[0005] The current ESC/ERS Guidelines for the treatment of PAH recommend initial double combination therapy or sequential combination therapy in patients with an inadequate clinical response to initial monotherapy. In patients at high risk, initial combination therapy including i.v. epoprostenol is recommended. More recently, the Proceedings from the 6th World Symposium on Pulmonary Hypertension propose initial oral combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase type 5 inhibitor (PDE-5i) in patients with low or intermediate risk of 1-year mortality, and initial combination therapy including i.v. prostacyclin in high risk patients.

SUMMARY

[0006] ~~In some embodiments, t~~The ~~invention~~ disclosure relates to methods of reducing the risk of disease progression in a patient with pulmonary arterial hypertension (PAH). These methods comprise administering to a patient in need thereof, an initial triple combination therapy of an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 (PDE-5) inhibitor, and a prostacyclin receptor agonist (IP receptor agonist).

[0006a] In one aspect, there is provided use of an endothelin receptor antagonist (ERA) in the manufacture of a first medicament, a phosphodiesterase type 5 (PDE-5) inhibitor in the manufacture of a second medicament and a prostacyclin receptor agonist (IP receptor agonist) in the manufacture of a third medicament, wherein the first medicament, second medicament and third medicament are to be used in an initial triple combination therapy for reducing the risk of disease progression of pulmonary arterial hypertension in a patient.

[0006b] In another aspect, there is provided an initial triple combination therapy of an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 (PDE-5) inhibitor, and a prostacyclin receptor agonist (IP receptor agonist) for use in reducing the risk of disease progression in a patient with pulmonary arterial hypertension (PAH).

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] Fig. 1 is a schematic showing the study periods at the subject level.

[0008] Fig. 2 is a schematic showing the planned duration at the study level.

[0009] Fig. 3 is a scatter plot of the change from baseline to Week 26 in PVR (versus baseline) Analysis Set: Full Analysis Set.

[0010] Fig. 4 is a Forest plot of ANCOVA: PVR ratio of Week 26 to baseline by subgroups Analysis Set: Full Analysis Set. In this figure, the vertical solid line references the overall treatment effect. Marker size for subgroups is based on number of subjects per group. P-values reflect treatment-by-subgroup interaction testing on extended main model, including stratification factors and baseline as covariate, with subgroup variable effect and its interaction with treatment added. * = interaction p-value; Sel=Selexipag; Plc=placebo.

[0011] Fig. 5 is a scatter plot of change from baseline to Week 26 in 6MWD (versus baseline).

[0012] Fig. 6 is a line graph showing time from randomization to first disease progression event up to EOMOP + 7 days Analysis Set: Full Analysis Set. In this figure, subjects are censored at EOMOP+7 days or end of study, whichever is earlier. Graph is cut

What is claimed:

1. Use of an endothelin receptor antagonist (ERA) in the manufacture of a first medicament, a phosphodiesterase type 5 (PDE-5) inhibitor in the manufacture of a second medicament and a prostacyclin receptor agonist (IP receptor agonist) in the manufacture of a third medicament, wherein the first medicament, second medicament and third medicament are to be used in ~~A method of reducing the risk of disease progression in a patient with pulmonary arterial hypertension (PAH), comprising administering to a patient in need thereof,~~ an initial triple combination therapy for reducing the risk of disease progression of pulmonary arterial hypertension in a patient~~of an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 (PDE-5) inhibitor, and a prostacyclin receptor agonist (IP receptor agonist)~~.

2. The ~~method~~ use of claim 1, wherein the reduced risk of disease progression is relative to a patient population with PAH that receives an initial double combination therapy of the ERA and the PDE-5 inhibitor.

3. The ~~method~~ use of claim 1 or 2, wherein the ERA is macitentan, bosentan, or ambrisentan, or a pharmaceutically acceptable salt thereof; the PDE-5 inhibitor is tadalafil, sildenafil, vardenafil, or udenafil, or a pharmaceutically acceptable salt thereof; and the IP receptor agonist is selexipag, 4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}acetic acid (MRE-269), or a pharmaceutically acceptable salt thereof.

4. The use ~~method~~ of claim 3, wherein the ERA is macitentan, the PDE-5 inhibitor is tadalafil, and the IP receptor agonist is selexipag.

5. The use ~~method~~ of any one of the preceding claims, wherein the patient is treatment naïve for PAH.

6. The use ~~method~~ of any one of the preceding claims, wherein an initial PAH diagnosis of the patient is made within six months of the start of the initial triple combination therapy.

7. The use ~~method~~ of any one of the preceding claims, wherein the patient has a mean pulmonary arterial hypertension (mPAP) of greater than or equal to about 25 mmHg at rest, a mean pulmonary arterial wedge pressure (PAWP) of less than or equal to about 15 mmHg, and a pulmonary vascular resistance (PVR) of greater than or equal to about 240 dyn·sec/cm^5 at the start of the initial triple combination therapy.

8. The use ~~method~~ of any one of the preceding claims, wherein the patient has a 6-minute walk distance (6MWD) of greater than or equal to about 50 meters at the start of the initial triple combination therapy.

9. The use ~~method~~ of any one of claims 4-8, wherein the macitentan is to be administered in an amount of about 10 mg once daily.

10. The ~~-~~use ~~method~~ of any one of claims 4-9, wherein the tadalafil is to be administered in an amount of from about 20 mg to about 40 mg once daily.

11. The use ~~method~~ of any one of claims 4-10, wherein the tadalafil is to be administered in an amount of about 40 mg once daily

12. The use ~~method~~ of any one of claims 4-11, wherein the selexipag is to be administered in an amount of from about 200 µg to about 1600 µg twice daily.

13. The use ~~method~~ of any one of claims 4-12, wherein each of the macitentan, the tadalafil, and the selexipag are to be administered orally in the form of one or more tablets.

14. The use ~~method~~ of any one of claims 4-12, wherein the macitentan and the tadalafil are to be administered orally in the form of a single tablet, and the selexipag is to be administered orally in the form of one or more separate tablets.

15. The use ~~method~~ of any one of claims 2-14, wherein the initial triple combination therapy reduced the risk of disease progression by about 30 to 40% relative to the initial double combination therapy.

16. The use ~~method~~ of any one of the preceding claims, wherein the disease progression comprises hospitalization for worsening of PAH, clinical worsening of PAH, or death.

17. An initial triple combination therapy of an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 (PDE-5) inhibitor, and a prostacyclin receptor agonist (IP receptor agonist) for use in reducing the risk of disease progression in a patient with pulmonary arterial hypertension (PAH).

18. The initial triple combination therapy for use of claim 17, wherein the reduced risk of disease progression is relative to a patient population with PAH that receives an initial double combination therapy of the ERA and the PDE-5 inhibitor.

19. The initial triple combination therapy for use of claim 17 or 18, wherein the ERA is macitentan, bosentan, or ambrisentan, or a pharmaceutically acceptable salt thereof; the PDE-5 inhibitor is tadalafil, sildenafil, vardenafil, or udenafil, or a pharmaceutically acceptable salt thereof; and the IP receptor agonist is selexipag, 4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}acetic acid (MRE-269), or a pharmaceutically acceptable salt thereof.

20. The initial triple combination therapy for use of claim 19, wherein the ERA is macitentan, the PDE-5 inhibitor is tadalafil, and the IP receptor agonist is selexipag.

21. The initial triple combination therapy for use of any one of claims 17-20, wherein the patient is treatment naïve for PAH.

22. The initial triple combination therapy for use of any one of claims 17-21, wherein an initial PAH diagnosis of the patient is made within six months of the start of the initial triple combination therapy.

23. The initial triple combination therapy for use of any one of claims 17-22, wherein the patient has a mean pulmonary arterial hypertension (mPAP) of greater than or equal to about 25 mmHg at rest, a mean pulmonary arterial wedge pressure (PAWP) of less than or equal to about 15 mmHg, and a pulmonary vascular resistance (PVR) of greater than or equal to about 240 dyn·sec/cm^5 at the start of the initial triple combination therapy.

24. The initial triple combination therapy for use of any one of claims 17-23, wherein the patient has a 6-minute walk distance (6MWD) of greater than or equal to about 50 meters at the start of the initial triple combination therapy.

25. The initial triple combination therapy for use of any one of claims 20-24, wherein the macitentan is formulated for administration in an amount of about 10 mg once daily.

26. The initial triple combination therapy for use of any one of claims 20-25, wherein the tadalafil is formulated for administration in an amount of from about 20 mg to about 40 mg once daily.

27. The initial triple combination therapy for use of any one of claims 20-26, wherein the tadalafil is formulated for administration in an amount of about 40 mg once daily

28. The initial triple combination therapy for use of any one of claims 20-27, wherein the selexipag is formulated for administration in an amount of from about 200 µg to about 1600 µg twice daily.

29. The initial triple combination therapy for use of any one of claims 20-28, wherein each of the macitentan, the tadalafil, and the selexipag are formulated for administration orally in the form of one or more tablets.

30. The initial triple combination therapy for use of any one of claims 20-28, wherein the macitentan and the tadalafil are formulated for administration orally in the form of a single tablet, and the selexipag is formulated for administration orally in the form of one or more separate tablets.

31. The initial triple combination therapy for use of any one of claims 18-30, wherein the initial triple combination therapy reduced the risk of disease progression by about 30 to 40% relative to the initial double combination therapy.

32. The initial triple combination therapy for use ~~method~~ of any one of claims 17-31, wherein the disease progression comprises hospitalization for worsening of PAH, clinical worsening of PAH, or death.