

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use WINREVAIR safely and effectively. See full prescribing information for WINREVAIR.

WINREVAIR™ (sotatercept-csrk) for injection, for subcutaneous use

Initial U.S. Approval: 2024

-----**RECENT MAJOR CHANGES**-----
Indications and Usage (1) 10/2025

-----**INDICATIONS AND USAGE**-----
WINREVAIR is an activin signaling inhibitor indicated for the treatment of adults with pulmonary arterial hypertension (PAH, WHO Group 1 pulmonary hypertension) to improve exercise capacity and WHO functional class (FC), and reduce the risk of clinical worsening events, including hospitalization for PAH, lung transplantation and death. (1)

-----**DOSAGE AND ADMINISTRATION**-----

- The recommended starting dose is 0.3 mg/kg by subcutaneous injection. (2.1)
- The recommended target dose is 0.7 mg/kg every 3 weeks by subcutaneous injection. (2.2)
- Dosage modifications due to increased hemoglobin (Hgb) and decreased platelets may be necessary. Check Hgb and platelets before each dose for the first 5 doses, or longer if values are unstable, and monitor periodically thereafter. (2.3)
- See full prescribing information for preparation and administration instructions. (2.4)

-----**DOSAGE FORMS AND STRENGTHS**-----

- For injection: 45 mg lyophilized cake or powder in a single-dose vial (3)
- For injection: 60 mg lyophilized cake or powder in a single-dose vial (3)

-----**CONTRAINDICATIONS**-----
None (4)

-----**WARNINGS AND PRECAUTIONS**-----

- Erythrocytosis: If severe, may increase the risk of thromboembolic events and 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. (5.1)
- Severe Thrombocytopenia: May increase the risk of bleeding. Monitor platelets before each dose for the first 5 doses, or longer if values are unstable, and periodically thereafter to determine if dose adjustments are required. (5.2)
- Serious Bleeding: Serious bleeding events were reported and were more likely with concomitant prostacyclin and/or antithrombotic agents, or with low platelet counts. Do not administer WINREVAIR if the patient is experiencing serious bleeding. (5.3)
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)
- Impaired Fertility: May impair female and male fertility. (5.5, 8.3, 13.1)

-----**ADVERSE REACTIONS**-----
The most common (≥10% in patients receiving WINREVAIR and 5% more than placebo) adverse reactions were infections, epistaxis, telangiectasia, diarrhea, headache, rash, increased hemoglobin, dizziness, erythema, and gingival bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

-----**USE IN SPECIFIC POPULATIONS**-----
Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Starting Dosage
- 2.2 Recommended Target Dosage
- 2.3 Dosage Modifications Due to Hemoglobin Increase or Platelet Count Decrease
- 2.4 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Erythrocytosis
- 5.2 Severe Thrombocytopenia
- 5.3 Serious Bleeding
- 5.4 Embryo-Fetal Toxicity
- 5.5 Impaired Fertility

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Post-marketing Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.6 Immunogenicity

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Pulmonary Arterial Hypertension

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

WINREVAIR™ is indicated for the treatment of adults with pulmonary arterial hypertension (PAH, Group 1 pulmonary hypertension) to improve exercise capacity and World Health Organization (WHO) functional class (FC), and reduce the risk of clinical worsening events including hospitalization for PAH, lung transplantation and death [see *Clinical Studies (14.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Starting Dosage

WINREVAIR is administered once every 3 weeks by subcutaneous injection according to patient body weight. The starting dose of WINREVAIR is 0.3 mg/kg.

Obtain hemoglobin (Hgb) and platelet count prior to the first dose of WINREVAIR. Do not initiate treatment if platelet count is <50,000/mm³ (<50 x 10⁹/L) [see *Dosage and Administration (2.3)*].

Injection volume for starting dose is calculated based on patient weight as follows:

$$\text{Injection Volume (mL)} = \frac{\text{Weight (kg)} \times 0.3 \text{ mg/kg}}{50 \text{ mg/mL}}$$

Injection volume should be rounded to the nearest 0.1 mL.

For example: (70 kg x 0.3 mg/kg) ÷ 50 mg/mL = 0.42 mL, rounds to 0.4 mL

See Table 1 for selecting the appropriate kit based on calculated injection volume for starting dose.

Table 1: Kit Type Based on Injection Volume for Dose of 0.3 mg/kg

Injection Volume (mL)	Kit Type
0.2 to 0.9	45 mg kit (containing 1 x 45 mg vial)
1 to 1.1	60 mg kit (containing 1 x 60 mg vial)

2.2 Recommended Target Dosage

After verifying acceptable Hgb and platelet count, increase to the target dose of 0.7 mg/kg. Continue treatment at 0.7 mg/kg every 3 weeks unless dosage adjustments are required [see *Dosage and Administration (2.3)*].

Injection volume for target dose is calculated based on patient weight as follows:

$$\text{Injection Volume (mL)} = \frac{\text{Weight (kg)} \times 0.7 \text{ mg/kg}}{50 \text{ mg/mL}}$$

Injection volume should be rounded to the nearest 0.1 mL.

For example: (70 kg x 0.7 mg/kg) ÷ 50 mg/mL = 0.98 mL, rounds to 1 mL

See Table 2 for selecting the appropriate kit based on calculated injection volume for target dose.

Table 2: Kit Type Based on Injection Volume for Dose of 0.7 mg/kg

Injection Volume (mL)	Kit Type
0.4 to 0.9	45 mg kit (containing 1 x 45 mg vial)
1 to 1.2	60 mg kit (containing 1 x 60 mg vial)
1.3 to 1.8	90 mg kit (containing 2 x 45 mg vials)
1.9 to 2.4	120 mg kit (containing 2 x 60 mg vials)

Missed Dose, Overdose, and Underdose

If a dose of WINREVAIR is missed, administer as soon as possible. If the missed dose of WINREVAIR is not administered 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* (10)].

2.3 Dosage Modifications Due to Hemoglobin Increase or Platelet Count Decrease

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 [see *Warnings and Precautions* (5.1, 5.2)].

Delay treatment for at least 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/mm³ (<50 x 10⁹/L).

Recheck Hgb and platelet count before reinitiating treatment. For treatment delays lasting >9 weeks, restart treatment at 0.3 mg/kg, and escalate to 0.7 mg/kg after verifying acceptable Hgb and platelet count.

2.4 Preparation and Administration

Administration is subject to monitoring of hemoglobin and platelet count [see *Dosage and Administration* (2.3), *Warnings and Precautions* (5.1, 5.2)].

WINREVAIR is intended for use under the guidance of a healthcare professional. Patients and caregivers may administer WINREVAIR when considered appropriate and when they receive training and follow-up from the healthcare provider (HCP) on how to reconstitute, prepare, measure, and inject WINREVAIR [see *Patient Counseling Information* (17)].

Confirm at subsequent visits that the patient and/or caregiver can correctly prepare and administer WINREVAIR, particularly if the dose changes or the patient requires a different kit [see *Warnings and Precautions* (5.1)].

Refer to the Instructions for Use (IFU) for detailed instructions on the proper preparation and administration of WINREVAIR.

Selecting the Appropriate Product Kit

If a patient's body weight requires the use of two 45 mg vials or two 60 mg vials of lyophilized product, use a 2-vial kit instead of two individual 1-vial kits. A 2-vial kit includes instructions to combine the contents of two vials, which aids in measuring the proper dosage and eliminates the need for multiple injections [see *How Supplied/Storage and Handling* (16.1)].

Reconstitution Instructions

- Remove the injection kit from the refrigerator and wait 15 minutes to allow the prefilled syringe(s) and drug product to come to room temperature prior to preparation.
- Attach the vial adapter to the vial.
- Visually inspect the pre-filled syringe for any damage or leaks and the Sterile Water for Injection inside to ensure there are no visible particles.
- Snap off the cap of the pre-filled syringe and attach the syringe to the vial adapter.
- Inject all of the Sterile Water for Injection from the attached syringe into the vial containing the lyophilized powder. 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.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- 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. Discard unused reconstituted solution.

Syringe Preparation

- Turn the syringe and vial upside-down and withdraw the appropriate volume for injection, based on the patient's weight.
 - If the dose amount requires the use of two vials, withdraw the entire contents of the first vial and slowly transfer full contents into the second vial.
 - Turn the syringe and vial upside-down and withdraw the required amount of drug product.
 - If necessary, remove excess drug product.
- If necessary, remove excess air from the syringe.

Administration Instructions

WINREVAIR is for subcutaneous injection.

- 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. Select a new site for each injection that is not scarred, tender, or bruised.
 - For administration by the patient or caregiver, use only the abdomen and upper thigh (see IFU).
- Perform subcutaneous injection.

3 DOSAGE FORMS AND STRENGTHS

- For injection: 45 mg white to off-white lyophilized cake or powder appearance in a single-dose vial.
- For injection: 60 mg white to off-white lyophilized cake or powder appearance in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Erythrocytosis

WINREVAIR may increase hemoglobin. Severe erythrocytosis may increase the risk of thromboembolic events or hyperviscosity syndrome. In clinical studies, moderate elevations in Hgb (>2 g/dL above ULN) occurred in 15% of patients taking WINREVAIR while no elevations ≥ 4 g/dL above ULN were observed. 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), *Adverse Reactions* (6.1)].

5.2 Severe Thrombocytopenia

WINREVAIR may decrease platelet count. Severe thrombocytopenia may increase the risk of bleeding. In clinical studies, severe thrombocytopenia (platelet count $<50,000/\text{mm}^3$ [$<50 \times 10^9/\text{L}$]) occurred in 3% to 6% of patients taking WINREVAIR. Thrombocytopenia occurred more frequently in patients also receiving prostacyclin infusion.

Do not initiate treatment if platelet count is $<50,000/\text{mm}^3$ [see *Dosage and Administration* (2.3)].

Monitor platelets 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), *Adverse Reactions* (6.1)].

5.3 Serious Bleeding

In clinical studies, serious bleeding (e.g., gastrointestinal, intracranial hemorrhage) was reported in 4% vs 1% (STELLAR) and 7% vs 5% (ZENITH) of patients taking WINREVAIR vs placebo, respectively [see *Clinical Studies* (14.1)]. Patients with serious bleeding 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 serious bleeding [see *Warnings and Precautions* (5.2), *Adverse Reactions* (6.1)].

5.4 Embryo-Fetal Toxicity

Based on findings in animal reproduction studies, WINREVAIR may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of WINREVAIR to pregnant rats and rabbits during organogenesis resulted in adverse developmental outcomes, including increased embryo-fetal mortality, alterations to growth, and structural variations at exposures 4-fold and 0.6-fold (based on area under the curve [AUC]) those occurring at the maximum recommended human dose (MRHD), respectively. 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* (8.1, 8.3)].

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* (8.3), *Nonclinical Toxicology* (13.1)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Erythrocytosis [see *Warnings and Precautions* (5.1)]
- Severe Thrombocytopenia [see *Warnings and Precautions* (5.2)]
- Serious Bleeding [see *Warnings and Precautions* (5.3)]
- Embryo-Fetal Toxicity [see *Warnings and Precautions* (5.4)]
- Impaired Fertility [see *Warnings and Precautions* (5.5)]

6.1 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.

STELLAR

The following data reflect exposure to WINREVAIR in the STELLAR trial. Adult PAH patients with WHO FC II or III (n=323) were randomized in a 1:1 ratio to receive WINREVAIR or placebo in combination with background standard of care 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 administered 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 randomized treatment assignment, until all patients completed the primary treatment period. The median duration of treatment was 273 days in the placebo group and 313 days in the WINREVAIR group [see *Clinical Studies* (14.1)].

The most common adverse reactions occurring in STELLAR ($\geq 10\%$ for WINREVAIR and at least 5% more than placebo) are shown in Table 3.

Table 3: Adverse Reactions $\geq 10\%$ in Patients Receiving WINREVAIR and at least 5% More Than Placebo in STELLAR*

Adverse reaction	WINREVAIR N=163	Placebo N=160
Headache	40 (24.5)	28 (17.5)
Epistaxis	36 (22.1)	3 (1.9)
Rash	33 (20.2)	13 (8.1)
Telangiectasia	27 (16.6)	7 (4.4)
Diarrhea	25 (15.3)	16 (10.0)
Dizziness	24 (14.7)	10 (6.3)
Erythema	22 (13.5)	5 (3.1)

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

Increased Hemoglobin

Increases in Hgb were managed by dose delays (10%), dose reductions (6%), or both (5%). Shifts in Hgb from normal to above normal levels occurred in 87 (53%) patients receiving WINREVAIR and in 23 (14%) patients receiving placebo.

Thrombocytopenia

Decreases in platelets were managed by dose delays (2%), dose reductions (2%), or both (2%). Shifts in platelet count from normal to below normal occurred in 40 (25%) patients receiving WINREVAIR and in 26 (16%) patients receiving placebo.

Telangiectasia

In patients exposed to WINREVAIR who experienced telangiectasia, the median time to onset was 36.1 weeks.

Increased Blood Pressure

In patients taking WINREVAIR, mean systolic/diastolic blood pressure increased from baseline by 2.2/4.9 mmHg at 24 weeks. In patients taking placebo, the change from baseline in mean blood pressure was -1.6/-0.6 mmHg.

Treatment Discontinuation

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

ZENITH

The following data reflect exposure to WINREVAIR in the ZENITH trial. Adult PAH patients with WHO FC III or IV at high risk of mortality (n=172) were randomized in a 1:1 ratio to treatment with WINREVAIR or placebo in combination with background standard of care therapies. Patients who did not experience a primary endpoint event remained in the Double-Blind Placebo-Controlled (DBPC) Treatment Period, while patients who experienced an event of PAH worsening-related hospitalization of ≥ 24 hours were eligible to enroll into the open-label, long-term follow-up (LTFU) study SOTERIA. The median duration of exposure was longer in the WINREVAIR group (435 days) than in the placebo group (268 days) [see *Clinical Studies* (14.1)].

The overall incidences of adverse reactions in both arms were higher in the ZENITH trial than in the STELLAR trial. Severe reduction in platelet count $<50,000/\text{mm}^3$ ($<50.0 \times 10^9/\text{L}$) occurred in 6% of patients taking WINREVAIR. In the WINREVAIR group, 1 patient (1%) discontinued study intervention due to an adverse event, compared with 4 patients (5%) in the placebo group.

Table 4: Adverse Reactions $\geq 10\%$ in Patients Receiving WINREVAIR and at least 5% More Than Placebo in ZENITH

Adverse reaction	WINREVAIR N=86	Placebo N=86
Infections	58 (67.4)	38 (44.2)
Epistaxis	39 (45.3)	8 (9.3)
Diarrhea	22 (25.6)	15 (17.4)
Telangiectasia	22 (25.6)	3 (3.5)
Increased hemoglobin	13 (15.1)	1 (1.2)
Rash	9 (10.5)	4 (4.7)
Erythema	9 (10.5)	3 (3.5)
Gingival bleeding	9 (10.5)	2 (2.3)

Uncontrolled Long-term Safety Data

Pooled long-term safety data are available from 431 patients who participated in multicenter phase 2 (PULSAR, SPECTRA) and phase 3 (STELLAR) clinical trials. A majority of these patients continued in SOTERIA, an ongoing, open-label follow-up study of the long-term safety and efficacy of WINREVAIR.

The safety profile with long-term exposure was generally similar to that observed in the STELLAR study. The mean duration of exposure to WINREVAIR was 173 weeks with a maximum exposure of 335 weeks.

Intrapulmonary Right-to-Left Shunting: Cases of intrapulmonary right-to-left shunting have been reported in a clinical trial with WINREVAIR. In SOTERIA, right-to-left intrapulmonary shunting has been reported in 3 participants ($<0.7\%$) who developed worsening hypoxemia despite improved PAH hemodynamics. Post-marketing cases have also been reported.

Partial to complete improvement in oxygenation has been observed following discontinuation of WINREVAIR.

6.2 Post-marketing Experience

The following adverse reaction has been reported during post-approval use of WINREVAIR. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: pericardial effusion

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal reproduction studies, WINREVAIR may cause fetal harm when administered to a pregnant woman. There are risks to the mother and the fetus associated with pulmonary arterial hypertension in pregnancy (*see Clinical Considerations*). There are no available data on WINREVAIR use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

In animal reproduction studies, administration of WINREVAIR to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes, including embryo-fetal mortality, alterations to growth, and structural variations at exposures 4-fold and 0.6-fold (based on area under the curve [AUC])

above those occurring at the maximum recommended human dose (MRHD), respectively (*see Data*). Advise pregnant women of the potential risk to a fetus [*see Use in Specific Populations (8.3)*].

The background risk of major birth defects and miscarriage for the indicated population is not known. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Report exposure during pregnancy or lactation to the Merck Sharp & Dohme, LLC Adverse Event reporting line at 1-877-888-4231.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

In patients with pulmonary arterial hypertension, pregnancy is associated with an increased rate of maternal and fetal morbidity and mortality, including spontaneous abortion, intrauterine growth restriction, and premature labor.

Data

Animal Data

In embryo-fetal developmental toxicity studies, pregnant animals were dosed subcutaneously with sotatercept-csrk during the period of organogenesis. Sotatercept-csrk 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 prenatal and postnatal development study in rats, sotatercept-csrk 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) $\geq$ 2-fold the MRHD.

8.2 Lactation

Risk Summary

There are no data on the presence of sotatercept-csrk 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.

8.3 Females and Males of Reproductive Potential

WINREVAIR may cause fetal harm when administered to pregnant women [*see Use in Specific Populations (8.1)*].

Pregnancy Testing

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

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with WINREVAIR and for at least 4 months after the final dose if treatment is discontinued [*see Use in Specific Populations (8.1)*].

Infertility

Based on findings in animals, sotatercept-csrk may impair female and male fertility [see *Nonclinical Toxicology* (13.1)]. In male rats, although adverse histologic changes in reproductive organs were not reversible after a 13-week period, functional fertility demonstrated reversibility.

8.4 Pediatric Use

The safety and effectiveness of WINREVAIR have not been established in patients less than 18 years of age.

8.5 Geriatric Use

A total of 127 patients ≥65 years of age participated in clinical studies for PAH, of which 99 (78%) were treated with WINREVAIR. No differences in efficacy of WINREVAIR were 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, but with no imbalance between age subgroups for any specific bleeding event.

Clinical studies of WINREVAIR did not include sufficient numbers of patients aged 75 and older to determine whether they respond differently from younger patients.

10 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.

11 DESCRIPTION

Sotatercept-csrk is a homodimeric recombinant 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-csrk is approximately 78 kDa as a homodimer.

Sotatercept-csrk for injection is a sterile, preservative-free, white to off-white lyophilized cake or powder appearance in single-dose vials for subcutaneous administration after reconstitution.

Each 45 mg single-dose vial provides 45 mg of sotatercept-csrk and citric acid monohydrate (0.40 mg), polysorbate 80 (0.18 mg), sodium citrate (1.84 mg), and sucrose (72 mg) at pH 5.8. After reconstitution with 1 mL Sterile Water for Injection, the resulting concentration is 50 mg/mL of sotatercept-csrk and the nominal deliverable volume is 0.9 mL.

Each 60 mg single-dose vial provides 60 mg of sotatercept-csrk and citric acid monohydrate (0.53 mg), polysorbate 80 (0.24 mg), sodium citrate (2.45 mg), and sucrose (96 mg) at pH 5.8. After reconstitution with 1.3 mL Sterile Water for Injection, the resulting concentration is 50 mg/mL of sotatercept-csrk and the nominal deliverable volume is 1.2 mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sotatercept-csrk, a recombinant activin receptor type IIA-Fc (ActRIIA-Fc) fusion protein, is an activin signaling inhibitor that binds to activin A and other TGF- β superfamily ligands. As a result, sotatercept-csrk improves the balance between 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-csrk analog reduced inflammation and inhibited proliferation of endothelial and smooth muscle cells in diseased vasculature. These cellular changes were associated with thinner vessel walls, partial reversal of right ventricular remodeling, and improved hemodynamics.

12.2 Pharmacodynamics

STELLAR

A greater decrease from baseline in pulmonary vascular resistance (PVR) was observed in the WINREVAIR group compared to the placebo group. The median treatment difference in PVR between sotatercept-csrk and placebo was $-235 \text{ dynes}\cdot\text{sec}/\text{cm}^5$ (95% CI: $-288, -181$). Sotatercept-csrk steady state exposure at 0.7 mg/kg dose was associated with near maximal reduction in PVR based on exposure-response analysis. A greater decrease from baseline in NT-proBNP was observed in the WINREVAIR group compared to the placebo group. The median treatment difference in NT-proBNP between the sotatercept-csrk and placebo was -442 pg/mL (95% CI: $-574, -310$).

ZENITH

The median treatment difference in change in PVR from baseline between the sotatercept and placebo groups after 24 weeks was $-340 \text{ dynes}\cdot\text{sec}/\text{cm}^5$ (95% CI: $-511, -168$). The median treatment difference in change in NT-proBNP from baseline between the sotatercept-csrk and placebo groups after 24 weeks was -2339 pg/mL (95% CI: $-3379, -1299$). The median treatment difference in change from baseline in mean pulmonary artery pressure (mPAP) between the sotatercept-csrk and placebo groups after 24 weeks was -21.2 mm Hg (95% CI: $-27.8, -14.6$).

12.3 Pharmacokinetics

Following subcutaneous administration of 0.7 mg/kg WINREVAIR every three weeks to PAH patients (PULSAR, SPECTRA, and STELLAR), the steady state geometric mean (%CV) area under the time concentration curve (AUC) is $171.3 \text{ mcg}\cdot\text{d/mL}$ (34.2%), and peak concentration (C_{max}) is 9.7 mcg/mL (30%). Sotatercept-csrk AUC and C_{max} increased proportionally with dose. Steady state is achieved after approximately 15 weeks following initiation of multiple dosing. The accumulation ratio of sotatercept-csrk AUC is approximately 2.2. Sotatercept-csrk pharmacokinetics were similar in PAH participants in ZENITH.

Absorption

Following subcutaneous administration, the absolute bioavailability of sotatercept-csrk is approximately 66%. The sotatercept-csrk median time to peak drug concentration (T_{max}) is approximately 7 days (range from 2 to 8 days) following multiple SC administration every 4 weeks.

Distribution

The population PK model estimated volume of distribution (%CV) of sotatercept-csrk at steady state is approximately 5.3 L (27.3%) in patients with PAH.

Elimination

The sotatercept-csrk effective half-life is approximately 24 days and its clearance is approximately 0.18 L/day .

Metabolism

Sotatercept-csrk is expected to be metabolized into small peptides by catabolic pathways.

Specific Populations

No clinically significant differences in sotatercept-csrk pharmacokinetics (PK) were observed based on age (18 to 81 years of age), sex, race, mild to moderate (eGFR ranging from 30 to 89 mL/min) renal impairment (PAH patients), or end-stage kidney disease (eGFR $<15 \text{ mL/min}$) with dialysis. Based on limited data, severe renal impairment (eGFR ranging from 15 to 30 mL/min , $n=3$) had no impact on the PK of sotatercept-csrk. Sotatercept-csrk is not dialyzable. The effect of hepatic impairment on the PK of sotatercept-csrk has not been studied.

Body Weight

The clearance (CL) and central volume of distribution (V_c) increase with increase in body weight. This effect is not clinically significant when sotatercept-csrk is administered using weight-based dosing as recommended.

12.6 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 studies described below with the incidence of anti-drug antibodies in other studies, including those of WINREVAIR or of other sotatercept-csrk products.

During the 24-week treatment period in STELLAR, 27% (44/163) of sotatercept-csrk-treated patients developed anti-sotatercept-csrk antibodies (ADA). Among the 44 ADA-positive patients, 12 (27%) tested positive for neutralizing antibodies against sotatercept-csrk.

During the ZENITH trial, with a median sotatercept treatment duration of 435 days, 43% (36/84) of patients developed anti-sotatercept antibodies. Among these 36 patients, 20 (56%) tested positive for neutralizing antibodies against sotatercept.

There were no identified clinical effects of anti-sotatercept-csrk antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of sotatercept-csrk over the treatment duration of 24 weeks at the recommended dosage in these studies.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies have been conducted with sotatercept-csrk.

In a fertility and early embryonic development study in female rats, sotatercept-csrk 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 preimplantation and postimplantation 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-csrk 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 functional fertility endpoints occurred at 30 mg/kg (20-fold the MRHD, based on estimated AUC).

14 CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension

STELLAR

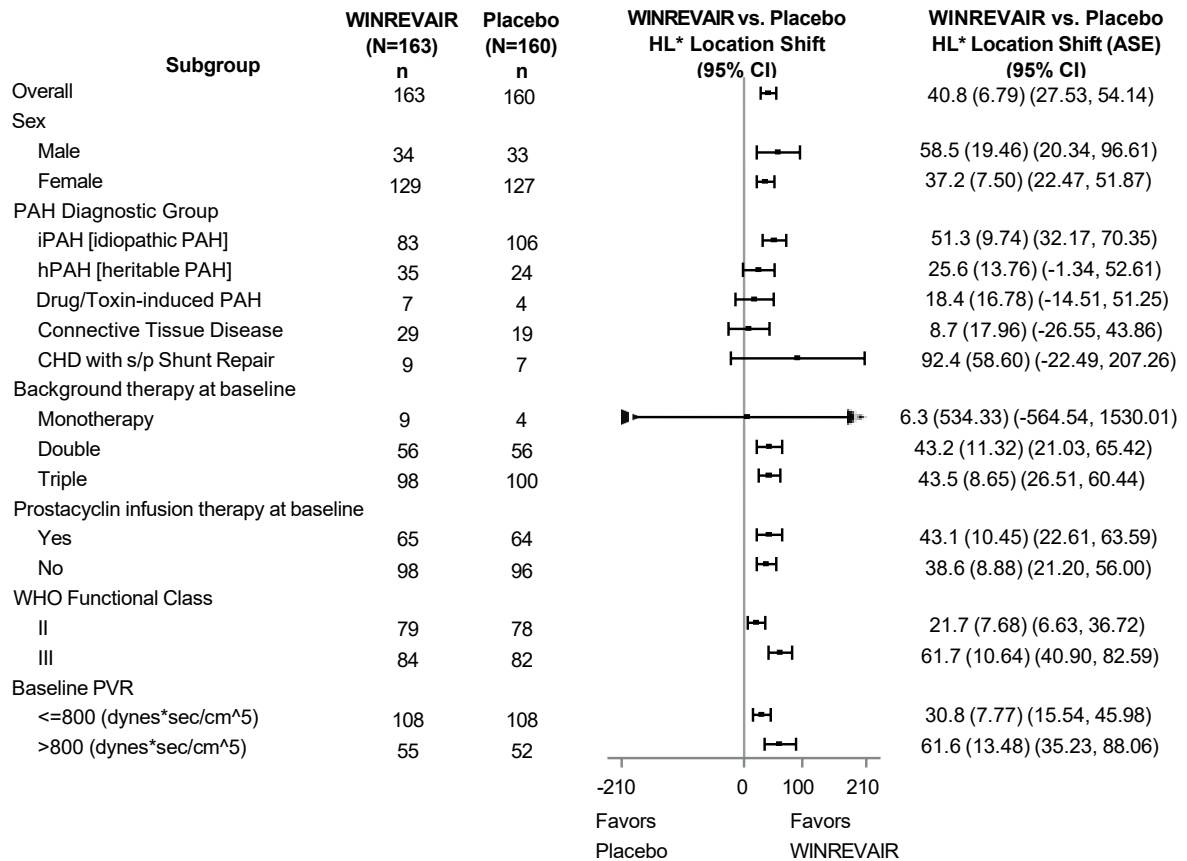
The efficacy of WINREVAIR was evaluated in adult patients with PAH in the STELLAR trial (NCT04576988). STELLAR was a global, double-blind, placebo-controlled, multicenter, parallel-group clinical trial in which 323 patients with PAH (WHO Group 1, FC II or III) were randomized 1:1 to WINREVAIR (target dose 0.7 mg/kg) (n=163) or placebo (n=160) administered subcutaneously once every 3 weeks.

Participants were: 79% female; had a median age of 48 years (range: 18 to 82 years), and median body weight of 68 kg (range 38 to 141 kg); and 89% White, 2% Black/African American, 2% Asian, 0.3% American Indian or Alaska Native, 0.3% Native Hawaiian or Other Pacific Islander, 6% Missing/Other races. The most common PAH etiologies were idiopathic PAH (59%), heritable PAH (18%), and PAH associated with connective tissue diseases (CTD) (15%). STELLAR excluded patients with human immunodeficiency virus (HIV)-associated PAH, PAH associated with portal hypertension, schistosomiasis-associated PAH,

and pulmonary veno occlusive disease. The mean time from PAH diagnosis to screening was 8.8 years. Most participants were receiving either three (61%) or two (35%) background drugs for PAH, and 40% were receiving prostacyclin infusions. Patients had a WHO FC II (49%) or III (51%) at baseline.

The primary efficacy endpoint was the change from baseline at Week 24 in 6-Minute Walk Distance (6 MWD). In the WINREVAIR group, the placebo-adjusted median increase in 6 MWD was 41 meters (95% CI: 28, 54; $p < 0.001$). Figure 1 displays placebo-adjusted changes in 6 MWD at Week 24 in relevant subgroups.

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



*Hodges-Lehmann location shift from placebo estimate (median of all paired differences). ASE = asymptotic standard error.

Change from baseline in 6 MWD at Week 24 for subjects who died was imputed to -2000 meters to receive the worst rank. Change from baseline in 6 MWD at Week 24 for subjects who had missing data due to a non-fatal clinical worsening event was imputed to -1000 meters to receive the next-worst rank.

Treatment with WINREVAIR led to an improvement from baseline by at least 1 WHO FC at Week 24 in 29% of patients compared to 14% of patients treated with placebo ($p<0.001$).

Treatment with WINREVAIR resulted in an 84% reduction in the occurrence of death from any cause or PAH clinical worsening events compared to placebo (see Table 5 and Figure 2). These outcomes were captured until the last patient completed the Week 24 visit (data up to the data cutoff; median duration of exposure 33.6 weeks).

Table 5: Death from Any Cause or PAH Clinical Worsening Events in STELLAR

	WINREVAIR (N=163) n (%)	Placebo (N=160) n (%)	Hazard Ratio (95% CI)
Number of subjects who experienced death or at least one clinical worsening event	9 (5.5)	42 (26.3)	0.16 (0.08, 0.35) p<0.001
Assessment of clinical worsening events*			
Death	2 (1.2)	7 (4.4)	
Worsening-related listing for lung and/or heart transplant	1 (0.6)	2 (1.3)	
Need to initiate rescue therapy with an approved PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more	2 (1.2)	17 (10.6)	
Need for atrial septostomy†	0 (0.0)	0 (0.0)	
PAH-specific hospitalization (≥24 hours)	0 (0.0)	8 (5.0)	
Deterioration of PAH‡	4 (2.5)	15 (9.4)	

* A subject can have more than one assessment recorded for their clinical worsening.

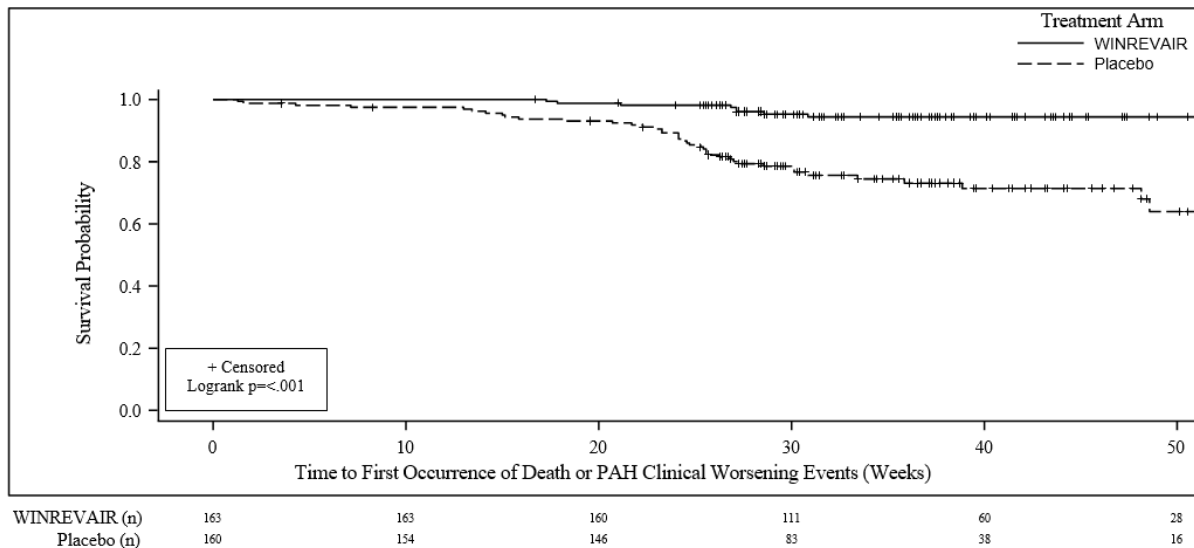
† There were no events of atrial septostomy.

‡ Deterioration of PAH 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 6 MWD by ≥15% (confirmed by two 6 MWTs at least 4 hours apart but no more than one week).

N = number of subjects in the category.

6 MWT = 6-Minute Walking Test

Figure 2: Time to Death from Any Cause or First Occurrence of PAH Clinical Worsening Event Kaplan-Meier Plot in STELLAR



ZENITH

The efficacy of WINREVAIR was evaluated in adult PAH patients with WHO FC III or IV at high risk of mortality in the ZENITH trial (NCT04896008). ZENITH was a global, double-blind, placebo-controlled, multicenter, parallel-group clinical trial in which 172 patients were randomized 1:1 to WINREVAIR (target dose 0.7 mg/kg) (n=86) or placebo (n=86) administered subcutaneously once every 3 weeks. Efficacy

was evaluated at the pre-specified interim analysis which occurred when 61 patients experienced a primary endpoint event and median patient time on study was 273 days.

The demographic and baseline clinical characteristics were similar between the WINREVAIR and placebo groups. Participants were: 77% female; had a median age of 58 years (range: 18 to 75 years); and 87% White, 5% Black/African American, 4% Asian, 1% American Indian or Alaska Native, 3% Missing/Other race, 74% were FC III and 26% were FC IV. The most common PAH etiologies were idiopathic PAH (50%), PAH associated with connective tissue diseases (CTD) (28%), and heritable PAH (11%). The mean time since PAH diagnosis to screening was 8 years. Participants were on background PAH treatment, 72% on triple therapy, 28% on double therapy, and 59% on prostacyclin infusion therapy. The REVEAL Lite 2 risk score was <9 for 2% of participants, 9 to 10 for 67% of participants, and ≥11 for 30% of participants. The ZENITH trial excluded patients diagnosed with human immunodeficiency virus (HIV)-associated PAH, PAH associated with portal hypertension, pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis or overt signs of capillary and/or venous involvement.

The primary efficacy endpoint was time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours. In the WINREVAIR treatment group, the risk of a first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours was 76% lower compared with the placebo group (HR: 0.24; 95% CI: 0.13, 0.43; p<0.0001) (see Table 6). Fewer participants in the WINREVAIR group (15 [17%]) than in the placebo group (47 [55%]) had a primary endpoint event as of the data cutoff. Based on the primary endpoint result, the study was stopped for favorable efficacy at the interim analysis.

The treatment effect of WINREVAIR was consistent across the prespecified subgroups (see Figure 4).

Table 6: Primary Endpoint Results in ZENITH

	WINREVAIR (N=86) n (%)	Placebo (N=86) n (%)	Hazard Ratio (95% CI) p-value
Number of participants with at least 1 primary event*	15 (17.4)	47 (54.7)	0.24 (0.13, 0.43) <0.0001
Components of primary endpoint†			
All-cause death	7 (8.1)	13 (15.1)	
Lung transplantation	1 (1.2)	6 (7.0)	
PAH worsening-related to hospitalization (≥24 hours)	8 (9.3)	43 (50.0)	

* The primary composite endpoint analysis includes the first occurrence of an adjudicated morbidity-mortality event up to the data cutoff. All deaths up to the data cutoff are included, regardless of adjudication and regardless of whether they occurred during or post-ZENITH, except for those occurring after lung transplantation or enrollment in SOTERIA.

† Shows each component of the composite primary endpoint as a standalone outcome. A participant is included in more than one row if multiple events meeting primary endpoint definition were observed.

Figure 3: Time to First Event in ZENITH of All-cause Death, Lung Transplantation, or PAH Worsening-related Hospitalization of ≥ 24 Hours Kaplan-Meier Plot

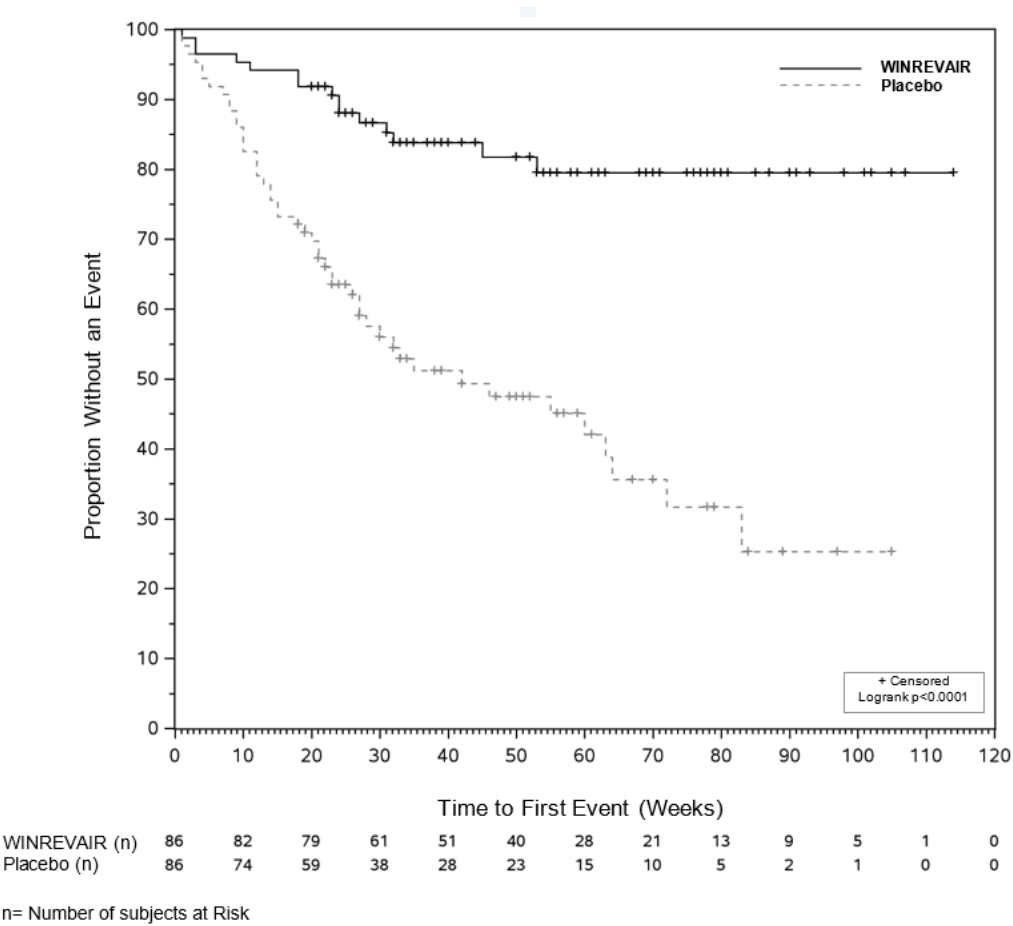
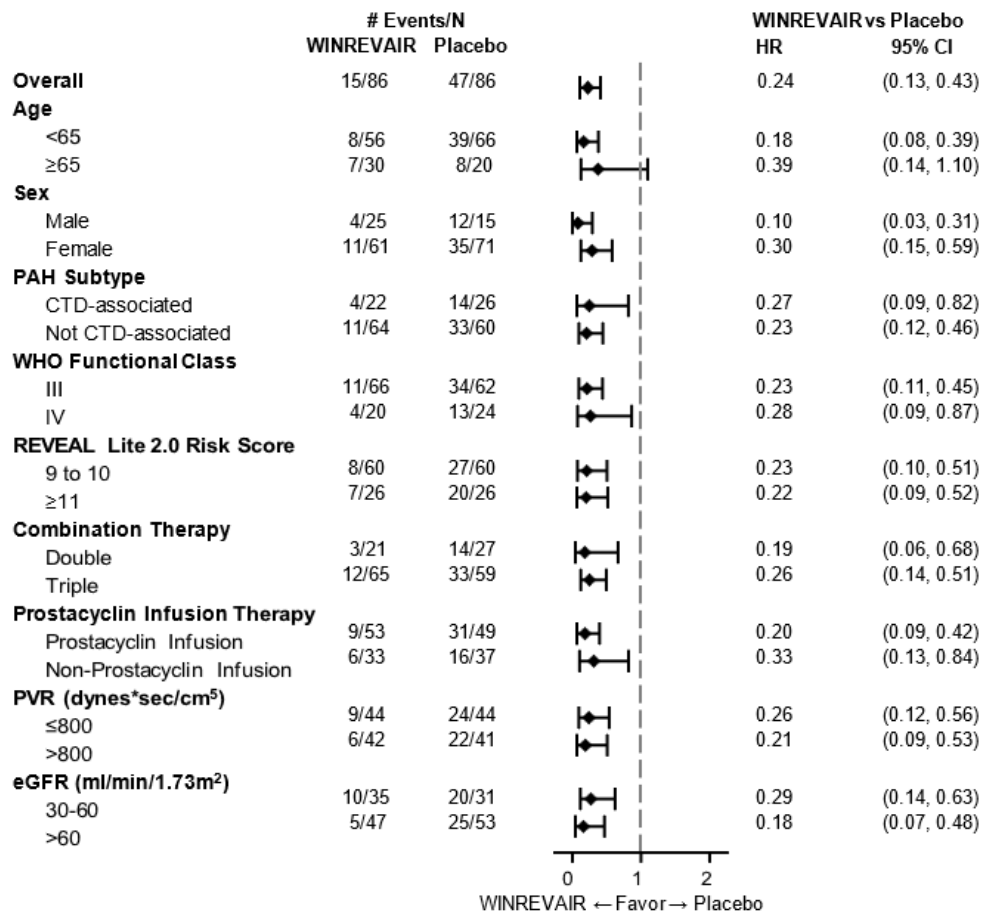


Figure 4: Hazard Ratio for the Primary Endpoint in Subgroups in ZENITH



Subgroup analyses were not displayed if the number of participants in subgroup category was less than 10% of FAS.
For participants with REVEAL Lite 2.0 risk score <9 at screening, they were grouped under "9 to 10" for the analyses.

The secondary endpoint of overall survival (OS) included all deaths up to the data cutoff, except for those occurring after lung transplantation or enrollment in a long-term follow-up study. Twenty OS events were observed (7 deaths in the WINREVAIR treatment group and 13 deaths in the placebo group). The point estimate for the OS HR favored the WINREVAIR treatment group over the placebo group.

Subsequent secondary endpoints were not eligible to be tested due to the hierarchical testing strategy.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

WINREVAIR (sotatercept-csrk) for injection is a white to off-white lyophilized cake or powder appearance supplied in single-dose vials (45 mg or 60 mg) packaged in kits that contain one measuring syringe and one safety needle. Each kit also contains Sterile Water for Injection in prefilled syringes necessary to reconstitute the product, vial adapter(s), and alcohol pads, as shown in Table 7.

Table 7: Kit Contents

Kit	Vial Adapters	Alcohol Pads	Sterile Water for Injection in prefilled syringes	NDC
(1) 45 mg vial	1	4	(1) 1 mL syringe	NDC # 0006-5090-01
(1) 60 mg vial	1	4	(1) 1.3 mL syringe	NDC # 0006-5091-01
(2) 45 mg vials	2	8	(2) 1 mL syringes	NDC # 0006-5087-01
(2) 60 mg vials	2	8	(2) 1.3 mL syringes	NDC # 0006-5088-01

16.2 Storage and Handling

Store vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze.

The kit should remain in the refrigerator until ready for use. The unused kit can be out of the refrigerator for (up to 25°C/77°F) up to 24 hours. For additional information on temperature excursions, call Merck Sharp & Dohme LLC at 1-800-672-6372.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information and IFU).

Discuss the following with patients prior to and during treatment with WINREVAIR.

Erythrocytosis

Caution patients that WINREVAIR may raise Hgb to levels that increase their risk of thrombotic events. Inform patients that Hgb levels will be assessed before at least the first 5 doses and then periodically, as dosage may need to be adjusted [see *Warnings and Precautions* (5.1)].

Severe Thrombocytopenia

Caution patients that WINREVAIR may cause platelet count to decrease, which if severe could cause bleeding. Inform patients that platelet count will be assessed before at least the first 5 doses and then periodically, as dosage may need to be adjusted [see *Warnings and Precautions* (5.2)].

Serious Bleeding

Inform patients of the possibility of serious bleeding, which is more likely to occur if they have low platelet counts or while on prostacyclin background therapy and/or antithrombotic agents. Advise patients to notify their healthcare provider about signs and symptoms of bleeding [see *Warnings and Precautions* (5.3)].

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving WINREVAIR and for at least 4 months after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected during treatment with WINREVAIR [see *Warnings and Precautions* (5.4), *Use in Specific Populations* (8.1)]. Report exposure during pregnancy or lactation to the Merck Sharp & Dohme, LLC Adverse Event reporting line at 1-877-888-4231.

Lactation

Advise females not to breastfeed during treatment with WINREVAIR and for 4 months after the final dose [see *Use in Specific Populations* (8.2)].

Females and Males of Reproductive Potential

Advise females and males of reproductive potential that WINREVAIR may impair fertility [see *Use in Specific Populations* (8.3), *Nonclinical Toxicology* (13.1)].

Administration by Patient or Caregiver

Review the IFU with the patient or caregiver step-by-step. Provide training to the patient or caregiver regarding proper preparation and administration of WINREVAIR and decide whether a patient or caregiver is capable of preparing and administering WINREVAIR independently [see *Dosage and Administration* (2.4)].

Make sure the patient or caregiver can do the following correctly:

- reconstitute the medicine,
- measure the correct amount of medicine according to the patient's prescription,
- select and prepare a proper injection site, and
- inject the medicine subcutaneously.

Incorrect Dose or Missed Dose

Inform patients to call their healthcare provider for further instruction if they take more than or less than the correct dose. Advise them about signs/symptoms to monitor for and what to do if any of these signs/symptoms should occur. Advise them that additional laboratory tests may be required prior to the next scheduled dose to ensure that the next dose can be safely administered.

Instruct the patient that if they miss the prescribed dose of WINREVAIR, they should take it within 3 days and maintain the original schedule for the next dose. If not taken within 3 days, instruct them to call their healthcare provider for guidance [see *Dosage and Administration* (2.2)].

Manufactured by:
Merck Sharp & Dohme LLC, Rahway, NJ 07065, USA

U.S. license number 0002

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