swissmedic

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Swiss Public Assessment Report

Winrevair

International non-proprietary name: sotatercept
Pharmaceutical form: powder for solution for injection
Dosage strength(s): 45 mg, 60 mg
Route(s) of administration: intravenous use
Marketing authorisation holder: MSD Merck Sharp & Dohme AG
Marketing authorisation no.: 69129
Decision and decision date: approved on 13.09.2024

Note:

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

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Table of contents

1 Terms, Definitions, Abbreviations

6-MWD	6-minute walking distance
ActRIIA/B	human activin receptor type IIA/B
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AEOI	Adverse event of interest
AUC	Area under the plasma concentration-time curve
BMP	Bone morphogenic protein
BMPR2	Bone morphogenetic protein receptor type II
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
DBPC	Double-blind placebo-controlled
EMA	European Medicines Agency
ESRD	End-stage renal disease
FDA	Food and Drug Administration (USA)
GDF	Growth differentiation factor
GLP	Good Laboratory Practice
Hgb	Haemoglobin
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
LTDB	Long-term double-blind
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
NAB	Neutralising antibody
NO(A)EL	No observed (adverse) effect level
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PCWP	Pulmonary capillary wedge pressure
PK	Pharmacokinetics
PLB	Placebo
PopPK	Population pharmacokinetics
PT	Preferred term
PVR	Pulmonary vascular resistance
PYAR	Person-years at risk
Q2W	Once every 2 weeks
Q3W	Once every 3 weeks
Q4W	Once every 4 weeks
RBC	Red blood cells
RMP	Risk management plan
SoC	Standard of care
SwissPAR	Swiss Public Assessment Report
TAR-EAIR	Time-at-risk exposure-adjusted incidence rate
TEAE	Treatment-emergent adverse event
TGF-β	Transforming growth factor-β
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)
ULN	Upper limit of normal
WHO FC	World Health Organization functional class

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for sotatercept in the above-mentioned medicinal product.

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 a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 11 October 2022.

Work-sharing procedure
The applicant requested a work-sharing procedure with Singapore, Canada, Australia, and Switzerland.
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), and Swissmedic – and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least 2 jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

Winrevair is indicated in combination with standard of care therapy for the treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II to III to improve exercise capacity, provide clinical improvement, improve WHO FC, and delay disease progression, including to reduce the risk of death and hospitalisation due to PAH.
Efficacy has been shown in a PAH population including aetiologies of idiopathic and heritable PAH, PAH associated with connective tissue disease, drug or toxin-induced PAH, or PAH associated with congenital heart disease with repaired shunts (see "Clinical efficacy").

2.2.2 Approved indication

Winrevair, in combination with standard pulmonary arterial hypertension (PAH) therapy, is indicated for the treatment of PAH in adult patients with WHO functional class (FC) II to III to improve exercise capacity and to delay disease progression (see "Clinical efficacy").
Efficacy has been shown in a PAH population including aetiologies of idiopathic and heritable PAH, PAH associated with connective tissue disease, drug or toxin-induced PAH, or PAH associated with congenital heart disease with repaired shunts (see "Clinical efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:
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.

Recommended target dosage in adults
The target dose of Winrevair is 0.7 mg/kg administered every 3 weeks.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	29 January 2024
Formal objection	2 February 2024
Response to formal objection	18 February 2024
Formal control completed	1 March 2024
Preliminary decision	14 August 2024
Response to preliminary decision	29 August 2024
Final decision	13 September 2024
Decision	approval

3 Medical context

Pulmonary arterial hypertension (PAH) is a debilitating disease leading to progressive limitations in patients' exercise capacities, failure of the right ventricle, and premature death. Advancing insight into the pathobiology of the disease has led to the development of efficacious pharmacotherapies including endothelin-1-receptor blockade, prostacyclin-receptor activation, and stimulation of the NO/cGMP pathway. Yet PAH remains incurable, and affected patients still face severe constraints in their physical abilities and marked reductions in life expectancy (median survival from diagnosis ~ 5 - 7 years). Novel therapies that target alternative pathophysiological aspects of the disease could help to further improve this situation.

Aberrant signalling in the transforming growth factor-β (TGF-β) system is known to contribute to pulmonary vasculature remodelling, a hallmark of PAH. Sotatercept is a fusion protein of the extra-cellular domain of the TGF-β (ActRIIA/B) receptor and the Fc domain of human IgG1. By dampening excessive pro-proliferative signalling via ActRIIA/B receptors, it may slow down (or partially reverse) the progression of PAH.

4 Quality aspects

4.1 Drug substance

Sotatercept is a recombinant homodimeric fusion protein consisting of the extracellular domain of human activin receptor type II (ActRII) linked to the Fc domain of human IgG1. Sotatercept functions as a soluble form of ActRII that traps TGF-β superfamily ligands, restoring the balance between the pro- and anti-proliferative signalling pathways.
Sotatercept is expressed in a Chinese hamster ovary (CHO) cell line and is manufactured using a fed-batch production process in a production bioreactor. The cell culture fluid is harvested and the antibody is purified by several chromatographic and filtration steps.
The drug substance manufacturing process is performed by AbbVie Bioresearch Center, Worcester, USA.
The fermentation and purification processes were validated using 3 consecutive batches, demonstrating a consistent manufacturing process that effectively reduces process-related impurities.
The characterisation of the physicochemical and biological properties of the drug substance and its impurities was performed.
The specifications for release include relevant tests and limits, e.g. for description, colour, clarity, identity, several purity/impurity tests, protein concentration, and a potency assay (functional cell-based bioassay).
Specifications are based on clinical data and batch analysis and are in conformance with current compendial or regulatory guidelines. Batch analysis data of development, clinical, and process validation batches were provided. All batch release data comply with the drug substance specifications valid at the time of batch release. All specific analytical methods are described and are fully validated.
The drug substance is stored frozen. No changes were observed within the proposed storage conditions. A shelf-life of 60 months (-80 +/-10°C) has been accepted.

4.2 Drug product

Winrevair for injection is a sterile, preservative-free, white to off-white lyophilised cake or powder in single-dose vials for subcutaneous administration after reconstitution. The drug product is reconstituted with water for injection (WFI) to obtain a solution with a protein concentration of 50 mg/mL in a citrate-based buffer for subcutaneous administration. Winrevair is available as 45 mg/vial or 60 mg/vial dosage strength. All excipients used comply with the European Pharmacopoeia.
The finished product manufacturing process consists of thawing the frozen substance, drug product compounding, bioburden reducing filtration, sterile filtration, filling and partial stoppering, lyophilisation, capping, and inspection.
Process validation studies were executed at commercial scale using 3 validation batches for each strength.
The release and stability specifications include relevant tests and limits, e.g. for appearance, identity, pH, osmolality, purity and impurities tests, a potency assay (functional cell-based bioassay), protein concentration, particulate matter, moisture content, reconstitution time, sterility, and bacterial endotoxins. All specific methods are validated in accordance with ICH guidelines. Batch analysis data of development, clinical, and process validation batches were provided. All batch release data comply with the drug product specifications valid at the time of batch release.
The drug product is packaged in 2R Type 1 glass vials stoppered with rubber stoppers, sealed with an aluminium seal and flip-off cap. All primary components comply with the European Pharmacopoeia.
The drug product is stored at 2-8°C, protected from light. A shelf-life of 36 months at 2-8°C has been accepted.

4.3 Quality conclusions

The manufacturing processes (drug substance and drug product) are well-described and demonstrate a consistent quality of drug substance and drug product. The shelf-lives of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk of adventitious agents is minimised.

5 Nonclinical aspects

The applicant submitted a comprehensive nonclinical package for Winrevair (sotatercept). Pivotal toxicity studies were conducted in compliance with GLP.

5.1 Pharmacology

Sotatercept is a soluble form of human activin receptor type IIA (ActRIIA) that traps activin A and B, growth differentiation factors (GDF)-11, GDF-8, and bone morphogenetic protein (BMP)-10. The amino acid sequence of ActRIIA and its ligands is highly conserved across nonclinical animal species. Sotatercept showed high-affinity binding (in the pM range) to activin A and B, GDF-11, GDF-8, and BMP-10, and lower affinity to other ligands of the TGF β superfamily. In cell-based reporter luciferase gene assays, sotatercept potently inhibited activin A, activin B, and GDF-11 (IC_{50} 4.4-630.7 ng/mL) signalling through the Smad 2/3 pathway, with minimal inhibition of BMP-6, BMP-9, and BMP-10 that signal through the Smad 1/5/8 pathway. This confirmed the higher specificity of sotatercept for the Smad 2/3 pathway, although inhibition of other ligands/pathways cannot be excluded considering the maximum plasma concentrations in humans (C_{max}) of 9.7 µg/mL.
In vivo pharmacology studies were conducted with the sotatercept murine surrogate, RAP-011. Efficacy was tested in well-established rat models of PAH (Sugen-hypoxia-normoxia and monocrotaline models).
Proof of concept was also demonstrated in *Bmpr2*$^{+/R899X}$ PAH mice (a model of heritable PAH arising from Bmpr2 haploinsufficiency) and in a mouse model of pressure overload-induced right ventricular failure (pulmonary artery banding). RAP-011 showed the ability to prevent and reverse pulmonary vascular remodelling, reduce pulmonary hypertension, and improve right heart remodelling and function. A secondary pharmacology study in mice showed that RAP-011 and erythropoietin induced erythropoiesis. The effect of sotatercept on haematopoiesis was observed across nonclinical and clinical studies.
Sotatercept did not induce antibody-dependent cell-mediated cytotoxicity or complement-dependent cytotoxicity.
Sotatercept concentration-dependently inhibited the hERG potassium current (33.8% at 1000 µg/mL >100-fold human C_{max}). No sotatercept-related effects on cardiovascular, respiratory, or central nervous system function were observed in the 9-month study in cynomolgus monkeys at exposure 16-fold higher than clinical C_{max}.

5.2 Pharmacokinetics

The pharmacokinetics (PK) of sotatercept was characterised in the nonclinical species used for safety assessment (rat, monkey, and rabbit). PK parameters are considered typical for a fusion protein, characterised by low clearance (0.3-0.8 mL/h/kg) and volume of distribution (98-260 mL/kg), and long half-life ($t_{1/2}$). $T_{1/2}$ in nonclinical species was faster (7-9 days in monkeys; 4-8 days in rats) compared to humans (20-30 days).
Systemic exposure of sotatercept after repeated doses increased in an approximately dose-proportional manner with no sex differences. No or only little accumulation was observed.
Sotatercept was immunogenic in all nonclinical species. The incidence of ADAs was 46%, 40%, and 16.7-33.3% in rats, rabbits, and monkeys, respectively. In some animals (mostly rats and rabbits), the presence of ADAs correlated with reduced sotatercept plasma exposure and short half-life. The exposure achieved across repeat-dose studies was sufficient to induce pharmacological activity and to detect the main toxicities induced by sotatercept.
In line with ICH S6(R1), studies of distribution, metabolism, and extraction were not conducted.
Sotatercept levels were detected in pooled rabbit fetal plasma samples, suggesting that sotatercept can cross the placental barrier. Sotatercept was excreted into the milk according to the results of the pre- and postnatal developmental toxicity study in rats. Therefore, breastfeeding is not recommended during treatment and for 4 months after the final dose, as stated in the Information for healthcare professionals.

5.3 Toxicology

Toxicology studies were conducted in rats, rabbits, and cynomolgus monkeys, considered to be relevant species based on the highly conserved sequence homology of the ActRIIA ligands.
Nonclinical safety assessment included repeat-dose toxicity studies in rats and monkeys, reproductive and development toxicity studies in rats and/or rabbits, and juvenile toxicity studies in rats.
The clinical administration route (subcutaneous injection) was used in the pivotal studies.
Rats were treated with up to 30 mg/kg sotatercept once weekly for up to 3 months (up to 2 months' recovery). Long-term studies in rats were not conducted due to the high incidences of ADAs and kidney toxicity. To support chronic use in patients, studies with a duration of 6 and 9 months (up to 13 weeks' recovery) were conducted in young, sexually immature monkeys dosed with up to 50 mg/kg or 10 mg/kg sotatercept once every 2 (Q2W) or 4 weeks (Q4W).
Main findings in the repeat-dose toxicity studies in both species included pharmacology-mediated haematological changes and kidney toxicity. Rat-specific target organs included the adrenal gland, testes, and heart. The choroid plexus was a target organ in cynomolgus monkeys only.
All nonclinical species demonstrated pharmacological responsiveness characterised by increased erythroid cell parameters (red blood cells (RBC), haemoglobin (Hgb), and haematocrit (HCT)) as a result of activin A and GDF-11 inhibition. Findings persisted in the recovery phase and there is no safety margin for these changes. Sotatercept occasionally induced a decreas in platelet counts in both species. An increase in HGB and a decrease in platelets were observed in patients, and measurement of both parameters is required prior to treatment with sotatercept.
Histological changes in the kidneys (renal tubular degeneration/atrophy with tubular dilatation, interstitial fibrosis, and membranoproliferative glomerulonephritis) were dose-dependent and correlated with increases in blood urea nitrogen, creatinine, and urinary protein. There was only a low or no safety margin for kidney toxicity. Findings were only (partially) reversible during the recovery period. Based on the results from immunohistochemistry and additional investigations, the findings in the kidney are considered to be directly sotatercept-induced and not related to immunocomplex formation. The mechanism of sotatercept-induced kidney toxicity and its relevance for human remain unclear. No effects on renal function parameters were observed in the clinical trials.
In monkeys, treatment with sotatercept also led to microscopic changes in the choroid plexus, including minimal to slight accumulation of foamy macrophages and/or inflammatory cells in most animals dosed at ≥1 mg/kg sotatercept every 4 weeks (exposure comparable to clinical exposure). This was associated with minimal intimal thickening of small arteries and arterioles predominately at 10 mg/kg. The change showed evidence of reversibility at the end of the recovery period. Immunohistochemical evaluation of the choroid plexus confirmed that foamy macrophages and vascular alterations in the small arteries and/or arterioles were associated with the deposition of monkey IgG, IgM, and/or C3, but accumulation of sotatercept could not be determined. The finding is considered to be sotatercept-mediated. However, in the absence of associated behavioural (clinical examination) and histopathological changes and reversibility at all dosages it is not considered adverse. The clinical relevance of the choroid plexus findings in monkeys is unknown. No effects on the central nervous system were observed in clinical trials. Specific monitoring is not possible due to lack of an adequate biomarker.
Genotoxicity and carcinogenicity studies were not conducted, which is acceptable according to ICH S6(R1).
Based on the weight of evidence assessment provided by the applicant, sotatercept is considered to have a low carcinogenic potential.
Sotatercept showed effects on male reproductive organs and fertility, which is in line with the known consequence of activin inhibition. Histological changes in the efferent ducts, testes, and epididymides in rats correlated with hypospermatogenesis and/or aspermatogenesis observed at ≥ 0.3 mg/kg (0.4-fold the clinical exposure at the maximum recommended human dose, MRHD) and did not show complete reversibility. Findings correlated with decreased fertility and pregnancy indices observed at 30 mg/kg (20-fold the clinical exposure at the MRHD). In a female fertility study, no effects were observed on the reproductive organs, but prolonged oestrous cycles were observed at 50 mg/kg (21-fold the clinical exposure at the MRHD), which correlated with a lower mean number of cycles and a lower mating index. Additionally, there was a decrease in the fertility rate, a lower pregnancy rate, a

decrease in implantation sites, and an increase in pre- and post-implantation loss. The NOAEL was considered to be 5 mg/kg (2-fold the clinical exposure at the MHRD).
Embryo-fetal development studies were conducted in rats (doses of 5, 15, and 50 mg/kg on gestation days (GD) 6 and 13) and rabbits (doses of 0.5, 1.5, and 5 mg/kg on GD 7 and 14). No maternal toxicity was observed.
In both species, increased resorption and post-implantation loss, a reduced number of live fetuses, lower fetal weight, and delays in ossification were observed.
The maternal exposure at the embryo-fetal NOAEL (5 mg/kg in rats and 0.5 mg/kg in rabbits) was about 2-fold and 0.4-fold the clinical exposure at the MRHD in rats and rabbits, respectively.
In a pre- and postnatal development study, pregnant female rats received sotatercept once weekly during the gestation period (GD 6 and 13; 1.5, or 5.0 mg/kg) or lactation period (LD 1, 8, and 15; 0, 1.5, 5.0, or 10 mg/kg). The maternal NOAEL was 5.0 mg/kg when administered either during gestation or lactation (2-fold the clinical exposure at the MHRD). In the F1 offspring from the maternal lactation dose groups (≥5 mg/kg; 2-fold the clinical exposure at the MHRD), sotatercept-related effects were observed on pup body weight and/or sexual maturation. There were no effects on pup survival clinical signs, motor activity, learning and memory, and reproductive performance. The NOAEL for effects on growth and maturation in the offspring when sotatercept was administered to pregnant rats during lactation was 1.5 mg/kg (0.6-fold the clinical exposure at the MHRD).
Due to the observed reproduction toxicity in nonclinical species, sotatercept is not recommended during pregnancy, and women of child-bearing potential should use contraception. This is adequately addressed in the Information for healthcare professionals.
In the juvenile toxicity study in rats (treatment with 1, 3, or 10 mg/kg from postnatal day (PND) 7 to PND 91), most sotatercept-related findings were similar to those observed in the adult animals. Additional adverse findings exclusively observed in the juvenile rats included delays in sexual maturation and changes in bone density. This needs to be taken into account if the indication is extended to paediatric patients; the current indication includes only adult patients.
There are no safety concerns with regard to excipients or impurities.
The submitted description of key safety findings from nonclinical studies in the RMP is considered adequate.
Due to the protein nature of sotatercept, no significant risk for the environment is anticipated.

5.4 Nonclinical conclusions

The pharmacological properties and the toxicity profile of sotatercept were sufficiently characterised. Thus, from a nonclinical perspective, approval may be granted for sotatercept in the proposed indication.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Absorption and biopharmaceutical development

The median sotatercept tmax after subcutaneous (s.c.) administration was 7 days. The estimated absolute bioavailability of sotatercept after s.c. administration was 65%. S.c. injection into the abdomen, thigh, or upper arm is supported by the available pharmacokinetic data.

Dose proportionality

There was a dose-proportional increase in sotatercept exposures after administration of single i.v. doses between 0.01 mg/kg and 3.0 mg/kg, single s.c. doses between 0.03 mg/kg and 0.1 mg/kg, and single s.c. doses between 0.1 mg/kg and 1.0 mg/kg in healthy postmenopausal female subjects.

Pharmacokinetics after multiple dosing

The estimated time to steady state after a starting dose of 0.3 mg/kg followed by 0.7 mg/kg Q3W was approximately 15 weeks. The accumulation ratios in a typical patient were predicted to be 2.24, 2.17, and 2.04 for AUC, C_{max} and C_{trough}, respectively.

Distribution

The mean sotatercept volume of distribution was 5.54 L.

Metabolism & elimination

No studies regarding the metabolism of sotatercept have been conducted in view of the biological nature of the molecule.

The mean sotatercept clearance was 0.186 L/d and the mean half-life was 22.5 days.

Special populations

Sotatercept PK in subjects with end-stage renal disease (ESRD) on dialysis were comparable to healthy postmenopausal women (not demographically matched) and a virtual, matched control group with normal renal function.

Sotatercept was not removed from serum by haemodialysis.

The pharmacokinetics of sotatercept in PAH patients was investigated in a PopPK analysis.

The dataset included 350 subjects, of whom 64 (18.3%) were healthy postmenopausal women and the remaining subjects (286, 81.7%) were PAH patients. The mean age of all subjects was 50.2 years (range 18 to 81 years). As expected, the PAH patients were younger than the healthy postmenopausal women. The majority (83.2%) of the PAH patients were less than 65 years old. The dataset included 14.3% and 2.4% of PAH patients between 65 and < 75 years and between 75 and 81 years, respectively.

The mean baseline body weight of all subjects was 71 kg (range 39.6 to 136 kg). The majority of the subjects (82.9%) were Caucasian, female (85.1%), and received sotatercept s.c. (91.4%). The dataset included 116 (33.1%) subjects with normal renal function, 183 (52.3%) subjects with mild renal impairment, and 51 (14.6%) subjects with moderate renal impairment. In the final dataset, 3.83% of the sotatercept PK samples were ADA positive.

The final PopPK model was a 2-compartment model with first-order absorption of s.c. administration, zero-order input for i.v. administration, and first-order elimination. The covariates planned to be investigated for their impact on sotatercept PK were body weight, baseline age, sex, disease status,

race, baseline eGFR, baseline albumin, and ADA. Of these, the final model included body weight as a covariate of CL and Vc and albumin as a covariate of CL.

Sotatercept CL and Vc increased with increasing body weight and CL decreased with increasing albumin concentrations. The impact of body weight on exposure is covered by the weight-based dosing of sotatercept. The impact of the remaining covariates on sotatercept exposures was small, i.e. from a pharmacokinetic point of view, no dose adjustments are required.

The number of ADA/NAB-positive samples was too low for inclusion in the formal covariate analysis. However, descriptive analyses of the data indicated slightly lower sotatercept concentrations in ADA/NAB-positive subjects. Considering the variability of the data, the differences due to ADA/NAB were not clinically relevant.

The final model slightly under-estimated the sotatercept concentrations in healthy postmenopausal women, but it described the data of PAH patients reasonably well.

Interactions
No interaction studies have been conducted in view of the biological nature of the molecule.

Pharmacodynamics
Secondary pharmacology (safety)
No tQT study or exposure-response analysis investigating the impact of sotatercept on QTc has been conducted in view of the biological nature of the molecule.

Exposure efficacy/safety relationship
The covariates investigated in the different exposure-response analyses included body weight, baseline age, sex, disease status, racial classification, region of enrolment, baseline eGFR, Hgb, PAH disease duration, PAH etiological subgroup, baseline standard of care (SoC) therapy, baseline (prostacyclin) infusion therapy, baseline 6-minutes walking distance (6-MWD), baseline pulmonary vascular resistance (PVR), baseline WHO functional class, iron supplementation, and ethnicity. It was planned to investigate ADA and baseline bone morphogenetic protein receptor type II (BMPR2) genotype as well, but the available data were not sufficient for a formal statistical assessment.

EFFICACY

6-minute walking distance (6-MWD)

The dataset included 449 PAH patients receiving placebo (PLB) + SoC 0.3 mg/kg only, 0.7 mg/kg only, or 0.3 mg/kg followed by 0.7 mg/kg sotatercept. The mean age of the patients was 47.9 years (range 18 to 82 years). The mean body weight was 72.4 kg (range 38 to 141 kg). The majority (82.1%) of the patients were female and not Hispanic/Latino (75.5%). Approximately 50% of the patients belonged to WHO functional class II or III at baseline, respectively, and most of them (59.7%) received triple SoC therapy at baseline. The percentage of patients with baseline SoC, especially triple therapy, was considerably lower in Hispanic/Latino patients compared to non-Hispanic/Latino patients.

The final model comprised an E_{max} model to describe the PLB effect. Sotatercept C_{avg} was added as a power function. It included the following covariate relationships: WHO functional class, age, and Hgb on baseline 6-MWD. The 6-MWD change (increase) from baseline at Week 24 was larger in patients ≤ 48 compared to older patients, slightly larger in WHO class III compared to class II, and larger in patients with baseline Hgb > 13.9 g/L compared to lower Hgb values.

Overall, the model described the data reasonably well. The final model predicted a sotatercept concentration-dependent increase of 6-MWD with the exposures achieved after 0.7 mg/kg approaching, but not fully reaching, the plateau of the exposure-response curve.

The therapeutic window of sotatercept was defined as 0.6 to 1.4-fold the median C_{avg} at Week 24. The median predicted 6-MWD at 0.6, median, and 1.4- fold sotatercept C_{avg} at Week 24 was 439, 444, and 448 m, respectively. The corresponding median predicted change from baseline was 36.1, 41.0, and 45.3 m, respectively.

The median predicted 6-MWD at 0.6, median, and 1.4- fold sotatercept C_{avg} at Week 24 was 433, 441, and 446 m, respectively. The corresponding median predicted change from baseline was 33.8, 40.6, and 46.4 m, respectively.

Pulmonary vascular resistance (PVR)

The dataset included 449 PAH patients receiving PLB + SoC 0.3 mg/kg only, 0.7 mg/kg only, or 0.3 mg/kg followed by 0.7 mg/kg sotatercept. The mean age of the patients was 47.6 years (range 18 to 82 years). The mean body weight was 72.9 kg (range 38 to 147 kg). The majority (82.1%) of the patients were female. The majority (74.1%) of the patients were not Hispanic or Latino. Approximately 50% of the patients belonged to WHO functional class II or III at baseline, respectively, and most of them (59.4%) were receiving triple SoC therapy at baseline.

The final PVR model consisted of an intercept and sotatercept C_{avg} as a power function, as no significant change in PVR was observed under PLB + SoC. PVR decreased with increasing sotatercept concentrations, approaching a plateau at the exposures reached after 0.7 mg/kg. The model described the data reasonably well.

Covariates affecting the impact of sotatercept on PVR were the duration of PAH disease, baseline PVR, and prostacyclin infusions. PVR increased with increasing duration of PAH disease. For each 5 years of disease duration, an increase in PVR of approximately 7% is expected. With every 100 dynes*sec/cm^5 increase in baseline PVR, post-dose PVR was estimated to be approximately 2% lower.

PVR was estimated to be approximately 16% lower in patients with prostacyclin infusions compared to patients without them.

The predicted PVR change from baseline (decrease) at Week 24 was larger in patients with PAH duration ≤ 7 years compared to longer disease duration, in patients with prostacyclin infusions compared to patients without prostacyclin infusions, and in patients with baseline PVR ≥ 664 dynes*s/cm^5 compared to patients with lower baseline PVR.

The therapeutic window of sotatercept was defined as 0.6 to 1.4-fold the median C_{avg} at Week 24. The median predicted PVR at 0.6, median, and 1.4- fold sotatercept C_{avg} at Week 24 was 567, 557, and 551 dynes*s/cm^5, respectively. The corresponding median predicted PVR change from baseline was -207, -217, and -223 dynes*s/cm^5, respectively.

SAFETY (Hgb)

The dataset included 528 subjects, of whom 79 (15%) were healthy postmenopausal women, who were older than the PAH patients. The mean age of all subjects was 49.9 years (range 18 to 82 years). The mean baseline body weight was 71.3 kg (range 38 to 141 kg). The majority (83.7%) of the subjects were White and female (83.9%). The majority (90.2%) of the subjects did not receive iron supplementation. The dataset included 177 (33.5%) subjects with normal renal function, 271 (51.3%) subjects with mild renal impairment, 80 (15.2%) subjects with moderate renal impairment, and no

subjects with severe renal impairment or ESRD. While most of the haematological markers were comparable between healthy subjects and PAH patients, the mean baseline reticulocyte count was approximately doubled in PAH patients compared to healthy subjects.

The model describing the effect of sotatercept on Hgb dynamics was a semi-mechanistic model fitting simultaneously the observed data for reticulocyte counts, RBC counts, and Hgb concentrations. It included 4 sequential catenary compartments describing a) the irreversible maturation of the RBC line from progenitor cells in the bone marrow to the mature RBCs, b) the saturable, sotatercept-driven stimulation of production and maturation of the most immature progenitor cell population, and c) the inhibitory or stimulatory feedback driven by the change in predicted Hgb concentrations from baseline.

The final model included the differences in baseline reticulocyte count between healthy subjects and PAH patients and the effect of iron supplementation on the zero-order input rate of early progenitors. The model tended to over-predict the central tendency and the variability of the data in healthy subjects, but it described the data in PAH patients under sotatercept reasonably well.

Simulations with the final model indicated a sotatercept C_{avg}-dependent Hgb increase in PAH patients. The applicant defined the therapeutic window of sotatercept as 0.6 to 1.4-fold the median C_{avg} at Week 24. The median predicted Hgb at Week 24 at the median C_{avg} after the therapeutic dosing regimen was 15.4 g/dL, which increased to 15.5 g/dL after a 40% increase in the median C_{avg}. The corresponding median Hgb changes from baseline were 1.75 g/dL and 1.87 g/dL, respectively.

At the median sotatercept C_{avg} at Week 24, the 95th percentile of patients exceeding a Hgb threshold of 18 g/dL was 17.6%. A 40% increase in C_{avg} resulted in an increase in this value to 18.6% of patients.

The predicted Hgb at baseline and at Week 24 was lower in patients on iron supplement, but the change from baseline was higher.

6.2 Dose finding and dose recommendation

Pharmacometrics aspects
In order to support the therapeutic window for sotatercept as proposed (0.6 to 1.4-fold the median C_{avg} at Week 24), simulations were provided for 6-MWD, PVR, and Hgb. The changes in 6-MWD are pivotal for judging sotatercept's clinical benefit, while PVR and Hgb function are pathophysiological surrogate and safety parameter, respectively.

The justification of the proposed dosing regimen is generally conclusive as all exposure-response (ER) relationships come close to their plateau at the dose of sotatercept 0.7 mg/kg Q3W, without fully reaching it. In other words, the models predict somewhat larger effects on 6-MWD and PVR with higher sotatercept doses. However, the pay-off for such additional beneficial effects on 6-MWD and PVR would be undue increases in Hgb which, ultimately, represent the limiting factor for further dose escalation (cf. safety section).

Clinical aspects
Two Phase 2 studies further consolidated the dose finding: the exploratory SPECTRA trial and the 3-arm, double-blind, randomised, controlled PULSAR trial.

The open-label, single-arm SPECTRA trial showed a mean **increase in VO_2 max** of 1.23 mL/min/kg (12.54%) in patients with PAH (n=21) following treatment with 1 dose of sotatercept 0.3 mg/kg plus 8 cycles of sotatercept 0.7 mg/kg 3-weekly (QW3).

The PULSAR trial investigated the efficacy of sotatercept 0.7 mg/kg Q3W (n=42), sotatercept 0.3 mg/kg Q3W (n=32), and placebo Q3W (n=32). The mean treatment differences [95% CI] for the primary endpoint (change from baseline to Week 24 in PVR [dynes*sec/cm^5]) were -151.1 [-249.6, -52.6] and -269.4 [-365.8, -173.0] for sotatercept 0.3 mg/kg Q3W and sotatercept 0.7 mg/kg Q3W,

respectively. The mean treatment difference for the secondary endpoint ∆6-MWD [95% CI] was 24.6 m [**-2.8**, 52.0] (0.3 mg/kg) and 22.3 m [4.8, 49.3] (0.7 mg/kg).

6.3 Efficacy

The applicant submitted the pivotal study STELLAR to support the proposed indication.

STELLAR is a pivotal Phase 3 study investigating the efficacy and safety of sotatercept in adults with PAH (including idiopathic, heritable, drug/toxin-induced, due to connective tissue disease, or congenital systemic-to-pulmonary shunts; excluding PAH associated with HIV, portal hypertension, or schistosomiasis, and pulmonary veno-occlusive disease as well as pulmonary hypertension Groups 2-5) on top of their preexisting PAH pharmacotherapy. The main inclusion criteria were a PVR ≥ 5 Wood units, pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and a 6-MWD within the range of ≥ 150 m - ≤ 500 m, while the trial excluded patients with haemoglobin (Hgb) above the ULN and a platelet count <50•10^9/L.

The study comprised a 24-week double-blind-controlled (DBPC) period and a subsequent long-term double-blind (LTDB) period lasting a maximum of 72 weeks until completion of the DBPC period by the last study participant (i.e. until study unblinding). Randomisation to treatment with sotatercept (n=163) or placebo (PLB) (n=160) occurred in a 1:1 ratio stratified by baseline WHO functional class (FC II or III) and background pharmacotherapy (mono, double, or triple).

As per protocol, dose escalation, delay, reduction, or discontinuation were to be performed depending on Hgb level and platelet count. Except for Visit 1 (0.3 mg/kg s.c.), the planned treatment intervention was sotatercept 0.7 mg/kg subcutaneously given Q3W and matching PLB. All but 1 sotatercept-treated patient (99.4%) initially reached the 0.7 mg/kg dose, 10 [6.1%] required dose reductions (median time to 1st dose reduction: 64.0 d), dose re-escalation occurred in 5 [3.0%] of them (median time to 1st re-escalation: 84.0 d).

The primary endpoint was the change from baseline to Week 24 in the 6-MWD. A difference of 25 m from PLB (∆6-MWD) was used for the sample size calculation of STELLAR. The protocol defined no explicit clinically relevant ∆6-MWD. The time to clinical worsening served as a secondary endpoint, where clinical worsening was defined as all-cause death or the first occurrence of a) listing for lung and/or heart transplant due to deterioration, b) the initiation of supplemental SoC PAH therapy for rescue, b) ≥10% increase in the dose of intravenous prostacyclin, c) need for atrial septostomy, d) hospitalisation (≥ 24 h) for PAH, and e) deterioration in the WHO FC and 6-MWD (decrease ≥ 15%). Other secondary endpoints comprised a) the proportion of patients with concurrent improvements in 6-MWD, NT-proBNP levels, and the WHO FC class meeting predefined margins, b) change in PVR, c) change in NT-proBNP, d) proportion of subjects with improvement in WHO FC, e) proportion of subjects achieving or maintaining a low-risk score, as well as f) a set of patient-reported outcomes.

Confirmatory statistical analyses (i.e. for the primary and other secondary efficacy endpoints) were generally planned and performed for the end of the 24-week DBPC treatment period, except for the analysis of the time to clinical worsening event based on the data up to the data cut-off (26 August 2022). To account for multiplicity, testing of the hypotheses for the endpoints occurred according to a predefined hierarchy.

The study design, endpoints chosen, and the study conduct were appropriate. Completion rates for the 24-week DBPC period (Visit 9) treatment arms were high, but slightly different between treatment arms (97.5% [sotatercept] vs. 92.5 [PLB]). Consistent with the beneficial effect of sotatercept claimed, discontinuation of the study treatment due to clinical worsening occurred more frequently in the PLB arm (10 [6.3%] patients) as compared with the sotatercept arm (only 1 [0.6%] patient). Demographics and other relevant baseline characteristics showed no meaningful imbalances between the treatment arms. Reflecting the known epidemiology, the study population were mostly female patients (~80%). At study start, the overall median age and body weight were 48 years and 68.2 kg, respectively.

The median time [range] since PAH diagnosis was ~7 [0.08 - 40.21] years; 48.6% and 51.4% were in WHO FC II and III, respectively. Medical history conditions for PAH were also largely comparable between treatment groups. Baseline background medication typically included a combination of ≥2 SoC PAH pharmacotherapies (198 [61.3%] patients received triple therapy, 112 [34.7%] patients

received double therapy, and only 13 [4.0%] patients received a monotherapy). In addition, about 40% of the study participants required prostacyclin infusion therapy at the time of their inclusion in the study. Apart from that, the most common concomitant medications were proton pump inhibitors (49.8%), sulfonamides (33.1%), and potassium (31.3%).

Sotatercept significantly improved the primary endpoint 6-MWD as compared with PLB (Hodges-Lehmann Location Shift [95% CI]: 40.8 m [27.53, 54.14]; p<0.001).

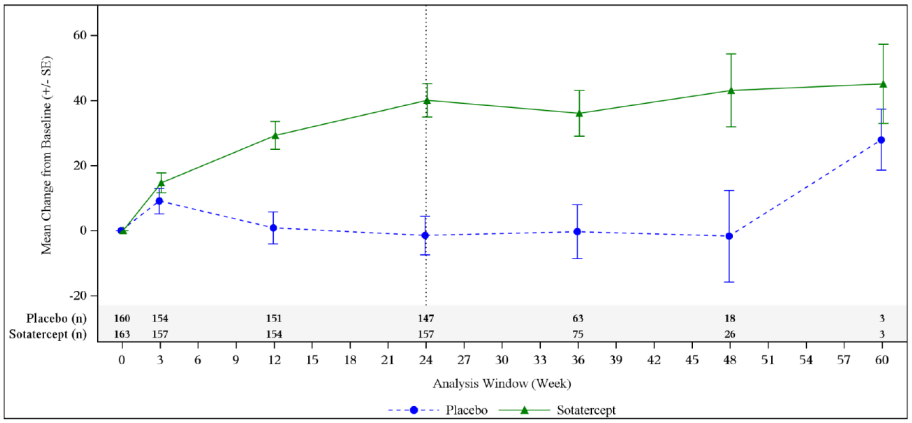


Fig. 14.2.2 CSR

In light of the 6-MWD changes achieved with other drugs approved for the treatment of PAH, this improvement can be considered as clinically relevant. Sensitivity analyses based on alternative methods of imputation support the robustness of this finding. Moreover, the treatment effect of sotatercept on Δ6-MWD was consistent across all prespecified subgroups.

Subgroup	Placebo (N=160) n	Sotatercept (N=163) n	Sotatercept vs. Placebo HL Location Shift (95% CI)	Sotatercept vs. Placebo HL Location Shift (ASE) [1] (95% CI)
Overall	160	163		40.8 (6.79) (27.53, 54.14)
Sex				
Male	33	34		58.5 (19.46) (20.34, 96.61)
Female	127	129		37.2 (7.50) (22.47, 51.87)
PAH Diagnostic Group				
iPAH [idiopathic PAH]	106	83		51.3 (9.74) (32.17, 70.35)
hPAH [heritable PAH]	24	35		25.6 (13.76) (-1.34, 52.61)
Drug/Toxin-induced PAH	4	7		18.4 (16.78) (-14.51, 51.25)
Connective Tissue Disease	19	29		8.7 (17.96) (-26.55, 43.86)
Congenital heart disease with s/p Shunt Repair	7	9		92.4 (58.60) (-22.49, 207.26)
Background therapy at baseline				
Monotherapy	4	9		6.3 (534.33) (-564.54, 1530.01)
Double	56	56		43.2 (11.32) (21.03, 65.42)
Triple	100	98		43.5 (8.65) (26.51, 60.44)
Prostacyclin infusion therapy at baseline				
Yes	64	65		43.1 (10.45) (22.61, 63.59)
No	96	98		38.6 (8.88) (21.20, 56.00)
WHO Functional Class				
II	78	79		21.7 (7.68) (6.63, 36.72)
III	82	84		61.7 (10.64) (40.90, 82.59)
Baseline PVR				
<=800 (dynes*sec/cm^5)	108	108		30.8 (7.77) (15.54, 45.98)
>800 (dynes*sec/cm^5)	52	55		61.6 (13.48) (35.23, 88.06)

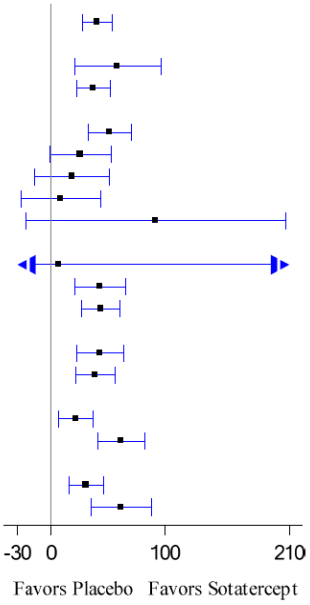


Figure 11-2 CSR

Results from the primary endpoint were corroborated by the outcomes for the secondary efficacy endpoints. In particular, sotatercept significantly (p<0.001) lowered the incidence of "death or first clinical worsening" events (9 [5.5%] versus 42 [26.3%] in the PLB control group; HR [95% CI]: 0.163 [0.076, 0.347]). Remarkably, this finding suggests a >20% absolute risk reduction and a >80% relative risk reduction.

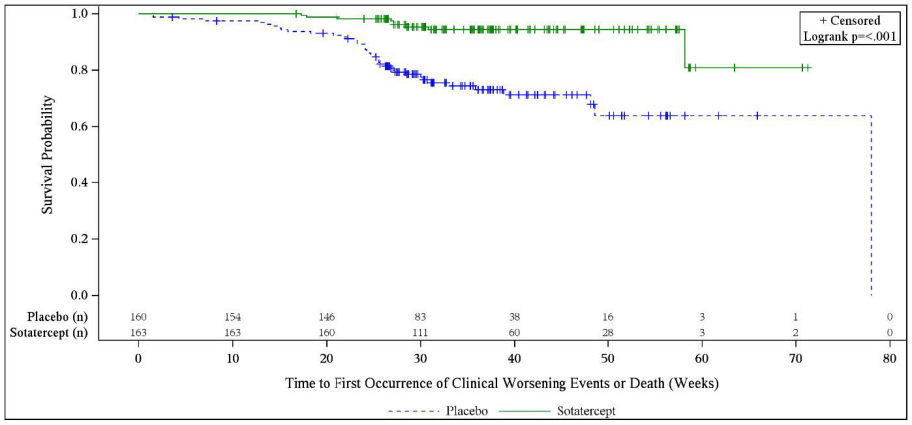


Fig. 11-5 CSR

An updated analysis of "mortality and clinical worsening events" (data cut-off 6 December 2022) with a mean duration [range] of exposure of 41.4 [3.0 - 80.9] weeks was consistent with the initial findings outlined above.

Moreover, sotatercept-treated patients were significantly (p<0.001) more likely than patients in the PLB control group to i) achieve improvements (to extents pre-defined in the protocol) concurrently for 6-MWD and NT-proBNP, and WHO FC (38.9% vs. 10.1%), or ii) maintain/achieve a low-risk score as defined per protocol up to Week 24 (39.5% vs. 18.2%). Equally, the percentage of subjects with improvement in the WHO FC during the 24-week DBPC treatment period was significantly (p<0.001) greater in the sotatercept arm (48 [29.4%] patients) compared with the PLB control arm (22 [13.8%] patients).

Of relevance from a pathophysiological perspective, sotatercept significantly (p<0.001) lowered both the PVR (Hodges-Lehmann Location Shift: -234.6 dynes*sec/cm^5) and the NT-proBNP level (Hodges-Lehmann Location Shift: - 441.6 pg/mL).

Concerning patient-reported outcomes, sotatercept significantly improved scores in the Physical Impacts Domain (Hodges-Lehmann Location Shift: -0.26) and the Cardiopulmonary Symptoms Domain (Hodges-Lehmann Location Shift: -0.13) of the PAH-SYMPACT® questionnaire.

6.4 Safety

Safety data were reported up to the data cut-off (26 August 2022) for STELLAR (DBPC period and cumulative data) and 2 pooled databases.

The PLB-controlled Pool A consists of the STELLAR and PULSAR trials in which >70% of the patients received 8 sotatercept doses (median treatment duration of 168 days cumulating to 114 person-years overall). Pool B consists of the cumulative data for sotatercept treatment in STELLAR, PULSAR, SPECTRA, and SOTERIA (i.e. it lacks an overall PLB control); it comprises 128 (39.9%) patients who received 9-16 doses of sotatercept and 96 (29.9%) patients who received >32 doses (median treatment duration of 315 days cumulating to 476.5 person-years overall).

Findings for Pool A and Pool B principally resembled those from the STELLAR trial.

In Pool A, treatment-emergent adverse events (TEAEs) of any grade were observed in 85.2% versus 88% of the patients treated with sotatercept and PLB, respectively. The incidence of TEAEs considered to be related to treatment was higher in sotatercept-treated patients (43.9%) compared with the PLB control (26%). This was reflected in a higher (as compared with PLB) incidence of TEAEs leading to dose reduction (3.4% vs. 1.0%) or to dose delay (10.5% vs. 2.6%).

Common TEAEs (reported in ≥5% of the patients in the DBPC period of STELLAR) with a significantly higher incidence in the sotatercept group compared with the PLB group were epistaxis (20 [12.3%] vs. 3 [1.9%]), telangiectasia (17 [10.4%] vs. 5 [3.1%]), and dizziness (17 [10.4%] vs. 3 [1.9%]). Nasal congestion was the only additional common TEAE more frequent in the sotatercept group (9 [5.5%]) than in the PLB group ([0.0%]) when analysing the data across the whole STELLAR trial.

In STELLAR, TEAEs more common in the sotatercept arm and considered to be related to the study intervention were telangiectasia (9.8% vs. 1.3% [PLB]), epistaxis (4.9% vs. 0.6% [PLB]), Hgb

increased (3.7% vs. 0.0% [PLB]), and injection site erythema (2.5% vs. 0.0% [PLB]). A corresponding analysis of the safety data Pool A identified thrombocytopenia (e.g. 4.6% vs. 1.0% [PLB]).

As illustrated below, the incidence of serious TEAEs was lower in the sotatercept group as compared with the PLB group, consistently across various pools and studies.

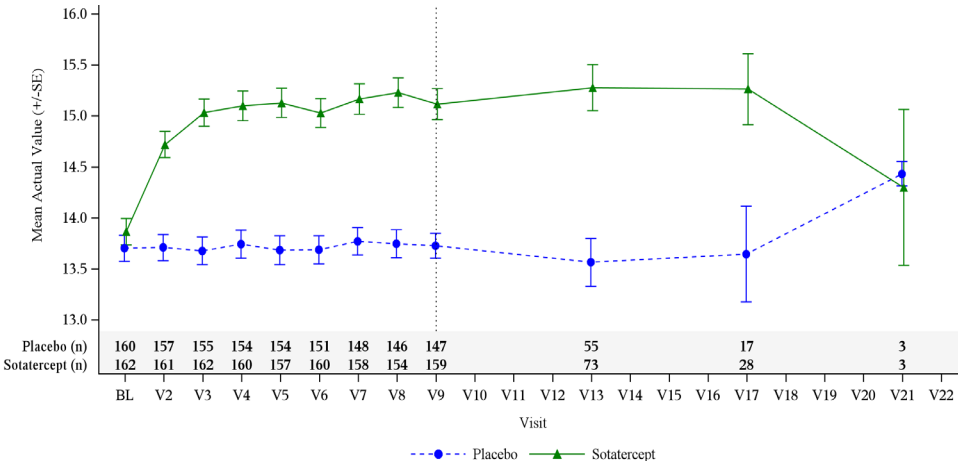
Pool / Study		Sotatercept	Placebo
		n (%) ¦ TAR-EAIR [95% CI] (100 PYAR)#	
STELLAR	DBPC period	23 (14.1%)	36 (22.5%)
	DBPC + LTDB period	36 (22.1%)	44 (27.5)
Pool A		34.6 [24.1, 48.1]	49.7 [35.3, 67.9]
Pool B		23.3 [18.7, 28.7]	- §

TAR-EAIR, time-at-risk exposure-adjusted incidence rate; PYAR, person-years at risk
§ Safety data Pool B contains no overall PLB group

No deaths were reported in the sotatercept group in the DBPC period of STELLAR compared with 6 deaths in the PLB group.

The following sections are dedicated to adverse events of interest (AEOIs), specifically "increased haemoglobin", "thrombocytopenia", "epistaxis and other bleeding events", and "increased blood pressure".

Increased haemoglobin (Hgb)



Laboratory data typically showed a robust and rapid rise in Hgb from baseline levels right after the first sotatercept dose, followed by a minor additional gain through Week 9 (Visit 4). Thereafter, Hgb remained more or less stable through Week 24 (Visit 9).

The mean increase from baseline at Week 24 was ~1.3 g/dL.

In STELLAR, the AEOI increased Hgb (preferred terms (PTs): Hgb increased, polycythaemia, and RBC count increased) was reported only for sotatercept-treated patients: 9 (5.5%) subjects in the 24-week DBPC period and 10 (6.1%) subjects overall up to the data cut-off (DBPC + LTDB period). In the overall sotatercept group of Pool A, the TAR-EAIR [95% CI] for the PT Hgb increased was 14.4/100 PYAR [8.0, 23.7] versus 0.0 in the overall PLB group.

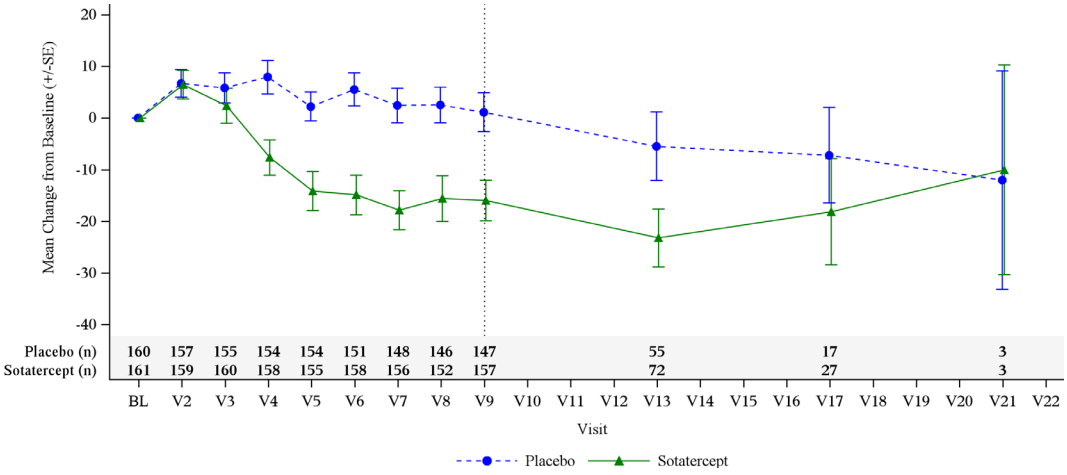
There were no increases in Hgb level >4 g/dL above the estimated ULN (CTCAE Grade 3).

Three events resulted in discontinuation of the study intervention and study withdrawal. One event (RBC count increased) was serious and required urgent phlebotomy. The 2 other events (polycythaemia and Hgb increased) were non-serious.

Thrombocytopenia

Thrombocytopenia (PTs reported: thrombocytopenia and platelet count decreased) was more common in sotatercept-treated than in PLB-treated patients in the DBPC period (10 [6.1%] vs. 4 [2.5%]) and up to the data cut-off of STELLAR (14 [8.6%] vs. 5 [3.1%]).

In Pool A, the TAR-EAIR [95% CI] for the PT thrombocytopenia in the overall sotatercept group was 14.3/100 PYAR [8.0, 23.5] compared with 3.5/100 PYAR [0.7, 10.1] in the overall PLB group.



The respective platelet counts showed a mean decrease of - 15.9 • 10^9/L from baseline to Week 24 (Visit 9) in the sotatercept arm, but only minimal changes in the PLB group.

Bleeding events including epistaxis

In the DBPC period of STELLAR, the incidence of the AEOI bleeding events (Standard MedDRA query Haemorrhage terms [excl. laboratory terms]) was markedly increased in the sotatercept group compared with the PLB group (35 [21.5%] vs. 20 [12.5%]). The most commonly reported AEOI bleeding event in the sotatercept group was epistaxis (followed by gingival bleeding).

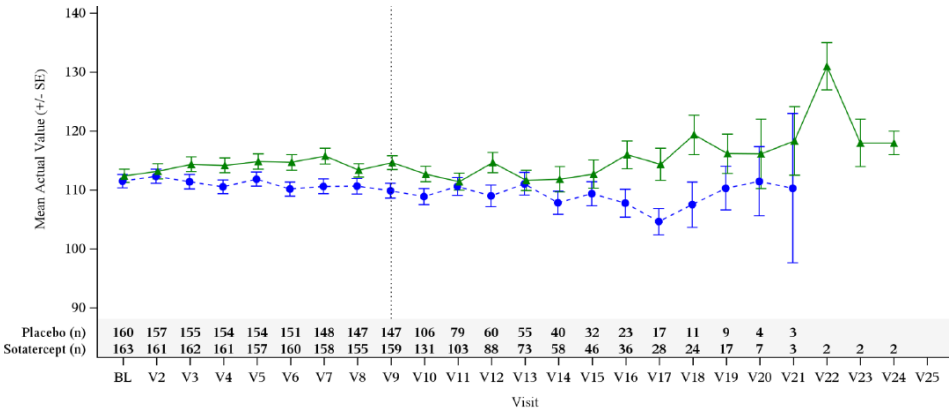
The TAR-EAIR [95% CI] for the PT epistaxis estimated for the overall sotatercept group of **Pool A** was 28.4/100 PYAR [19.0, 40.7], corresponding to a significant > 6-fold increase compared with the overall PLB group (4.6/100 PYAR [1.3, 11.9]).

In the overall sotatercept group of Pool B, 4 events led to discontinuation of the study intervention and study withdrawal. It is noteworthy that none of these events was concurrent with severe thrombocytopenia. Three events (gastrointestinal haemorrhage, haemoptysis, and haemorrhage intracranial) were serious and severe, 2 of which were fatal (gastrointestinal haemorrhage and haemorrhage intracranial). Two out of the 3 patients with a serious bleeding event (including the patient with intracranial bleeding) were receiving both an anticoagulant and a prostacyclin analogue.

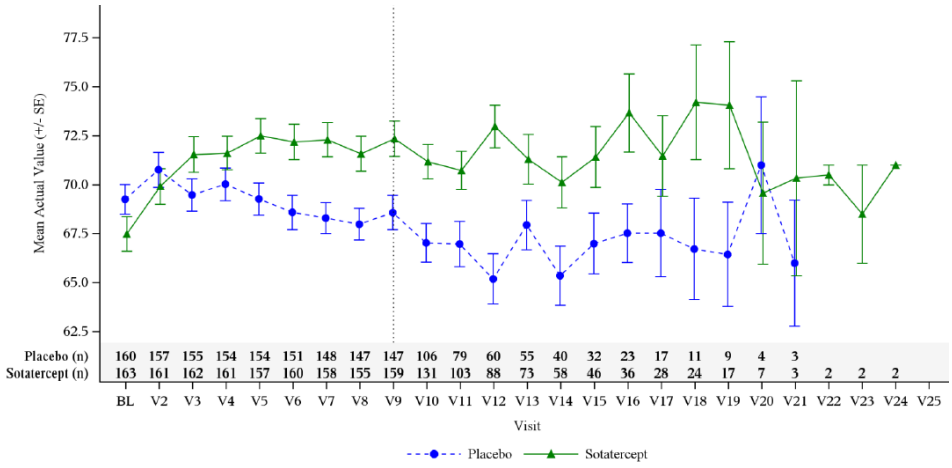
Increased blood pressure (hypertension)

In the DBPC period of STELLAR, increased blood pressure (PTs: hypertension, blood pressure diastolic increased, and blood pressure increased) was more common in the sotatercept (6 [3.7%]) than in the PLB (1 [0.6%]) group. The TAR-EAIR [95% CI] for the PT hypertension in the overall sotatercept group of **Pool A** was 4.6/100 PYAR [1.5, 10.8] versus 1.1/100 PYAR [0.0, 6.4] in the overall PLB group.

Systolic blood pressure (mmHg)



Diastolic blood pressure (mmHg)



Over time (from baseline to Week 24), small increases in blood pressure (BP) occurred in the sotatercept arm, on average amounting to 2.2 mmHg (systolic BP) and 4.9 mmHg (diastolic BP). The corresponding changes in the PLB group were -1.6 mmHg (systolic BP) and -0.6 mmHg (diastolic blood BP).

Please refer to the Information for healthcare professionals (Appendix) for further details of overall safety.

6.5 Final clinical benefit risk assessment

Sotatercept treatment on top of the current SoC PAH pharmacotherapy provides clinical benefits including improved exercise capacity (mean difference in the change in the 6-MWD [95% CI]: 40.8 m [27.53, 54.14]) and marked reductions in mortality and morbidity (decrease in "death or 1st clinical worsening" events documented for a duration of treatment ~45 weeks). Sotatercept treatment also triggered favourable changes in pathophysiological surrogates such as PVR and NT-proBNP.

Common and limiting risks associated with sotatercept treatment are increased Hgb and thrombo-cytopenia. In the pivotal STELLAR trial, these were manageable with a predefined algorithm for dose modifications. Other adverse drug reactions include bleeding events (mostly epistaxis), telangiectasia, and increased blood pressure.

The benefit-risk ratio can be considered positive for the population examined in the Phase 2/3 trials when adhering to the dose modification algorithm preventing excessive Hgb increases and drops in platelet count, respectively.

7 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.

8 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 for solution for injection.
Powder: white to off-white lyophilised powder.

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 treatment of PAH in adult patients with WHO Functional Class (FC) II to III, to improve exercise capacity and to delay disease progression (see «Clinical efficacy»).

Efficacy has been shown in a PAH population including aetiologies of idiopathic and heritable PAH, PAH associated with connective tissue disease, drug or toxin-induced PAH, or PAH associated with congenital heart disease with repaired shunts (see «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)	Dose Vial
30.0 – 40.8	0.2	45 mg
40.9 – 57.4	0.3	
57.5 – 74.1	0.4	
74.2 – 90.8	0.5	
90.9 – 107.4	0.6	
107.5 – 124.1	0.7	
124.2 – 140.8	0.8	
140.9 – 157.4	0.9	
157.5 – 174.1	1.0	60 mg
174.2 – 180.0	1.1	

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

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, 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. Sotatercept has not been studied 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 lyophilized powder vial(s) should be prepared and administered by a health care

professional (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 (>2 g/dL to <4g/dL above ULN in ~15% of study participants). 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’.

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 discontinuated 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 safety of Winrevair was evaluated in the pivotal trial STELLAR, a long-term placebo-controlled trial of 323 patients with PAH (see «Properties/Effects/Clinical efficacy»). After completing the primary 24-week treatment phase, patients continued into a long-term double-blind treatment period, maintaining their current therapy, until all patients completed the primary treatment period. The median duration of treatment with Winrevair was 252 days. 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 more often in the Winrevair group and with a frequency greater than 1%.

Among the adverse reactions observed, serious events were uncommon (<1.0%) (see description of selected adverse reactions). The most frequently reported adverse reactions were headache (24.5%), epistaxis (22.1%), and telangiectasia (16.6%), diarrhoea (15.3%), dizziness (14.7%), rash (12.3%), and thrombocytopenia (10.4%).

List of adverse reactions,

The adverse reactions reported with Winrevair in STELLAR are listed in the table below 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).

Table 3: Adverse reactions

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

[1] See “Warnings and precautions”
[2] See description of selected adverse reactions
[3] MedDRA High Level Terms (HLT)

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»)

Thrombocytopenia

The majority of events of thrombocytopenia (thrombocytopenia and platelet count decreased) were non-serious, mild, reversible, and have not been associated with discontinuation of therapy. Severe reduction in platelet count <50,000/mm3 (<50.0 x 109/L) occurred in 1.8% of patients taking Winrevair.

Telangiectasia

Events of telangiectasia were non-serious and did not progress in severity over time. In all patients exposed to Winrevair, the median time to onset was 47.1 weeks. Discontinuations of

therapy due to telangiectasia were 1% in the Winrevair group vs 0% in the placebo group. No episodes of serious bleeding have been associated with telangiectasia.

Increased Blood Pressure

Events of increased blood pressure (hypertension, blood pressure diastolic increased, blood pressure increased) were 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.

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.

Immunogenicity

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

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

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

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

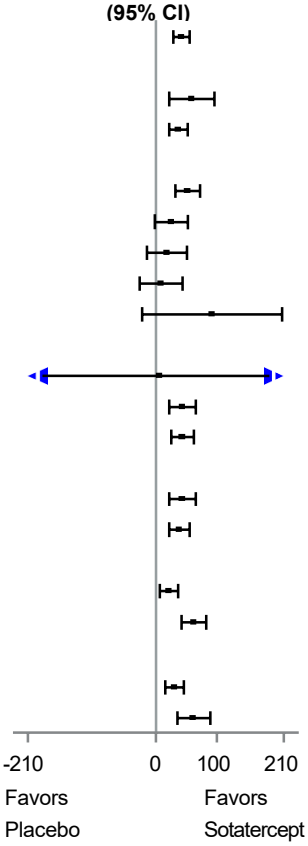
decrease from baseline in PVR was also significantly greater in the sotatercept 0.7 mg/kg group compared with the placebo group (see «Clinical efficacy»).
In rat models of PAH, a sotatercept analog reduced expression of pro-inflammatory markers at the pulmonary arterial wall, reduced leukocyte recruitment, 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

The efficacy of Winrevair was evaluated in adult patients with PAH in the STELLAR trial. STELLAR was a global, double-blind, placebo-controlled, multicenter, parallel-group clinical trial in which 323 patients with PAH (WHO Group 1 FC II or III) were randomized 1:1 to Winrevair (target dose 0.7 mg/kg) (n=163) or placebo (n=160) administered subcutaneously once every 3 weeks.
The demographic and baseline clinical characteristics were generally comparable between the Winrevair and placebo groups. Participants in this study were adults with a median age of 48.0 years (range: 18 to 82 years); median weight 68 kg (range: 38.0 to 141.3 kg); 89.2% of participants were White, and 79.3% were not Hispanic or Latino; and 79.3% were female. The most common PAH etiologies were idiopathic PAH (58.5%), heritable PAH (18.3%), and PAH associated with connective tissue diseases (CTD) (14.9%). The mean time since PAH diagnosis to screening was 8.76 years. Most participants were receiving either triple (61.3%) or double (34.7%) background PAH therapy, and more than one-third (39.9%) were receiving prostacyclin infusions. The proportions of participants in WHO FC II (48.6%) and WHO FC III (51.4%) were similar in both groups. The STELLAR trial excluded patients diagnosed with human immunodeficiency virus (HIV)-associated PAH, PAH associated with portal hypertension, schistosomiasis-associated PAH, and pulmonary veno occlusive disease.
The primary efficacy endpoint was the change from baseline at Week 24 in 6-Minute Walk Distance (6MWD). In the Winrevair treatment group, the median of the placebo-adjusted change in 6MWD from baseline at Week 24 was 40.8 meters (95% CI: 27.5, 54.1; p <0.001). The median of the placebo-adjusted changes in 6MWD at Week 24 were also evaluated in subgroups (see Figure 1).

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

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



CHD = Congenital heart disease

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

Clinical improvement was 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

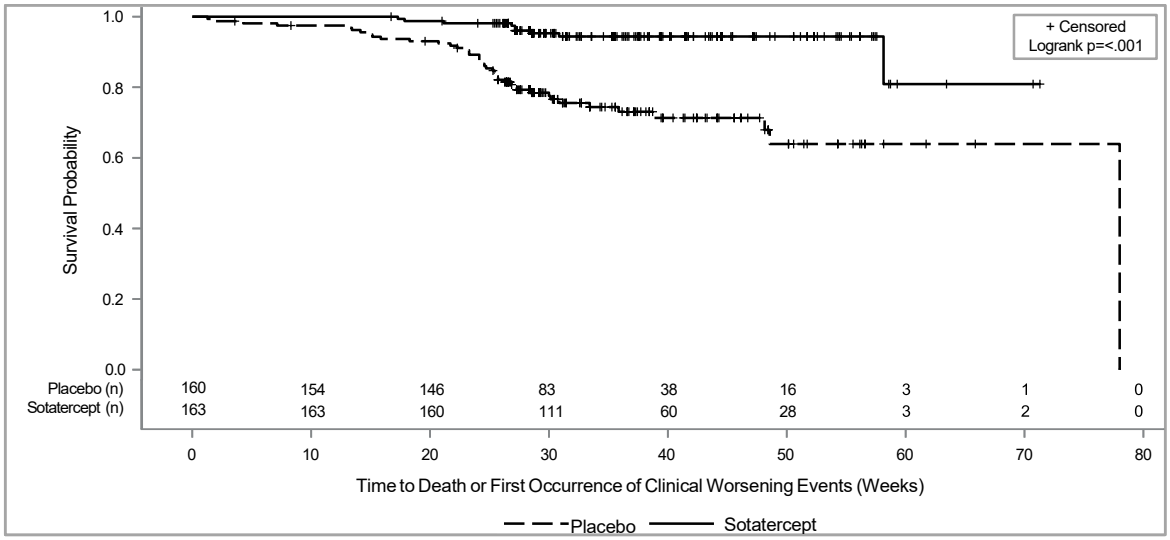
	Placebo (N=160)	Winrevair (N=163)
Total number of subjects who experienced death or at least one clinical worsening event, n (%)	42 (26.3)	9 (5.5)
Assessment of death or first occurrence of clinical worsening events*, n (%)		
Death	6 (3.8)	2 (1.2)
Worsening-related listing for lung and/or heart transplant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

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

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

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

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



n= Number of subjects at Risk

Pharmacokinetics

In patients with PAH, the geometric mean (%CV) steady-state AUC and steady-state peak concentration (C_{max}) at the dose of 0.7 mg/kg Q3W were 171.3 mcg×d/mL (34.2%) and 9.7 mcg/mL (30%CV), respectively. 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.

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

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

Winrevair lyophilized powder vial(s) should be prepared and administered by a health care professional. Step-by-step preparation and administration instructions are provided below.

Reconstitution Instructions

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

This will provide a final concentration of 50 mg/mL.

- Gently swirl the vial to reconstitute the drug product. DO NOT shake or vigorously agitate.
- Allow the vial to stand for up to 3 minutes to allow bubbles to disappear.
- Visually inspect the reconstituted solution. When properly mixed, Winrevair should be clear to opalescent and colorless to slightly brownish-yellow and does not have clumps or powder.
- If prescribed a 2-vial presentation, repeat the steps within this section to prepare the second vial.
- Use the reconstituted solution as soon as possible, but no later than 4 hours after reconstitution.

Administration Instructions

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

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

Authorisation number

69129

Packs

Type I glass vial sealed with a bromobutyl rubber stopper and aluminium seal with lime polypropylene flip-off cap

Winrevair 45 mg powder for solution for injection

Pack containing 1 vial. [B]

Pack containing 2 vials. [B]

Winrevair 60 mg powder for solution for injection

Pack containing 1 vial. [B]

Pack containing 2 vials. [B]

Marketing authorisation holder

MSD MERCK SHARP & DOHME AG

Luzern

Date of revision of the text

August 2024.