▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – WINREVAIR® (Sotatercept)

1 NAME OF THE MEDICINE

Sotatercept

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 45 mg single-use vial provides 55 mg of sotatercept and after reconstitution with 1.0 mL sterile water for injections, 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 injections, the resulting concentration is 50 mg/1.0 mL of sotatercept and the nominal deliverable volume is 1.2 mL.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

WINREVAIR is indicated for the treatment of adults with pulmonary arterial hypertension (PAH) in WHO Functional Class (FC) II, III, or IV, in combination with standard therapy.

Efficacy has been shown in idiopathic and heritable PAH, PAH associated with connective tissue disease, drug or toxin-induced PAH and PAH associated with congenital heart disease with repaired shunts.

4.2 DOSE AND METHOD OF ADMINISTRATION

WINREVAIR should only be initiated and monitored by a physician experienced in the diagnosis and treatment of PAH.

Recommended Starting Dosage in Adults

Obtain haemoglobin (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 section 4.2 Dose and Method of Administration (Dosage Modifications in Adults Due to Haemoglobin Increase or Platelet Count)]

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).

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

Patient Weight Range (kg)	Injection Volume (mL)	Administration Pack	Vial
30.0 – 40.8	0.2	45 mg pack (containing 1x 45mg vial)	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 pack (containing 1x 60mg vial)	60 mg
174.2 – 180.0	1.1		

Recommended Target Dosage in Adults

Three weeks after a single starting dose of 0.3 mg/kg, the dose should be escalated to the recommended target dose of 0.7 mg/kg after verifying acceptable Hgb and platelet count (see Section 4.2 Dosage Modification in Adults Due to Haemoglobin Increase or Platelet Count Decrease). Treatment should be continued at 0.7 mg/kg every 3 weeks unless dose adjustments are required.

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

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

Patient Weight Range (kg)	Injection Volume (mL)	Administration Pack	Vial
30.0 – 31.7	0.4	45 mg pack (containing 1x 45mg vial)	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 pack (containing 1x 60mg vial)	60 mg
74.7 – 81.7	1.1		
81.8 – 88.9	1.2		
89.0 – 96.0	1.3	90 mg pack (containing 2x 45 mg vial)	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	120 mg pack (containing 2x 60 mg vial)	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 Section 4.9 Overdose]. In case of overdose when WINREVAIR is administered by patient or caregiver, retrain the patient or caregiver if appropriate or consider ongoing administration by a healthcare professional (see Section 4.9 Overdose).

Dosage Adjustment

Dosage Modifications in Adults Due to Haemoglobin 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 Section 4.4 Special Warnings and Precautions for Use].

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).

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.

Renal Impairment
No dose adjustment of WINREVAIR is required based on renal impairment. Limited data are available on the use of sotatercept in PAH patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) [see Section 4.4 Special Warnings and Precautions for Use and Section 5.2 Pharmacokinetic Properties].

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 metabolised via cellular catabolism [see Section 4.4 Special Warnings and Precautions for Use and Section 5.2 Pharmacokinetic Properties].

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

Elderly Patients
No dose adjustment of WINREVAIR is required based on age [see Section 4.4 Special Warnings and Precautions for Use].

Method of Administration

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

Administration Pack Presentation
WINREVAIR is intended for use under the guidance of a health care professional. Patients and caregivers may administer WINREVAIR when considered appropriate and when they receive training and follow-up from the doctor in how to reconstitute, prepare, measure, and inject WINREVAIR.

Consider confirming at subsequent visits that the patient or caregiver can prepare and administer WINREVAIR correctly:

- if the dose changes or the patient requires a different administration pack
- if the patient develops erythrocytosis [see Section 4.4 Special Warnings and Precautions for Use].

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

Selecting the Appropriate Administration Pack
If a patient's weight requires the use of two 45 mg vials or two 60 mg vials of lyophilized product, a 2-vial administration pack should be used instead of two individual 1-vial administration packs. A 2-vial administration pack includes instructions to combine the contents of two vials, which aids in measuring the proper dosage and eliminates the need for multiple injections [see Section 6.5 Nature and Contents of

Container].

Reconstitution Instructions

- Remove the administration pack from the refrigerator and wait 15 minutes to allow the prefilled syringe(s) and 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.
- Attach the vial adapter to the vial.
- Visually inspect the pre-filled syringe for any damage or leaks and the sterile water 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 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.
- 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.
- Unscrew the syringe from the vial adapter and discard the emptied syringe into a sharps container.
- 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.

Syringe Preparation

- Swab the vial adapter with an alcohol wipe.
- Remove dosing syringe from packaging and attach the syringe to the vial adapter.
- 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, push plunger in to remove excess drug product or air from the syringe.
- Remove the syringe from the vial and attach the needle.

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.
- Discard the emptied syringe into a sharps container. Do not reuse the syringe.

4.3 CONTRAINDICATIONS

WINREVAIR is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Erythrocytosis

Hgb increases have been observed in patients during treatment with WINREVAIR. Severe erythrocytosis (high haemoglobin) 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 Section 4.2 Dose and Method of Administration and Section 4.8 Adverse Effects (Undesirable Effects)].

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/mm3 (<50 x 10^9/L) [see Section 4.2 Dose and Method of Administration].

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 Section 4.2 Dose and Method of Administration and Section 4.8 Adverse Effects (Undesirable Effects)].

Serious Bleeding
In clinical studies, serious bleeding events (e.g., gastrointestinal, intracranial hemorrhage) were reported in 4% versus 1% (STELLAR), 7% versus 7% (ZENITH), and 7% versus 2% (HYPERION) of patients taking WINREVAIR versus placebo, respectively. 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 Section 4.8 Adverse Effects (Undesirable Effects)].

Embryofetal 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 Section 4.6 Fertility, Pregnancy and Lactation].

Impaired Fertility
Based on findings in animals, WINREVAIR may impair female and male fertility. Advise patients on the potential effects on fertility [see Section 4.6 Fertility, Pregnancy and Lactation].

Use in Renal Impairment
No dose adjustment of WINREVAIR is required based on renal impairment. Limited data are available on the use of sotatercept in PAH patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) [see Section 4.2. Dose and Method of Administration and Section 5.2 Pharmacokinetic Properties].

Use in 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 metabolised via cellular catabolism [see Section 4.2. Dose and Method of Administration and Section 5.2 Pharmacokinetic Properties].

Use in the Elderly
No dose adjustment of WINREVAIR is required based on age. A total of 257 patients ≥65 years of age participated in clinical studies for PAH, of which 167 (65%) 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.

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

Effects on laboratory tests
Not applicable.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No other interaction studies have been performed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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 Pregnancy].

Infertility

Based on findings in animals, sotatercept may impair female and male fertility.

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 oestrous 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 functional fertility endpoints occurred at 30 mg/kg (20-fold the MRHD, based on estimated AUC).

Use in Pregnancy - Category D

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 embryofetal 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.

Animal Data

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 lower 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, lower pup weight and delays in sexual maturation were seen at estimated exposures (based on AUC) ≥ 2-fold the MRHD.

Use in Lactation

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. In a rat pre/postnatal study, lower weights and delayed sexual maturation were seen in breast-fed pups following maternal exposure to sotatercept. Since it is not known if sotatercept is excreted in human breast milk, breastfeeding is not recommended during treatment with sotatercept and for 4 months after the final dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of this medicine on a person's ability to drive and use machines were performed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Experience

STELLAR The following data reflect exposure to WINREVAIR in the pivotal STELLAR trial. Adult PAH patients with WHO FC II or III (n=323) were randomised 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 treatment assignment. The median duration of treatment was longer in the WINREVAIR group (313.0 days) than in the placebo group (273.0 days) [see Section 5.1 Pharmacodynamic Properties – Clinical Trials].

Adverse events occurring in STELLAR are summarised in Table 3.

Table 3: Treatment-Emergent Adverse Events Experienced by ≥5% in One or More Treatment Groups Term Week 24 Results (DBPC)*

Adverse Event	WINREVAIR N=163 n(%)	Placebo N=160 n(%)
Headache	33 (20.2)	24 (15.0)
COVID-19	24 (14.7)	21 (13.1)
Nausea	16 (9.8)	18 (11.3)
Diarrhea	20 (12.3)	12 (7.5)
Fatigue	17 (10.4)	12 (7.5)
Epistaxis	20 (12.3)	3 (1.9)
Telangiectasia	17 (10.4)	5 (3.1)
Injection site pain	11 (6.7)	10 (6.3)
Dizziness	17 (10.4)	3 (1.9)
Thrombocytopenia†	10 (6.1)	4 (2.5)
Dyspnoea	4 (2.5)	14 (8.8)
Oedema peripheral	8 (4.9)	10 (6.3)
Nasopharyngitis	7 (4.3)	9 (5.6)
Hypokalaemia	9 (5.5)	5 (3.1)
Rash	9 (5.5)	4 (2.5)
Flushing	9 (5.5)	3 (1.9)
Increased Haemoglobin‡	9 (5.5)	0 (0.0)

N = number of subjects in the treatment group. n = number of subjects in the category.
* Double-blind placebo-controlled period.
† Composites of preferred terms: Thrombocytopenia and Platelet Count increased.
‡ Composites of preferred terms: Haemoglobin increased and Polycythaemia.

Description of Selected Adverse Reactions from STELLAR (DBPC+LTDB)

Increased Haemoglobin
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 15.3% 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 were not associated with discontinuation of therapy. Severe reduction in platelet count <50,000/mm^3 (<50.0 x 10^9/L) occurred in 3.1% of patients taking WINREVAIR.

Telangiectasia
Events of telangiectasia were non-serious. In all patients exposed to WINREVAIR, the median time to onset was 36.1 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 nonserious 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.

ZENITH
The safety of WINREVAIR in adult PAH patients in WHO FC III or IV at high risk of mortality was based on data from 172 patients in the ZENITH trial who were randomised in a 1:1 ratio to treatment with WINREVAIR or placebo in combination with background standard of care (SOC) 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 hospitalisation 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 (434.5 days) than in the placebo group (267.5 days) [see Section 5.1 Pharmacodynamic Properties – Clinical Trials].

Overall, the incidence of adverse reactions observed in the ZENITH trial was higher than those observed in the STELLAR trial, reflecting the more advanced disease state of the population studied. The most commonly reported adverse reactions in the WINREVAIR group occurring at a frequency greater than placebo were: epistaxis (45.3%), telangiectasia (25.6%), thrombocytopenia (15.1%), increased haemoglobin (15.1%), gingival bleeding (10.5%), erythema (7.0%), and rash (5.8%). Severe reduction in platelet count <50,000/mm^3 (<50.0 x 10^9/L) occurred in 6% of patients taking WINREVAIR. Events of serious bleeding were balanced between the WINREVAIR and placebo groups. In the WINREVAIR group, 1% of patients discontinued study intervention due to an adverse event, compared with 5% of patients in the placebo group.

HYPERION
The safety of WINREVAIR in newly diagnosed adult PAH patients in WHO FC II or III at intermediate or high risk of disease progression was based on data from 320 patients in the HYPERION trial who were randomized in a 1:1 ratio to treatment with WINREVAIR or placebo in combination with background standard of care (SOC) therapies. The median duration of exposure was longer in the WINREVAIR group (442.5 days) than in the placebo group (350.0 days) [see Section 5.1 Pharmacodynamic Properties, Clinical Trials].

The adverse reactions observed in the HYPERION trial were generally consistent with those observed in the STELLAR trial. The most commonly reported adverse reactions in the WINREVAIR group occurring at a frequency greater than placebo were: epistaxis (31.9%), telangiectasia (26.3%), and increased hemoglobin (11.3%). No severe reductions in platelet count <50,000/mm^3 (<50.0 x 10^9/L) occurred in the WINREVAIR group. Treatment discontinuation due to an adverse event occurred in 3.1% and 0% of the WINREVAIR and placebo groups, respectively. The only adverse reaction causing treatment discontinuation at a frequency greater than 1% in the WINREVAIR group was epistaxis (1.9%).

Long-term Safety Data
Long-term safety data are available from pooled phase 2 and phase 3 clinical studies (n=431). The

median duration of exposure was 657 days. The safety profile was generally similar to that observed in the pivotal STELLAR study.

In SOTERIA, an ongoing open-label study of the long-term safety and efficacy of WINREVAIR, right-to-left intrapulmonary shunting has been reported in 2 participants (<0.5%) who developed worsening hypoxemia despite improved PAH haemodynamics.

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 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 neutralising antibodies against sotatercept. Anti-sotatercept antibodies generally had low titers with a median titer of 40 (range <20 to 2,560).

During the ZENITH study with a median sotatercept treatment duration of 434.5 days, 36/84 (43%) patients developed anti-sotatercept antibodies. Among these 36 patients, 20 (56%) tested positive for neutralising antibodies against sotatercept. Anti-sotatercept antibodies generally had low titers with a median titer of 10 (range 10 to 320).

During the HYPERION study with a median sotatercept treatment duration of 442.5 days, 63/159 (40%) patients developed anti-sotatercept antibodies. Among these 63 patients, 25 (40%) tested positive for neutralizing antibodies against sotatercept. Anti-sotatercept antibodies generally had low titers with a median titer of 20 (range: 10 to 1,280).

There were no identified clinical effects of anti-sotatercept antibodies on pharmacokinetics, safety, or effectiveness of sotatercept in these studies.

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

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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 dialysable during haemodialysis.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Sotatercept, a recombinant activin receptor type IIA-Fc (ActRIIA-Fc) fusion protein, is an activin signalling inhibitor that binds to activin A and other TGF- β superfamily ligands. As a result, sotatercept improves

the balance between the pro-proliferative (ActRIIA/Smad2/3-mediated) and anti-proliferative (BMPRII/Smad1/5/8-mediated) signalling to modulate vascular proliferation. In rodent-models of PAH, a sotatercept-csrk analogue reduced inflammation and inhibited proliferation of endothelial and smooth muscle cells in diseased vasculature. These cellular changes were associated with thinner vessel walls, reversal of right ventricular remodelling, and improved haemodynamics.

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. In ZENITH, the median treatment difference in change in PVR from baseline between the sotatercept and placebo groups after 24 weeks was -339.6 dynes*sec/cm^5 (95% CI: -511.09, -168.06) see Section 5.1 Pharmacodynamic Properties – Clinical Trials].

Clinical Trials

Pulmonary Arterial Hypertension

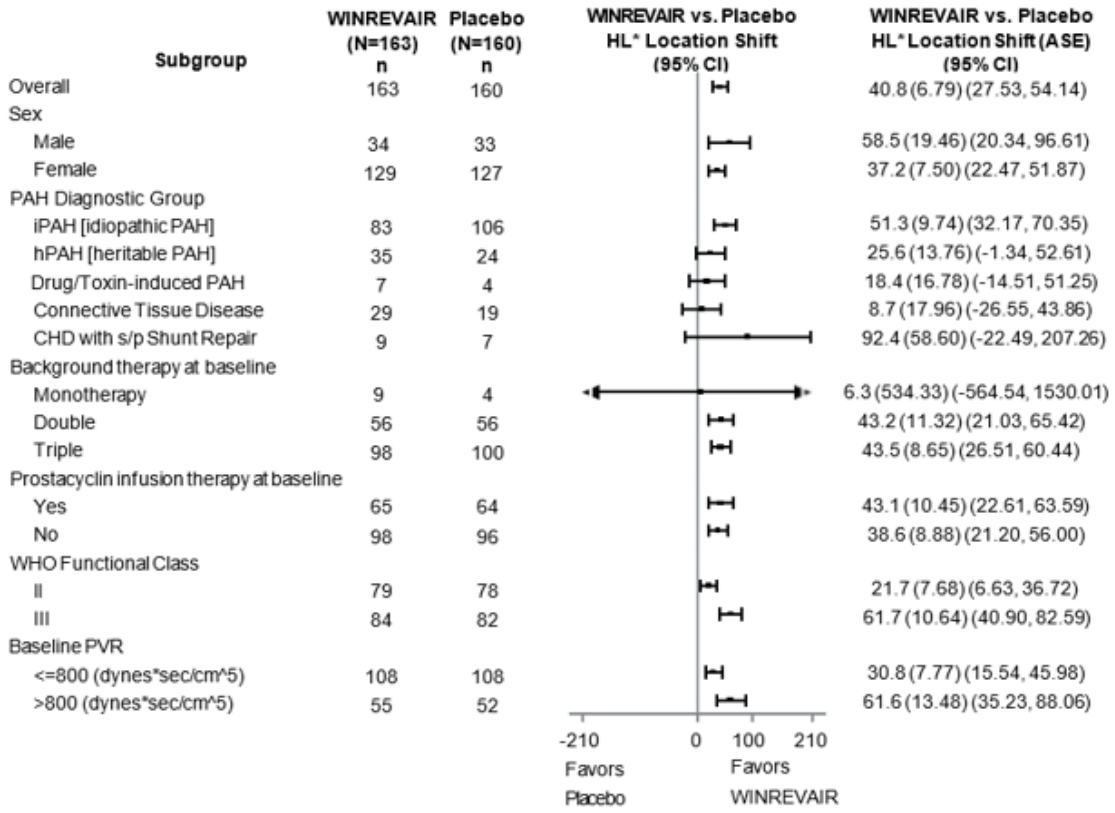
STELLAR

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 FC II or III) were randomised 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 in STELLAR



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 a pre-defined endpoint measured by 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 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 hospitalisation versus placebo-treated patients (see Table 4, Table 5, and Figure 2).

Table 4: Secondary Efficacy Results of STELLAR

Endpoint	WINREVAIR (N=163)	Placebo (N=160)	95% CI	p-value
Proportion of Patients Achieving Multicomponent Improvement* (MCI) from Baseline at Week 24, n (%)	63 (38.9)†	16 (10.1)	N/A	<0.001‡
Change from Baseline PVR at Week 24 (ASE) (dynes*sec/cm^5)	-234.6 (27.5)§	N/A	(-288.4, -180.8)	<0.001¶
Change from Baseline NT-proBNP Levels at Week 24 (ASE) (pg/mL)	-441.6 (67.3)#	N/A	(-573.5, -309.6)	<0.001¶
Proportion of Patients who Improve FC Class from Baseline at Week 24, n (%)	48 (29.4)†	22 (13.8)	N/A	<0.001‡
Time to Death or the First Occurrence of a Worsening Eventᵖ, n (%)	9 (5.5)	42 (26.3	0.163 (0.076, 0.347)ß	<0.001à
Proportion of Patients who Maintained or Achieved a Low Risk Scoeè at Week 24 vs. Baseline, n (%)	64 (39.5)	29 (18.2)	N/A	<0.001‡
Change from Baseline in the Physical Impacts Domain Score of PAH-SYMPACT®ð at Week 24 (ASE)	-0.26 (0.115)ø	N/A	(-0.490, -0.040)	0.010¶
Change from Baseline in the Cardiopulmonary Symptoms Domain Score of PAH-SYMPACT®ð at Week 24 (ASE)	-0.13 (0.062)ø	N/A	(-0.256, -0.014)	0.028¶
Change from baseline in the Cognitive/Emotional Impacts Domain Score of PAH-SYMPACT®ð at Week 24 (ASE)	-0.16 (0.123)ø	N/A	(-0.399, 0.084)	0.156¶

ASE= asymptotic standard error.

Note: Wherever stratified randomisation factors were used, the stratified randomisation 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 randomisation 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 randomisation 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.

ᵖ 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) hospitalisation 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 randomisation factors.

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

è Utilising 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 in STELLAR

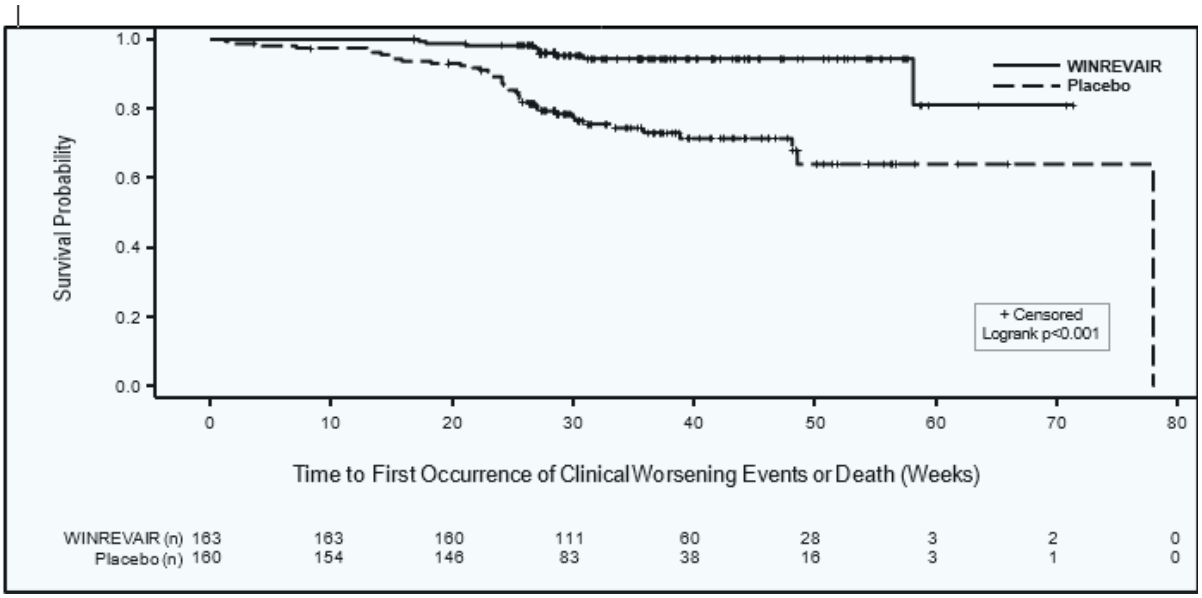
	WINREVAIR (N=163)	**Placebo (N=160)**
Total number of subjects who experienced death or at least one clinical worsening event, n (%)	9 (5.5)	42 (26.3)
Assessment of death or first occurrence of clinical worsening events*, n (%)		
Death	2 (1.2)	6 (3.8)
Worsening-related listing for lung and/or heart transplant	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	2 (1.2)	17 (10.6)
Need for atrial septostomy	0 (0.0)	0 (0.0)
PAH-specific hospitalisation (≥24 hours)	0 (0.0)	7 (4.4)
Deterioration of PAH†	4 (2.5)	15 (9.4)

* 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 in STELLAR Kaplan-Meier Plot



n= Number of subjects at Risk

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. ZENITH was a global, double-blind, placebo-controlled, multicenter, parallel-group clinical trial in which 172 patients were randomised 1:1 to WINREVAIR (target dose 0.7 mg/kg) (n=86) or placebo (n=86) 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 57.5 years (range: 18 to 75 years); 86.6% of participants were White, and 87.8% were not Hispanic or Latino; and 76.7% were female. The most common PAH etiologies were idiopathic PAH (50.0%), PAH associated with connective tissue diseases (CTD) (27.9%), and heritable PAH (10.5%). The mean time since PAH diagnosis to screening was 7.68 years. There were more participants on background PAH triple therapy (72.1%) compared with double therapy (27.9%), and 59.3% of participants were on prostacyclin infusion therapy. There were more participants in WHO FC III (74.4%) compared with WHO FC IV (25.6%). The REVEAL Lite 2 risk score was <9 for 2.3% of participants, 9 to 10 for 67.4% of participants, and ≥11 for 30.2% 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 the time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalisation of ≥24 hours. In the WINREVAIR treatment group, the risk of a first event of all-cause death, lung transplantation, or PAH worsening-related hospitalisation 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 treatment group (15 [17.4%]) than in the placebo group (47 [54.7%]) had a primary endpoint event as of the data cutoff.

The low event rate in the WINREVAIR treatment group precluded estimation of the median time to first event of the primary composite endpoint; the median time to first event was 9.6 months (95% CI: 6.2, 14.8) in the placebo group. The Kaplan-Meier curves began to separate at approximately Week 5, and the separation increased for the remainder of the study (see Figure 3). The treatment effect of WINREVAIR was consistent across the prespecified subgroups (see Figure 4).

Table 6: Components of the Primary Endpoint

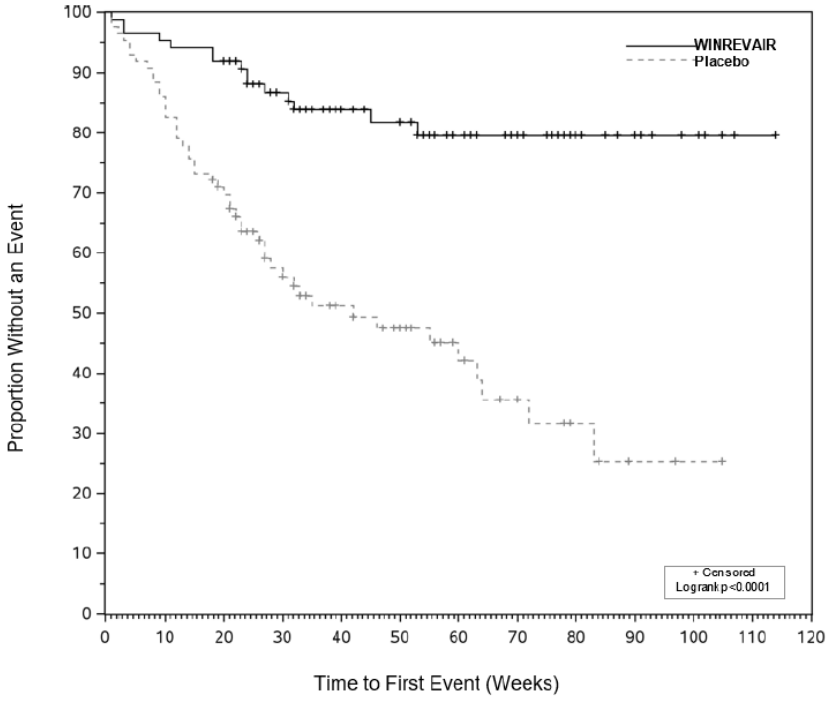
	WINREVAIR (N=86) n (%)	Placebo (N=86) n (%)	Hazard Ratio (95% CI) p-value*
Number (%) of participants with ≥ 1 primary event during or post ZENITH	15 (17.4)	47 (54.7)	0.24 (0.13, 0.43) <0.0001
Components of the primary endpoint†			
All-cause death‡	7 (8.1)	13 (15.1)	
Lung transplantation	1 (1.2)	6 (7.0)	
PAH worsening-related hospitalisation of ≥ 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.

† 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.

‡ Includes all deaths up to the data cutoff, except for those occurring after lung transplantation or enrollment in SOTERIA.

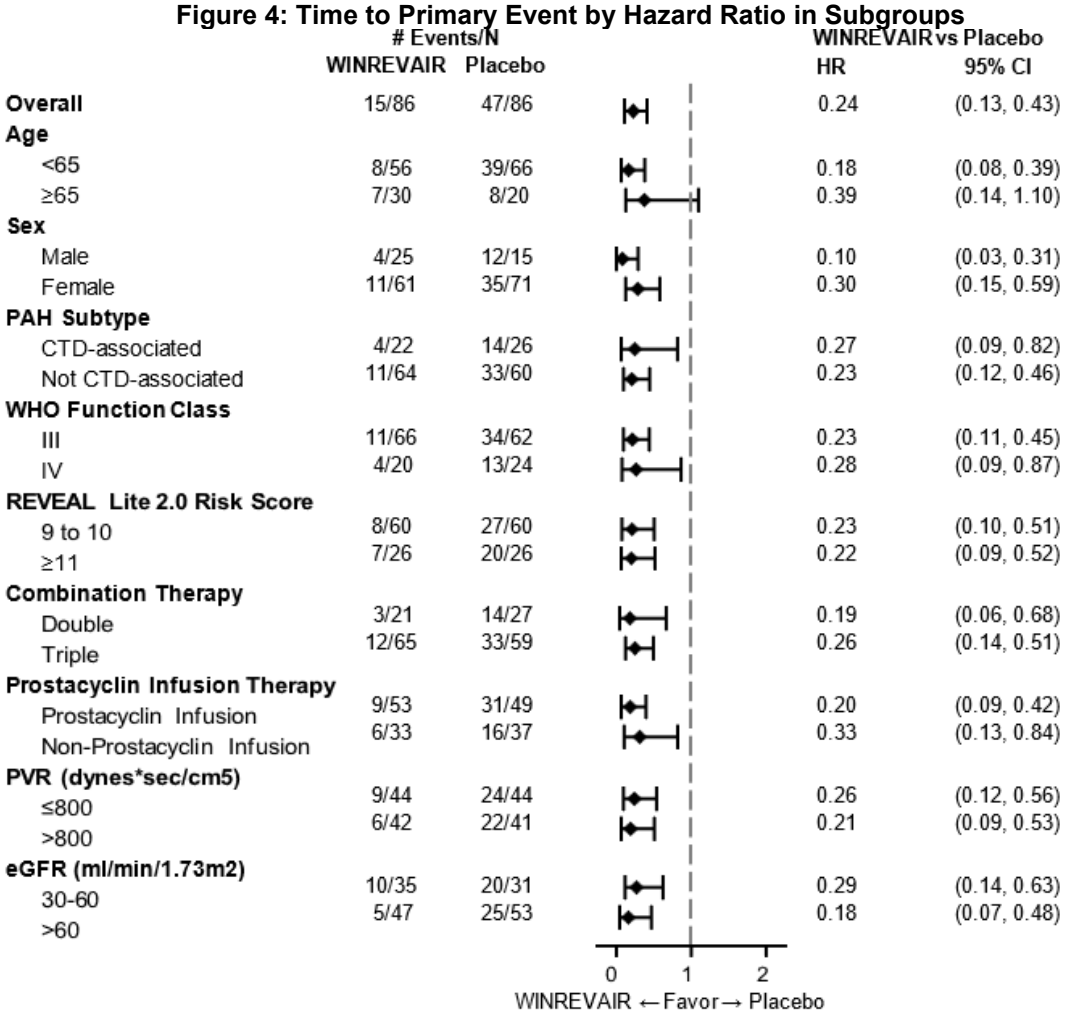
Figure 3: Time to First Event of All-cause Death, Lung Transplantation, or PAH Worsening-related Hospitalisation of ≥ 24 Hours Kaplan-Meier Plot



WINREVAIR (n)	86	82	79	61	51	40	28	21	13	9	5	1	0
Placebo (n)	86	74	59	38	28	23	15	10	5	2	1	0	0

n= Number of subjects at Risk

Figure 4: Time to Primary Event by Hazard Ratio in Subgroups



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

Based on the primary endpoint result, the study was stopped for favorable efficacy at the interim analysis. The primary analysis of the first secondary endpoint in the hierarchical testing strategy, 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 events were observed (7 events in the WINREVAIR treatment group and 13 events in the placebo group). The point estimate for the OS HR favored the WINREVAIR treatment group over the placebo group (HR: 0.42; 95% CI: 0.17, 1.07; p=0.0313), but the boundary for statistical significance at the interim analysis (p<0.0021) was not crossed. The Kaplan-Meier curves began to separate before Week 20 and remained separated for the remainder of the study (see Table 7 and Figure 5).

Results from the sensitivity analysis of OS, including all deaths up to the data cutoff, even those occurring after lung transplantation or enrollment in a long-term follow-up study, were consistent with results from the primary analysis.

The subsequent secondary endpoints were not eligible to be tested due to the hierarchical testing strategy (see Table 7).

Table 7: Secondary Endpoints

Endpoint*, †	WINREVAIR (N = 86)	Placebo (N = 86)
Overall Survival		
Number of Events (%)	7 (8.1)	13 (15.1)
Person-months	1020.6	769.1
Event Rate / 100 Person-months	0.7	1.7
Hazard ratio (95% CI)‡	0.42 (0.17 to 1.07)§	
Transplant-Free Survival		
Hazard ratio (95% CI)‡	0.34 (0.15 to 0.78)	
REVEAL Lite 2 risk score — unitless		
Median change estimate (min, max) from baseline at Week 24	-3.0 (-3, -2)	0.0 (0, 0)
Hodges-Lehmann location shift from placebo estimate (95% CI)¶, #, Þ	-3.1 (-4.3 to -1.9)	
REVEAL Lite 2 risk score — n/m (%)#		
Patients who achieved low or intermediate score (≤7) at Week 24 — no./total no. with REVEAL Lite 2 risk score >7 at baseline (%)	34/69 (49.3%)	11/72 (15.3%)
Between-group difference in proportions (95% CI)Þ	33.1% (18.4 to 47.0)	
NT-proBNP — pg/ml		
Median change estimate (min, max) from baseline at Week 24	-1233.0 (-1233, -1233)	255.4 (211, 263)
Hodges-Lehmann location shift from placebo estimate (95% CI)¶, Þ	-2339.1 (-3378.7 to -1299.4)	
Mean PAP — mm Hg		
Median change estimate (min, max) from baseline at Week 24	-13.6 (-14, -13)	5.5 (5, 6)
Hodges-Lehmann location shift from placebo estimate (95% CI)¶, Þ	-21.2 (-27.8 to -14.6)	
Pulmonary vascular resistance — dyn·sec·cm^{-5}		
Median change estimate (min, max) from baseline at Week 24	-156.6 (-160, -152)	46.6 (36, 104)
Hodges-Lehmann location shift from placebo estimate (95% CI)¶, Þ	-339.6 (-511.1 to -168.1)	
WHO-FC — n/m (%)		
Patients with improvement — no./total no. (%)	48/86 (55.8%)	24/86 (27.9%)
Between-group difference in proportions (95% CI)	27.4% (12.9 to 41.0)	
6-minute walk distance — m		
Median change estimate (min, max) from baseline at Week 24	45.4 (45.0, 46.0)	-5.4 (-9.5, -1.0)
Hodges-Lehmann location shift from placebo estimate (95% CI)¶, Þ	63.0 (23.2 to 102.7)	
Cardiac output — liters/min		
Median change estimate (min, max) from baseline at Week 24	-0.1 (-0.1, -0.1)	-0.4 (-0.4, -0.4)
Hodges-Lehmann location shift from placebo estimate (95% CI)¶, Þ	0.5 (-0.2 to 1.2)	
EQ-5D-5L™ Index Scoreß		
Median change estimate (min, max) from baseline at Week 24	0.060 (-1.020, 0.512)	0.007 (-0.358, 0.740)

* Except where noted otherwise, all analyses were conducted in the intention-to-treat population.

† Endpoints were statistically tested in the order presented in the table, whereby each endpoint was tested only if the previous end point achieved statistically significant superiority using a one-sided alpha level of 0.0021.

‡ Hazard ratio (sotatercept/placebo) was derived from a Cox proportional hazard regression model with treatment group as the covariate stratified by randomisation factors of REVEAL Lite 2 risk score (9-10 versus ≥11) and PAH subtype (CTD versus non-CTD). Analysis was based on the first adjudication-confirmed event prior to the interim analysis data-cutoff. Pre-cutoff deaths were included regardless of whether they occurred during or post-ZENITH, except for deaths occurring after lung transplantation or after rollover to SOTERIA.

§ P value = 0.0313, which did not meet the statistical criterion for superiority of sotatercept versus placebo at the interim analysis.

¶ Median of differences between all pairs of patients (with each pair consisting of one patient per treatment group).

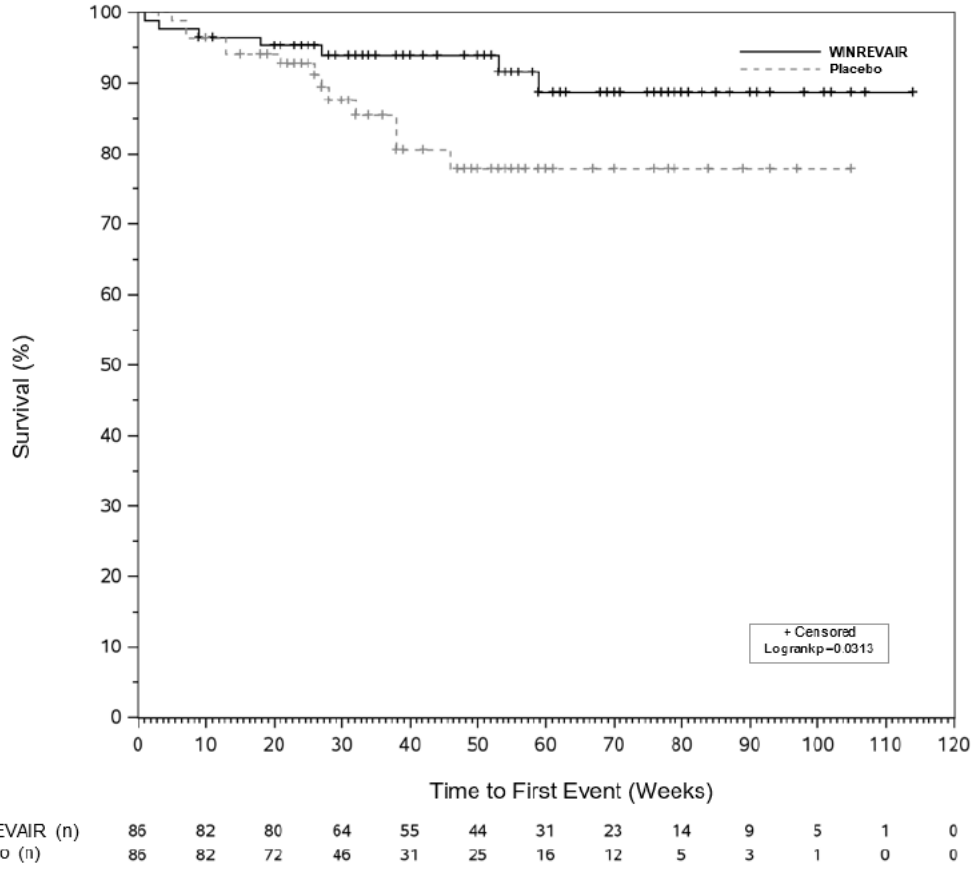
A higher REVEAL Lite 2 risk score indicates a greater risk of 1-year mortality. Patients with REVEAL Lite 2 risk score ≤7 at baseline were excluded from analysis.

Þ For endpoints associated with Week 24, only patients who were randomised more than 24 weeks prior to the interim analysis data-cutoff were included in the analysis.

ß EQ-5D-5L™ index score is a standardised measure of health-related quality of life, with higher scores indicating better overall health

status and well-being.
CTD: connective tissue disease; EQ-5D-5L: EuroQol 5-Dimension 5-Level Health Questionnaire; max: maximum; min: minimum; N: number of patients in the treatment group; no.: number of patients in the category; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PAP: pulmonary artery pressure; REVEAL: Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; WHO: World Health Organisation; WHO-FC: World Health Organisation functional class.

Figure 5: Overall Survival Kaplan-Meier Plot



n= Number of subjects at Risk

HYPERION

The efficacy of WINREVAIR was evaluated in adults with newly diagnosed PAH (WHO FC II or III, diagnosis within 12 months of study screening) at intermediate to high risk of disease progression in the HYPERION trial. HYPERION was a global, double-blind, placebo-controlled clinical trial in which 320 patients were randomized 1:1 to WINREVAIR (target dose 0.7 mg/kg) (n=160) or placebo (n=160) administered subcutaneously once every 3 weeks. HYPERION was stopped early based on the positive results from the interim analysis of the ZENITH trial and a review of the totality of data from the WINREVAIR clinical program.

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 60.0 years (range: 18 to 88 years); 86.3% of participants were White, and 76.6% were not Hispanic or Latino; and 72.5% were female. The most common PAH etiologies were idiopathic PAH (59.4%) and PAH associated with connective tissue diseases (CTD) (30.3%). The mean time since PAH diagnosis was 0.7 years (range: 0.1 to 1.2 years). All participants were on background standard of care therapy, with more participants on background PAH double therapy (72.2%) compared with triple therapy (27.8%), with a minority (16.6%) of participants on prostacyclin infusion therapy. There were more participants in WHO FC III (78.8%) compared with WHO FC II (21.3%). The REVEAL Lite 2 risk score was <6 for 20.6% of participants, 6 to 7 for 50.9% of participants, and ≥8 for 28.1% of participants. The COMPERA 2 risk score was low for 1.9% of participants, intermediate-low for 64.1% of participants, intermediate-high for 32.2% of participants, high for 1.6% of participants, and missing for 0.3% of participants. The HYPERION

trial excluded participants diagnosed with human immunodeficiency virus (HIV)-associated PAH, PAH associated with portal hypertension, schistosomiasis-associated PAH, pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis.

The primary efficacy endpoint was time to clinical worsening (TTCW), defined as the time to the first confirmed morbidity or mortality event. Events comprising this endpoint included all-cause death, non-planned PAH worsening-related hospitalization of ≥24 hours, atrial septostomy, lung transplantation, and deterioration in 6MWD from baseline combined with at least one of the following: worsening of WHO FC, signs/symptoms of increased right heart failure, or addition of a new background PAH therapy or change to a parenteral route of administration.

In the WINREVAIR treatment group, the risk of experiencing a first clinical worsening event was 76% lower compared with the placebo group (HR: 0.24; 95% CI: 0.14, 0.41; p<0.0001) (see Table 8). Fewer participants in the WINREVAIR group (17 [10.6%]) than in the placebo group (59 [36.9%]) had a primary endpoint event.

The low event rate in the WINREVAIR treatment group precluded estimation of the median TTCW; the median TTCW was 23.0 months (95% CI: 17.3, NR) in the placebo group. The Kaplan-Meier curves showed early separation beginning at approximately Week 5 and with increasing separation for the remainder of the study (see Figure 6). The treatment effect of WINREVAIR was consistent across the prespecified subgroups: age, sex, PAH subtype (idiopathic PAH, CTD-associated PAH), double versus triple background PAH therapy, WHO FC, prostacyclin infusion versus non prostacyclin infusion therapy, PVR, eGFR, REVEAL Lite 2 score, intermediate-low versus intermediate-high COMPERA 2 risk score.

Table 8: Components of the Primary Endpoint in HYPERION

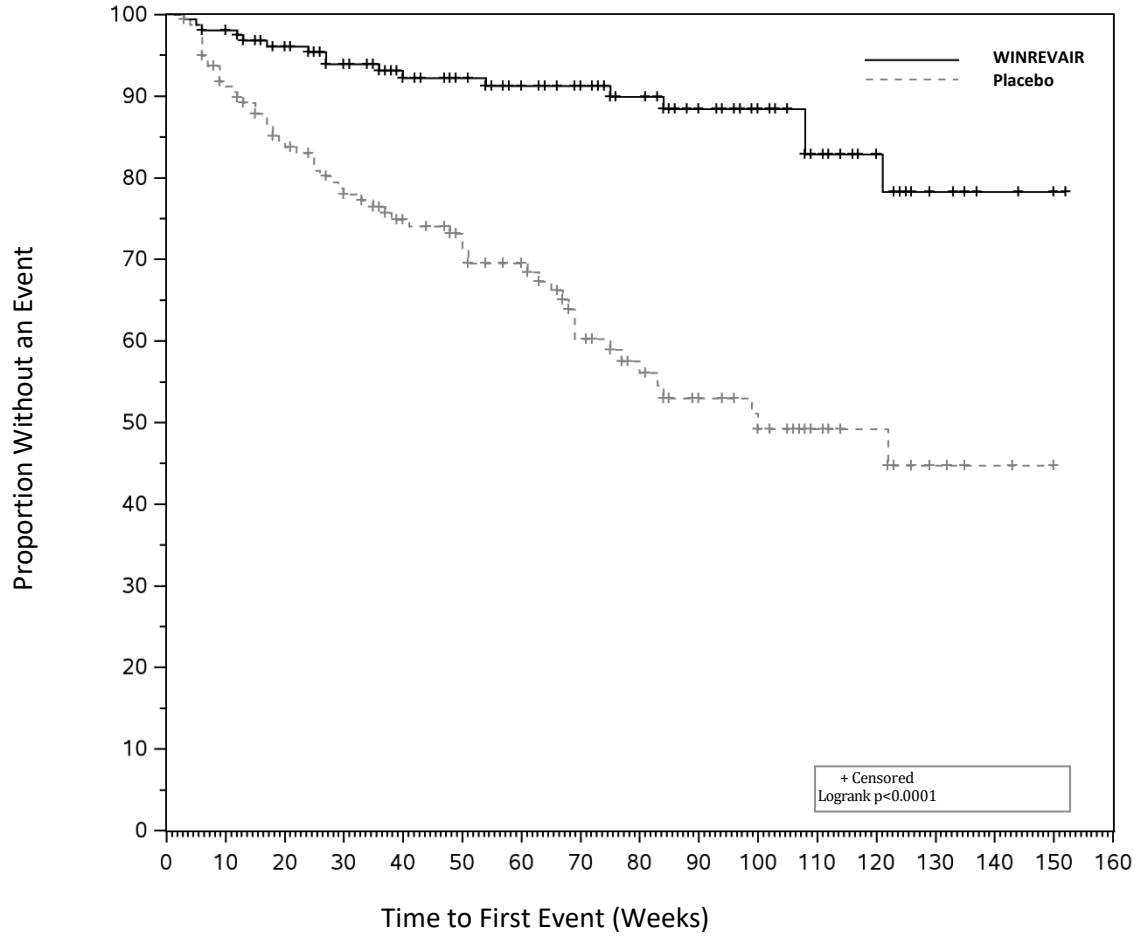
	WINREVAIR (N=160) n (%)	Placebo (N=160) n (%)	Hazard Ratio (95% CI) p-value
Number (%) of participants with ≥1 primary event during or post-HYPERION*	17 (10.6)	59 (36.9)	0.24 (0.14, 0.41) <0.0001
Components of the primary endpoint†			
All-cause death	7 (4.4)	6 (3.8)	
Non-planned PAH-related hospitalization of ≥24 hours	3 (1.9)	14 (8.8)	
Atrial septostomy	0	0	
Lung transplant	0	0	
Deterioration in performance in exercise due to PAH‡	8 (5.0)	46 (28.8)	

* The primary composite endpoint analysis includes the first occurrence of an adjudicated clinical worsening event. All deaths are included, regardless of adjudication and regardless of whether they occurred during or post-HYPERION, except for those occurring after 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.

‡ Defined as a decrease in 6MWD from the average of the screening on 2 consecutive tests (which must be at least 4 hours apart) and at least 1 of the following: worsening of WHO FC, signs/symptoms of increased right heart failure; or addition/change of a background PAH therapy.

Figure 6: Time to First Clinical Worsening Event in HYPERION Kaplan-Meier Plot



WINREVAIR (n)	160	152	138	125	109	95	87	75	63	53	40	26	21	10	4	2	0
Placebo (n)	160	142	122	107	92	80	70	50	40	31	27	16	11	5	2	1	0

n= Number of subjects at Risk

The secondary endpoints included improvements in multicomponent improvement (MCI), NT-proBNP, WHO FC, and 6MWD.

MCI was measured by the proportion of participants achieving all of the following at Week 24 relative to baseline: improvement in 6MWD (increase ≥30 m), improvement in 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. The proportion of participants who met all three MCI criteria was significantly greater in the WINREVAIR group (29.4%) than in the placebo group (14.6%) (p=0.0025). Additionally, the proportion of participants meeting each component of the MCI was higher in the WINREVAIR group compared with the placebo group. At week 24, the median treatment difference in 6MWD between the sotatercept and placebo groups was 21.4 m (95% CI: 4.65, 38.24). The median treatment difference in NT-proBNP between the sotatercept and placebo groups was -308.6 pg/mL (95% CI: -434.84, -182.37). Improvement in WHO FC from baseline occurred in 55.2% of patients in the sotatercept group versus 38.9% in the placebo group.

5.2 PHARMACOKINETIC PROPERTIES

In patients with PAH, in the phase 2 and phase 3 studies PULSAR, SPECTRA, and STELLAR, 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. For a typical patient weighing 70 kg (with a baseline albumin of 4.5g/dL), the accumulation

ratio of sotatercept AUC should be approximately 2.2. Sotatercept exposure in PAH participants in the phase 3 HYPERION study were consistent with the above data.

In the phase 3 ZENITH study, following subcutaneous administration of sotatercept at the dose of 0.7 mg/kg once every 3 week (Q3W), the geometric mean (%CV) steady-state AUC and steady-state peak concentration (Cmax) were 129.6 mcg*d/mL (44.9%) and 7.3 mcg/mL (42.5%CV), which were consistent with the above data, respectively.

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%).

Metabolism
Sotatercept is catabolised by general protein degradation processes.

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

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). Severe renal impairment (eGFR ranging from 15 to 30 mL/min/1.73m^2, n=3) had no impact on the PK of sotatercept. Additionally, sotatercept PK is comparable between non-PAH end-stage kidney disease (ESKD) patients (eGFR <15 mL/min/1.73m^2) and patients with normal renal function. WINREVAIR is not dialysable during haemodialysis. No dose adjustment is recommended for renally impaired patients. Limited data are available on the use of sotatercept 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 metabolised via cellular catabolism. Sotatercept has not been studied in PAH patients with hepatic impairment (Child-Pugh Classification A to C).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No data available. As a high molecular weight protein, sotatercept is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity
No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

45 mg single-use vial: citric acid monohydrate (0.48 mg), polysorbate 80 (0.22 mg), sucrose (88 mg), and sodium citrate dihydrate (2.56 mg).

60 mg single-use vial: citric acid monohydrate (0.64 mg), polysorbate 80 (0.29 mg), sucrose (116 mg), and sodium citrate dihydrate (3.37 mg).

The product does not contain antimicrobial preservative.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in Section 4.2 Dose and Method of Administration.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store vials refrigerated at 2°C to 8°C in original carton to protect from light. Do not freeze.

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

6.5 NATURE AND CONTENTS OF CONTAINER

WINREVAIR is a sterile, preservative-free, white to off-white lyophilised powder for injection available in 45 mg and 60 mg single-use vials.

The product is for single use in one patient only. Discard any residue.

WINREVAIR supplied in the following packaging configurations:

WINREVAIR 45 mg – carton containing 1 or 2 vials.
WINREVAIR 60 mg – carton containing 1 or 2 vials.

WINREVAIR 45 mg administration pack contains:

- 1 or 2 vials of powder for injection, 1 or 2 pre-filled syringes of sterile Water for Injections (1.0 mL each), 1 or 2 vial adaptors, 1 syringe for injection (3.0 mL), 1 needle, 4 or 8 alcohol wipes.

WINREVAIR 60 mg administration pack contains:

- 1 or 2 vials of powder for injection, 1 or 2 pre-filled syringes of sterile Water for Injections (1.3 mL each), 1 or 2 vial adaptors, 1 syringe for injection (3.0 mL), 1 needle, 4 or 8 alcohol wipes.

Not all presentations may be supplied.
None of the components contain natural rubber latex.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

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.

CAS number

1001080-50-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

8 November 2024

10 DATE OF REVISION

20 October 2026

Summary table of changes

Section changed	Summary of new information
All	Editorial changes
4.4	Updated information on *Serious Bleeding* and *Use in the Elderly*
4.8	Addition of HYPERION data Update to STELLAR data under *Immunogenicity*
5.1	Addition of HYPERION data
5.2	Addition of statement regarding HYPERION study

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