swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Winrevair

International non-proprietary name:	sotatercept
Pharmaceutical form:	powder and solvent for solution for injection
Dosage strength(s):	45 mg, 60 mg
Route(s) of administration:	subcutaneous use
Marketing authorisation holder:	MSD Merck Sharp & Dohme AG
Marketing authorisation no.:	69787
Decision and decision date:	approved on 05.02.2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DBPC	Double-blind placebo-controlled
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FC	Functional class
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
mPAP	Mean pulmonary artery pressure
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PAH	Pulmonary arterial hypertension
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
PVR	Pulmonary vascular resistance
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
WHO	World Health Organization

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA. Orphan drug status was granted on 11 October 2022.

2.2 Indication and dosage

2.2.1 Requested indication

Winrevair, in combination with standard pulmonary arterial hypertension (PAH) therapy, is indicated for long-term treatment of PAH in adult patients with WHO functional class (FC) II, III, and IV (see "Clinical efficacy").

2.2.2 Approved indication

Winrevair, in combination with standard pulmonary arterial hypertension (PAH) therapy, is indicated for the long-term treatment of PAH in adult patients with WHO functional class (FC) II, III, and IV (see "Warnings and precautions" and "Clinical efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	18 June 2025
Formal control completed	19 June 2025
List of Questions (LoQ)	19 August 2025
Response to LoQ	15 October 2025
Preliminary decision	2 December 2025
Response to preliminary decision	8 January 2026
Final decision	5 February 2026
Decision	approval

3 Medical context

Pulmonary arterial hypertension (PAH) is a debilitating disease leading to progressive limitations in exercise capacities, failure of the right ventricle (RV), and premature death. Sotatercept acts as a ligand trap for so-called activins and other growth-differentiation factors involved in vascular remodelling, a key feature in the pathobiology of PAH. Hitherto, its use has been limited to patients in WHO functional classes (FC) II and III. The present application extends sotatercept's use to patients in WHC FC IV while cancelling prior restrictions by PAH aetiology.

4 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable. Since sotatercept is a protein, the extension of the indication will not be associated with a significant risk for the environment.

5 Clinical aspects

5.1 Clinical pharmacology

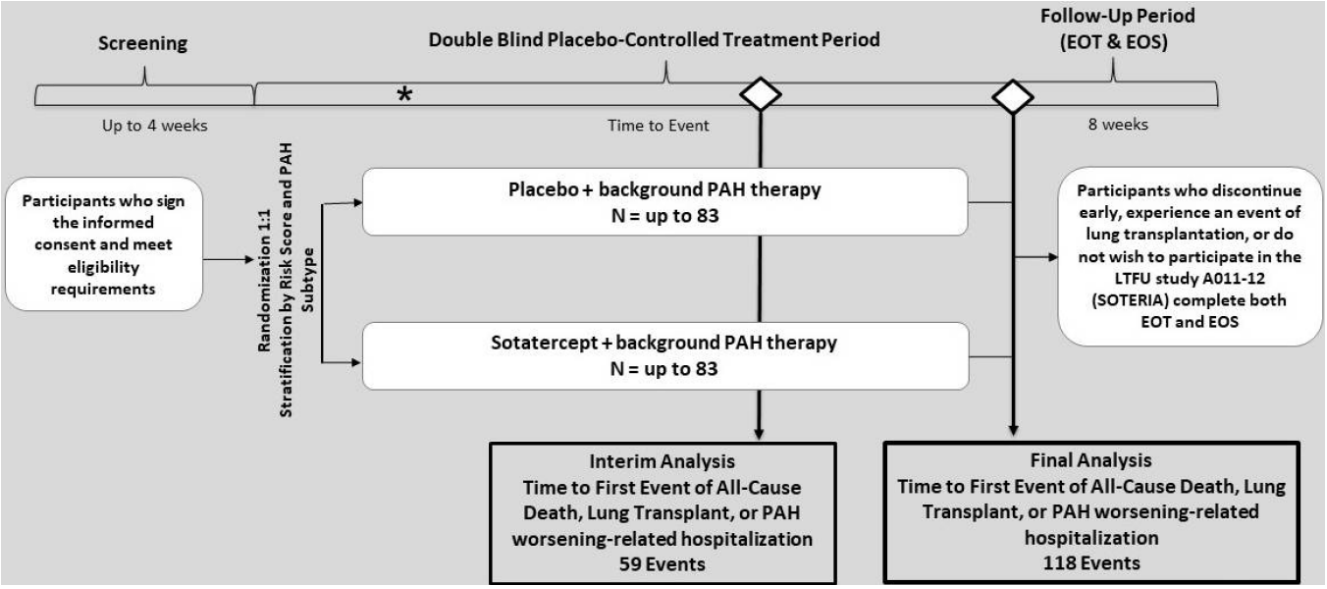
This application for an extension of the indication was based on PK data of sotatercept collected in patients with pulmonary arterial hypertension Class III and IV enrolled in ZENITH. A PopPK analysis was performed to compare the PK of sotatercept between participants with PAH class III and II and participants with PAH class III and IV. SC administration of a starting dose of 0.3 mg/kg followed by a target dose of 0.7 mg/kg Q3W sotatercept in patients with PAH class III or IV (ZENITH) resulted in exposures similar with those observed in patients with PAH class II or III (PULSAR, SPECTRA, and STELLAR). For details, refer to the Information for healthcare professionals.

5.2 Dose finding and dose recommendation

The dosing scheme of sotatercept (starting dose of 0.3 mg/kg sc followed by a target dose of 0.7 mg/kg Q3W sc) in patients with pulmonary arterial hypertension, World Health Organization functional class IV (PAH WHO FC IV) resulted in exposures similar to those observed in patients with PAH class II or III.

5.3 Efficacy

The new indication is supported by data from the ZENITH trial, a global, Phase 3, randomised, double-blind, placebo-controlled study investigating the treatment effect of sotatercept in patients with advanced PAH (WHO FC III – IV). The trial consisted of a screening period (up to 4 weeks) followed by a double-blind placebo-controlled (DBPC) treatment period.



The major treatment benefit is a marked delay (reduction in the incidence) of first “disease worsening” events (composite primary endpoint: all-cause death, lung transplantation, or PAH worsening-related hospitalisation of ≥24 h duration).

	Sotatercept (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 primary endpoint events[a]			
All-cause death[b]	7 (8.1)	13 (15.1)	
Lung transplantation	1 (1.2)	6 (7.0)	
PAH worsening-related hospitalization of ≥ 24 hours	8 (9.3)	43 (50.0)	

Sotatercept treatment was also associated with numerical or statistically significant improvement of the secondary endpoints, including overall survival, transplant-free survival, 6-minute walk distance (6MWD), and important pathophysiologic surrogates such as mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), the REVEAL Lite 2.0 risk score, and change in WHO FC.

Secondary Endpoint	Sotatercept Group	Placebo Group	Comparison vs. Placebo (HR, Difference, or Hodges-Lehmann Location Shift, 95% CI)
Overall Survival (OS)	7 events (8.1%)	13 events (15.1%)	HR: 0.42 (95% CI: 0.17, 1.07)
Transplant-Free Survival	8 events (9.3%)	19 events (22.1%)	HR: 0.34 (95% CI: 0.15, 0.78)
Mortality Event at End of Study (EOS)	7 events (8.1%)	13 events (15.1%)	Difference: -7.29% (95% CI: -17.65, 2.41)
6-Minute Walk Distance (6MWD)	Median change: +45.39 m	Median change: -5.36 m	Hodges-Lehmann shift: +63.0 m (95% CI: 23.22, 102.73)
Mean Pulmonary Artery Pressure (mPAP)	Median change: -13.6 mmHg	Median change: +5.5 mmHg	Hodges-Lehmann shift: -21.2 mmHg (95% CI: -27.78, -14.59)
Pulmonary Vascular Resistance (PVR)	Median change: -156.6 dynes*sec/cm^5	Median change: +46.6 dynes*sec/cm^5	Hodges-Lehmann shift: -339.6 dynes*sec/cm^5 (95% CI: -511.09, -168.06)
Cardiac Output (CO)	Median change: -0.10 L/min	Median change: -0.38 L/min	Hodges-Lehmann shift: +0.5 L/min (95% CI: -0.18, 1.16)
REVEAL Lite 2.0 Risk Score	Median change: -2.9	Median change: 0.0	Hodges-Lehmann shift: -3.0 (95% CI: -4.10, -1.91)
WHO Functional Class (FC) Improvement	48 participants (55.8%) improved	24 participants (27.9%) improved	Difference: 27.41% (95% CI: 12.85, 40.98)

Sensitivity analyses support the robustness of this finding, and subgroup analyses for the primary endpoint revealed no heterogeneity.

5.4 Safety

The ZENITH trial confirmed the known safety profile of sotatercept in patients with PAH WHO FC III – IV. All safety concerns originating from the ZENITH trial are already covered adequately in the Swiss Information for healthcare professionals.

The most common and/or relevant AEs related to sotatercept treatment include increased haemoglobin, telangiectasia, and bleeding events (primarily epistaxis). There was no clinically meaningful impact (either on safety or efficacy) of the observed immunogenicity. It was concluded that leukopenia, neutropenia, hepatic toxicity, and renal toxicity do not represent significant safety concerns.

5.5 Final clinical benefit-risk assessment

The benefit-risk ratio can be considered positive.

For further details concerning efficacy and safety, please see the Appendix of this report.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Winrevair was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reaction. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

Winrevair®

Composition

Active substances

Sotatercept

Excipients

Citric acid monohydrate (E330), Trisodium citrate dihydrate (E331), Polysorbate 80 (E433), Sucrose.

Each ml of the reconstituted solution contains 0.55 mg sodium.

Pharmaceutical form and active substance quantity per unit

Powder and solvent for solution for injection.

Powder: white to off-white lyophilised powder.

Solvent: water for injection.

A vial with powder for solution for injection contains 45 mg and 60 mg of sotatercept, respectively.

After reconstitution of a 45 mg sotatercept single-dose vial, the resulting concentration is 50 mg/mL of sotatercept. The nominal deliverable volume is 0.9 mL. For subcutaneous injection. After reconstitution of a 60 mg sotatercept single-dose vial, the resulting concentration is 50 mg/mL of sotatercept. The nominal deliverable volume is 1.2 mL. For subcutaneous injection.

Indications/Uses

Winrevair, in combination with standard pulmonary arterial hypertension (PAH) therapy, is indicated for the long term treatment of PAH in adult patients with WHO Functional Class (FC) II, III, and IV (see “Warnings and precautions” and "Clinical efficacy").

Dosage/Administration

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

Posology

Recommended starting dosage in Adults

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

Obtain hemoglobin (Hgb) and platelet count prior to the first dose of Winrevair. In patients with a platelet count of <50,000/mm^3 (<50,0 x 10^9/L) no treatment with WINREVAIR should be initiated (see “Dosage/Administration”, “Dosage Modification in Adults due to Hemoglobin Increase or Platelet Count Decrease”). Rapid increases in Hgb of more than 2 g/dL have been observed after initiating treatment.

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

Patient Weight Range (kg)*	Injection Volume (mL)	Kit Type
30.0 – 40.8	0.2	45 mg kit (containing 1 x 45 mg vial)
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 kit (containing 1 x 60 mg vial)
174.2 – 180.0	1.1	

Recommended Target Dosage in Adults

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

Obtain and review hemoglobin (Hgb) and platelet count prior to increasing to the target dose. Continue treatment at 0.7 mg/kg every 3 weeks unless dosage adjustments are required (see "Dosage/Administration", "Dosage modifications due to haemoglobin increase and platelet count decrease").

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

Patient Weight Range (kg)*	Injection Volume (mL)	Kit Type
30.0 – 31.7	0.4	45 mg kit (containing 1 x 45 mg vial)
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 kit (containing 1 x 60 mg vial)
74.7 – 81.7	1.1	
81.8 – 88.9	1.2	
89.0 – 96.0	1.3	90 mg kit (containing 2 x 45 mg vials)
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 kit (containing 2 x 60 mg vials)
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	

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

Increases in Hgb to levels greater than 2 g/dL above the upper limit of normal (ULN) and decreases in platelet count <50,000/mm^3 (<50.0 x 10^9/L) have been observed. Check Hgb and

platelet count before each dose for the first 5 doses, or longer if values are unstable. Thereafter, monitor Hgb and platelet count regularly. Consider the benefit-risk ratio for the individual patient in determining whether dose modification is appropriate (see “Warnings and Precautions”, “Erythrocytosis”, “Severe Thrombocytopenia”).

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

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

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

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 taken within 3 days of the scheduled date, adjust the schedule to maintain 3-week dosing intervals. In case of an overdose or underdose, consider retraining the patient or caregiver on proper administration as appropriate. In case of an overdose, monitor for erythrocytosis (see “Overdose”).

Special patient groups

Patients with hepatic impairment

Winrevair use has not been studied in patients with hepatic impairment (Child-Pugh Classification A to C). Hepatic impairment is not expected to influence sotatercept metabolism since sotatercept is metabolized via cellular catabolism (see “Pharmacokinetics”).

Patients with 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 “Pharmacokinetics”).

Geriatric patients

No dose adjustment of Winrevair is required based on age (see “Pharmacokinetics”).

Paediatric patients

Safety and efficacy of Winrevair have not been demonstrated in patients less than 18 years of age.

Mode of administration

Winrevair should be reconstituted before use and administered by subcutaneous injection in the abdomen (at least 5 cm away from navel), upper arm, or upper thigh.
Winrevair kit is intended for use under the guidance of a healthcare professional (HCP).
Patients and caregivers may administer Winrevair when considered appropriate and when they receive training and follow-up from the HCP in how to reconstitute prepare, measure and inject Winrevair. Refer to the “Other information/Instruction for handling” and the *Instructions for Use* (IFU) for the kit for detailed instructions on the proper preparation and administration of 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 kit
- if the patient develops erythrocytosis (see “Warnings and Precautions”, “Erythrocytosis”)

Selecting the appropriate product kit
If a patient’s weight requires the use of two 45 mg or two 60 mg vials of lyophilised product, a 2-vial kit should be used 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 dose and also eliminates the need for multiple injections (see “Other information/Instruction for handling”).
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in “Composition”.

Warnings and precautions

Erythrocytosis
Hgb increases have been observed in patients during treatment with Winrevair. Severe erythrocytosis may increase the risk of thromboembolic events or hyperviscosity syndrome. Monitor Hgb before each dose for the first 5 doses, or longer if values are unstable, and periodically thereafter to determine if dose adjustments are required (see “Dosage/Administration”, “Dosage Modifications in Adults Due to Hemoglobin Increase or Platelet Count Decrease” and “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/mm^3 (<50 x 10^9/L) (see “Dosage /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 “Dosage/Administration”, “Modifications in Adults Due to Hemoglobin Increase or Platelet Count Decrease” and “Undesirable effects”).

Serious Bleedings

In clinical studies, serious bleeding events (e.g., gastrointestinal, intracranial hemorrhage) were reported in 4% of patients taking Winrevair and 1% of patients taking placebo. Patients with serious bleeding events were more likely to be on prostacyclin background therapy and/or antithrombotic agents, or have low platelet counts. Advise patients about signs and symptoms of blood loss. Evaluate and treat bleeding accordingly. Do not administer Winrevair if the patient is experiencing a serious bleeding event (see “Warnings and precautions/Severe Thrombocytopenia“ and “Undesirable effects”).

Embryo-Fetal Toxicity

Based on findings in animal reproduction studies, Winrevair may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with Winrevair and for at least 4 months after the final dose (see “Pregnancy, lactation”, “Pregnancy” and “Preclinical data/Reproductive toxicity”).

Impaired Fertility

Based on findings in animals, Winrevair may impair female and male fertility. Advise patients on the potential effects on fertility (see “Pregnancy, lactation/Fertility” and “Preclinical data/Reproductive toxicity”).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium free’.

Limitation of the clinical data

The clinical studies did not include participants with human immunodeficiency virus (HIV)-, portal hypertension-, schistosomiasis-, or pulmonary veno occlusive disease (PVOD)-associated PAH.

Interactions

No interaction studies have been performed.

Pregnancy, lactation

Women of childbearing potential/Contraception in females

Pregnancy testing is recommended for women of childbearing potential before starting treatment with Winrevair. Women of childbearing potential should use effective contraception during treatment with Winreviar and for ≥4 months after the last dose (end of treatment) (see “Preclinical data”).

Pregnancy

There are no data from the use of sotatercept in pregnant women. Studies in animals have shown reproductive toxicity (see “Preclinical data”).

Winrevair is not recommended during pregnancy and in women of childbearing potential not using contraception.

Clinical Considerations

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

Lactation

It is unknown whether sotatercept/metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with Winrevair and restarted 4 months after the last dose of treatment.

Fertility

Based on findings in animals, sotatercept may impair female and male fertility (see “Preclinical data”).

Effects on ability to drive and use machines

Sotatercept has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of safety profile

The most frequently reported adverse reactions in either STELLAR or ZENITH were epistaxis (45.3%), headache (26.7%), telangiectasia (25.6%), diarrhoea (25.6%), increased haemoglobin

(15.1%), thrombocytopenia (15.1%), dizziness (14.7%), rash (12.3%), and gingival bleeding (10.5%).
The most frequently reported serious adverse reactions were thrombocytopenia (<1.2%), epistaxis (<1.2%) and dizziness (<1.2%).
The most common adverse reaction leading to discontinuation were epistaxis and telangiectasia.

Tabulated list of adverse reactions

The safety of Winrevair was evaluated in the pivotal placebo-controlled studies STELLAR and ZENITH, which included 163 and 86 patients with PAH treated with Winrevair, respectively (see "Properties/Effects/Clinical efficacy"). The median duration of treatment with Winrevair was 313 days in STELLAR and 434.5 days in ZENITH.

Table 3 shows the adverse reactions reported with Winrevair in placebo-controlled clinical studies and post-marketing surveillance. These are listed by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), and very rare (<1/10,000), and not known (cannot be estimated from available post-marketing data).

Table 3: Adverse reactions

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Very common	Thrombocytopenia[1,2] Increased haemoglobin[1]
Nervous system disorders	Very common	Dizziness Headache
Respiratory, thoracic and mediastinal disorders	Very common	Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea Gingival bleeding[3]
Skin and subcutaneous tissue disorders	Very common	Telangiectasia[1] Rash
	Common	Erythema
Investigations	Common	Increased blood pressure[1,4]

[1] See description of selected adverse reactions
[2] Includes 'thrombocytopenia' and 'platelet count decreased'
[3] The frequency category is based on ZENITH
[4] Includes 'hypertension', 'blood pressure diastolic increased' and 'blood pressure increased'

Description of specific adverse reactions and additional information

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

- Erythrocytosis (see "Warnings and precautions/Erythrocytosis")
- Severe Thrombocytopenia (see "Warnings and precautions/Severe Thrombocytopenia")
- Serious Bleedings (see "Warnings and precautions/Serious Bleedings")
- Embryo-Fetal Toxicity (see "Warnings and precautions/Embryo-Fetal Toxicity")
- Impaired Fertility (see "Warnings and precautions/Impaired Fertility")

Increased Hemoglobin

The majority of events of increased Hgb (Hgb increased, polycythemia) were non-serious, mild, and reversible, and were not associated with discontinuation of therapy. Moderate elevations in Hgb (>2 g/dL above ULN) occurred in 15.3% of patients taking Winrevair. No severe elevations (≥4 g/dL above ULN) were observed. The extent of Hgb increase was 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 Wiinrevair, 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.

Long-term Safety Data

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

The mean duration of exposure to Winrevair in PULSAR and the long-term follow-up study was 151 weeks, with a maximum exposure of 218 weeks. The safety profile was generally similar to that observed in the pivotal STELLAR study. However, telangiectasia was not observed during the double-blind, placebo-controlled treatment period in PULSAR. Telangiectasia was first reported in the open-label extension, occurring in 27% of patients at study completion, with a median time to onset of 106 weeks.

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 hemodynamics.

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 neutralizing antibodies against sotatercept. Anti-sotatercept antibodies generally had low titers with a median titer of 30 (range <20 to 640).

During the ZENITH study with a median sotatercept treatment duration of 322.0 days, 33 of 84 evaluable (39%) patients developed anti-sotatercept antibodies. Among these 33 patients, 16 (48%) tested positive for neutralizing antibodies against sotatercept. Anti-sotatercept antibodies generally had low titers with a median titer of 10 (range 10 to 320).

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

Elderly population

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.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reaction online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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 dialyzable during hemodialysis.

Properties/Effects

ATC code

C02KX06

Mechanism of action

Sotatercept, a recombinant activin receptor type IIA-Fc (ActRIIA-Fc) fusion protein, is an activin signaling inhibitor that binds to activin A and other TGF- β superfamily ligands. As a result, sotatercept improves the balance between the pro-proliferative (ActRIIA/Smad2/3-mediated) and anti-proliferative (BMPRII/Smad1/5/8-mediated) signaling to modulate vascular proliferation.

Pharmacodynamics

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

compared with the placebo group (see “Clinical efficacy”). 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 “Clinical efficacy”).
In rat models of PAH, a sotatercept analog reduced expression of pro-inflammatory markers at the pulmonary arterial wall, reduced leukocyte recruitment, inhibited proliferation of endothelial and smooth muscle cells, and promoted apoptosis in diseased vasculature. These cellular changes were associated with thinner vessel walls, reversed arterial and right ventricular remodeling, and improved hemodynamics.

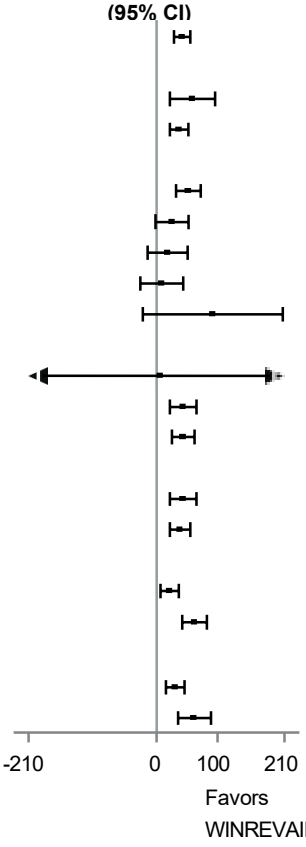
Clinical efficacy

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 randomized 1:1 to Winrevair (target dose 0.7 mg/kg) (n=163) or placebo (n=160) administered subcutaneously once every 3 weeks. The demographic and baseline clinical characteristics were generally comparable between the Winrevair and placebo groups. Participants in this study were adults with a median age of 48.0 years (range: 18 to 82 years); median weight 68 kg (range: 38.0 to 141.3 kg); 89.2% of participants were White, and 79.3% were not Hispanic or Latino; and 79.3% were female. The most common PAH etiologies were idiopathic PAH (58.5%), heritable PAH (18.3%), and PAH associated with connective tissue diseases (CTD) (14.9%). The mean time since PAH diagnosis to screening was 8.76 years. Most participants were receiving either triple (61.3%) or double (34.7%) background PAH therapy, and more than one-third (39.9%) were receiving prostacyclin infusions. The proportions of participants in WHO FC II (48.6%) and WHO FC III (51.4%) were similar in both groups. The STELLAR trial excluded patients diagnosed with human immunodeficiency virus (HIV)-associated PAH, PAH associated with portal hypertension, schistosomiasis-associated PAH, and pulmonary veno occlusive disease.
The primary efficacy endpoint was the change from baseline at Week 24 in 6-Minute Walk Distance (6MWD). In the Winrevair treatment group, the median of the placebo-adjusted change in 6MWD from baseline at Week 24 was 40.8 meters (95% CI: 27.5, 54.1; p <0.001). The median of the placebo-adjusted changes in 6MWD at Week 24 were also evaluated in subgroups (see Figure 1).

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

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



CHD = Congenital heart disease

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

Clinical improvement was 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 included worsening-related listing for lung and/or heart transplant, need to initiate rescue therapy with an approved background PAH therapy or the need to increase the

dose of infusion prostacyclin by ≥10%, need for atrial septostomy, hospitalization for worsening PAH (≥24 hours), or deterioration of PAH (worsened WHO FC and decrease in 6MWD ≥15% with both events occurring at the same time or different times). Clinical worsening events and death were captured until the last patient completed the week 24 visit (data up to the data cutoff; median duration of exposure 33.6 weeks).

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

At Week 24, 38.9% of sotaterceptttreated patients showed improvement in MCI versus 10.1% in the placebo group (p <0.001). The median treatment difference in PVR between sotatercept and placebo group was -234.6 dyn*sec/cm^5 (95% CI: -288.4, -180.8; p <0.001). The median treatment difference in NT-proBNP between the sotatercept and placebo groups was -441.6 pg/mL (95% CI: -573.54, -309.61; p <0.001). Improvement in functional class from baseline occurred in 29% of patients in the sotaterceptgroup versus 13.8% in the placebo group (p <0.001).

Table 4: Death or Clinical Worsening Events

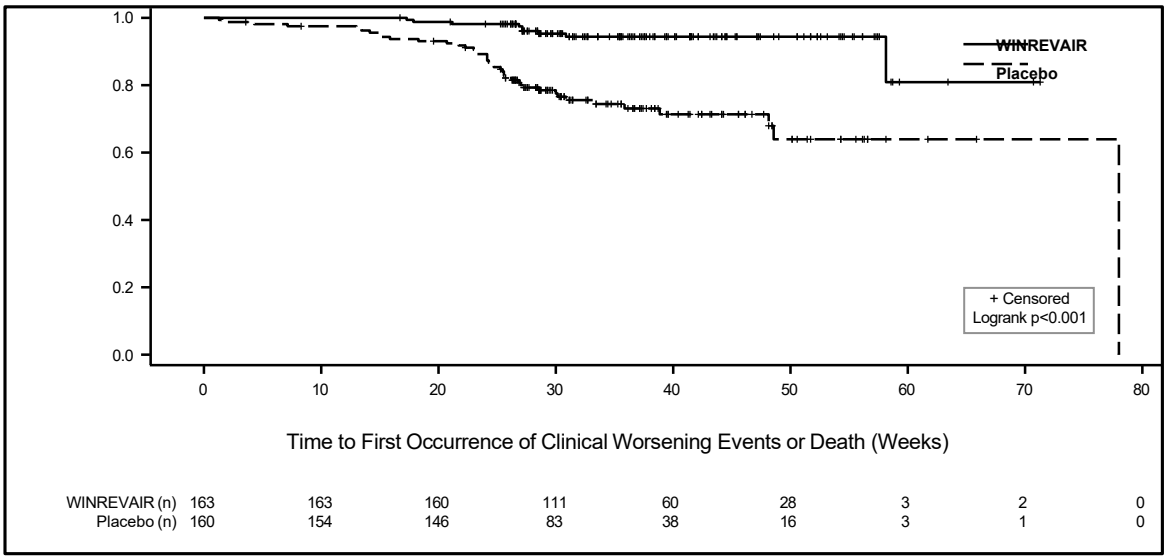
	Winrevair (N=163)	Placebo (N=160)
Total number of subjects who experienced death or at least one clinical worsening event, n (%)	9 (5.5)	42 (26.3)
Assessment of death or first occurrence of clinical worsening events*, n (%)		
Death	2 (1.2)	6 (3.8)
Worsening-related listing for lung and/or heart transplant	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 hospitalization (≥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 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 randomized 1:1 to WINREVAIR (target dose 0.7 mg/kg) (n=86) or placebo (n=86) 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. At the start of the trial, 72.1% and 27.9% of patients were already receiving a triple or a double combination as PAH background therapy, and 59.3% of participants were receiving a prostacyclin infusion therapy. There were 74.4% of the participants in WHO FC III and 25.6% in WHO FC IV. 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 a composite endpoint, i.e., until (i) all-cause death, (ii) lung transplantation, or (iii) PAH worsening-related hospitalization of ≥24 hours. WINREVAIR reduced the risk for the primary endpoint versus placebo by 76% (HR: 0.24; 95% CI: 0.13; 0.43; p<0,0001) (see table 5). 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 5: Components of the Primary Endpoint

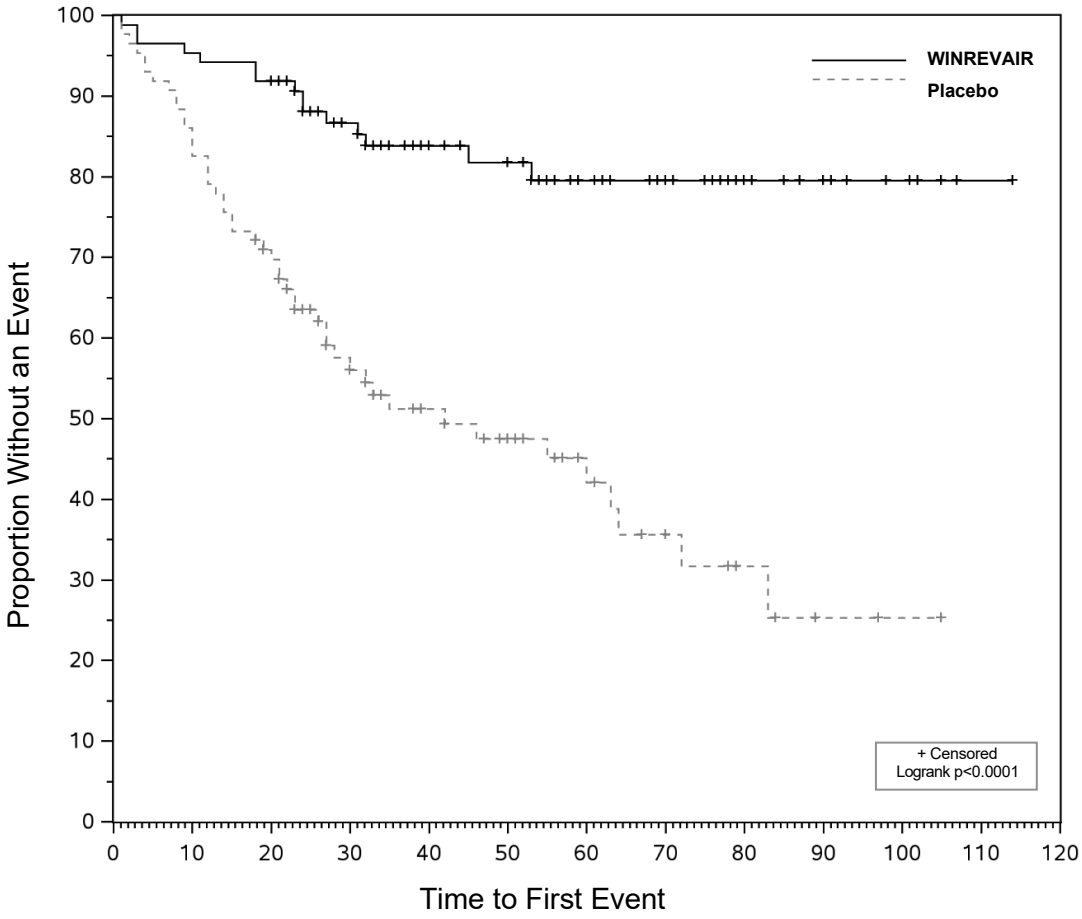
	WINREVAIR (N=86) n (%)	Placebo (N=86) n (%)	Hazard Ratio (95% CI) p-value*
Number (%) of participants with ≥ 1 primary event during or post ZENITH	15 (17.4)	47 (54.7)	0.24 (0.13, 0.43) <0.0001
Components of the primary endpoint†			
All-cause death‡	7 (8.1)	13 (15.1)	
Lung transplantation	1 (1.2)	6 (7.0)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

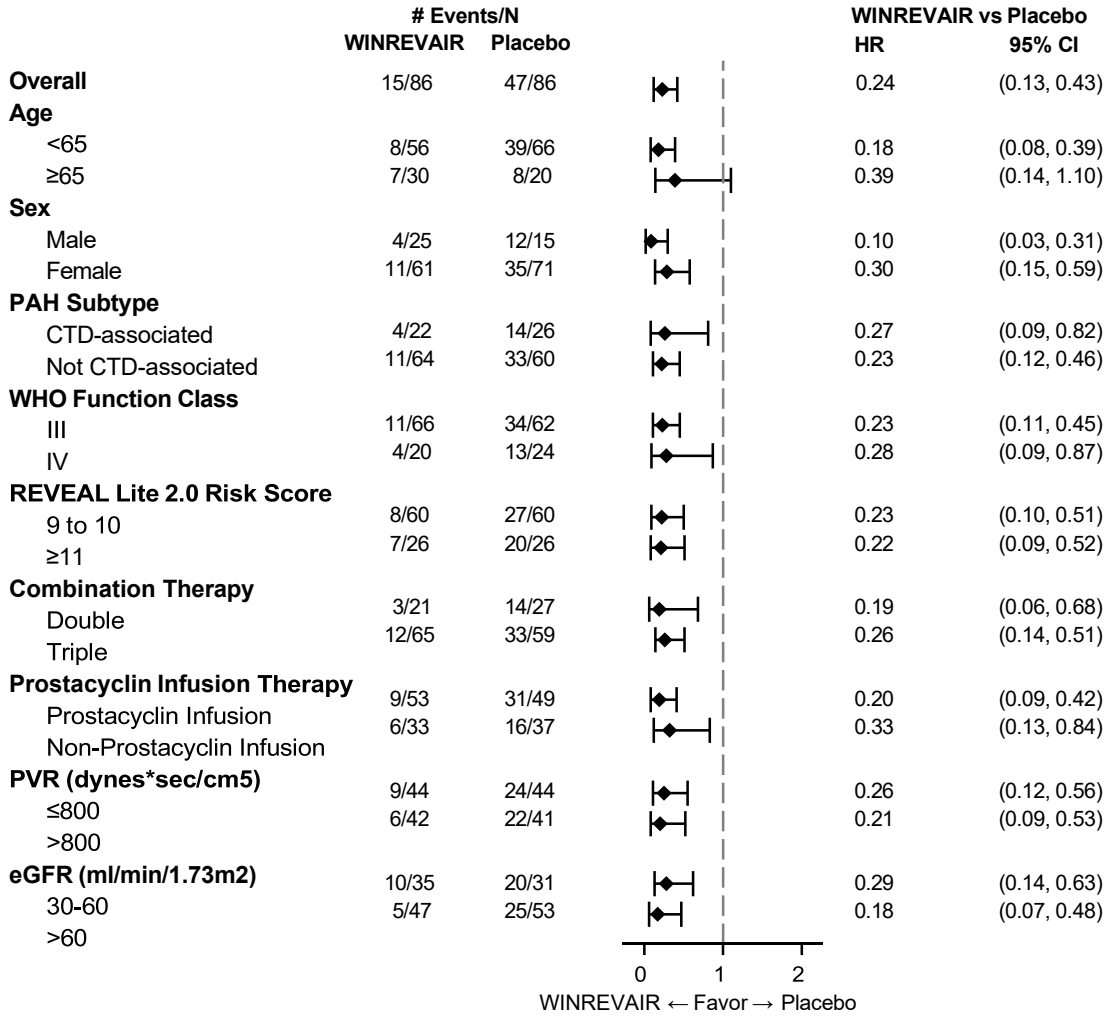
Figure 3: Time to First Event of All-cause Death, Lung Transplantation, or PAH Worsening-related Hospitalization of ≥ 24 Hours Kaplan-Meier Plot



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.

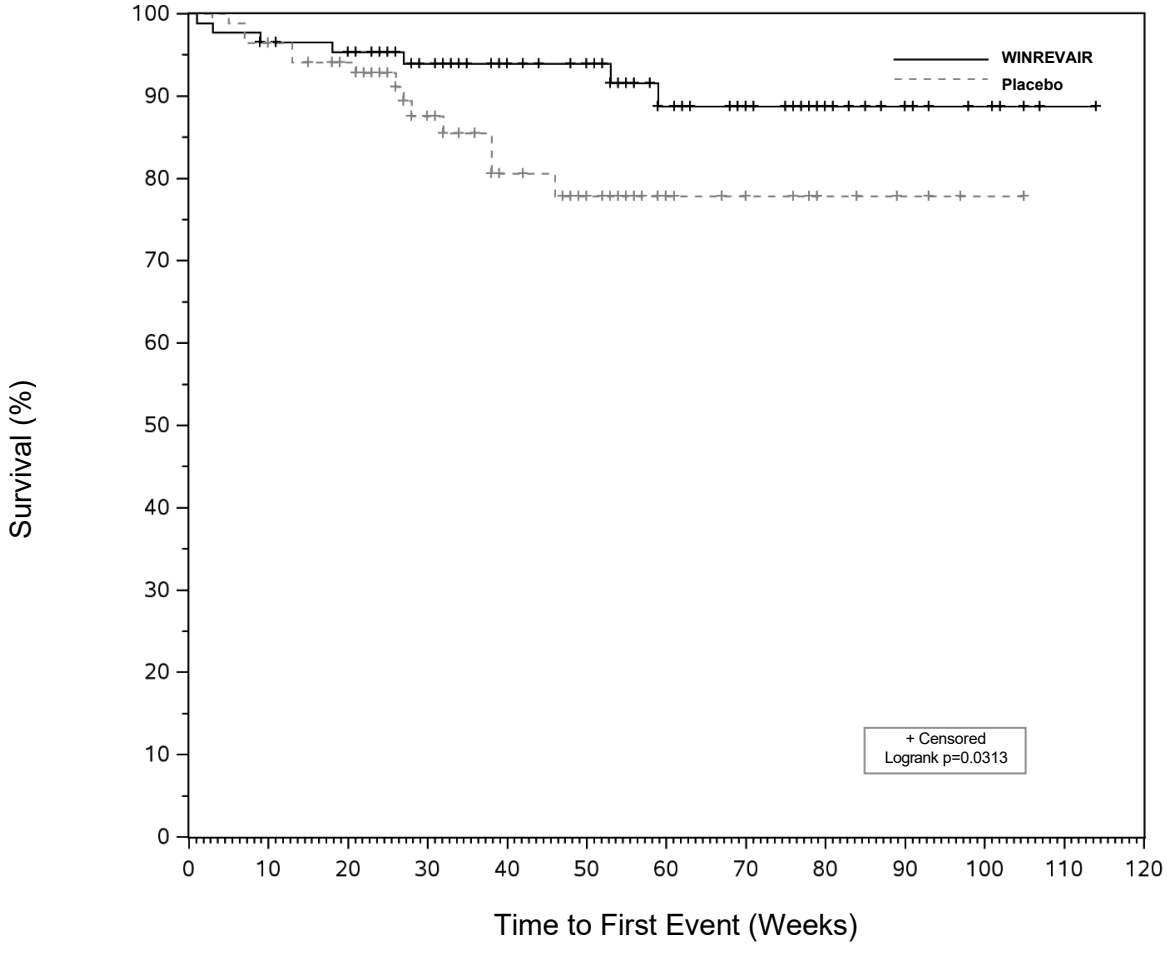
According to prespecified criteria the study was stopped for favorable efficacy of the primary endpoint at the interim analysis. The primary analysis of the first secondary endpoint in the hierarchical testing strategy, overall survival (OS), included all deaths up to the data cutoff, except for those 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 statistical significance at the interim analysis (p<0.0021) was not reached. The Kaplan-Meier curves began to separate before Week 20 and remained separated for the remainder of the study (see Figure 5).

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

Other secondary endpoints included improvements in transplant-free survival, NT-proBNP, mean pulmonary arterial pressure (PAP), PVR, 6MWD, cardiac output, and WHO FC.

At Week 24, the point estimate for the transplant-free survival favoured the WINREVAIR treatment group over the placebo group (HR: 0.42; 95% CI: 0.17, 1.07). The median treatment difference in NT-proBNP between the WINREVAIR and placebo groups was 2339.1 pg/mL (95% CI: 3378.7 to 1299.4). The median treatment difference in mean PAP between the WINREVAIR and placebo groups was 21.2 mm Hg (95% CI: 27.8 to 14.6). The median treatment difference in PVR between the WINREVAIR and placebo groups was 339.6 dyn*sec/cm5 (95% CI: 511.1 to 168.1). The median treatment difference in 6MWD between the WINREVAIR and placebo groups was 63 m (95% CI: 23.2 to 102.7). The median treatment difference in cardiac output between the WINREVAIR and placebo groups was 0.5 L/min (95% CI: 0.2 to 1.2). Improvement in WHO FC from baseline occurred in 55.8% of patients in WINREVAIR versus 27.9% in placebo.

Figure 5: Overall Survival Kaplan-Meier Plot



WINREVAIR (n)	86	82	80	64	55	44	31	23	14	9	5	1	0
Placebo (n)	86	82	72	46	31	25	16	12	5	3	1	0	0

n= Number of subjects at Risk

Pharmacokinetics

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. After administration of subcutaneous single doses between 0.1 mg/kg and 1.0 mg/kg, sotatercept AUC and C_{max} increase proportionally with dose. Steady state is achieved after approximately 15 weeks upon multiple Q3W dosing. The accumulation ratio of sotatercept AUC was approximately 2.2. Sotatercept exposure in PAH participants in the phase 3 ZENITH study were consistent with the above data.

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 catabolized 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%).

Kinetics in specific patient groups

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

Hepatic impairment

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

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 dialyzable during hemodialysis. 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).

Preclinical data

Repeated dose toxicity

In rats and monkeys, the longest duration SC toxicity studies were 3-months and 9-months in duration, respectively. In rats administered once weekly doses of 0.3, 3, and 30 mg/kg for 3 months, adverse findings included efferent duct/testicular degeneration, adrenal gland congestion/necrosis, and membranoproliferative glomerulonephritis and tubulointerstitial nephritis in the kidneys. Both the adrenal and kidney changes demonstrated partial reversibility following a 1-month recovery period. In monkeys administered 1, 2.6, and 10 mg/kg once every 4 weeks and 10 mg/kg once every 2 weeks, adverse changes included glomerulonephritis and tubulointerstitial nephritis in the kidneys. Kidney changes in monkeys partially resolved following a 3-month recovery period. In monkeys at the clinical exposure, inflammatory infiltrates were present in the choroid plexus. At the no observed adverse effect level (NOAEL) in rats and monkeys, sotatercept exposures were ≤2-times the clinical exposure at the maximum recommended human dose (MRHD).

Genotoxicity and Carcinogenicity

No carcinogenicity or mutagenicity studies have been conducted with sotatercept.

Reproductive toxicity

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

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

non-reversible histologic changes in the efferent ducts, testes, and epididymides. Reversible decreases in fertility occurred at 30 mg/kg (20-fold the MRHD, based on estimated AUC).
In embryo-fetal developmental toxicity studies, pregnant animals were dosed subcutaneously with sotatercept during the period of organogenesis. Sotatercept was administered to rats on gestation days 6 and 13 at doses of 5, 15, or 50 mg/kg and to rabbits on gestation days 7 and 14 at doses of 0.5, 1.5, or 5 mg/kg. Effects in both species included reductions in numbers of live fetuses and fetal body weights, delays in ossification, and increases in resorptions and post-implantation losses. In rats and rabbits, these effects were observed at exposures (based on area under the curve (AUC)) approximately 4-fold and 0.6-fold the MRHD, respectively. In rats only, skeletal variations (increased number of supernumerary ribs and changes in the number of thoracic or lumbar vertebrae) occurred at an exposure 15-fold the human exposure at the MRHD.
In a pre- and postnatal development study in rats, sotatercept was administered subcutaneously at doses of 1.5 and 5 mg/kg on gestation days 6 and 13, or at dosages of 1.5, 5, or 10 mg/kg during lactation on days 1, 8, and 15. There were no adverse effects in first filial generation (F1) pups from dams dosed during gestation at estimated exposures up to 2-fold the MRHD. In F1 pups from dams dosed during lactation, decreases in pup weight correlated with delays in sexual maturation at estimated exposures (based on AUC) ≥ 2-fold the MRHD.

Other information

Incompatibilities

This medicinal product may be mixed only with those medicinal products listed under Instructions for handling.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.
From a microbiological point of view, the medicinal product should be used immediately or no longer than 4 hours after reconstitution.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze.
Store in the original carton in order to protect the contents from light.
For storage conditions after reconstitution of the medicinal product, see “Shelf life”.
Keep out of the reach of children.

Instructions for handling

Kit presentation

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

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.
- 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. The vials contain excess volume of sotatercept, so that after reconstitution with 1 mL and 1.3 mL, the nominal amount that can be removed, is 45 mg/0.9 mL and 60 mg/1.2 mL, respectively.
- 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.

Authorisation number

69787

Packs

Type I glass vial, sealed with a bromobutyl rubber stopper and aluminium seal with lime polypropylene flip-off cap as well as pre-filled syringe (type I glass cartridge closed with a bromobutyl rubber) with 1 mL of water for injections (WFI) for 45 mg/vial kits or 1.3 mL of WFI for 60 mg/vial kits.

Winrevair 45 mg powder and solvent for solution for injection

- Pack with 1 vial with powder, 1 pre-filled syringe with solvent, 1 dosing syringe with 0.1 mL graduations, 1 vial adapter (13 mm), 1 needle for injection and 4 alcohol wipes. [B]
- Pack with 2 vials with powder, 2 pre-filled syringe with solvent, 1 dosing syringe with 0.1 mL graduations, 2 vial adapters (13 mm), 1 needle for injection and 7 alcohol wipes. [B]

Winrevair 60 mg powder and solvent for solution for injection

- Pack with 1 vial with powder, 1 pre-filled syringe with solvent, 1 dosing syringe with 0.1 mL graduations, 1 vial adapter (13 mm), 1 needle for injection and 4 alcohol wipes. [B]
- Pack with 2 vials with powder, 2 pre-filled syringe with solvent, 1 dosing syringe with 0.1 mL graduations, 2 vial adapters (13 mm), 1 needle for injection and 7 alcohol wipes. [B]

Marketing authorisation holder

MSD MERCK SHARP & DOHME AG

Luzern

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