

## 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

### INDICATIONS AND USAGE

WINREVAIR is an activin signaling inhibitor indicated for the treatment of adults with pulmonary arterial hypertension (PAH, WHO Group 1) to increase exercise capacity, improve WHO functional class (FC) and reduce the risk of clinical worsening events. (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 ( $\geq 10\%$  in patients receiving WINREVAIR and 5% more than placebo) adverse reactions were headache, epistaxis, rash, telangiectasia, diarrhea, dizziness, and erythema. (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](http://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: 03/2024

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

WINREVAIR™ is indicated for the treatment of adults with pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1) to increase exercise capacity, improve WHO functional class (FC), and reduce the risk of clinical worsening events.

### 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  $<50,000/\text{mm}^3$  ( $<50 \times 10^9/\text{L}$ ) [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:  $(70 \text{ kg} \times 0.3 \text{ mg/kg}) \div 50 \text{ mg/mL} = 0.42 \text{ mL}$ , 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:  $(70 \text{ kg} \times 0.7 \text{ mg/kg}) \div 50 \text{ mg/mL} = 0.98 \text{ mL}$ , 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/mm<sup>3</sup> (<50 x 10<sup>9</sup>/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  $\geq$ 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% 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% of patients taking WINREVAIR and 1% of patients taking placebo. 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.

The following data reflect exposure to WINREVAIR in the STELLAR trial. Patients (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	Placebo N=160	WINREVAIR N=163
Headache	28 (17.5)	40 (24.5)
Epistaxis	3 (1.9)	36 (22.1)
Rash	13 (8.1)	33 (20.2)
Telangiectasia	7 (4.4)	27 (16.6)
Diarrhea	16 (10.0)	25 (15.3)
Dizziness	10 (6.2)	24 (14.7)
Erythema	5 (3.1)	22 (13.5)

\* 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 47.1 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.

#### Uncontrolled Long-term Safety Data

The safety profile in the long-term uncontrolled extension period of the PULSAR study was generally similar to that observed in the STELLAR study. Patients were treated with WINREVAIR 0.3 mg/kg or 0.7 mg/kg (n=104) and had a mean duration of exposure of 151 weeks (maximum 218 weeks).

## **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 81 patients  $\geq 65$  years of age participated in clinical studies for PAH, of which 52 (16%) were treated with WINREVAIR. No differences in efficacy of WINREVAIR were observed between the  $< 65$ -year-old and  $\geq 65$ -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  $\geq 65$ -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- $\beta$  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

PVR:

A statistically significantly greater decrease from baseline in PVR was observed in the WINREVAIR group compared to the placebo group in the Phase 3 STELLAR study. The median treatment difference in PVR between sotatercept-csrk and placebo was -235 dynes\*sec/cm<sup>5</sup> (95% CI: -288, -181; p<0.001). Sotatercept-csrk steady state exposure at 0.7 mg/kg dose was associated with near maximal reduction in PVR based on exposure-response analysis.

NT-proBNP:

A statistically significantly greater decrease from baseline in NT-proBNP was observed in the WINREVAIR group compared to the placebo group in the Phase 3 STELLAR study. The median treatment difference in NT-proBNP between the sotatercept-csrk and placebo was -442 pg/mL (95% CI: -574, -310; p<0.001).

### 12.3 Pharmacokinetics

Following subcutaneous administration of 0.7 mg/kg WINREVAIR every three weeks to PAH patients, the steady state geometric mean (%CV) area under the time concentration curve (AUC) is 172 mcg\*d/mL (34.2%), and peak concentration (C<sub>max</sub>) is 9.7 mcg/mL (30%). Sotatercept-csrk AUC and C<sub>max</sub> 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.

#### Absorption

Following subcutaneous administration, the absolute bioavailability of sotatercept-csrk is approximately 66%. The sotatercept-csrk median time to peak drug concentration (T<sub>max</sub>) 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 mL/min) with dialysis. Severe renal impairment (eGFR ranging from 15 to 30 mL/min) is not expected to impact 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<sub>c</sub>) 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 study 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.

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.

## **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  $\geq 15$  mg/kg ( $\geq 9$  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  $\geq 0.3$  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**

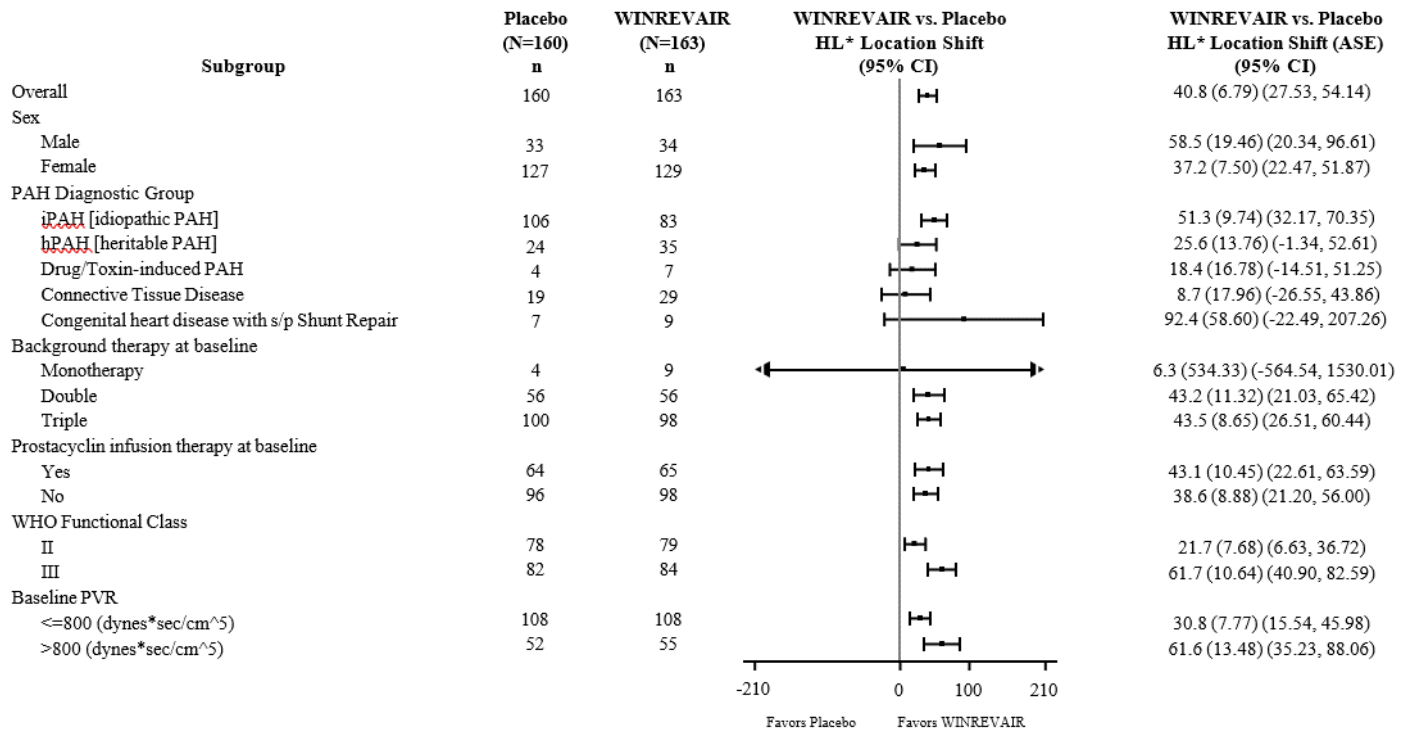
### **14.1 Pulmonary Arterial Hypertension**

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/Caucasian, 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**



\*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 4 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 4: Death from Any Cause or PAH Clinical Worsening Events**

	<b>Placebo (N=160) n (%)</b>	<b>WINREVAIR (N=163) n (%)</b>	<b>Hazard Ratio (95% CI)</b>
Number of subjects who experienced death or at least one clinical worsening event	42 (26.3)	9 (5.5)	0.16 (0.08, 0.35) p<0.001
<b>Assessment of clinical worsening events*</b>			
Death	7 (4.4)	2 (1.2)	
Worsening-related listing for lung and/or heart transplant	2 (1.3)	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 <sup>†</sup>	0 (0.0)	0 (0.0)	
PAH-specific hospitalization (≥24 hours)	8 (5.0)	0 (0.0)	
Deterioration of PAH <sup>‡</sup>	15 (9.4)	4 (2.5)	

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

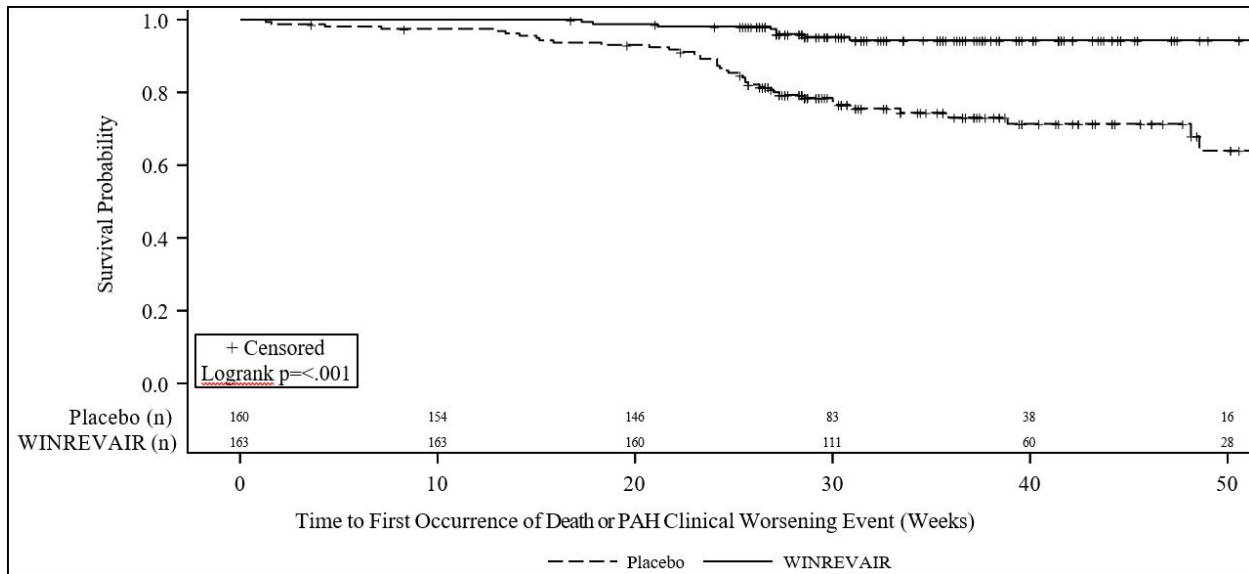
<sup>†</sup> There were no events of atrial septostomy.

<sup>‡</sup> 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**



## 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 5.

**Table 5: 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)*].

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Manufactured by:  
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