

What is claimed:

1. 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 of an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 (PDE-5) inhibitor, and a prostacyclin receptor agonist (IP receptor agonist).
2. The method 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 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 method of claim 3, wherein the ERA is macitentan, the PDE-5 inhibitor is tadalafil, and the IP receptor agonist is selexipag.
5. The method of any one of the preceding claims, wherein the patient is treatment naïve for PAH.
6. The 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 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/cm⁵ at the start of the initial triple combination therapy.

8. The 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 method of any one of claims 4-8, wherein the macitentan is administered in an amount of about 10 mg once daily.
10. The method of any one of claims 4-9, wherein the tadalafil is administered in an amount of from about 20 mg to about 40 mg once daily.
11. The method of any one of claims 4-10, wherein the tadalafil is administered in an amount of about 40 mg once daily
12. The method of any one of claims 4-11, wherein the selexipag is administered in an amount of from about 200 µg to about 1600 µg twice daily.
13. The method of any one of claims 4-12, wherein each of the macitentan, the tadalafil, and the selexipag are administered orally in the form of one or more tablets.
14. The method of any one of claims 4-12, wherein the macitentan and the tadalafil are administered orally in the form of a single tablet, and the selexipag is administered orally in the form of one or more separate tablets.
15. The 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 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 reducing the risk of disease progression in a patient with pulmonary arterial hypertension (PAH).

18. The initial triple combination therapy 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 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 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 of any one of claims 17-20, wherein the patient is treatment naïve for PAH.
22. The initial triple combination therapy 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 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/cm⁵ at the start of the initial triple combination therapy.
24. The initial triple combination therapy 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 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 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 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 of any one of claims 20-27, wherein the selexipag is formulated for administration in an amount of from about 200 μ g to about 1600 μ g twice daily.
29. The initial triple combination therapy 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 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 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 method of any one of claims 17-31, wherein the disease progression comprises hospitalization for worsening of PAH, clinical worsening of PAH, or death.