant according to a conventional method; and then granulating the mixture with e.g., a roller compactor (TF mini, Vector). And also, the granules containing olmesartan medoxomil may be prepared according to a wet granulation method. That is, the granules containing olmesartan medoxomil may be prepared by mixing olmesartan medoxomil, a binder, an additive (diluent), a disintegrant; granulating the mixture with a high speed mixer (MIC Developer-5, COMASA); and then drying and sieving the resulting granules.

Representative double-layer tablets can be prepared as described below.

Step 1. Preparation of granules containing rosuvastatin.

Rosuvastatin calcium, lactose monohydrate, Prosolv™, dibasic calcium phosphate dihydrate, crospovidone, croscarmellose sodium, light anhydrous silicic acid, and magnesium stearate (85% of the total amount used in the rosuvastatin-layer) were sieved through a 24 mesh and then mixed. The resulting mixture was granulated using a roller compactor (TF mini, Vector). The obtained granules were sieved through a 24 mesh and then mixed with magnesium stearate pre-sieved though a 35 mesh (15% of the total amount used in the rosuvastatin-layer) to prepare a rosuvastatin-containing granule mixture.

Step 2. Preparation of granules containing olmesartan medoxomil.

Olmesartan medoxomil, hydroxypropyl cellulose, lactose monohydrate, microcrystalline cellulose, and low substituted hydroxypropyl cellulose were sieved through a 24 mesh and then mixed. The resulting mixture was granulated using a high speed mixer (MIC Developer-5, COMASA). The resulting dry granules were sieved

through a 24 mesh and then mixed with magnesium stearate pre-sieved though a 35 mesh and yellow iron oxide pre-sieved through an 80 mesh to prepare a olmesartan medoxomil-containing granule mixture.

Step 3. Preparation of double-layered tablets.

The rosuvastatin-containing granule mixture prepared in Step 1 and the olmesartan medoxomil-containing granule mixture prepared in Step 2 were compressed with a double-layer tablet-press machine (BB-11, RIVA) to obtain double-layered tablets. The resulting tablets were film-coated with Opadry™ in a pan coating machine (LDCS, VECTOR).

The following is a description of a rosuvastatin clinical trials that demonstrates race (non-Asian/Caucasian) is an important factor in rosuvastatin pharmacokinetics (PK) and pharmacodynamics (PD).

Hyperlipidemia, Hypertriglyceridemia, Dysbetalipoproteinemia, Hypercholesterolemia, and Atherosclerosis

Hyperlipidemia is a condition in which blood lipid levels increase due to abnormal lipid metabolism of triglycerides, cholesterol, and other fatty acids. Hyperlipidemia can be caused by genetic factors or by secondary factors such as hypothyroidism, hepatic disease, nephrotic syndrome, or diabetes mellitus. Serum lipids primarily comprise cholesterol, triglycerides, phospholipids, and free fatty acids transported in a lipoprotein form. Lipoproteins are categorized into 4 types as follows: chylomicrons, very low-density lipoprotein (VLDL), LDL, and HDL. VLDLs are synthesized by the liver in the fasting state and are responsible for transporting triglycerides to peripheral tissues where some are converted to LDLs. LDLs are the major carriers of cholesterol to peripheral tissues; however, they are also a major risk factor for coronary arteriosclerosis.

In the US, approximately 73.5 million adults (31.7%) have high LDL, and only 29.5% of affected adults have the condition under control (Mozaffarian et al. 2015; CDC MMWR 2014). An estimated 48.1% of US adults with high LDL cholesterol receive treatment to decrease their levels (Mozaffarian et al. 2015). Individuals with elevated cholesterol have an approximately 2-times greater risk of developing heart disease compared with individuals with normal cholesterol levels (CDC 2011a).

Treatment for hyperlipidemia includes lifestyle changes such as dietary modification, weight management, and physical activity to decrease LDL levels.

Cholesterol-lowering agents (e.g., statins, bile acid sequestrants, nicotinic acid, fibrates, and ezetimibe) can be prescribed in addition to enacting lifestyle changes. Rosuvastatin calcium is a statin drug (HMG-CoA reductase inhibitor) that decreases LDL cholesterol by inhibiting HMG-CoA reductase, which is an enzyme in the metabolic pathway for cholesterol production (Olsson et al. 2002b).

PK Studies

A series of PK studies were performed to characterized the PK of rosuvastatin in Asian and non-Asian populations. The first clinical bioequivalent (BE) study was conducted in Korean population (Korean BE study). This was a randomized, open Label, single-dose, 2-way cross-over clinical trial to compare the safety and pharmacokinetic characteristics of combination therapy of rosuvastatin calcium (RC) 20 mg and olmesartan medoxomil (OM) 40 mg (Reference drug, RC+OM) to monotherapy of ST-101 (as used herein "ST-101" refers to Test drug, fixed dose combination of OM 40 mg and RC 20 mg) in healthy male volunteers. 54 subjects in total had completed the study. In terms of pharmacokinetic assessment, the geometric mean ratios of test drug and the reference drug in connection of AUC_{last} and C_{max} for rosuvastatin were 91.31% and 90.37%, respectively. The 90% confidence intervals of the geometric mean ratios of test drug and the reference drug were within the bioequivalence acceptance range (80.00-125.00%).

The second BE study was conducted in Indian population (Indian BE study). This was an open label, balanced, randomized, two-treatment, two-sequence, two-period, crossover, single-dose oral BE study of ST-101 (Test drug, fixed dose combination of RC/OM 10/20 mg) and co-administration of RC 10 mg and OM 20 mg (Reference drug) in healthy, adult, male, human subjects under fasting conditions. 26 subjects had completed the study. The geometric mean ratios of test drug and the reference drug in connection of AUC_{last} and C_{max} for rosuvastatin were 99.80% and 99.40%, respectively. The 90% confidence intervals of the geometric mean ratios of test drug and the reference drug were within the bioequivalence acceptance range.

The third BE study was conducted in non-Asian population in Czech Republic (EU BE study). This was a single-dose, randomized, two-period, two-treatment, two-sequence, crossover BE study on ST-101 (test drug, fixed dose combination of OM/RC 40 mg/20 mg) versus two co-administered reference products OM 40 mg and RC 20 mg in healthy volunteers under fasting conditions. 56 subjects had completed the

study. The geometric mean ratios of test drug and the reference drug in connection of AUC_{last} and C_{max} for rosuvastatin were 100.16 % and 98.54 %, respectively. The 90% confidence intervals of the geometric mean ratios of test drug and the reference drug were within the bioequivalence acceptance range.

The PK data from the three BE studies are summarized in the Table 1 and FIGURE 1.

Table 1. The median and mean AUC of rosuvastatin from the Korean, Indian and EU BE study.

	Korean BE study		Indian BE study		EU BE study	
	RC 20mg	ST-101 OM40mg/RC20mg	RC 10mg	ST-101 OM20mg/RC10mg	RC 20mg	ST-101 OM40mg/RC20mg
Number of subjects	54	54	26	26	56	56
AUC Median	191.5	181.3	149.1	143.5	75.73	79.41
AUC Mean	207.4	190.6	152.7	145	89	86.78
Std. Deviation of AUC	88.47	79.78	66.11	41.58	53.07	42.95

The target AUC was defined as Caucasian median AUC at 20 mg/day. This was rounded up to 80 mg*hr/mL.

Analysis of rosuvastatin PK-demonstration of higher drug exposure and dose non-proportional PK for Asian population

PubMed database was searched to identify relevant scientific and review articles from October 2002 to March 2015 using the search term rosuvastatin PK. Reference lists of included articles were reviewed to locate additional references of interest. PK studies

with single dose AUC of rosuvastatin calcium in healthy subjects were selected. Rosuvastatin AUC from co-administration of rosuvastatin calcium with other drugs were also included if there was no known DDI. More than 50% of the studies reported AUC in geometric mean. Thus, to make comparable analysis, only studies with AUC calculated by geometric mean were included in the analysis. PK and demographic data from a total of 745 healthy subjects in 11 clinical studies were included in the final analysis: CSR Synopsis DW_DWJ1276002; Cooper et al. 2002; Martin et al. 2003a; Martin et al. 2003b; Schneck et al. 2004; Lee et al. 2005; Li et al. 2007; Li et al. 2010b; Trabelsi et al. 2012; Birmingham et al. 2015b). Birmingham et al 2015b reported rosuvastatin PK in Korean subjects.

Dose proportional analysis was performed to confirm reported dose proportional nature of rosuvastatin PK. The AUC/dose was then used in multivariate correlation to define the variable that has significant impact on PK. The analysis yielded significant correlation between weight and race to AUC/dose, but not age. ANCOVA analysis was then performed to show that race is a significant factor even after weight was taken in consideration. However, there was no observed difference between rosuvastatin PK in ST-101 population versus Asian population. This allowed us to bridge ST-101 PK data to Asian PK data and to Caucasian PK data.

The mean AUC_{last} of rosuvastatin from each study were plotted versus dose (FIGURE 2). The plot showed that the mean AUCs of rosuvastatin in Asian subjects are higher than the mean AUCs in non-Asian subjects at the same dose. Rosuvastatin AUC from subjects treated with ST-101 overlapped with AUC from 20 mg of rosuvastatin in Asian subjects.

There is a linear dose-dependent increase in AUC from 5 to 80 mg of rosuvastatin in non-Asian and from 5 to 40 mg in Asian subjects. Dose proportional analysis was performed by demonstrating constant AUC/dose across doses. The dose-normalized AUC was plotted versus dose (FIGURE 3). The linear regression line of AUC/dose against dose was horizontal with 95% CIs of slopes close to 0 for both Asian (-0.24 to 0.05; p=0.20) and non-Asian groups (-0.02 to 0.02; p = 0.92). The observed dose proportionality is similar to previous reports (Martin et al. 2003a, CRESTOR® Prescribing Information 2014). The dose proportionality nature of rosuvastatin PK validated the use of dose-normalized AUC for ANCOVA.

Compared to Asian subjects, non-Asian subjects have a significantly lower dose-normalized AUC of rosuvastatin ($p < 0.0001$), while dose-normalized AUCs of rosuvastatin from ST-101 administered or from olmesartan medoxomil/rosuvastatin calcium co-administered in Korean subjects are comparable to reported AUCs of rosuvastatin of Asian subjects ($p = 0.50$) (FIGURE 4A). Additionally, Asian and non-Asian subjects were significantly different in BW ($p < 0.0001$), with BWs of Korean subjects in the ST-101 studies being similar to other Asian subjects ($p = 0.34$) (FIGURE 4B).

After confirming no significant interaction between BW and race, ANCOVA was conducted to determine whether there was a significant difference between Asian and non-Asian subjects on dose-normalized AUC after controlling for BW, using Fit Model Platform (JMP version 11.2.1 clinical software). The number of subjects in each study was used to assign a weight to each study in the analysis. The slopes of the regression lines of dose-normalized AUC of rosuvastatin against BW are significantly different between Asian and non-Asian groups ($p = 0.02$) (FIGURE 5). This implies that dose-normalized AUC of rosuvastatin are different between Asian and non-Asian groups even after taking BW into account, indicating that race is an important determinant of drug exposure. This finding is well described in a population PK model (Tzeng et al. 2008). In this model, Asians were assigned 2 times greater drug exposure than Caucasians. Similar differences have been observed between Asian and white subjects living in Singapore, suggesting that these ethnic differences are independent of geographic residence (Lee et al. 2005). Birmingham et al. (2015a) affirmed a higher exposure to rosuvastatin in Asian subjects (Chinese, Filipinos, Asian Indians, Koreans, Vietnamese, and Japanese) residing in the US than in white subjects. Even though the differences in rosuvastatin exposure between Asian and non-Asian existed, rosuvastatin AUC from Korean subjects treated with ST-101 is the same as rosuvastatin AUC from Korean and other Asian subjects treated with rosuvastatin (FIGURE 4A), which is well understood.

The above results demonstrate that race is an important factor in rosuvastatin PK even after weight was taken into consideration.

Analysis of Rosuvastatin PD response

PubMed database was searched to identify relevant scientific and review articles from September 2001 to June 2015 using the search terms rosuvastatin efficacy, response, effect/clinical trial. Reference lists of included articles were reviewed to locate additional

references of interest. PD studies with rosuvastatin calcium dose range from 1 to 80 mg monotherapy were selected. PD response and demographic data from a total of 17,395 patients with dyslipidemia in 52 clinical studies were included in the analysis: Clinical Study Report DW_DWJ1276003 Synopsis 2013; Olsson et al., 2001; Paoletti et al., 2001; Davidson et al., 2002; Brown et al. 2002; Olsson et al. 2002b; Blasetto et al., 2003; Ballantyne et al. 2003; Capuzzi et al., 2003; Saito et al., 2003; Jones et al., 2003; Schneck et al., 2003; Ballantyne et al. 2004; Durrington et al., 2004; Lu et al., 2004; Strandberg et al., 2004; Schuster et al., 2004; Schwartz et al., 2004; Bots and Kastelein 2005; Jukema et al., 2005; Fonseca et al., 2005; Clearfield et al., 2006; Glueck et al., 2006; Ballantyne et al., 2006; Catapano et al., 2006; Milionis et al., 2006; Wongwiwatthananukit et al., 2006; Asztalos et al., 2007; Insull et al., 2007; Leiter et al., 2007; Betteridge et al., 2007; Deedwania et al., 2007; Ballantyne et al., 2007; Saito et al., 2007; Zhu et al., 2007; Stein et al., 2007; Mazza et al., 2008; Talini et al., 2008; Faergeman et al., 2008; Sviridov et al., 2008; Underhill et al., 2008; Laks et al., 2008; Kurabayashi M and Yamazaki 2008; Riesen et al. 2008; Pirro et al., 2009; Qu et al., 2009; McCormack et al., 2010; Saku et al., 2011; Yanagi et al., 2011; Pitt et al., 2012; Hong et al. 2011, and Jang et al., 2015). Hong et al. (2011) and Jang et al. (2015) are studies conducted in Korea.

The mean reduction rate in LDL-C in patients from each study was plotted versus dose (FIGURE 6). The LDL-C reduction rate by ST-101 is similar to the effects by 20 mg of rosuvastatin calcium in Korean, other Asian, and non-Asian patients. Regression analysis showed a significant correlation between LDL-C reduction and dose ($p<0.0001$) (FIGURE 6). This dose-related response for rosuvastatin calcium has been reported previously (CRESTOR® Prescribing Information 2014).

The interaction between dose and race on the LDL-C reduction was evaluated. The number of subjects in each study was used to assign a weight to each study in the analysis. The slopes of the regression lines relate LDL-C reduction to dose were significantly different between Asian and non-Asian patients ($p = 0.02$; FIGURE 7). The slope for dose-response in Asian patients is much steeper than that in non-Asian patients, therefore, race is an important determinant of PD response for rosuvastatin.

A dose-related response for rosuvastatin has been described previously in both Asian and non-Asian patients in a rosuvastatin PD model (Yang et al. 2011). The model has shown that the race differences in PD response of rosuvastatin are consistent with PK,

and there is no significant difference in the exposure-response relationship for LDL-C reduction between the 2 groups.

The above results demonstrate that race is an important factor in rosuvastatin PD.

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While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

CLAIMS

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method for rosuvastatin dosing by AUC, comprising:

(a) administering rosuvastatin at a first dose to a subject in need of therapy;

(b) determining the concentration of rosuvastatin in the subject's blood at one or more time points after rosuvastatin administration to provide a set of rosuvastatin concentration/time data points;

(c) transforming the set of rosuvastatin concentration/time data points to provide area-under-the-curve (AUC); and

(d) administering rosuvastatin to the subject at one or more subsequent doses to achieve a target rosuvastatin AUC of 80 ng*hr/mL.

2. The method of Claim 1, wherein the target AUC is ±15% of the target value.

3. The method of Claim 1, wherein the target AUC is ±20% of the target value.

4. The method of Claim 1, wherein the target AUC is ±30% of the target value.

5. The method of Claim 1, wherein the second dose is substantially the same as the first dose.

6. The method of Claim 1, wherein the second dose is greater than the first dose.

7. The method of Claim 1, wherein the second dose is less than the first dose.

8. The method of Claim 1 further comprising repeating steps (a)-(d) until target rosuvastatin AUC is achieved.

9. The method of Claim 1, wherein the subject is in need of treatment for hypertension and dyslipidemia, and the method comprises administration of a single dosage form that comprises olmesartan and an anti-dyslipidemia drug.

10. The method of Claim 9, wherein single dosage form comprises olmesartan and rosuvastatin.

11. The method of Claim 1, wherein the hypertension is resistant hypertension.

12. A method for anti-dyslipidemia drug dosing by one or more pharmacokinetic parameters, comprising:

(a) administering an anti-dyslipidemia drug at a first dose to a subject in need of therapy;

(b) determining the concentration of the anti-dyslipidemia drug in the subject's blood at one or more time points after anti-dyslipidemia drug administration to provide a set of anti-dyslipidemia drug concentration/time data points;

(c) transforming the set of anti-dyslipidemia drug concentration/time data points to provide one or more pharmacokinetic parameters; and

(d) administering the anti-dyslipidemia drug to the subject at one or more subsequent doses to achieve a target optimal value for the one or more pharmacokinetic parameters.

13. The method of Claim 12, wherein the one or more pharmacokinetic parameters is selected from the group consisting of concentration time course, peak concentration (C_{max}), and time after administration to peak concentration, terminal half-life, area-under-the-curve (AUC), bioavailability, absorption, distribution, metabolism, excretion, biotransformation, and combinations thereof.

14. The method of Claim 12, wherein the one or more pharmacokinetic parameters is area-under-the-curve (AUC).

15. The method of Claim 12, wherein the target optimal value is ±15% of the target optimal value.

16. The method of Claim 12 further comprising repeating steps (a)-(d) until dyslipidemia control is achieved.

17. The method of Claim 12, wherein the anti-dyslipidemia drug is a statin.

18. The method of Claim 12, wherein the anti-dyslipidemia drug is rosuvastatin.

19. The method of Claim 12, wherein the subject is in need of treatment for hypertension and dyslipidemia, and the method comprises administration of an antihypertensive drug and an anti-dyslipidemia drug.

20. The method of 12, wherein the subject is in need of treatment for hypertension and dyslipidemia, and the method comprises administration of a single dosage form that comprises an antihypertensive drug and an anti-dyslipidemia drug.

21. The method of Claim 20, wherein single dosage form comprises olmesartan and rosuvastatin.

22. The method of Claim 12, wherein the hypertension is resistant hypertension.

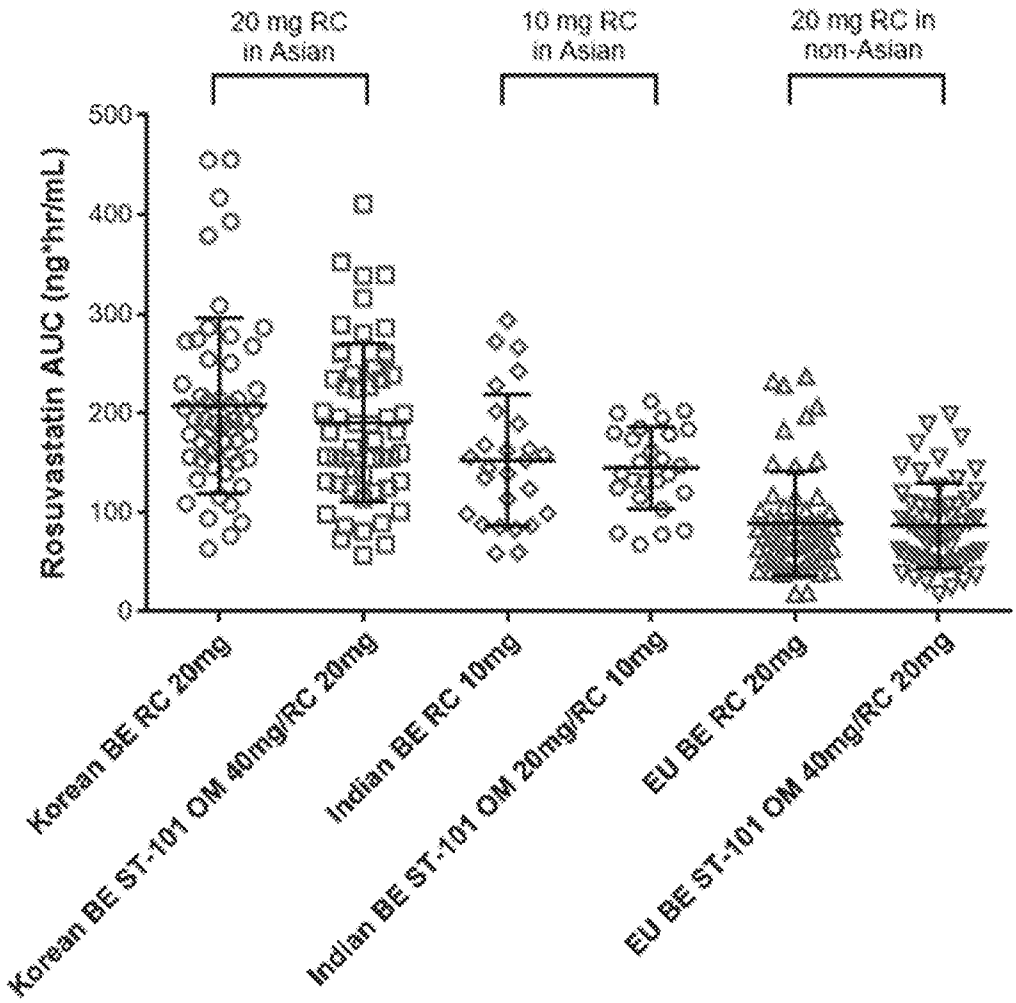
20 mg RC in Asian
10 mg RC in Asian
20 mg RC in non-Asian
Rosuvastatin AUC (ng*hr/mL)
500
400
300
200
100
0
Korean BE RC 20mg
Korean BE ST-101 OM 40mg/RC 20mg
Indian BE RC 10mg
Indian BE ST-101 OM 20mg/RC 10mg
EU BE RC 20mg
EU BE ST-101 OM 40mg/RC 20mg

Fig. 1

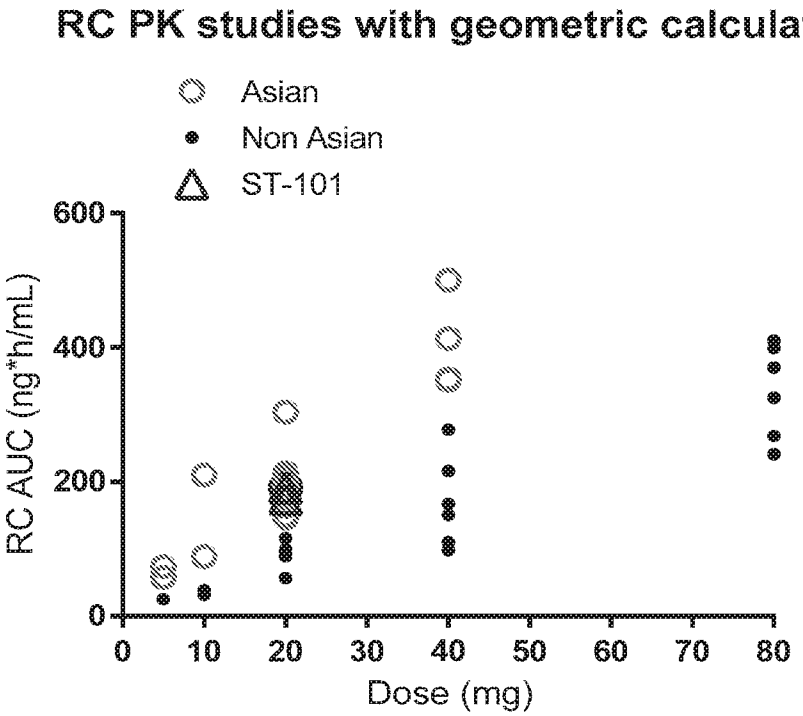
RC PK studies with geometric calculation
Asian
Non Asian
ST-101
RC AUC (ng*h/mL)
600
400
200
0
0
10
20
30
40
50
60
70
80
Dose (mg)

Fig. 2.

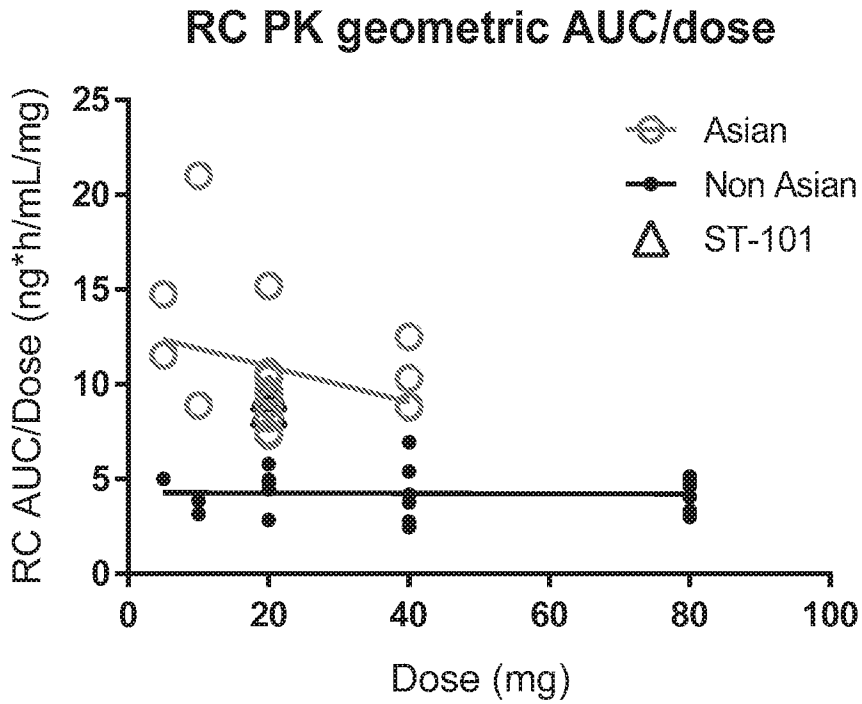
RC PK geometric AUC/dose
RC AUC/Dose (ng*h/mL/mg)
25
20
15
10
5
0
0
20
40
60
80
100
Dose (mg)
Asian
Non Asian
ST-101

Fig. 3

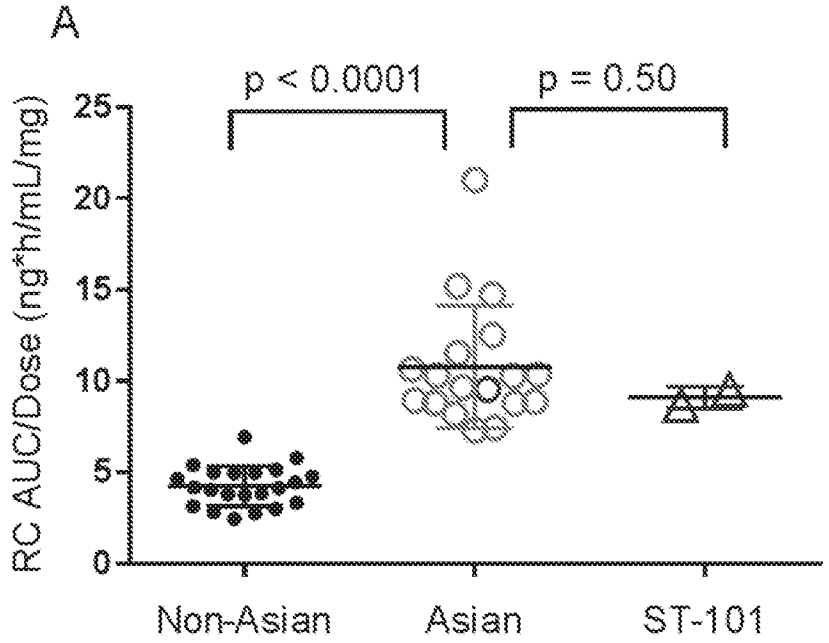
A
p < 0.0001
p = 0.50
RC AUC/Dose (ng*h/mL/mg)
25
20
15
10
5
0
Non-Asian
Asian
ST-101

Fig. 4A

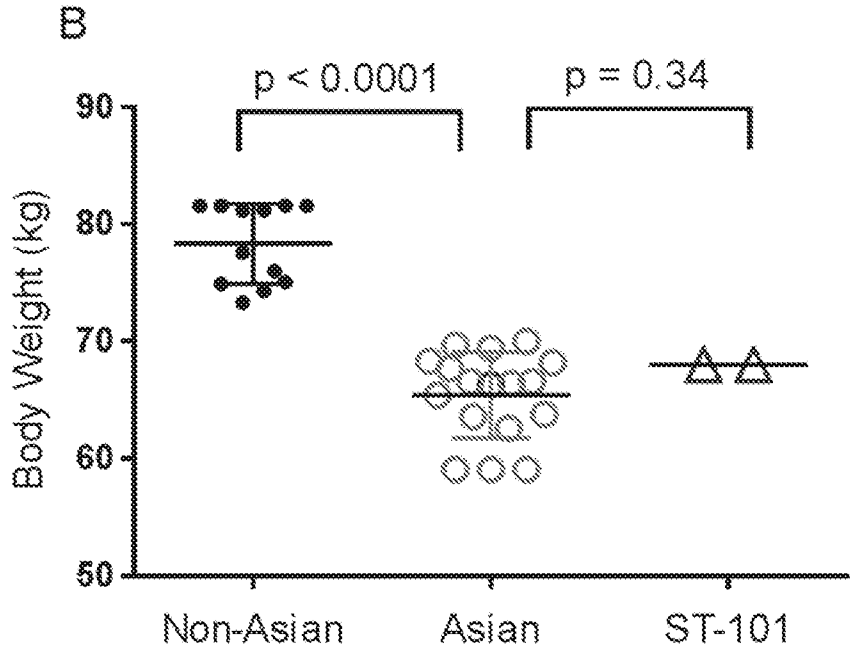
B
p < 0.0001
p = 0.34
Body Weight (kg)
90
80
70
60
50
Non-Asian
Asian
ST-101

Fig. 4B

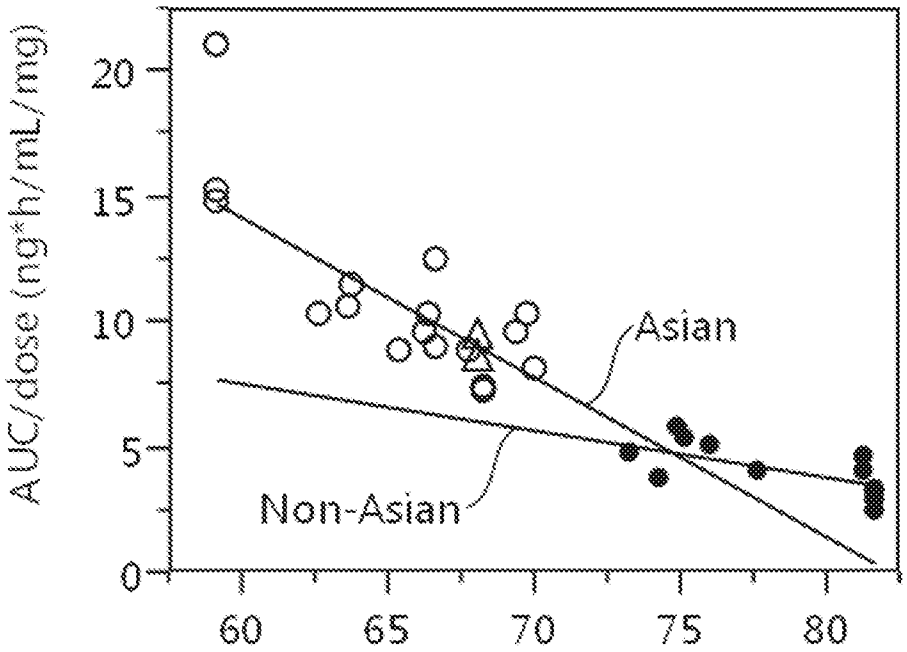
AUC/dose (ng*h/mL/mg)
20
15
10
5
0
60
65
70
75
80
Asian
Non-Asian

Fig. 5

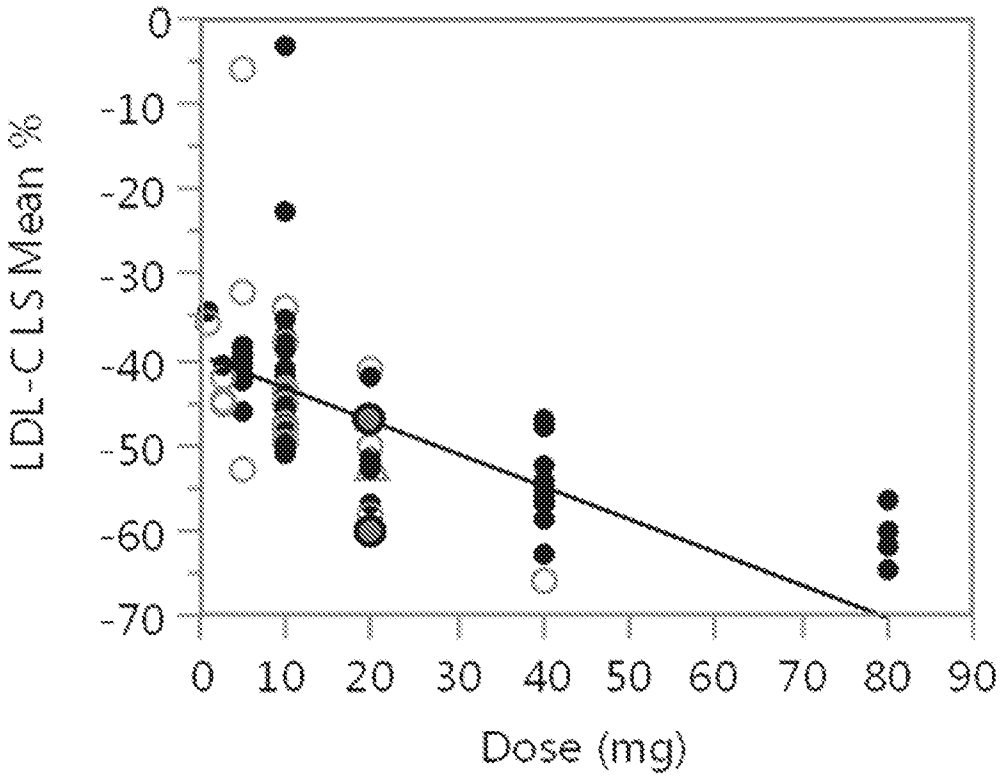
LDL-C LS Mean %
0
-10
-20
-30
-40
-50
-60
-70
0
10
20
30
40
50
60
70
80
90
Dose (mg)

Fig. 6

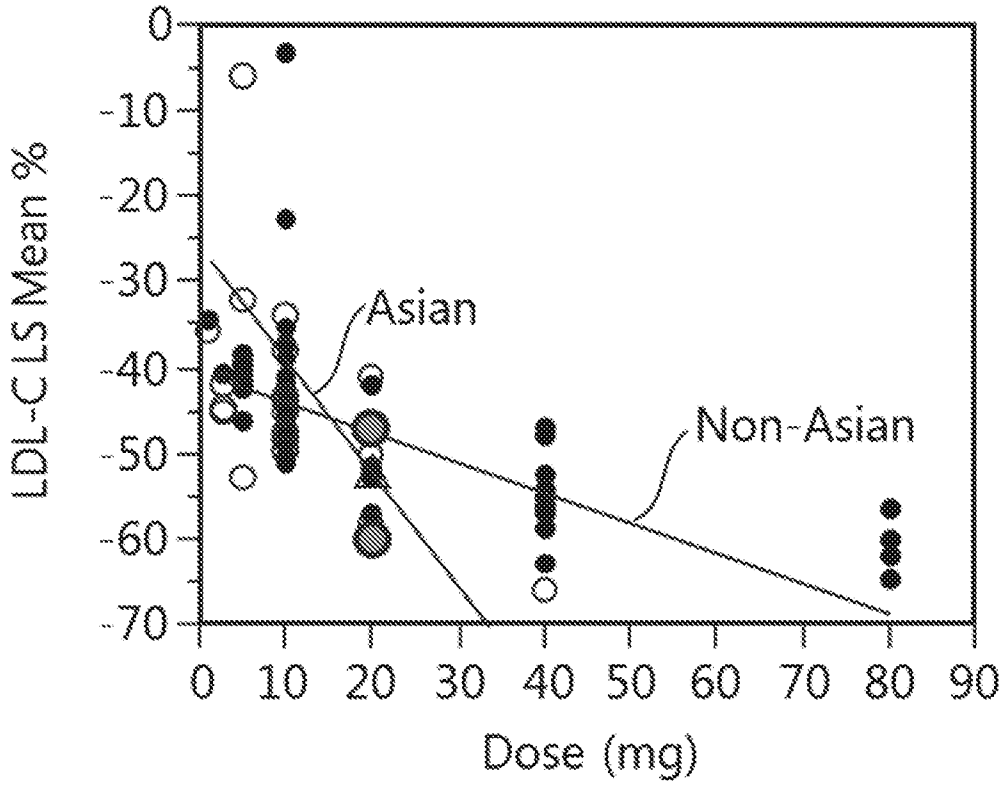
LDL-C LS Mean %
0
-10
-20
-30
-40
-50
-60
-70
Asian
Non-Asian
0 10 20 30 40 50 60 70 80 90
Dose (mg)

Fig. 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/041162

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/41; A61K 31/4164; A61K 31/44; G01N 33/53 (2017.01)

CPC - A61K 31/41; A61K 31/4164; A61K 31/44; A61K 2300/00; G01N 33/53; G01N 33/54366 (2017.08)

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)

See Search History document

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

USPC - 424/464; 424/468; 514/248; 514/275; 514/383; 544/297; 548/159; 548/311.1 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/0349862 A1 (TRIEU) 27 November 2014 (27.11.2014) entire document	12-18
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Y		1-11, 19-22
Y	HARAHAP et al. "Bioequivalence study of two rosuvastatin tablet formulations in healthy Indonesian subjects," Int J Clin Pharmacol Ther, 15 June 2015 (15.06.2015), Vol. 54, No. 3, Pgs. 212-216. entire document	1-11
Y	US 2015/0050333 A1 (DAEWOONG PHARMACEUTICAL CO., LTD.) 19 February 2015 (19.02.2015) entire document	9, 10, 19-21
Y	WO 2013/101830 A1 (IRONWOOD PHARMACEUTICALS, INC. et al) 04 July 2013 (04.07.2013) entire document	11, 22
A	SON et al. "Pharmacokinetics of rosuvastatin/olmesartan fixed-dose combination: a single-dose, randomized, open-label, 2-period crossover study in healthy Korean subjects," Clin Ther, 27 June 2013 (27.06.2013), Vol. 35, No. 7, Pgs. 915-922. entire document	1-22
A	ZAID et al. "Investigation of the Bioequivalence of Rosuvastatin 20 mg Tablets after a Single Oral Administration in Mediterranean Arabs Using a Validated LC-MS/MS Method," Sci Pharm, 30 June 2016 (30.06.2016), Vol. 84, No. 3, Pgs. 536-546. entire document	1-22

☐ Further documents are listed in the continuation of Box C. ☐ 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 application or patent 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
30 August 2017	02 OCT 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774