WINREVAIR® (sotatercept)
Powder for Solution for Injection

1. INDICATIONS AND USAGE

WINREVAIR is indicated for the treatment of adults with pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1; Functional Class [FC] II to III) to increase exercise capacity, improve WHO functional class, and delay disease progression.

2. DOSAGE

2.1 Recommended Starting Dosage in Adults

WINREVAIR is administered once every 3 weeks by subcutaneous (SC) injection according to patient weight. The starting dose of WINREVAIR is 0.3 mg/kg (see Table 1).

Obtain hemoglobin (Hgb) and platelet count prior to the first dose of WINREVAIR. Rapid increases in Hgb of more than 2 g/dL have been observed after initiating treatment. It is not recommended to initiate treatment if platelet count is <50,000/mm^3 (<50.0 x 10^9/L) *[see Dosage and Administration (2.3)]*.

Table 1: Injection Volume for Dose of 0.3 mg/kg

Patient Weight Range (kg)	Injection Volume (mL)	Dose Vial
30.0 – 40.8	0.2	45 mg
40.9 – 57.4	0.3	
57.5 – 74.1	0.4	
74.2 – 90.8	0.5	
90.9 – 107.4	0.6	
107.5 – 124.1	0.7	
124.2 – 140.8	0.8	
140.9 – 157.4	0.9	

157.5 – 174.1	1.0	60 mg
174.2 – 180.0	1.1	

2.2 Recommended Target Dosage in Adults

The target dose of WINREVAIR is 0.7 mg/kg (see Table 2) administered every 3 weeks.

Obtain and review hemoglobin (Hgb) and platelet count prior to increasing to the target dose. Continue treatment at 0.7 mg/kg every 3 weeks unless dosage adjustments are required *[see Dosage and Administration (2.3)]*.

Table 2: Injection Volume for Dose of 0.7 mg/kg

Patient Weight Range (kg)	Injection Volume (mL)	Dose Vial(s)
30.0 – 31.7	0.4	45 mg
31.8 – 38.9	0.5	
39.0 – 46.0	0.6	
46.1 – 53.2	0.7	
53.3 – 60.3	0.8	
60.4 – 67.4	0.9	
67.5 – 74.6	1.0	60 mg
74.7 – 81.7	1.1	
81.8 – 88.9	1.2	
89.0 – 96.0	1.3	2 x 45 mg
96.1 – 103.2	1.4	
103.3 – 110.3	1.5	
110.4 – 117.4	1.6	
117.5 – 124.6	1.7	
124.7 – 131.7	1.8	
131.8 – 138.9	1.9	2 x 60 mg
139.0 – 146.0	2.0	
146.1 – 153.2	2.1	
153.3 – 160.3	2.2	
160.4 – 167.4	2.3	
167.5 and above	2.4	

Missed Dose or Overdose

If a dose of WINREVAIR is missed, administer as soon as possible. If the missed dose of WINREVAIR is not taken within 3 days of the scheduled date, adjust the schedule to maintain 3-week dosing intervals. In case of an overdose, monitor for erythrocytosis *[see Overdosage (9)]*.

2.3 Dosage Modifications in Adults Due to Hemoglobin Increase or Platelet Count Decrease

Increases in Hgb to levels greater than 2 g/dL above the upper limit of normal (ULN) and decreases in platelet count <50,000/mm^3 (<50.0 x 10^9/L) have been observed. Check Hgb and platelet count before each dose for the first 5 doses, or longer if values are unstable. Thereafter, monitor Hgb and platelet count periodically. Consider assessment of benefit-risk for the individual patient in determining whether dose modification is appropriate *[see Warnings and Precautions (5.1, 5.2)]*.

Delay treatment for 3 weeks if any of the following occur:

- Hgb increases >2.0 g/dL from the previous dose and is above ULN.
- Hgb increases >4.0 g/dL from baseline.
- Hgb increases >2.0 g/dL above ULN.
- Platelet count decreases to <50,000/mm^3 (<50.0 x 10^9/L).

For treatment delays lasting >9 weeks, restart treatment at 0.3 mg/kg.

2.4 Pediatric Patients

Safety and efficacy of WINREVAIR have not been established in patients less than 18 years of age.

2.5 Geriatric Patients

No dose adjustment of WINREVAIR is required based on age *[see 7. Use in Specific Populations (7.5) and Clinical Pharmacology (11.4)]*.

2.6 Renal Impairment

No dose adjustment of WINREVAIR is required based on renal impairment. Sotatercept has not been studied in PAH patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) *[see 7. Use in Specific Populations (7.6) and Clinical Pharmacology (11.4)]*.

2.7 Hepatic Impairment

WINREVAIR use has not been studied in patients with hepatic impairment (Child-Pugh Classification A to C). Hepatic impairment is not expected to influence sotatercept metabolism since sotatercept is metabolized via cellular catabolism *[see 7. Use in Specific Populations (7.7) and Clinical Pharmacology (11.4)]*.

3. PREPARATION AND ADMINISTRATION

WINREVAIR Lyophilized powder should be prepared and administered by a health care professional. Step-by-step preparation and administration instructions are provided below.

Reconstitution Instructions

- Remove the vial(s) from the refrigerator and wait 15 minutes to allow the drug product to come to room temperature prior to preparation.
- Check the vial to ensure the product is not expired. The powder should be white to off-white and may look like a whole or fragmented cake.
- Remove the lid from the vial containing the WINREVAIR lyophilized powder and swab the rubber stopper with an alcohol wipe.
- Reconstitute the content of the vial with sterile water:
    - For each vial of WINREVAIR 45 mg, inject 1.0 mL of sterile water
    - For each vial of WINREVAIR 60 mg, inject 1.3 mL of sterile water

  This will provide a final concentration of 50 mg/mL.
- Gently swirl the vial to reconstitute the drug product. DO NOT shake or vigorously agitate.
- Allow the vial to stand for up to 3 minutes to allow bubbles to disappear.
- Visually inspect the reconstituted solution. When properly mixed, WINREVAIR should be clear to opalescent and colorless to slightly brownish-yellow and does not have clumps or powder.

- If prescribed a 2-vial presentation, repeat the steps within this section to prepare the second vial.
- Use the reconstituted solution as soon as possible, but no later than 4 hours after reconstitution.

Administration Instructions

- Withdraw the appropriate dose of WINREVAIR from one or two vials, depending on the volume to inject.
- Select the injection site on the abdomen (at least 2 inches away from navel), upper thigh, or upper arm, and swab with an alcohol wipe. For each injection, select a new site that is not scarred, tender, or bruised.
- Perform subcutaneous injection.
- Discard the emptied syringe into a sharps container. Do not reuse the syringe.

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 Erythrocytosis

Hgb increases have been observed in patients during treatment with WINREVAIR. Severe erythrocytosis may increase the risk of thromboembolic events or hyperviscosity syndrome. Monitor Hgb before each dose for the first 5 doses, or longer if values are unstable, and periodically thereafter to determine if dose adjustments are required *[see Dosage and Administration (2.3) and Adverse Reactions (8.1)]*.

5.2 Severe Thrombocytopenia

Decreased platelet count has been observed in some patients taking WINREVAIR and severe thrombocytopenia (platelet count <50,000/mm^3 (<50.0 x 10^9/L)) has been observed. Thrombocytopenia occurred more frequently in patients also receiving prostacyclin infusion.

Do not initiate treatment if platelet count is <50,000/mm^3 (<50 x 10^9/L) *[see Dosage and Administration (2.3)]*.

Monitor platelet count before each dose for the first 5 doses, or longer if values are unstable, and periodically thereafter to determine whether dose adjustments are required *[see Dosage and Administration (2.3) and Adverse Reactions (8.1)]*.

5.3 Serious Bleeding

In clinical studies, serious bleeding events (e.g., gastrointestinal, intracranial hemorrhage) were reported in 4% of patients taking WINREVAIR and 1% of patients taking placebo. Patients with serious bleeding events were more likely to be on prostacyclin background therapy and/or antithrombotic agents, or have low platelet counts. Advise patients about signs and symptoms of blood loss. Evaluate and treat bleeding accordingly. Do not administer WINREVAIR if the patient is experiencing a serious bleeding event *[see Warnings and Precautions (5.2), Adverse Reactions (8.1)]*.

5.4 Embryo-Fetal Toxicity

Based on findings in animal reproduction studies, WINREVAIR may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with WINREVAIR and for at least 4 months after the final dose *[see Use in Specific Populations (7.1, 7.3) and Animal Toxicology (12.6)]*.

5.5 Impaired Fertility

Based on findings in animals, WINREVAIR may impair female and male fertility. Advise patients on the potential effects on fertility *[see Use in Specific Populations (7.3) and Animal Toxicology (12.5)].*

6. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No interaction studies have been performed.

7. USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

Risk Summary

There are no available data on WINREVAIR use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. However, based on animal embryo-fetal toxicity studies, WINREVAIR may cause post-implantation loss or fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is not known. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively *(see Clinical Considerations)*.

Clinical Considerations

Pregnant women with PAH are at risk for heart failure, preterm delivery, and maternal and fetal death.

Data

Animal Data

In pregnant rats and rabbits, sotatercept exposures ≥4-fold and ≥0.6-fold the MRHD, respectively, resulted in decreases in fetal weights, delays in ossification, and increases in resorptions and post-implantation loss. At 15-fold the MRHD, rat fetuses had an increased incidence of skeletal variations (increased number of supernumerary ribs and changes in the number of thoracic or lumbar vertebrae). In a pre- and postnatal development study, rat pups from lactating dams exposed to sotatercept levels ≥2-fold the MRHD had decreased body weights that correlated with delays in sexual maturation *[see Animal Toxicology (12.6)]*.

7.2 Nursing Mothers

Risk Summary

There are no data on the presence of sotatercept in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in

the breastfed child, advise patients that breastfeeding is not recommended during treatment with WINREVAIR, and for 4 months after the final dose.

7.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential before starting treatment.

Contraception

Females

Females of reproductive potential should use effective contraception during treatment with WINREVAIR and for at least 4 months after the last dose if treatment is discontinued *[see Use in Specific Populations (7.1) and Animal Toxicology (12.5)]*.

Infertility

Based on findings in animals, sotatercept may impair female and male fertility *[see Animal Toxicology (12.5)]*.

7.4 Pediatric Use

Safety and efficacy of WINREVAIR have not been established in patients less than 18 years of age.

7.5 Geriatric Use

No dose adjustment of WINREVAIR is required based on age. A total of 81 patients ≥65 years of age participated in clinical studies for PAH, of which 52 (16%) were treated with WINREVAIR.

No overall differences in efficacy of WINREVAIR have been observed between the <65-year-old and ≥65-year-old subgroups.

With the exception of bleeding events (a collective group of adverse events of clinical interest), there were no differences in safety between the <65-year-old and ≥65-year-old subgroups. Bleeding events occurred more commonly in the older WINREVAIR subgroup; however, there was no notable imbalance between age subgroups for any specific bleeding event.

7.6 Renal Impairment

No dose adjustment of WINREVAIR is required based on renal impairment. Sotatercept has not been studied in PAH patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) *[see 2. Dosage and Administration (2.6) and Clinical Pharmacology (11.4)]*.

7.7 Hepatic Impairment

WINREVAIR use has not been studied in patients with hepatic impairment (Child-Pugh Classification A to C). Hepatic impairment is not expected to influence sotatercept metabolism since sotatercept is metabolized via cellular catabolism *[see 2. Dosage and Administration (2.7) and Clinical Pharmacology (11.4)]*.

8. ADVERSE REACTIONS

8.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following data reflect exposure to WINREVAIR in the pivotal STELLAR trial. Patients (n=323) were randomized in a 1:1 ratio to receive WINREVAIR or placebo in combination with background standard of care (SOC) therapies. Patients received a starting dose of 0.3 mg/kg via SC injection and the dose was increased to the target dose of 0.7 mg/kg once every 3 weeks for 24 weeks. After completing the primary 24-week treatment phase, patients continued into a long-term double-blind (LTDB) treatment period, maintaining their current therapy, until all patients completed the primary treatment period. The median durations of treatment were similar between the placebo and WINREVAIR groups (229.5 days vs 252.0 days, respectively) *[see Clinical Studies (10.1)]*.

Adverse reactions occurring in STELLAR by the time all patients completed the primary 24-week period of the study are summarized in Table 3.

Table 3: Adverse Reactions in Patients Receiving WINREVAIR (DBPC + LTDB)*

Adverse reaction	Placebo N=160	WINREVAIR N=163
Headache	17.5%	24.5%
Epistaxis	1.9%	22.1%
Telangiectasia	4.4%	16.6%
Diarrhea	10.0%	15.3%
Dizziness	6.3%	14.7%
Rash†	4.4%	12.3%
Thrombocytopenia‡	3.1%	10.4%
Increased hemoglobin‡	0.6%	8.6%
Increased blood pressure‡	0.6%	4.3%
Erythema†	0.6%	3.1%

* Double-blind placebo-controlled period + Long-term double-blind period of STELLAR.

† MedDRA HLT

‡ Composites of preferred terms (PT) or Standardized MedDRA Queries (SMQ). Increased hemoglobin: Hemoglobin increased; Hematocrit increased; Polycythemia. Thrombocytopenia: SMQ Hematopoietic thrombocytopenia (narrow). Increased blood pressure: SMQ Hypertension (broad).

Increased Hemoglobin

The majority of events of increased Hgb (Hgb increased, polycythemia) were non-serious, mild, and reversible, and were not associated with discontinuation of therapy. Moderate elevations in Hgb (>2 g/dL above ULN) occurred in 12.3% of patients taking WINREVAIR. No severe elevations (≥4 g/dL above ULN) were observed. Increases in Hgb were manageable by dose delays, dose reductions, or both.

Thrombocytopenia

The majority of events of thrombocytopenia (thrombocytopenia and platelet count decreased) were non-serious, mild, reversible, and have not been associated with discontinuation of therapy.

Severe reduction in platelet count <50,000/mm^3 (<50.0 x 10^9/L) occurred in 1.8% of patients taking WINREVAIR.

Telangiectasia

Events of telangiectasia were non-serious and did not progress in severity over time. In all patients exposed to WINREVAIR, the median time to onset was 47.1 weeks. Discontinuations of therapy due to telangiectasia were 1% in the WINREVAIR group vs 0% in the placebo group. No episodes of serious bleeding have been associated with telangiectasia.

Increased Blood Pressure

Events of increased blood pressure (hypertension, blood pressure diastolic increased, blood pressure increased) were non-serious and no severe events were reported. In patients taking WINREVAIR, mean systolic blood pressure increased from baseline by 2.2 mmHg and diastolic blood pressure increased by 4.9 mmHg at 24 weeks. In patients taking placebo, the change from baseline in mean systolic blood pressure was -1.6 mmHg and -0.6 mmHg change in diastolic blood pressure.

Treatment Discontinuation

The overall incidence of treatment discontinuations due to an adverse reaction was 4% in the WINREVAIR group and 7% in the placebo group. There were no specific adverse reactions causing treatment discontinuations that occurred with a frequency greater than 1% and more often in the WINREVAIR group.

Long-term Safety Data

Long-term safety data are available from a Phase 2 clinical trial (PULSAR) that comprised a 24-week, double-blind, placebo-controlled treatment period followed by a 30-month, open-label extension period (n=104). A majority of these patients then continued into a long-term follow-up study.

The mean duration of exposure to WINREVAIR in PULSAR and the long-term follow-up study was 151 weeks, with a maximum exposure of 218 weeks. The safety profile was generally similar to that observed in the pivotal STELLAR study. However, telangiectasia was not observed during the double-blind, placebo-controlled treatment period in PULSAR. Telangiectasia was first

reported in the open-label extension, occurring in 27% of patients at study completion, with a median time to onset of 106 weeks.

9. OVERDOSAGE

In healthy volunteers, WINREVAIR dosed at 1 mg/kg resulted in increases in Hgb associated with hypertension; both improved with phlebotomy. In the event of overdose, monitor closely for increases in Hgb and blood pressure, and provide supportive care as appropriate. WINREVAIR is not dialyzable during hemodialysis.

10. CLINICAL STUDIES

10.1 Pulmonary Arterial Hypertension Adult Subjects

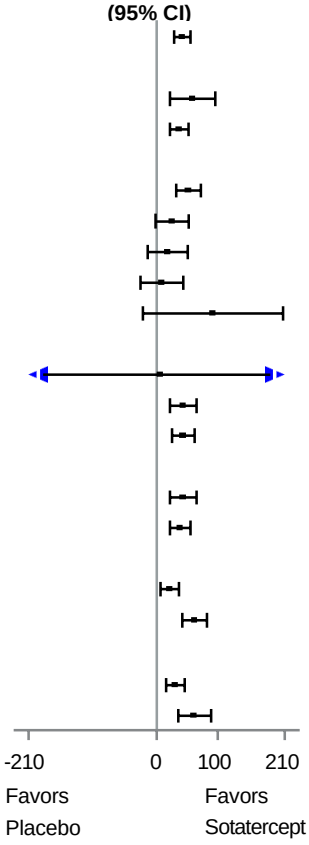
The efficacy of WINREVAIR was evaluated in adult patients with PAH in the STELLAR trial. STELLAR was a global, double-blind, placebo-controlled, multicenter, parallel-group clinical trial in which 323 patients with PAH (WHO Group 1 FC II or III) were randomized 1:1 to WINREVAIR (target dose 0.7 mg/kg) (n=163) or placebo (n=160) administered subcutaneously once every 3 weeks.

The demographic and baseline clinical characteristics were generally comparable between the WINREVAIR and placebo groups. Participants in this study were adults with a median age of 48.0 years (range: 18 to 82 years); median weight 68 kg (range: 38.0 to 141.3 kg); 89.2% of participants were White, and 79.3% were not Hispanic or Latino; and 79.3% were female. The most common PAH etiologies were idiopathic PAH (58.5%), heritable PAH (18.3%), and PAH associated with connective tissue diseases (CTD) (14.9%). The mean time since PAH diagnosis to screening was 8.76 years. Most participants were receiving either triple (61.3%) or double (34.7%) background PAH therapy, and more than one-third (39.9%) were receiving prostacyclin infusions. The proportions of participants in WHO FC II (48.6%) and WHO FC III (51.4%) were similar in both groups. The STELLAR trial excluded patients diagnosed with human immunodeficiency virus (HIV)-associated PAH, PAH associated with portal hypertension, schistosomiasis-associated PAH, and pulmonary veno-occlusive disease.

The primary efficacy endpoint was the change from baseline at Week 24 in 6-Minute Walk Distance (6MWD). In the WINREVAIR treatment group, the median of the placebo-adjusted change in 6MWD from baseline at Week 24 was 40.8 meters (95% CI: 27.5, 54.1; p <0.001). The median of the placebo-adjusted changes in 6MWD at Week 24 were also evaluated in subgroups (see Figure 1).

Figure 1: Change from Baseline in 6-Minute Walk Distance (meters) at Week 24 in Subgroups

Subgroup	Placebo (N=160) n	Sotatercept (N=163) n	Sotatercept vs. Placebo HL* Location Shift (95% CI)	Sotatercept vs. Placebo HL* Location Shift (ASE) (95% CI)
Overall	160	163		40.8 (6.79) (27.53, 54.14)
Sex				
Male	33	34		58.5 (19.46) (20.34, 96.61)
Female	127	129		37.2 (7.50) (22.47, 51.87)
PAH Diagnostic Group				
iPAH [idiopathic PAH]	106	83		51.3 (9.74) (32.17, 70.35)
hPAH [heritable PAH]	24	35		25.6 (13.76) (-1.34, 52.61)
Drug/Toxin-induced PAH	4	7		18.4 (16.78) (-14.51, 51.25)
Connective Tissue Disease	19	29		8.7 (17.96) (-26.55, 43.86)
CHD with s/p Shunt Repair	7	9		92.4 (58.60) (-22.49, 207.26)
Background therapy at baseline				
Monotherapy	4	9		6.3 (534.33) (-564.54, 1530.01)
Double	56	56		43.2 (11.32) (21.03, 65.42)
Triple	100	98		43.5 (8.65) (26.51, 60.44)
Prostacyclin infusion therapy at baseline				
Yes	64	65		43.1 (10.45) (22.61, 63.59)
No	96	98		38.6 (8.88) (21.20, 56.00)
WHO Functional Class				
II	78	79		21.7 (7.68) (6.63, 36.72)
III	82	84		61.7 (10.64) (40.90, 82.59)
Baseline PVR				
<=800 (dynes*sec/cm^5)	108	108		30.8 (7.77) (15.54, 45.98)
>800 (dynes*sec/cm^5)	52	55		61.6 (13.48) (35.23, 88.06)



CHD = Congenital heart disease

* Hodges-Lehmann location shift from placebo estimate (median of all paired differences). ASE = asymptotic standard error. Change from baseline in 6MWD at Week 24 for subjects who died was assigned a value of to -2000 meters to receive the worst rank. Change from baseline in 6MWD at Week 24 for subjects who have missing data due to a non-fatal clinical worsening event was imputed to -1000 meters to receive the next worst-rank.

Clinical improvement was assessed by a pre-defined endpoint, multicomponent improvement (MCI), defined as the proportion of patients achieving all three of the following criteria at Week 24 relative to baseline: improvement in 6MWD (increase ≥30 m), improvement in N-terminal pro-B-

type natriuretic peptide (NT-proBNP) (decrease in NT-proBNP ≥30% or maintenance/achievement of NT-proBNP level <300 ng/L), and improvement in WHO FC or maintenance of WHO FC II. Disease progression was measured by the time to death or first occurrence of a clinical worsening event. Clinical worsening events included worsening-related listing for lung and/or heart transplant, need to initiate rescue therapy with an approved background PAH therapy or the need to increase the dose of infusion prostacyclin by ≥10%, need for atrial septostomy, hospitalization for worsening PAH (≥24 hours), or deterioration of PAH (worsened WHO FC and decrease in 6MWD ≥15% with both events occurring at the same time or different times). Clinical worsening events and death were captured until the last patient completed the week 24 visit (data up to the data cutoff; median duration of exposure 33.6 weeks).

WINREVAIR-treated patients experienced statistically significant clinical improvement, improvement in WHO FC, and delayed disease progression, including reduced risk of death and hospitalization versus placebo-treated patients (see Table 4, Table 5, and Figure 2).

Table 4: Secondary Efficacy Results of STELLAR

Endpoint	Placebo (N=160)	WINREVAIR (N=163)	95% CI	p-value
Proportion of Patients Achieving Multicomponent Improvement* (MCI) from Baseline at Week 24, n (%)	16 (10.1)	63 (38.9)†	N/A	<.001‡
Change from Baseline PVR at Week 24 (ASE) (dynes*sec/cm^5)	N/A	-234.6 (27.5)§	(-288.4, -180.8)	<.001¶
Change from Baseline NT-proBNP Levels at Week 24 (ASE) (pg/mL)	N/A	-441.6 (67.3)#	(-573.5, -309.6)	<.001¶
Proportion of Patients who Improve FC Class from Baseline at Week 24, n (%)	22 (13.8)	48 (29.4)†	N/A	<.001‡
Time to Death or the First Occurrence of a Worsening Eventᵖ, n (%)	42 (26.3)	9 (5.5)	0.163 (0.076, 0.347)ß	<.001à

Proportion of Patients who Maintained or Achieved a Low Risk Scoreè at Week 24 vs. Baseline, n (%)	29 (18.2)	64 (39.5)	N/A	<.001‡
Change from Baseline in the Physical Impacts Domain Score of PAH-SYMPACT®ð at Week 24 (ASE)	N/A	-0.26 (0.115)ø	(-0.490, -0.040)	0.010¶
Change from Baseline in the Cardiopulmonary Symptoms Domain Score of PAH-SYMPACT®ð at Week 24 (ASE)	N/A	-0.13 (0.062)ø	(-0.256, -0.014)	0.028¶
Change from baseline in the Cognitive/Emotional Impacts Domain Score of PAH-SYMPACT®ð at Week 24 (ASE)	N/A	-0.16 (0.123)ø	(-0.399, 0.084)	0.156¶

ASE= asymptotic standard error.

Note: Wherever stratified randomization factors were used, the stratified randomization factors were baseline WHO FC (Class II or III) and background PAH therapy (mono/double or triple therapy).

* A patient satisfies the MCI if all of the following occur at Week 24 relative to baseline: Improvement in 6MWD (increase ≥30 m), improvement in NT-proBNP (decrease ≥30% or maintenance/achievement of NT-proBNP <300 pg/mL), and improvement in WHO FC or maintenance of WHO FC II.

† A missing result at Week 24 not due to COVID-19 was considered a non-responder. Subjects who missed assessments due to COVID-19 were removed from the denominator.

‡ Comparison with placebo uses Cochran-Mantel-Haenszel (CMH) method stratified by randomization factors.

§ Hodges-Lehmann location shift from placebo estimate (median of all paired differences). Change from baseline in PVR at Week 24 for subjects who died was assigned as 20000 to receive the worst rank. Change from baseline in PVR at Week 24 for subjects who had missing data due to a non-fatal clinical worsening event was imputed as 15000 to receive the next-worst rank.

¶ Wilcoxon p-value refers to p-value from the aligned rank-stratified Wilcoxon test with randomization factors as strata.

Hodges-Lehmann location shift from placebo estimate (median of all paired differences). Change from baseline in NT-proBNP at Week 24 for subjects who died was assigned as 200000 to receive the worst rank. Change from baseline in NT-proBNP at Week 24 for subjects who had missing data due to a non-fatal clinical worsening event was imputed as 150000 to receive the next-worst rank.

Þ Time to death or the first occurrence of any of the following clinical worsening events: a) worsening-related listing for lung and/or heart transplant, b) need to initiate rescue therapy with an approved background PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more, c) need for atrial septostomy, d) hospitalization for

worsening of PAH (≥24 hours), e) deterioration of PAH defined by both of the following events occurring at any time (even if they began at different times) as compared to their baseline values: worsened WHO FC and decrease in 6MWD by ≥15% confirmed by 2 tests at least 4 hours apart but no more than 1 week.

ß The hazard ratio (WINREVAIR / placebo) was derived from a Cox proportional hazard model with treatment group as the covariate stratified by the randomization factors.

à Log-rank test comparison with placebo stratified by the randomization factors.

è Utilizing French Risk score calculator

ð Pulmonary Arterial Hypertension-Symptoms and Impact

ø Hodges-Lehmann location shift from placebo estimate (median of all paired differences). Change from baseline in SYMPACT scores at Week 24 for subjects who died was assigned as 200 to receive the worst rank. Change from baseline in SYMPACT scores at Week 24 for subjects who had missing data due to a non-fatal clinical worsening event was imputed as 150 to receive the next-worst rank.

Table 5: Death or Clinical Worsening Events

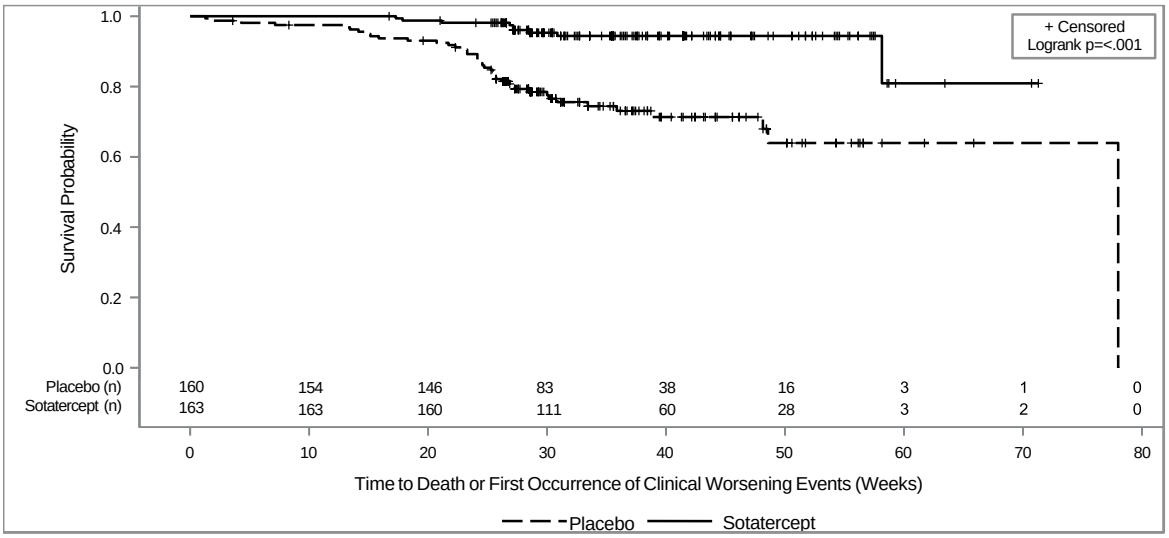
	Placebo (N=160)	WINREVAIR (N=163)
Total number of subjects who experienced death or at least one clinical worsening event, n (%)	42 (26.3)	9 (5.5)
Assessment of death or first occurrence of clinical worsening events*, n (%)		
Death	6 (3.8)	2 (1.2)
Worsening-related listing for lung and/or heart transplant	1 (0.6)	1 (0.6)
Need to initiate rescue therapy with an approved PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more	17 (10.6)	2 (1.2)
Need for atrial septostomy	0 (0.0)	0 (0.0)
PAH-specific hospitalization (≥24 hours)	7 (4.4)	0 (0.0)
Deterioration of PAH†	15 (9.4)	4 (2.5)

* A subject can have more than one assessment recorded for their first event of clinical worsening. There were 3 placebo subjects and 0 sotatercept subjects who had more than one assessment recorded for their first event of clinical worsening.

† Deterioration of PAH therapy is defined by both of the following events occurring at any time, even if they began at different times, as compared to their baseline values: (a) Worsened WHO functional class (II to III, III to IV, II to IV, etc.); and (b) Decrease in 6MWD by ≥15% (confirmed by two 6MWTs at least 4 hours apart but no more than one week).

N = number of subjects in FAS population; n = number of subjects in the category. Percentages are calculated as (n/N)*100.

Figure 2: Time to Death or First Occurrence of Clinical Worsening Events Kaplan-Meier Plot



n= Number of subjects at Risk

11. CLINICAL PHARMACOLOGY

11.1 Therapeutic Class

WINREVAIR (sotatercept) is an activin signaling inhibitor.

11.2 Mechanism of Action

Sotatercept is an activin signaling inhibitor with high selectivity for Activin-A, a dimeric glycoprotein which belongs to the transforming growth factor-β (TGF-β) superfamily of ligands. Activin A binds to the activin receptor type IIA (ActRIIA) regulating key signaling for inflammation, cell proliferation, apoptosis, and tissue homeostasis.

Activin A levels are increased in PAH patients. Activin binding to ActRIIA promotes proliferative signaling while there is a decrease in anti-proliferative bone morphogenetic receptor type II (BMPR-II) signaling. The imbalance of ActRIIA-BMPRII signaling underlying PAH results in vascular cell hyperproliferation causing pathological remodeling of the pulmonary arterial wall, narrowing the arterial lumen, increasing pulmonary vascular resistance, and leads to increased pulmonary artery pressure and right ventricular dysfunction.

Sotatercept consists of a recombinant homodimeric activin receptor type IIA-Fc (ActRIIA-Fc) fusion protein which acts as a ligand trap that scavenges excess activin A and other ligands for ActRIIA to inhibit activin signaling. As a result, Sotatercept rebalances the pro-proliferative (ActRIIA/Smad2/3-mediated) and anti-proliferative (BMPRII/Smad1/5/8-mediated) signaling to modulate vascular proliferation. In rat models of PAH, a sotatercept analog reduced expression of pro-inflammatory markers at the pulmonary arterial wall, reduced leukocyte recruitment, inhibited proliferation of endothelial and smooth muscle cells, and promoted apoptosis in diseased vasculature. These cellular changes were associated with thinner vessel walls, reversed arterial and right ventricular remodeling, and improved hemodynamics. In PAH clinical studies, WINREVAIR decreased pulmonary vascular resistance and reversed right ventricular remodeling.

11.3 Pharmacodynamics

A Phase 2 clinical study assessed pulmonary vascular resistance (PVR) in patients with PAH after 24 weeks of treatment with sotatercept. The decrease from baseline in PVR was significantly greater in the sotatercept 0.7 mg/kg and 0.3 mg/kg groups compared with the placebo group. The placebo-adjusted least squares (LS) mean difference from baseline was -269.4 dynes*sec/cm^5 (95% CI: -365.8, -173.0) for the sotatercept 0.7 mg/kg group and -151.1 dynes*sec/cm^5 (95% CI: -249.6, -52.6) for the sotatercept 0.3 mg/kg group. In STELLAR, the decrease from baseline in PVR was also significantly greater in the sotatercept 0.7 mg/kg group compared with the placebo group *[see Clinical Studies (10.1)]*.

11.4 Pharmacokinetics

In patients with PAH, the geometric mean (%CV) steady-state AUC and steady-state peak concentration (C_{max}) at the dose of 0.7 mg/kg Q3W were 171.3 mcg×d/mL (34.2%) and 9.7 mcg/mL (30%CV), respectively. Sotatercept AUC and C_{max} increase proportionally with dose. Steady state is achieved after approximately 15 weeks upon multiple Q3W dosing. The accumulation ratio of sotatercept AUC was approximately 2.2.

Absorption

The SC formulation has an absolute bioavailability of approximately 66%. The maximum sotatercept concentration is achieved at a median time to peak drug concentration (T_{max}) of approximately 7 days (range from 2 to 8 days) after multiple (0.1 mg/kg every 4 weeks) SC doses in post menopausal women.

Distribution

The central volume of distribution (%CV) of sotatercept is approximately 3.6 L (24.7%). The peripheral volume of distribution (%CV) is approximately 1.7 L (73.3%).

Elimination

Sotatercept clearance is approximately 0.18 L/day. The geometric mean terminal half-life (%CV) is approximately 21 days (33.8%).

Metabolism

Sotatercept is catabolized by general protein degradation processes.

Specific Populations

Age, Sex, and Race

No clinically significant differences in sotatercept pharmacokinetics (PK) were observed based on age (18 to 81 years of age), sex, or race.

Body Weight

The clearance (CL) and central volume of distribution (Vc) of sotatercept increased with increasing body weight. The recommended weight-based dosing regimen results in consistent sotatercept exposures regardless of body weight.

Renal Impairment

Sotatercept PK was comparable in PAH patients with mild to moderate renal impairment (eGFR ranging from 30 to 89 mL/min/1.73m^2) to those with normal renal function (eGFR ≥90 mL/min/1.73m^2). Additionally, sotatercept PK is comparable between non-PAH end-stage kidney disease (ESKD) patients and patients with normal renal function. WINREVAIR is not dialyzable during hemodialysis. No dose adjustment is recommended for renally impaired patients. Sotatercept has not been studied in PAH patients with severe renal impairment (eGFR <30 mL/min/1.73m^2).

Hepatic Impairment

Hepatic impairment (determined by Child-Pugh Classification) is not expected to influence sotatercept metabolism since sotatercept is metabolized via cellular catabolism. Sotatercept has not been studied in PAH patients with hepatic impairment (Child-Pugh Classification A to C).

11.5 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the study described below with the incidence of anti-drug antibodies in other studies, including those of WINREVAIR or of other sotatercept products.

During the 24-week treatment period in the pivotal study (STELLAR), 44/163 (27%) of sotatercept-treated patients developed anti-sotatercept antibodies. Among these 44 patients, 12 (27%) tested positive for neutralizing antibodies against sotatercept. Anti-sotatercept antibodies generally had low titers with a median titer of 30 (range <20 to 640).

There were no identified clinical effects of anti-sotatercept antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of sotatercept over the treatment duration of 24 weeks.

12. ANIMAL TOXICOLOGY

12.1 Acute Toxicity

No acute toxicity was observed in repeated-dose SC toxicity studies at dosages up to 30 mg/kg in rats and 50 mg/kg in monkeys (single doses provided exposures approximately 15-fold and 38-fold, respectively, the human exposure at the MRHD (based on estimated AUC)).

12.2 Chronic Toxicity

In rats and monkeys, the longest SC toxicity studies were 3 months and 9 months in duration, respectively. In rats, adverse findings included efferent duct/testicular degeneration, adrenal gland congestion/necrosis, and membranoproliferative glomerulonephritis and tubulointerstitial nephritis in the kidneys. Kidney changes were not reversible following a 1-month recovery period. In monkeys, adverse changes included increased interstitial matrix at the corticomedullary junction, decreased glomerular tuft size, glomerulonephritis and tubulointerstitial nephritis in the

kidney. Kidney changes in monkeys partially resolved following a 3-month recovery period. At the no observed adverse effect level (NOAEL) in rats and monkeys, sotatercept exposures were ≤2-times the clinical exposure at the maximum recommended human dose (MRHD).

12.3 Carcinogenesis

No carcinogenicity studies have been conducted with sotatercept.

12.4 Mutagenesis

No mutagenicity studies have been conducted with sotatercept.

12.5 Reproduction

In a fertility and early embryonic development study in female rats, sotatercept was administered SC once weekly at doses of 5, 15, and 50 mg/kg beginning 2 weeks prior to mating and through gestation day 7. At doses ≥15 mg/kg (≥9-fold the MRHD, based on estimated AUC), pregnancy rates were decreased and there were increases in pre-implantation and post-implantation loss and reductions in live litter size. Increased estrous cycle duration occurred at 50 mg/kg only (21-fold the MRHD, based on estimated AUC).

In a fertility study in male rats, sotatercept was administered SC once weekly at doses of 0.3, 3, and 30 mg/kg for 13 weeks (beginning 10 weeks prior to mating). A subset of animals was examined after a 13-week recovery period. At ≥0.3 mg/kg (0.5-fold the MRHD, based on estimated AUC) there were non-reversible histologic changes in the efferent ducts, testes, and epididymides. Reversible decreases in fertility occurred at 30 mg/kg (20-fold the MRHD, based on estimated AUC).

12.6 Development

In embryo-fetal developmental toxicity studies, pregnant animals were dosed subcutaneously with sotatercept during the period of organogenesis. Sotatercept was administered to rats on gestation days 6 and 13 at doses of 5, 15, or 50 mg/kg and to rabbits on gestation days 7 and 14 at doses of 0.5, 1.5, or 5 mg/kg. Effects in both species included reductions in numbers of live fetuses and fetal body weights, delays in ossification, and increases in resorptions and post-implantation losses. In rats and rabbits, these effects were observed at exposures (based on area under the curve (AUC)) approximately 4-fold and 0.6-fold the maximum recommended human dose

(MRHD), respectively. In rats only, skeletal variations (increased number of supernumerary ribs and changes in the number of thoracic or lumbar vertebrae) occurred at an exposure 15-fold the human exposure at the MRHD.

In a pre- and postnatal development study in rats, sotatercept was administered subcutaneously at doses of 1.5 and 5 mg/kg on gestation days 6 and 13, or at dosages of 1.5, 5, or 10 mg/kg during lactation on days 1, 8, and 15. There were no adverse effects in first filial generation (F1) pups from dams dosed during gestation at estimated exposures up to 2-fold the MRHD. In F1 pups from dams dosed during lactation, decreases in pup weight correlated with delays in sexual maturation at estimated exposures (based on AUC) ≥2-fold the MRHD.

13. NAME OF THE DRUG

WINREVAIR (sotatercept)

14. PHARMACEUTICAL FORM

Sotatercept for injection is a sterile, preservative-free, white to off-white lyophilized powder available in 45 mg and 60 mg single-dose vials for SC administration after reconstitution.

15. PHARMACEUTICAL PARTICULARS

15.1 Chemistry

Sotatercept is a recombinant human homodimeric fusion protein consisting of the extracellular domain of the human activin receptor type IIA (ActRIIA) linked to the human IgG1 Fc domain. The molecular weight based on the amino acid sequence of sotatercept is approximately 78 kDa as a homodimer.

15.2 Composition

Active Ingredient

Each 45 mg single-dose vial provides 55 mg of sotatercept and after reconstitution with 1.0 mL Sterile Water for Injection, the resulting concentration is 50 mg/1.0 mL of sotatercept and the nominal deliverable volume is 0.9 mL.

Each 60 mg single-dose vial provides 72.5 mg of sotatercept and after reconstitution with 1.3 mL Sterile Water for Injection, the resulting concentration is 50 mg/1.0 mL of sotatercept and the nominal deliverable volume is 1.2 mL.

Inactive Ingredients (List of excipients)

45 mg single-dose vial: citric acid monohydrate, polysorbate 80, sucrose, and tri-sodium citrate dihydrate at pH 5.8.

60 mg single-dose vial: citric acid monohydrate, polysorbate 80, sucrose, and tri-sodium citrate dihydrate at pH 5.8.

15.3 Storage

Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. For reconstituted solution, store up to 4 hours at 30°C.

15.4 Shelf Life

Refer to outer carton for expiry.

Use the reconstituted solution as soon as possible, but no later than 4 hours after reconstitution.

15.5 Availability (a.k.a. Nature and contents of container)

Sotatercept lyophilized powder is supplied in a Type I glass vial with bromobutyl stopper. Available in

- One 45 mg powder vial
- Two 45 mg powder vials
- One 60 mg powder vial
- Two 60 mg powder vials

Not all presentations may be available locally.

Product Owner:

Merck Sharp & Dohme LLC

126 East Lincoln Ave.

P.O. Box 2000
Rahway, New Jersey 07065
USA

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