The present invention will be illustrated further by means of the following non-limiting examples.

EXAMPLES

Example 1:

A Mendelian randomization analysis was carried of 470.471 participants with individual level data from UK Biobank and dbGAP. From these participants 44.321 suffered from a major cardiovascular event (CHD death, MI, stroke or coronary revascularization). After analysis it was found that CETP inhibition is causally associated with decreased risk of major cardiovascular events. It was further found that a substantial attenuation of effect (i.e. the reduction of ApoB/LDL-C lowering) occurred when CETP inhibition is added to HMGCR inhibition. However, it was surprisingly found that a similar attenuation of CETP effect did not occur when added to NPC1L1 (i.e. CETP stratified by NPC1L1 inhibition). Hence, other than would have been expected on the basis of HMGCR inhibition by statins, the use of background ezetimibe does not lead to a attenuation in effect of CETP on lowering ApoB/ LDL-C and thereby on cardiovascular events. This makes said combination very suitable for lowing the ApoB/ LDL-C concentration in statin intolerant patients.

The results of the analysis are depicted below in Figures 1 and 2, wherein tertile 1 represents the lowest degree of inhibition of either HMGCR or NPC1LI and tertile 3 represents the highest degree of inhibition of said receptors. From these results it is clear that the more inhibition of HMGCR takes place, the smaller the effect of CETP inhibition on APO-B/LDL-C becomes. Remarkably, increased inhibition of NPC1L1 does not lead to a smaller effect of CETP inhibition on APO-B/LDL-C:

Example 2a:

Placebo-Controlled, Double-Blind, Randomized Phase 2 Study to Evaluate the Effect of Obicetrapib in Combination with Ezetimibe in Participants with Mild dyslipidaemia and potential statin intolerance (Protocol)

CLAIMS

1. Use of a Ppharmaceutical composition comprising obicetrapib and ezetimibe or pharmaceutically acceptable salts or solvates thereof and a pharmaceutically acceptable carrier for use in thein the manufacture of a medicament for treatment of subjects suffering or having an increased risk for hyperlipidemia or mixed dyslipidemia and wherein said subjects are partially or completely intolerant to statins.

2. The use Pharmaceutical composition according to claim 1, wherein the treatment of subjects suffering or having an increased risk for hyperlipidemia or mixed dyslipidemia for use incomprises reducing the risk for cardiovascular events.

3. The Pharmaceutical composition for use according to any of the previous claims, wherein the subjects suffer from mild dyslipidemia.

4. The Pharmaceutical composition for use according to any of the previous claims, wherein the medicament is a subject in need thereof is administeredadapted for administering between 1 to 10 mg per day obicetrapib and between 5 to 20 mg ezetimibe per day, preferably said subject is administered 5 mg obicetrapib per day and 10 mg ezetimibe per day or 10 mg obicetrapib per day and 10 mg ezetimibe per day.

5. The Pharmaceutical composition for use according to any of the previous claims, wherein said composition reduces the apolipoprotein B (ApoB) concentration in the blood of said subjects.

6. The Pharmaceutical composition for use according to any of the previous claims, wherein said composition reduces the LDL-C concentration in the blood of said subjects.

7. The Pharmaceutical composition for use according to any of the previous claims, wherein the composition does not attenuate the LDL-C lowering effect of obicetrapib,

when compared to obicetrapib monotherapy.

8. The ~~Pharmaceutical composition for~~ use according to any of the previous claims, wherein the relative LDL-C reduction by obicetrapib when administered in combination with ezetimibe is similar to the relative LDL-C reduction by the same dose of obicetrapib administered as monotherapy.

9. The ~~Pharmaceutical composition for~~ use according to any of the previous claims, wherein the relative LDL-C reduction by a daily dose 5 mg obicetrapib when administered in combination with 10 mg ezetimibe is similar to the relative LDL-C reduction by a daily dose of 5 mg obicetrapib administered as monotherapy.

10. The ~~Pharmaceutical composition for~~ use according to any of the previous claims, wherein the relative LDL-C reduction by a daily dose of 10 mg obicetrapib when administered in combination with 10 mg ezetimibe is similar to the relative LDL-C reduction by a daily dose of 10 mg obicetrapib administered as monotherapy.

11. The ~~Pharmaceutical composition for~~ use according to any of the previous claims, wherein the composition is formulated as an oral free dose or oral fixed dose combination, preferably as an oral fixed dose combination.

12. The ~~Pharmaceutical composition for~~ use according to any of the previous claims, wherein the oral fixed dose combination is a solid dosage form, such as a capsule or tablet.

13. The ~~Pharmaceutical composition for~~ use according to any of the previous claims, wherein the composition is an oral fixed dose combination comprising 1 to 10 mg obicetrapib and 5 to 20 mg ezetimibe, preferably said composition comprises 5 mg obicetrapib and 10 mg ezetimibe or 10 mg obicetrapib and 10 mg ezetimibe.

14. Use of a ~~T~~therapeutic combination comprising obicetrapib and ezetimibe or pharmaceutically acceptable salts or solvates thereof ~~for use~~ in the manufacture of a medicament for treatment of subjects suffering from hyperlipidemia or mixed dyslipidemia or having an increased risk for hyperlipidemia or mixed dyslipidemia

and wherein said subjects are partially or completely intolerant to statins.

15. The ~~Therapeutic combination according to the previous claim for~~ use according to claim 14, wherein the treatment comprises ~~in~~ reducing the risk for cardiovascular events.

16. The ~~Therapeutic combination for~~ use according to ~~the previous~~ claim 14 or 15, wherein the subjects suffer from mild dyslipidemia.

17. The ~~Therapeutic combination for~~ use according to any of ~~the previous~~ claims 14 to 16, wherein the medicament is adapted for administering to a subject in need thereof ~~is administered~~ between 1 to 10 mg per day obicetrapib and between 5 to 20 mg ezetimibe per day, preferably ~~said subject is administered~~ 5 mg obicetrapib per day and 10 mg ezetimibe per day or 10 mg obicetrapib per day and 10 mg ezetimibe per day.

18. The ~~Therapeutic combination for~~ use according to any of ~~the previous~~ claims 14 to 17, wherein said combination reduces the apolipoprotein B (ApoB) concentration in the blood of said subjects.

19. The ~~Therapeutic combination for~~ use according to any of ~~the previous~~ claims 14 to 18, wherein the combination does not attenuate the LDL-C lowering effect of obicetrapib, when compared to obicetrapib monotherapy.

20. The ~~Therapeutic combination for~~ use according to any of ~~the previous~~ claims 14 to 19, wherein the relative LDL-C reduction by obicetrapib when administered in combination with ezetimibe is similar to the relative LDL-C reduction by the same dose of obicetrapib administered as monotherapy.

21. The ~~Therapeutic combination for~~ use according to any of ~~the previous~~ claims 14 to 20, wherein the relative LDL-C reduction by a daily dose 5 mg obicetrapib when administered in combination with 10 mg ezetimibe is similar to the relative LDL-C reduction by a daily dose of 5 mg obicetrapib administered as monotherapy.

22. The ~~Therapeutic combination for~~ use according to any of ~~the previous~~ claims 14 to 21, wherein the relative LDL-C reduction by a daily dose of 10 mg obicetrapib when administered in combination with 10 mg ezetimibe is similar to the relative LDL-C reduction by a daily dose of 10 mg obicetrapib administered as monotherapy.

23. The ~~Therapeutic combination for~~ use according to any of ~~the previous~~ claims 14 to 22, wherein the combination is as an oral free dose or an oral fixed dose combination.

24. The ~~Therapeutic combination for~~ use according to any of ~~the previous~~ claims 14 to 23, wherein the combination comprises a first unit dosage form comprising 1 to 10 mg obicetrapib and a second unit dosage comprising 5 to 20 mg ezetimibe, preferably the first unit dosage comprises 5 mg obicetrapib and the second unit dosage 10 mg ezetimibe or the first unit dosage comprises 10 mg obicetrapib and the second unit dosage 10 mg ezetimibe.

25. The use ~~Therapeutic combination~~ according to any of ~~the previous~~ claims 14 to 24, wherein the combination comprises a package comprising said unit dosage forms, preferably in the form of tablets or capsules.

~~26. Method of treating a partially or completely statin intolerant subject suffering from or having an increased risk for hyperlipidemia or mixed dyslipidemia, the method comprising administering to said subject in need thereof an effective dosage amount of the pharmaceutical composition or therapeutic combination according to any of the previous claims.~~

~~27. Method according to the previous claim, wherein said method reduces the risk for cardiovascular events.~~

~~28. Use of a pharmaceutical composition or therapeutic combination according to any of the previous claims in the manufacture of a medicament for use in the treatment of partially or completely statin intolerant subjects suffering from or having an increased risk for hyperlipidemia or mixed dyslipidemia.~~

29. Use according to the previous claims, wherein said use reduces the risk for cardiovascular events.

30. Pharmaceutical composition or therapeutic combination comprising a CETP-inhibitor, preferably obicetrapib, and ezetimibe for use in the treatment of partially or completely statin intolerant subjects suffering from cardiovascular diseases or having an increased risk for cardiovascular diseases.

31. Pharmaceutical composition or therapeutic combination for use according to the previous claim, for reducing the risk for cardiovascular events.

32. Pharmaceutical composition or therapeutic combination for use according to claims 27 or 28, for reducing the apolipoprotein B (ApoB) concentration in the blood of said subjects.

33. Pharmaceutical composition or therapeutic combination for use according to claims 27-29, wherein the relative LDL-C reduction by obicetrapib when administered in combination with ezetimibe is similar to the relative LDL-C reduction by the same dose of obicetrapib administered as monotherapy.

34. Pharmaceutical composition or therapeutic combination for use according to claims 27-29, wherein said combination does not attenuate the LDL-C lowering effect of obicetrapib, when compared to obicetrapib monotherapy.