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(54) Title: METHODS FOR TREATING OBESITY WITH A COMBINATION COMPRISING A MTP INHIBITOR AND A CHOLESTEROL ABSORPTION INHIBITOR

(57) Abstract: The invention is directed to methods for treating and/or controlling obesity in a patient. The methods involve combination therapies using a microsomal triglyceride transfer protein (MTP) inhibitor (for example, AEGR-733 and implitapide) and a cholesterol absorption inhibitor (CAI) (for example, ezetimibe).



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## METHODS FOR TREATING OBESITY WITH A COMBINATION COMPRISING A MTP INHIBITOR AND A CHOLESTEROL ABSORPTION INHIBITOR

### RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/876,280 filed December 21, 2006, the entire disclosure of which is incorporated by reference herein

### FIELD OF THE INVENTION

5 [0002] This invention relates generally to methods of treating and/or controlling obesity in a patient. More particularly, the invention relates to therapies using a microsomal triglyceride transfer protein (MTP) inhibitor in combination with a cholesterol absorption inhibitor (CAI).

### BACKGROUND

10 [0003] Obesity is a major public health concern and is now recognized as a chronic disease that requires treatment to reduce its associated health risks. It is understood that more than 100 million adults in the United States are overweight or obese. The medical problems caused by overweight and obesity can be serious and often life-threatening, and include diabetes, shortness of breath, gallbladder disease, hypertension, elevated blood cholesterol levels, cancer, arthritis, other orthopedic problems, reflux esophagitis (heartburn), snoring, sleep apnea,  
15 menstrual irregularities, infertility and heart trouble. Moreover, obesity and overweight substantially increase the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis and endometrial, breast, prostate, and colon cancers. Higher body weights are also associated with increases in all-cause mortality. Most or all of these problems are alleviated or improved by permanent  
20 significant weight loss. Longevity is likewise significantly increased by permanent significant weight loss. Hence, it is believed that a 2-10% intentional reduction in body weight may reduce morbidity and mortality. There is a clear on-going need for methods for treating obesity that effectively reduce body mass in a patient in need thereof.

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[0004] Microsomal triglyceride transfer protein (MTP) inhibitors have been developed as potent inhibitors of MTP-mediated neutral lipid transfer activity. MTP catalyzes the transport of triglyceride, cholesteryl ester, and phosphatidylcholine between small unilamellar vesicles.

[0005] Cholesterol absorption inhibitors such as ezetimibe impair the intestinal reabsorption of both dietary and hepatically-excreted biliary cholesterol. Ezetimibe, for example, is used for reducing low density lipoprotein cholesterol in patients. Cholesterol absorption inhibitors are not known to be effective, when used in monotherapy, for use in treating obesity or for use as a weight loss agent.

### SUMMARY OF THE INVENTION

[0006] The invention provides methods for treating and/or controlling obesity. The method includes administering an MTP inhibitor, such as AEGR-733 or implitapide, in combination with a cholesterol absorption inhibitor (CAI), such as ezetimibe. The MTP inhibitors can be administered at certain lower dosages that are still therapeutically effective when combined with a CAI but yet create fewer or reduced adverse effects when compared to therapies using therapeutically effective dosages of the MTP inhibitors during monotherapy. The administration of one or more MTP inhibitors, when administered in combination with one or more CAIs, may provide an additive or synergistic therapeutic effect, e.g. may result in patient weight loss that is greater than the sum of the expected weight loss due to administration of a MTP inhibitor and CAI when administered alone. In some embodiments, disclosed methods can result in fewer incidences of gastrointestinal adverse events in a patient as compared to administration of a MTP inhibitor alone.

[0007] An exemplary method includes a method of treating obesity comprising administering to a patient in need thereof a MTP inhibitor in combination with a cholesterol absorption inhibitor, wherein the administration of the combination results in a greater reduction in body mass of the patient after 12 weeks of daily administration as compared to 12 weeks of daily administration of a cholesterol absorption inhibitor or a MTP inhibitor alone.

[0008] For example, a method of treating obesity is disclosed that comprises administering to a patient in need thereof a MTP inhibitor in combination with a cholesterol absorption inhibitor, wherein the administration of the combination results in a greater reduction in body mass of the patient after 12 weeks of daily administration as compared to 12 weeks of daily administration

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of a cholesterol absorption inhibitor or a MTP inhibitor alone, and wherein the method results in fewer incidences of gastrointestinal adverse events in the patient as compared to administration of a MTP inhibitor alone.

[0009] Another exemplary method contemplated by this disclosure includes a method of inducing weight loss in a patient comprising administering to the patient an MTP inhibitor in combination with a cholesterol absorption inhibitor so as to induce weight loss in the patient. In some embodiments, the weight loss achieved, after e.g. 4 weeks, 8 weeks, 12 weeks, or even 6 months, is greater than that achieved by administering the cholesterol inhibitor alone or the MTP inhibitor alone. In an embodiment, weight loss achieved by the disclosed methods is greater than the additive effect of administering the MTP inhibitor alone and the cholesterol absorption inhibitor alone.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Throughout this entire disclosure, including the figures and claims, the terms “AEGR-733” and “BMS-201038” have the same meaning and are used interchangeably.

[0011] Figure 1 depicts body mass reduction at 4 weeks, 8 weeks, and 12 weeks of daily administration of AEGR-733 and ezetimibe in the patient study described in Example 1.

[0012] Figure 2 depicts the occurrence rate of gastrointestinal adverse events and the GSRS results of patients assessed at 12 weeks in the patient study described in Example 1.

[0013] Figure 3 depicts body mass reduction at 4 weeks, 8 weeks, and 12 weeks of daily administration of AEGR-733 and ezetimibe for those patients with an initial BMI greater than 30 kg/m<sup>2</sup> in the patient study as described in Example 1.

[0014] Figure 4 depicts body mass reduction at 4 weeks, 8 weeks, and 12 weeks of daily administration of AEGR-733 and ezetimibe for those patients with an initial BMI less than or equal to 30 kg/m<sup>2</sup> in the patient study as described in Example 1.

## DETAILED DESCRIPTION

[0015] The invention relates, in part, to methods of treating and/or controlling obesity comprising administering to a patient in need thereof a MTP inhibitor in combination with a cholesterol absorption inhibitor. Such a patient may have, for example, a body mass index greater than or equal to about 30 kg/m<sup>2</sup>, e.g. between about 30 kg/m<sup>2</sup> and about 60 kg/m<sup>2</sup> before treatment. Alternatively, a patient may have a body mass index between about 25 kg/m<sup>2</sup> and about 30 kg/m<sup>2</sup> before treatment.

[0016] The methods described herein result in a greater reduction in body mass of a patient after, for example, four, eight and/or twelve weeks of daily administration, or 4, 5, and/or 6 months or 1 year of substantially daily administration, as compared to daily administration of a cholesterol absorption inhibitor or a MTP inhibitor alone for the same time interval.

[0017] Administering combinations of a MTP inhibitor and a cholesterol absorption inhibitor, under certain circumstances, provide an additive and/or synergistic therapeutic effect, e.g. provide a total reduction in body mass that is greater than the sum of the reduction in body mass resulting from administering a MTP inhibitor or a cholesterol absorption inhibitor alone.

### 1. Definitions

[0018] For convenience, certain terms used in the specification, examples, and appended claims are collected in this section.

[0019] The phrase "combination therapy," as used herein, refers to co-administering an MTP inhibitor, for example, AEGR-733 and implitapide, or a combination thereof, and CAI, for example, ezetimibe, as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually weeks, months or years depending upon the combination selected). Combination therapy is intended to embrace administration of multiple therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous

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