EU RISK MANAGEMENT PLAN (RMP)

for

Sotatercept Subcutaneous Injection

RMP version to be assessed as part of this application:

RMP Version number: 3.0

Data lock point for this RMP: 13-JUN-2025

Date of final sign off: 30-APR-2026

Rationale for submitting an updated RMP:

The RMP was updated to align sotatercept ADRs, per section 4.8 of the SmPC, included in PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S).

Summary of significant changes in this RMP:

The RMP was updated to align sotatercept ADRs, per section 4.8 of the SmPC, included in PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S); there are no changes to the risk profile in Modules SVII and SVIII.

Other RMP versions under evaluation:

Not applicable.

QPPV name: Peter De Veene, MD

QPPV signature: see signature page

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LIST OF ABBREVIATIONS

ActRIIA	activin receptor type IIA
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
ATC	anatomical therapeutic chemical classification system
AUC	area under the curve
BID	twice a day
BMI	body mass index
BMPR2	bone morphogenetic protein receptor type II
BMS	Bristol-Myers Squibb
BP	blood pressure
CBC	complete blood count
CCB	calcium channel blocker
CCDS	company core data sheet
CCSI	company core safety information
CHD-PAH	congestive heart disease-pulmonary arterial hypertension
CHO	Chinese hamster ovary
CI	confidence interval
CMML	chronic myelomonocytic leukemia
COMP	Committee for Orphan Medicinal Products
COMPERA	Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
CSR	clinical study report
CTD-PAH	connective tissue disease-pulmonary arterial hypertension
CVA	cerebrovascular accident
DBPC	double-blind placebo-controlled
dL	deciliter
ECD	extracellular domain
ECG	electrocardiogram
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EHR	electronic health records
EMA	European Medicines Agency
EPAR	European Public Assessment Report

ERA	endothelin receptor antagonist
ESC/ERS	European Society of Cardiology and European Respiratory Society
ESKD	end-stage kidney disease
EU	European Union
FC	functional class
Fc	fragment crystallizable
FDA	Food and Drug Administration
FVC	forced vital capacity
g	gram
GDF	growth differentiation factor
HCP	healthcare professional
HD	hemodialysis
HGB	hemoglobin
HIV	human immunodeficiency virus
HPAH	heritable pulmonary arterial hypertension
I/HPAH	idiopathic/heritable pulmonary arterial hypertension
ICH	international conference on harmonization
IFU	instructions for use
IgG1 Fc	immunoglobulin G1 fragment crystallizable
IMP	investigational medicinal product
INN	international nonproprietary name
IPAH	idiopathic pulmonary arterial hypertension
IQR	interquartile range
IV	intravenous(ly)
kDA	kilodalton
kg	kilogram
KORPAH	Korean Registry of Pulmonary Arterial Hypertension
L	liter
LQTS	long QT syndrome
LTDB	long-term double-blind
LTFU	long-term follow-up
MAA	marketing authorisation application
MDRD	modification of diet in renal disease
MDS	myelodysplastic syndrome
MedDRA	medical dictionary for regulatory activities

mg	milligram
mm	millimeter
mL	milliliter
M.W.	molecular weight
6MWD	6 minute walk distance
N/A	not applicable
NHS	National Health Service
NOAEL	no observed adverse effect level
NT-proBNP	N-terminal pro b-type natriuretic peptide
PAES	post-authorisation efficacy study
PAH	pulmonary arterial hypertension
PD	pharmacodynamic
PDCO	Paediatric Committee
PDE5	phosphodiesterase type 5
PFT	pulmonary function test
PH	pulmonary hypertension
PIP	paediatric investigation plan
PK	pharmacokinetics
PMW	post-menopausal women
PO	oral(ly)
PT	preferred term
PYT	patient-years of treatment
Q3W	every 3 weeks
RBC	red blood cell
RECOPILAR	Registro Colaborative de Hipertension Pulmonar en Argentina
REVEAL	Registry to Evaluate Early and Long-term PAH Disease Management
RHC	right heart catheterization
RMP	risk management plan
SAE	serious adverse event
SPAHR	Swedish Pulmonary Arterial Hypertension Registry
Smad	small mothers against decapentaplegic
SC	subcutaneous
SLR	systemic literature review
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query

SMR	Scottish Morbidity Record
SoC	standard of care
SPVU	Scottish Pulmonary Vascular Unit
TAR-EAIR/100 PYAR	time-at-risk exposure-adjusted incidence rate per 100 person-years at risk
ULN	upper limits of normal
UK	United Kingdom
US	United States
WHO	World Health Organization
WOCBP	women of child-bearing potential

PART I: PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s) (INN or Generic name)	Sotatercept
Pharmacotherapeutic group(s) (ATC Code)	Antihypertensives, antihypertensives for pulmonary arterial hypertension. (C02KX06)
Marketing Authorisation Applicant	Merck Sharp & Dohme B.V.
Number of medicinal products to which this RMP refers	One
Invented name in the European Economic Area (EEA)	Winrevair
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: a recombinant homodimeric fusion protein consisting of the extracellular domain of human activin receptor type IIA (ActRIIA) linked to the Fc domain of human IgG1, produced in Chinese Hamster Ovary cells by recombinant DNA technology.
	Summary of mode of action: Sotatercept is an activin signalling inhibitor with high selectivity for Activin-A, a dimeric glycoprotein which belongs to the transforming growth factor-β (TGF-β) superfamily of ligands. Activin-A binds to the ActRIIA regulating key signalling for inflammation, cell proliferation, apoptosis, and tissue homeostasis.
	Important information about its composition: Sotatercept is a homodimeric recombinant fusion protein expressed in CHO cells and consisting of the ECD of the human ActRIIA linked to the human IgG1 Fc domain. Each 45 mg single-dose vial provides 55 mg of sotatercept, and after reconstitution with 1.0 mL Sterile Water for Injection, the resulting concentration is 50 mg/1.0 mL of sotatercept and the nominal deliverable volume is 0.9 mL. Each 60 mg single-dose vial provides 72.5 mg of sotatercept, and after reconstitution with 1.3 mL Sterile Water for Injection, the resulting concentration is 50 mg/1.0 mL of sotatercept and the nominal deliverable volume is 1.2 mL. **Inactive Ingredients (List of excipients)** Citric acid monohydrate, sodium citrate, polysorbate 80, and sucrose.
Hyperlink to the Prescribing Information	See proposed Prescribing Information in Module 1.3
Indication(s) in the EEA	Current: Winrevair, in combination with other pulmonary arterial hypertension (PAH) therapies, is indicated for the treatment of PAH in adult patients with WHO Functional Class (FC) II, III, and IV.
	Proposed: Not applicable.

Table I.1: Product Overview

Dosage in the EEA	Current: Winrevair is administered once every 3 weeks as a single subcutaneous (SC) injection according to patient weight. Hgb and platelet count should be obtained prior to the first dose. It is contraindicated to initiate treatment if platelet count is consistently < 50 x 10^9/L. Treatment is initiated with a single dose of 0.3 mg/kg. Three weeks after a single starting dose of 0.3 mg/kg, the dose should be escalated to the recommended target dose 0.7 mg/kg after verifying acceptable Hgb and platelet count. Treatment should be continued at 0.7 mg/kg every 3 weeks unless dose adjustments are required.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: Winrevair powder and solvent for solution for injection is a white to off-white powder and a clear colourless water for injections available in 45 mg and 60 mg single-dose vials for SC administration after reconstitution. The single-dose vials are packaged in the following configurations: 1 x 45 mg vial, 1 x 60 mg vial, 2 x 45 mg vials, and 2 x 60 mg vials.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

PH is a chronic disease with many contributing etiologies. PH is characterized by an elevated mean pulmonary arterial pressure at rest. The 2022 ESC/ERS Guidelines classify PH into five groups based on the WHO Group classification: Group 1 (PAH), Group 2 (PH due to left heart disease), Group 3 (PH due to lung disease and/or hypoxia), Group 4 (PH associated with pulmonary artery obstructions), and Group 5 (PH with unclear and/or multifactorial mechanisms) [Ref. 5.4: 084PF5].

Indication:

Winrevair (sotatercept), in combination with other pulmonary arterial hypertension (PAH) therapies, is indicated for the treatment of PAH in adult patients with WHO Functional Class (FC) II, III, and IV.

Epidemiology:

Limited data have been published on the incidence and prevalence of PAH in the US, Europe, or the world. Many of the studies are not population-based or are poorly designed. Furthermore, many studies do not describe PAH prevalence overall. Instead, they describe the prevalence of specific PAH subtypes or by WHO FC, report on the prevalence of PAH in patients with a specific underlying condition or describe the prevalence of various disease manifestations or comorbidities. The complexity of the diagnosis of PAH may explain, to some extent, the variability in estimates of incidence and prevalence.

To provide the best estimate of the epidemiology, the Company conducted a SLR to summarize the incidence and prevalence of PAH and to describe key demographic and clinical characteristics [Ref. 5.4: 086S2S].

Incidence:

Based on the SLR [Ref. 5.4: 086S2S], estimates of the incidence of PAH ranged from 1.5 to 32.0 cases per million per year with a weighted average of 3.7 cases per million per year. The estimates based on RHC fell on the lower end of this range, with the lowest bound representing a likely underestimate from the US REVEAL registry. The upper bound originated from a claims-based review that identifies likely PAH cases via a diagnostic algorithm.

Table SI.1: Incidence Estimates for Group 1 PAH

Study Name	Country	Study Incidence Rate (cases per million per year)
RHC-based estimates		
Sweden (SPAHR)	Swedish PAH Registry [Ref. 5.4: 085DRC]	5.3
United States	Dubroff 2020 [Ref. 5.4: 05LKQH]	14.5
Poland	Kopec 2020 [Ref. 5.4: 084P4X]	5.2
RECOPILAR	Coronel 2018 [Ref. 5.4: 0877Z5]	4.4
Portugal (Northern Portugal)	Santos 2018 [Ref. 5.4: 085CJJ]	2.3
Latvia	Skride 2018 [Ref. 5.4: 085CKK]	13.7
Germany	Hoeper 2016 [Ref. 5.4: 05LF7B]	3.9
Republic of Korea (KORPAH)	Chung 2015 [Ref. 5.4: 0877Z4]	1.9
Switzerland	Mueller-Mottet 2015 [Ref. 5.4: 085CH9]	7.1
Czechia (Czech Republic)	Jansa 2014 [Ref. 5.4: 085CLG]	10.7
Spain	Escribano-Subias 2012 [Ref. 5.4: 05LF6Z]	3.7
United States (REVEAL)	Badesch 2010 [Ref. 5.4: 0886NV]	1.5
United Kingdom (SPVU)	Peacock 2007 [Ref. 5.4: 05LKQJ]	7.6
France	Humbert 2006 [Ref. 5.4: 00WDQY]	2.4
Echocardiogram or Claims-Based Algorithm Estimates		
United Kingdom (England)	Beaudet 2019 [Ref. 5.4: 0877Z3])	5.0
Republic of Korea	Song 2018 [Ref. 5.4: 0877ZC]	4.8
Canada (Ontario)	Wijeratne 2018 [Ref. 5.4: 05LF88]	32.0
United Kingdom (SMR)	Peacock 2007 [Ref. 5.4: 05LKQJ]	7.1

Source: [Ref. 5.4: 086S2S]

Prevalence:

The primary global meta-analysis based on the SLR [Ref. 5.4: 086S2S] using all PAH case definitions predicted 57.0 prevalent PAH cases per million population [95% CI: 44.6, 69.4], equivalent to roughly 330,231 adult PAH cases worldwide in 2025.

Table SI.2: Country-Specific RHC Prevalence Estimates for Adult Group 1 PAH

Country	Source	PAH Definition	PAH Prevalence Rate (cases per million)
Australia	Naing 2021 [Ref. 5.4: 0877ZB]	Echo + EHR Review	368.3
Australia	Strange 2012 [Ref. 5.4: 0877ZD]	Echo + EHR Review	150.0
Republic of Korea	Song 2018 [Ref. 5.4: 0877ZC]	Claims Analysis	20.2
Republic of Korea	Chung 2015 [Ref. 5.4: 0877Z4]	RHC	13.0
UK	NHS Digital 2021 [Ref. 5.4: 085DQS]	RHC	54.1
UK	Beaudet 2019 [Ref. 5.4: 0877Z3]	Claims Analysis	31.7
UK	Peacock 2007 (SPVU) [Ref. 5.4: 05LKQJ]	RHC	26.0
UK	Peacock 2007 (SMR) [Ref. 5.4: 05LKQJ]	Claims Analysis	52.0
US	Dubroff 2020 [Ref. 5.4: 05LKQH]	RHC	92.8
US	Kirson 2011 [Ref. 5.4: 05LF7T]	Claims Analysis	150.5
US	Badesch 2010 [Ref. 5.4: 0886NV]	RHC	10.8
Sweden	SPAHR 2021 [Ref. 5.4: 085DRC]	RHC	48.8
Poland	Kopec 2020 [Ref. 5.4: 084P4X]	RHC	30.8
Colombia	Miranda-Machado 2019 [Ref. 5.4: 0877Z9]	RHC	28.0
Argentina	Coronel 2018 [Ref. 5.4: 0877Z5]	RHC	9.2
Latvia	Skride 2018 [Ref. 5.4: 085CKK]	RHC	45.7
Canada	Wijeratne 2018 [Ref. 5.4: 05LF88]	Claims Analysis	268.0
Germany	Hoeper 2016 [Ref. 5.4: 05LF7B]	RHC	25.9
Japan	Kasahara 2015 [Ref. 5.4: 0877Z8]	Claims Analysis	15.6
Switzerland	Mueller-Mottet 2015 [Ref. 5.4: 085CH9]	RHC	8.6
Czechia	Jansa 2014 [Ref. 5.4: 085CLG]	RHC	22.4
Spain	Escribano-Subias 2012 [Ref. 5.4: 05LF6Z]	RHC	16.0
Israel	Fruchter 2008 [Ref. 5.4: 0877Z6]	Echo	56.0
France	Humbert 2006 [Ref. 5.4: 00WDQY]	RHC	15.0

Source: [Ref. 5.4: 086S2S]

For broader investigation into the possible range of PAH prevalence, secondary analyses specific to PAH definition were also conducted as part of the SLR. An RHC-confirmed estimate was provided as a lower bound of PAH diagnosed cases globally, while an estimate using exclusively studies with broader definitions (ie, echocardiogram diagnosis or claims-based algorithms) provided an upper estimate of PAH prevalence. The RHC-confirmed estimate included 15 studies and provided a prevalence rate of 33.3 cases per million population [95% CI: 27.4, 39.3], equating to a projected 193,054 cases globally in 2025. This estimate is consistent with a recently published systematic literature review reporting a mean prevalence based on RHC of 37 cases per million population [Ref. 5.4: 08SJ9Z]. The echocardiogram and claims-based estimate included nine studies and provided a prevalence rate of 113.1 cases per million population [95% CI: 71.5, 154.7], equating to a projected 654,902 cases globally in 2025.

The European prevalence of all forms of PAH is estimated to be 9 to 54 cases per million population (0.09 to 0.54 per 10,000). The mean prevalence is 0.29 per 10,000 with a median of 0.26 per 10,000. The incidence estimates range from 2.3 to 13.7 per million (0.023 to 0.137 per 10,000) with a mean and median of 0.06 and 0.05 per 10,000 per year.

The COMP Orphan Maintenance Assessment Report (EMADOC-1700519818-1497234), which re-evaluated the Orphan Designation in parallel with the original MAA, included a prevalence calculation using a sensitivity analysis to estimate the worst-case scenario. This calculation, which includes a multiplier to account for the prevalence in children and adolescents, results in an estimate of the upper limit of the prevalence rate of 1.6 per 10,000 (see Table SI.3). It should be noted that the proportion of diagnosed participants has been increasing as have the registry coverage and subgroups included, so some of the correction factors may not be necessary and 1.6 per 10,000 is likely to be an overestimate.

Table SI.3: Sensitivity Analysis for European Prevalence

Variable	Assumption	Correction Factor	Prevalence (Number per 10,000)
Base estimate			0.29 (based on mean prevalence estimate from the literature)
PAH subgroups	HPAH and IPAH account for only half of PAH patients	x2	0.58
Age groups	Approximately 15% of EU population is <15 years of age	x1.15	0.667
Undiagnosed subjects	Approximately 21% of PAH patients go undiagnosed for 2 years	x1.21	0.807
Registry coverage	Only 50% of PAH patients captured by regional registries	x2	1.61

Source: [Ref. 5.4: 08F9LD]

Demographics of the population in the proposed indication [Ref. 5.4: 086S2S]:

Gender: Across 97 studies, the median proportion of females is 70%, with an IQR of 64-75%.

Race/Ethnicity: Table SI.4 provides race/ethnicity estimates for the US. There were very few studies of race/ethnicity in non-US populations. In France, the percentages of White, Black, and Asian patients were 83.9%, 8.6%, and 5.4%, respectively. In the UK, across 2-3 studies, the corresponding percentages were 78.7-90.0%, 2.8-4.0%, and 6.0-14.7%. One study in Brazil found 66.3% Caucasian, 26.0% Mixed, 5.8% Black, and 1.9% Asian, while studies in Australia/New Zealand found 80.1-84.8% Caucasian, 6.1% Middle Eastern (single study), 4.6-5.1% Asian, and 5-10% Other.

Table SI.4: Race/Ethnicity of PAH Populations - United States

Metric	Estimate (Representative Studies)		
	Median (IQR)	Range	Number of Estimates
% White	73.0% (72.1%-82.8%)	48.7%-89.0%	27
% Black/African American	12.5% (10.8%-13.4%)	4.5%-14.6%	18
% Hispanic/ Latino	12.2% (8.9%-17.5%)	3.6%-35.7%	14
% Asian/Pacific Islander	3.4% (2.1%-4.4%)	0.6%-6.2%	10

Source: [Ref. 5.4: 086S2S]

Age at Diagnosis: Across 89 studies, the median age at diagnosis was 53.4 years with an IQR of 46.3 – 60.0 years.

Time to Diagnosis: Mean duration between age at symptom onset and diagnosis was calculated from 11 studies, with a median of 2.7 years and an IQR of 1.0-3.0 years.

Distribution of PAH subtypes:

Table SI.5: Group 1 PAH Sub-type Mean Prevalence Values and Ranges

PAH Sub-Type	Mean Prevalence Rate (Cases per 1 M)	Prevalence Range (Cases per 1 M)	Sources N of Source Estimates
IPAH*	15.0	3.0 – 27.7	19
HPAH	0.3	0.1 – 0.6	2
CHD-PAH	15.5	1.7 – 157.0	18
CTD-PAH	14.0	2.2 – 102.9	16
Drugs/Toxins	4.3	0.0 – 19.3	5
HIV-PAH	0.5	0.2 – 0.9	4
Portopulmonary hypertension	2.2	0.8 – 7.8	8

* Includes some I/HPAH combined rates when data were not separated – HPAH is typically a very small portion of disease within this category and so the cases should primarily reflect IPAH

Source: [Ref. 5.4: 086S2S]

WHO Functional Class: Among the studies reporting functional class, FC II and III account for the majority of patients (see Table SI.6). Therefore, most patients have more advanced disease at the time a diagnosis of PAH is established.

Table SI.6: Functional Class at PAH Diagnosis – Excluding Studies Without FC I Data

Functional Class	Median (IQR)	Number of Estimates
FC I	2.3% (1.0%-4.1%)	31
FC II	22.8% (17.4%-31.3%)	31
FC III	61.0% (50.9%-69.2%)	43
FC IV	10.9% (6.2%-12.9%)	43
Note: Because not every study reported all FCs, the medians do not add to 100%.		

Source: [Ref. 5.4: 086S2S]

Risk factors for the disease:

Sex: Females are at higher risk for developing PAH [Ref. 5.4: 084N78].

Family history: 10-27% of patients have HPAH, which is characterized by a pathogenic variant in one of the known genes related to PAH. The most common genetic mutation is bone morphogenetic protein receptor type II (BMPR2) mutation, which is inherited as an autosomal dominant trait with variable penetrance. These estimates may vary depending on whether the diagnosis is based on family history or genotyping [Ref. 5.4: 084R0F, 07YQ8J].

Disease history: Common etiologies underlying PAH in registries include scleroderma or other connective tissue diseases, and congenital heart disease [Ref. 5.4: 084R0F]. Other risk factors for PAH include systemic hypertension, portal hypertension, splenectomy, HIV infection, and Osler-Weber-Rendu syndrome (also known as hereditary hemorrhagic telangiectasia) [Ref. 5.4: 084N78, 084P4Q].

Drugs and toxins: Risk factors for PAH include exposure to certain drugs and toxins (eg, aminorex, fenfluramine, dexfenfluramine, benfluorex, methamphetamine, dasatinib, toxic rapeseed oil) [Ref. 5.4: 05J4R0].

The main existing treatment options:

Clinical evaluation (6MWD, WHO FC, and NT-proBNP), assessment of right ventricular function, and hemodynamic parameters are used to determine whether patients are of low-, intermediate-, or high-risk status, according to their expected 1-year mortality. The patient's risk status is used to determine appropriate treatment: the primary goal is to achieve low-risk status. PAH treatment guidelines also recommend that most PAH patients be managed with combination drug therapy [Ref. 5.4: 083NSM].

A treatment-naïve PAH patient should adopt general measures (eg, physical activity in stable patients) and supportive therapy (eg, oral anticoagulants, diuretics, oxygen therapy). Acute vasoreactivity testing should be performed for patients with IPAH, HPAH, or PAH associated with drugs or toxins, and vasoreactive patients should be treated with CCBs. Vasoreactive patients who do not have an adequate response to CCBs should be treated with approved PAH medications.

Most current PAH therapies act via the prostacyclin, endothelin, or nitric oxide pathways and primarily mediate their effects through pulmonary vasodilation [Ref. 5.4: 083Y64, 083Y7G]. Approved PAH therapies affecting these pathways including ERAs, PDE5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists.

Recently, sotatercept, an activin signaling inhibitor, was approved as a new PAH therapy. Sotatercept rebalances the pro-proliferative and anti-proliferative signaling to modulate vascular proliferation [Ref. 5.4: 07YQ8J]. Known adverse reactions of currently approved PAH therapies include the following: ERAs are associated with embryo-foetal toxicity, hepatoxicity, edema and anemia. PDE5 inhibitors can result in non-arteritic ischemic optic neuropathy, prolonged erection and hearing impairment. Riociguat, a guanylate cyclase stimulator, is associated with haemoptysis. Catheter-related infections and infusion interruptions of parenteral prostanoids can be life-threatening. Known adverse reactions associated with sotatercept include headache**,** epistaxis, telangiectasia, diarrhoea, dizziness, rash, thrombocytopenia, injection site pruritus, increased hemoglobin, gingival bleeding, increased blood pressure, erythema, urinary tract infection, back pain, colonic angioectasia, skin hypopigmentation, gastrointestinal tract bleeding, pericardial effusion, and intrapulmonary shunt.

Furthermore, PDE5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues all cause systemic vasodilation that may result in symptomatic hypotension or ischemia. Additive systemic hypotensive effects limit or contraindicate the use of these drugs in combination.

Despite the availability of several approved therapies, including ERAs, PDE5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists, many patients do not achieve low-risk status and/or individual treatment goals, and their long-term prognosis remains poor, with an estimated 5- to 7-year survival of approximately 50% after diagnosis [Ref. 5.4: 080ZZX, 05LZLF, 080JN8]. Lung transplantation is an option in severe cases [Ref. 5.4: 083NSM].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The progressive nature of PAH means that patients may initially experience mild symptoms but will eventually require treatment to maintain their quality of life. If left untreated, PAH can lead to right ventricular failure [Ref. 5.4: 084NP8]. The median survival of patients with untreated IPAH is 2.8 years. The median 1, 3, and 5-year survival rate for patients with untreated IPAH is 68%, 48%, and 34%, respectively [Ref. 5.4: 080JN8]. The median survival for patients with untreated PAH associated with systemic sclerosis is 1 year [Ref. 5.4: 084PF7].

While treatment advances over the last decade have favorably impacted life expectancy, survival among PAH patients is still poor. Based on the SLR, which included 56 studies with survival information [Ref. 5.4: 086S2S], 1-year post-diagnosis survival ranged from 79.6% to 100.0% (median 89.7%, IQR 86.3%-94.1%). At 3 years, the range was 53.0% to 95.4% (median 75.8%; IQR 67.1%-81.3%), and at 5 years, the range was 32.2% to 95.3% (median

66.1%, IQR 55.6%-72.9%). These estimates are largely consistent with a recently published SLR reporting global 1, 3, and 5 year survival ranging from 85% to 99%, 65% to 95%, and 50% to 86%, respectively [Ref. 5.4: 08SH9D]. These survival estimates do not include patient experience with sotatercept as the time period of these studies pre-dates the availability of this new PAH therapy.

Survival rates for FC I and II patients are considerably higher than those for FC III and IV patients. Five-year survival by functional class in newly diagnosed PAH patients from the REVEAL registry was reported as 72.2%, 71.7%, 60.0%, and 43.8% for functional classes I-IV, respectively [Ref. 5.4: 05KRZR]. A meta-analysis of published observational PAH registry studies reported a survival rate at 1 year of 93.3% (95% CI: 90.7,95.2) for WHO FC I or II patients compared with 81.2% (95% CI: 77.8,84.2) for FC III or IV patients. Two-year survival rates were reported as 85.5% (95% CI: 81.5,88.7) and 66.7% (95% CI: 62.2,71.0) for those in FC I or II and FC III or IV, respectively, with 3 year survival rates for FC I or II patients of 78.4% (95% CI: 73.1,82.9) and 54.8% (95% CI: 50.4,59.2) for those in FC III or IV [Ref. 5.4: 08ST6W]. However, as noted, a diagnosis of PAH is not typically confirmed until a patient presents with advanced disease. Thus, early diagnosis and measures to stabilize or improve a patient's FC are key goals in the management of PAH [Ref. 5.4: 083Y7G].

Complications of PAH include arrhythmias, hemoptysis, and mechanical complications [Ref. 5.4: 083NSM]. Mechanical complications in PAH are typically related to progressive dilatation of the pulmonary artery, such as pulmonary artery aneurysms, rupture and dissection, and compression of intrathoracic structures [Ref. 5.4: 084PF5].

Important co-morbidities:

In the US-based REVEAL registry, common comorbidities were systemic hypertension (40%), obesity defined as a BMI $\geq$ 30 kg/m^2 (33%), clinical depression (25%), obstructive airways disease not considered to be the cause of PH (22%), sleep apnoea (21%) and diabetes mellitus (12%) [Ref. 5.4: 084QWW].

Common comorbidities in the PAH population in the European COMPERA registry (n= 4,445) were systemic hypertension (52%), coronary heart disease (23%), diabetes mellitus (23%), thyroid disease (19%), venous thromboembolism (8%), and obstructive sleep apnoea (7%) [Ref. 5.4: 0888S7].

Based on the Company's SLR [Ref. 5.4: 086S2S], the most common comorbid conditions (reported in at least 5 studies with a median prevalence rate >15%) are shown in Table SI.7.

Table SI.7: Comorbid Conditions – Descriptive Findings for Frequently Identified Conditions

Comorbid Condition	Number of Studies Reporting Comorbid Condition	Median Prevalence Rate % (IQR %-%)
Diabetes	60	15.9 (8.5-24.2)
Hypertension [a]	53	40.0 (26.7-48.1)
Obesity	32	20.8 (18.3-29.8)
Pericardial effusion	30	29.0 (18.0-40.2)
Smoking and/or tobacco use	24	35.6 (8.8-46.4)
Sleep apnea	19	18.9 (13.0-20.9)
Heart failure [b]	11	38.9 (26.7-44.0)
Hypothyroidism	10	16.5 (8.6-17.7)
Interstitial lung disease	9	20.0 (16.0-29.7)
Connective tissue diseases	9	15.3 (8.8-19.0)
Chronic renal/kidney disease	9	15.2 (10.5-33.6)
Down Syndrome/Trisomy 21	6	18.3 (6.2-25.7)
Current alcohol use	5	35.0 (32.7-35.9)
Renal dysfunction	5	26.5 (17.3-37.8)
History of drug use [c]	5	16.4 (10.2-25.2)

[a] Includes essential hypertension, systemic hypertension, arterial hypertension.

[b] Includes congestive heart failure, heart failure, ventricular failure.

[c] Including psychoactive substances, weight loss drugs; excludes one study reporting lifetime methamphetamine use (89.8%) among meth-PAH patients.

Source: [Ref. 5.4: 086S2S]

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
General Toxicity Increases in measures of RBC mass (RBC, hematocrit, and hemoglobin) that were non-adverse and reversible occurred in rats and monkeys. At the NOAEL for these changes in rats and monkeys, sotatercept exposures were 18-fold and 13-fold, respectively, the clinical AUC at 0.7 mg/kg.	Based on the mechanism of action of sotatercept, increases in RBC count, hematocrit and hemoglobin are expected to occur. Mild to moderate increases in hemoglobin within the normal range may not be associated with any untoward effects and may be of benefit to PAH patients due to improved oxygen carrying capacity at higher hemoglobin levels. However, at levels significantly above the normal range, erythrocytosis may be associated with adverse effects including thromboembolic events, increased blood pressure, or hyperviscosity syndrome.
ActRIIA-dependent adrenal remodeling occurs after birth. In primates, this process is complete within the first year of life. In rats this process continues into early adulthood. In sotatercept-treated adolescent rats and adolescent monkeys, adrenal gland congestion, necrosis, and/or mineralization occurred in rats only. At the NOAEL for rat adrenal toxicity, sotatercept exposure was 2-fold the clinical exposure at 0.7 mg/kg.	These findings are unlikely to have relevance for adult human usage.
Adverse histologic changes occurred in the kidney (glomeruli and renal tubules) of rats and monkeys treated with sotatercept. These changes increased in a dose and time-dependent manner. Immune complex deposition was also noted in the kidney. However, kidney toxicity appeared to be a direct effect of sotatercept in animals. In monkeys, histologic changes in the kidney sometimes correlated with increases in blood urea nitrogen, creatinine, and/or urinary protein. At the NOAEL for kidney changes in rats and monkeys, sotatercept exposures were 2-fold the clinical exposure at 0.7 mg/kg.	The relevance of these findings to human usage is unclear. No signal of glomerulonephritis or tubulointerstitial nephritis has emerged in the clinical development programme.
Nonadverse mononuclear cell infiltrates and perivascular accumulations of foamy macrophages were present in the choroid plexus of monkeys treated with sotatercept. Findings in the choroid plexus did not correlate with neurobehavioral changes and were reversible after a 3-month treatment-free period. At the NOAEL for choroid plexus changes, sotatercept exposure was ≥13-fold that achieved clinically at 0.7 mg/kg.	The relevance of these findings to human usage is unclear. No signals of serious adverse nervous system events have emerged in the clinical development programme.
Mononuclear cell infiltrates were present in the liver of monkeys treated with sotatercept. This finding did not correlate with increases in liver enzymes or evidence of tissue injury and was reversible after a 3-month treatment-free period. At the NOAEL for mononuclear cell infiltrates in the liver, sotatercept exposure was similar to that achieved clinically at 0.7 mg/kg.	The relevance of these findings to human usage is unclear. No signal of liver injury has emerged in the clinical development programme.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Juvenile Rat Toxicity Sotatercept-mediated toxicities were similar in adult (see General Toxicity) and juvenile rats but generally occurred at higher severity and lower dosages in juvenile animals. The NOAEL in juvenile rats dosed on postnatal days 7 through 91 was <2-fold the clinical AUC at 0.7 mg/kg.	These findings are unlikely to have relevance for adult human usage.
Reproductive and Developmental Toxicity In the male rat fertility study, fertility and pregnancy indices were decreased (reversible), and testis and/or epididymis degeneration/atrophy (with hypospermatogenesis or aspermatogenesis) occurred secondary to outflow obstruction of the efferent ducts. The risk of testicular toxicity resulting from efferent duct blockage in humans is low. In contrast to rat efferent ductules that merge into a single duct, human efferent ductules enter the epididymis at several sites, allowing fluid outflow even if several ductules become occluded. A NOAEL for histologic changes in the male rat reproductive tract was not identified. At the NOAEL for male fertility functional changes, sotatercept exposure was 2-fold the clinical AUC at 0.7 mg/kg. In the female fertility study, fertility and fecundity indices were decreased, estrous cycle length was increased, and there were increases in pre- and postimplantation loss. At the NOAEL for female fertility endpoints, sotatercept exposure was 2-fold the clinical AUC at 0.7 mg/kg.	The effects of sotatercept on fertility in humans are not known. Based on findings in animals, sotatercept may compromise both male and female fertility.
In embryo-foetal developmental toxicology studies in pregnant rats and rabbits, there were increases in resorptions and postimplantation loss, and decreases in liter size and fetal weights. There was also an increased incidence of skeletal effects in rats (delays in ossification, increase in the incidence of supernumerary ribs with increases or decreases in thoracic and lumbar vertebrae) and rabbits (lower mean numbers of ossification sites). At the NOAEL in rats and rabbits, sotatercept exposures were 2-fold and 0.4-fold, respectively, the clinical exposure at 0.7 mg/kg.	Sotatercept may cause fetal harm if administered to pregnant women.
In the perinatal/postnatal rat toxicity study where rats were administered sotatercept during either pregnancy or lactation, there were drug-related adverse effects on pup body weight, pup body weight gain and/or sexual maturation in the offspring of dams dosed during lactation. There were no similar effects in offspring from dams that were dosed during gestation. Maternal administration of sotatercept during gestation or lactation did not cause effects on pup mortality, clinical signs, motor activity, learning and memory, mating and fertility, or ovarian and uterine parameters. At the NOAEL for effects on growth and maturation in pups exposed to sotatercept via milk, sotatercept exposure was 0.6-fold the clinical AUC at 0.7 mg/kg).	The risks to a nursing infant from maternal exposure to sotatercept are not known.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Carcinogenicity Carcinogenicity studies were not conducted with sotatercept, as these studies are not appropriate for biotechnology-derived therapeutics. In a weight-of-evidence risk assessment, sotatercept was determined to have a low risk for carcinogenicity due to the absence of proliferative changes in the nonclinical studies, its demonstrated low potential to suppress normal immune function in animals, and the absence of any potential for genotoxic metabolites. Based on the published literature, decreased availability of the sotatercept ligands activin A, activin B, and/or GDF-11 is generally associated with decreases in abnormal cell growth, migration, and invasion, and can decrease the tumor promoting function of activin A in immune cells.	Carcinogenicity has not been studied in animals. Given the weight of evidence, carcinogenicity is unlikely to be a relevant concern for human usage.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1 Clinical Study Information

Based on its RBC-stimulating pharmacological effects, sotatercept was previously evaluated for the treatment of refractory anemia in oncology, renal, and β-thalassemia indications. However, further development of sotatercept for these indications is not planned.

Given the effects of sotatercept's murine ortholog, RAP-011, on the vascular smooth muscle cell layer of the pulmonary vessel wall and improvements in mean pulmonary arterial pressure observed in a rodent model, sotatercept has also been evaluated for the treatment of patients with PAH.

In the PAH clinical development programme, encompassing completed studies and a long-term extension study, 742 participants have been treated with sotatercept at varying doses. These include participants from 2 Phase 2 studies (P001/A011-09/PULSAR and P002/A011-10/SPECTRA) and 4 Phase 3 studies (P003/A011-11/STELLAR, and MK-7962-006/A011-14/ZENITH, MK-7962-005/A011-13/HYPERION, and MK-7962-004/A011-12/SOTERIA). These studies are hereafter referred to by their study names PULSAR, SPECTRA, STELLAR, ZENITH, HYPERION, and SOTERIA, respectively.

In addition to the 742 PAH participants, there were 64 participants from 2 completed Phase 1 studies in healthy post-menopausal women as well as 286 participants from trials on the treatment of refractory anemia in oncology, renal, and β-thalassemia indications. Overall, approximately 1092 study participants have been treated with sotatercept in clinical studies at varying doses.

SIII.2 Patient Exposure

Duration of exposure by indication for all unblinded Company-sponsored completed studies as of 13-JUN-2025 is provided in Table SIII.2.1. Data for the ongoing Phase 3 PAH study, SOTERIA, are provided as of 15-AUG-2024. Participants in PAH studies include those from PULSAR, SPECTRA, STELLAR, ZENITH, HYPERION, and SOTERIA. Safety findings in non-PAH indications were not considered relevant to this RMP given the confounding by indication and comorbidities observed in these studies.

Our Company is pursuing development and marketing authorisation approval of sotatercept in PAH patients. Therefore, exposure by sub-groups of age and gender, dose, ethnic origin, and race is provided for only the PAH indication in Table SIII.2.2, Table SIII.2.3, Table SIII.2.4, and Table SIII.2.5.

Table SIII.2.1: Clinical Trial Exposure by Duration in Participants Treated with Sotatercept

	Healthy Volunteer (N=64)		Oncology (N=152)		Renal (N=88)		Beta-thal (N=46)		PAH (N=742)		Total (N=1092)	
Duration of Exposure (months)	n (%)	Participant-Years	n (%)	Participant-Years	n (%)	Participant-Years	n (%)	Participant-Years	n (%)	Participant-Years	n (%)	Participant-Years
< 1	40 (62.5)	0.11	9 (5.9)	0.69	17 (19.3)	1.19	0 (0.0)	NE	11 (1.5)	1.10	77 (7.1)	3.09
1 - < 3	16 (25.0)	3.04	48 (31.6)	9.32	21 (23.9)	3.42	9 (19.6)	1.74	29 (3.9)	4.70	123 (11.3)	22.22
3 - < 6	8 (12.5)	2.47	73 (48.0)	25.26	39 (44.3)	12.17	2 (4.3)	0.71	49 (6.6)	18.60	171 (15.7)	59.21
6 - < 12	0 (0.0)	NE	6 (3.9)	3.44	10 (11.4)	5.81	6 (13.0)	4.19	88 (11.9)	64.50	110 (10.1)	77.95
>= 12	0 (0.0)	NE	16 (10.5)	40.68	1 (1.1)	1.10	29 (63.0)	160.24	565 (76.1)	1468.90	611 (56.0)	1670.92
Total Participant-Years		5.62		79.40		23.69		166.89		1557.80		1833.39

Participants in PAH studies include those from PULSAR, SPECTRA, STELLAR, ZENITH, HYPERION and SOTERIA. SOTERIA with data cut as of 15-August-2024. Other PAH studies and all non-PAH studies are completed.

The total participant-years is defined as the sum of the treatment duration exposure in years for all participants for each pooled treatment group.

NE = Not Estimable.

Source: [RMP: sdtm-ex dm ds]

Table SIII.2.2: Clinical Trial Exposure by Age/Gender Group in PAH Participants Treated with Sotatercept

	0.3 mg/kg (N=47)		0.7 mg/kg (N=695)		Total (N=742)	
	n (%)	Participant -Year	n (%)	Participant -Year	n (%)	Participant -Year
18 - <45 y	20 (42.6)	97.1	239 (34.4)	526.5	259 (34.9)	623.6
M	3 (6.4)	12.7	37 (5.3)	70.3	40 (5.4)	83
F	17 (36.2)	84.4	202 (29.1)	456.2	219 (29.5)	540.6
45 - <65 y	21 (44.7)	86.7	273 (39.3)	522.9	294 (39.6)	609.6
M	2 (4.3)	5.2	68 (9.8)	126.3	70 (9.4)	131.5
F	19 (40.4)	81.5	205 (29.5)	396.6	224 (30.2)	478.1
65 - <75 y	5 (10.6)	25.2	149 (21.4)	245.5	154 (20.8)	270.7
M	0 (0.0)	NE	42 (6.0)	60.6	42 (5.7)	60.6
F	5 (10.6)	25.2	107 (15.4)	184.9	112 (15.1)	210.1
>=75 y	1 (2.1)	5.7	34 (4.9)	48.2	35 (4.7)	53.9
M	1 (2.1)	5.7	12 (1.7)	16.2	13 (1.8)	21.9
F	0 (0.0)	NE	22 (3.2)	32	22 (3.0)	32
Total	47 (100.0)	214.7	695 (100.0)	1343.1	742 (100.0)	1557.8
M	6 (12.8)	23.6	159 (22.9)	273.4	165 (22.2)	297
F	41 (87.2)	191.1	536 (77.1)	1069.7	577 (77.8)	1260.8

Participants from PULSAR, SPECTRA, STELLAR, ZENITH, HYPERION and SOTERIA are included. SOTERIA with data cut as of 15-August-2024. Other studies are completed studies.

The total participant-years is defined as the sum of the treatment duration exposure in years for all participants for each pooled treatment group.

Exposure data from participants receiving a starting dose of sotatercept of 0.3 mg/kg then escalating to a target of 0.7 mg/kg is summarized in the 0.7 mg/kg group.

Source: [RMP: sdtm-ex dm ds]

Table SIII.2.3: Clinical Trial Exposure by Dose in PAH Participants Treated with Sotatercept

Dose of Exposure	Participants	Mean Duration (days)	Participant-Years
0.3 mg/kg	47 (6.3)	1667.3	214.70
0.7 mg/kg	695 (93.7)	707.2	1343.10
Total	742 (100.0)	768.1	1557.80

Participants from PULSAR, SPECTRA, STELLAR, ZENITH, HYPERION and SOTERIA are included. SOTERIA with data cut as of 15-August-2024. Other studies are completed studies.

Each participant is counted once on each applicable dose category row.

Treatment duration (days) = Last dose date - First dose date + 1. Last dose date is the minimum value of [(the last dose date + 20), study discontinuation date, data cutoff date].

The total participant-years is defined as the sum of the treatment duration exposure in years for all participants for each pooled treatment group.

Source: [RMP: sdtm-ex dm ds]

Table SIII.2.4: Clinical Trial Exposure by Ethnic Origin in PAH Participants Treated with Sotatercept

	0.3 mg/kg (N=47)		0.7 mg/kg (N=695)		Total (N=742)	
	n (%)	Participant -Years	n (%)	Participant -Years	n (%)	Participant -Years
Hispanic Or Latino	13 (27.7)	57.2	118 (17.0)	273.1	131 (17.7)	330.3
Not Hispanic Or Latino	29 (61.7)	133.7	549 (79.0)	1022.4	578 (77.9)	1156.1
Unknown	0 (0.0)	NE	5 (0.7)	9.6	5 (0.7)	9.6
Not Reported	5 (10.6)	23.8	23 (3.3)	38	28 (3.8)	61.8
All	47 (100.0)	214.7	695 (100.0)	1343.1	742 (100.0)	1557.8

Participants from PULSAR, SPECTRA, STELLAR, ZENITH, HYPERION and SOTERIA are included. SOTERIA with data cut as of 15-August-2024. Other studies are completed studies.

The total participant-years is defined as the sum of the treatment duration exposure in years for all participants for each pooled treatment group.

Exposure data from participants receiving a starting dose of sotatercept of 0.3 mg/kg then escalating to a target of 0.7 mg/kg is summarized in the 0.7 mg/kg group.

Source: [RMP: sdtm-ex dm ds]

Table SIII.2.5: Clinical Trial Exposure by Race in PAH Participants Treated with Sotatercept

	0.3 mg/kg (N=47)		0.7 mg/kg (N=695)		Total (N=742)	
	n (%)	Participant -Years	n (%)	Participant -Years	n (%)	Participant -Years
White	45 (95.7)	205.6	615 (88.5)	1178.6	660 (88.9)	1384.2
Black Or African American	1 (2.1)	4.1	16 (2.3)	36.5	17 (2.3)	40.6
Asian	0 (0.0)	NE	20 (2.9)	32.6	20 (2.7)	32.6
American Indian Or Alaska Native	0 (0.0)	NE	2 (0.3)	7.1	2 (0.3)	7.1
Native Hawaiian Or Other Pacific Islander	1 (2.1)	5	2 (0.3)	6.7	3 (0.4)	11.7
Other	0 (0.0)	NE	27 (3.9)	43.2	27 (3.6)	43.2
Multiple	0 (0.0)	NE	4 (0.6)	15.4	4 (0.5)	15.4
Not Reported	0 (0.0)	NE	9 (1.3)	23	9 (1.2)	23
All	47 (100.0)	214.7	695 (100.0)	1343.1	742 (100.0)	1557.8

Participants from PULSAR, SPECTRA, STELLAR, ZENITH, HYPERION and SOTERIA are included. SOTERIA with data cut as of 15-August-2024. Other studies are completed studies.

The total participant-years is defined as the sum of the treatment duration exposure in years for all participants for each pooled treatment group.

Exposure data from participants receiving a starting dose of sotatercept of 0.3 mg/kg then escalating to a target of 0.7 mg/kg is summarized in the 0.7 mg/kg group.

Source: [RMP: sdtm-ex dm ds]

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Diagnosis of pulmonary hypertension WHO Groups 2, 3, 4, or 5	Sotatercept was studied only in PH WHO Group 1 (PAH).	No	No claims will be made for the effects of sotatercept in patients with PH WHO Groups 2, 3, 4, or 5.
Diagnosis of the following PAH Group 1 subtypes: HIV-associated PAH, PAH associated with portal hypertension, schistosomiasis associated PAH and pulmonary venoocclusive disease	These specific etiologies of PAH could confound interpretation of study efficacy results.	No	Based on the known safety profile and mechanism of action, it is not expected that the safety profile will be different in these subtypes.
Hgb at screening above gender-specific upper limit of normal, per local laboratory test	Patients with Hgb levels above the upper limit of normal were excluded from trial participation to avoid risks associated with erythrocytosis and to avoid confounding the interpretation of study results.	No	Erythrocytosis is an important identified risk for sotatercept. Instructions are provided in the label to obtain Hgb prior to first dose and to continue monitoring during treatment.
Uncontrolled systemic hypertension; as evidenced by sitting systolic BP > 160 mmHg or sitting diastolic BP > 100 mmHg.	This concomitant condition could confound the interpretation of study results.	No	Physicians who treat patients with PAH are experienced in managing hypertension.
Baseline systolic BP < 90 mmHg at screening.	Systolic BP < 90 mmHg indicates unstable hemodynamics which could affect interpretation of study results.	No	The safety profile of sotatercept does not suggest a need for its limitation in PAH patients with low systolic BP. Mean systolic BP increased by 2.2 mmHg in patients on sotatercept.
eGFR < 30 mL/min/1.73m^2 (as assessed by MDRD equation).	Comorbidities associated with severe renal impairment could influence the interpretation of study efficacy results.	No	Sotatercept has not been studied in PAH patients with severe renal impairment (eGFR <30 mL/min/1.73m^2). Sotatercept PK is comparable between non-PAH ESKD patients and patients with normal renal function. No dose adjustment is recommended for renally impaired patients.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Serum alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels > 3 × ULN. Known history of portal hypertension or chronic liver disease, including hepatitis B and/or hepatitis C (with evidence of recent infection and/or active virus replication), defined as mild to severe hepatic impairment (Child-Pugh Class A-C).	Baseline hepatic impairment could influence the interpretation of study results.	No	Hepatic impairment is not expected to influence sotatercept metabolism since sotatercept is metabolized via cellular catabolism.
History of full pneumonectomy. History of atrial septostomy within 180 days prior to the screening visit.	These concomitant procedures and conditions could influence interpretation of study results. The hemodynamics of patients who have had a pneumonectomy or a recent atrial septostomy are unstable and thus including these patients could confound data for important efficacy endpoints.	No	The safety profile of sotatercept in PAH does not suggest a safety concern in these patients.
PFT values of FVC < 60% predicted at the screening visit or within 6 months prior to the screening visit. Mild obstructive sleep apnea that is untreated.	These concomitant conditions could confound the interpretation of study results.	No	These requirements for PFT and other pulmonary criteria further ensure that studies were conducted in WHO Group 1 PH patients only and did not include patients with pulmonary disease of other classifications or etiologies. The safety profile of sotatercept in PAH does not suggest a safety concern in patients with reduced FVC (< 60% predicted) or untreated sleep apnea.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Initiation of an exercise programme for cardiopulmonary rehabilitation within 90 days prior to the screening visit or planned initiation during the study.	Patients undergoing cardiopulmonary rehabilitation programmes may experience changes in PAH disease severity or symptoms independent of PAH standard of care treatments or sotatercept, thereby confounding clinical trial data interpretation.	No	The safety profile of sotatercept in PAH does not suggest a safety concern in patients who have initiated an exercise programme for cardiopulmonary rehabilitation.
Received intravenous inotropes (eg, dobutamine, dopamine, norepinephrine, vasopressin) within 30 days prior to the screening visit.	Patients who have recently required any of these treatments for circulatory support may be at risk of recurrent hemodynamic instability that could confound data interpretation.	No	The safety profile of sotatercept in PAH does not suggest a safety concern in patients who have recently received intravenous inotropes.
Significant (≥ 2+ regurgitation) mitral regurgitation or aortic regurgitation valvular disease. Cerebrovascular accident within 3 months prior to the screening visit. Any symptomatic coronary disease events (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain) within 6 months prior to the screening visit. Left ventricular ejection fraction < 45% on historical echocardiogram within 6 months prior to the screening visit. Acutely decompensated heart failure within 30 days prior to the screening visit. History of restrictive, constrictive, or congestive cardiomyopathy.	The presence of these comorbidities could confound the interpretation of study results.	No	Sotatercept has not been studied in PAH patients with left heart valvular disease, cerebrovascular disease, symptomatic coronary disease, left heart failure and cardiomyopathies. The safety profile is not expected to be different in PAH patients with these comorbidities. Requirements excluding participants with valvular heart disease, left heart failure and cardiomyopathies further ensure that studies were conducted in WHO Group 1 PH patients only and did not include patients with PH of other classifications or etiologies. The safety profile of sotatercept in PAH does not suggest a safety concern in patients with recent CVA or coronary disease.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
ECG with Fridericia's corrected QT interval > 500 ms during the screening period. Personal or family history of LQTS or sudden cardiac death.	Prolongation of QT interval or history of LQTS can predispose to potentially fatal ventricular arrhythmias. This could confound interpretation of clinical trial.	No	The safety profile is not expected to be different in PAH patients with these comorbidities. In general, biologics have low potential for QT prolongation.
Baseline platelet count < 50,000/mm^3 (< 50.0 x 10^9/L) at screening.	This concomitant condition could confound interpretation of study results.	No	It is contraindicated to initiate treatment if the platelet count is consistently <50,000/mm^3 (<50.0 x 10^9/L) as specified in the product labeling. Severe thrombocytopenia is an important potential risk for sotatercept.
Pregnant or breastfeeding women.	Pregnant and lactating females are excluded to avoid potential harm to the unborn fetus or breastfeeding newborn.	No	Women who are pregnant or breastfeeding should not receive sotatercept as specified in the product labeling. Embryo-foetal toxicity is an important potential risk for sotatercept.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programme

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programme

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Paediatric Population	The use of sotatercept in participants less than 18 years of age is under investigation. A study is being conducted in accordance with the paediatric investigation plan (PIP) (EMEA-002756-PIP01-19) in participants 1 year to less than 18 years of age with PAH (WHO Group 1). The paediatric study is ongoing.
Elderly Population	In pooled PAH studies, 154/742 (20.8%; 270.7 person-years) participants treated with sotatercept were aged 65 - < 75 years and 35/742 (4.7%; 53.9 person-years) participants were aged ≥ 75 years.
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with a disease severity different from inclusion criteria in clinical trials	The use of sotatercept in participants with hepatic impairment has not been investigated. Hepatic impairment is not expected to influence sotatercept metabolism since sotatercept is metabolized via cellular catabolism. No dedicated PK studies of sotatercept in patients with renal impairment have been conducted in the PAH population. Renal impairment is not expected to affect the systemic exposures to sotatercept given its size (M.W. >69 kDa); eGFR (>30) was not a covariate affecting PK per population PK analysis. In PAH participants treated with sotatercept: • 203/675 (30.1%; 458.10 person-years) participants had eGFR ≥ 90 (normal) at baseline • 312/675 (46.2%; 733.50 person-years) participants had eGFR > 60 - 90 (mild renal impairment) • 150/675 (22.2%; 309.70 person-years) participants had eGFR 30 – 60 (moderate renal impairment) • 10/675 (1.5%; 13.30 person-years) participants had eGFR < 30 (severe renal impairment) Outside of the PAH population, exposure in ESKD participants with refractory anaemia was 23.69 person-years. As of the data cutoff, no studies have been completed in patients with a disease severity different from those who met the inclusion criteria in the initial registration studies.
Population with relevant different ethnic origin	Refer to Table SIII.2.4 and Table SIII.2.5.
Subpopulations carrying relevant genetic polymorphisms	No formal studies have been conducted.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

A summary of the worldwide distribution of sotatercept for the cumulative period from market introduction to 28-FEB-2025 is presented in Table SV1.2.1 based on the available data.

SV.1.1 Method Used to Calculate Exposure

The estimated patient exposure was based upon the assumption that a kit, whether containing 1 or 2 vials, is intended for a single subcutaneous injection administered once every 3 weeks according to patient weight. In order to estimate the PYT, the number of kits distributed was divided by 17.33 weeks, based on 52 weeks divided by 3.

It is important to note that the estimated PYT are not equivalent to the absolute numbers of patients treated.

SV.1.2 Exposure

Table SV1.2.1: Estimated Patient Exposure: Kit Distribution and Patient-Years of Treatment with Sotatercept to 28-FEB-2025

Strength	Distribution (total number of kits)		Patient-Years of Treatment
	Cumulative to 28-FEB-2025		Cumulative to 28-FEB-2025
	1-vial kit	2-vial kit	1-vial kit & 2-vial kit
45 mg	21,439	8,684	1,738
60 mg	14,211	1,139	886
Total	**35,650**	**9,823**	**2,624**

The estimate of patient exposure from market introduction is based on the availability of monthly drug distribution figures; hence, this estimate has been calculated from market introduction to 28-FEB-2025.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Sotatercept is available only through prescribing physicians and other health care providers with prescriptive authority. Neither sotatercept nor its components are known to possess addictive properties.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Table SVII.1.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Erythrocytosis
Important potential risks	Severe thrombocytopenia
	Embryo-foetal toxicity
Missing information	Long-term safety

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Thrombocytopenia, epistaxis, telangiectasia, increased blood pressure/hypertension and dizziness, headache, diarrhoea, erythema, rash, gingival bleeding, and injection site pruritus

These risks are further delineated as follows with frequencies derived from STELLAR DBPC+LTDB as per the SmPC:

Thrombocytopenia

Thrombocytopenia was reported in 10.4% of patients taking sotatercept. The majority of events were non-serious, mild, reversible, and were not associated with discontinuation of treatment. Thrombocytopenia was reported more frequently in patients also receiving prostacyclin infusion (21.5%) taking sotatercept compared with patients who were not receiving prostacyclin infusion (3.1%). Thrombocytopenia was managed by dose adjustments. No additional risk minimisation measures or additional pharmacovigilance activities are warranted; furthermore, severe thrombocytopenia is classified as an important potential risk.

Epistaxis

Most bleeding events were non-serious epistaxis. Epistaxis was reported in 22.1% of patients taking sotatercept. No additional risk minimisation measures or additional pharmacovigilance activities are warranted.

Telangiectasia

Telangiectasia was observed in 16.6% of patients taking sotatercept. Discontinuations of treatment due to telangiectasia were 1% in the sotatercept group. No additional risk minimisation measures or additional pharmacovigilance activities are warranted.

Increased blood pressure

Increased blood pressure was reported in 4.3% of patients taking sotatercept. In patients taking sotatercept, mean systolic blood pressure increased from baseline by 2.2 mmHg and diastolic blood pressure increased by 4.9 mmHg at 24 weeks. No additional risk minimisation measures or additional pharmacovigilance activities are warranted.

Dizziness

Dizziness was reported in 14.7% of patients taking sotatercept. No additional risk minimisation measures or additional pharmacovigilance activities are warranted.

Headache

Headache was reported in 24.5% of patients taking sotatercept. No additional risk minimisation measures or additional pharmacovigilance activities are warranted.

Diarrhoea

Diarrhoea was reported in 15.3% of patients taking sotatercept. No additional risk minimisation measures or additional pharmacovigilance activities are warranted.

Erythema

Erythema was reported in 3.1% of patients taking sotatercept. No additional risk minimisation measures or additional pharmacovigilance activities are warranted.

Rash

Rash was reported in 12.3% participants taking sotatercept. No additional risk minimisation measures or additional pharmacovigilance activities are warranted.

Gingival bleeding

Gingival bleeding was reported in 4.3% participants taking sotatercept. No additional risk minimisation measures or additional pharmacovigilance activities are warranted.

Injection site pruritus

Injection site pruritus was reported in 1.8% participants taking sotatercept. No additional risk minimisation measures or additional pharmacovigilance activities are warranted.

Table SVII.1.1.1 lists ADRs reported in patients receiving sotatercept in STELLAR as reflected in the SmPC.

Table SVII.1.1.1: Adverse Reactions

System organ class	Frequency	Adverse reaction
Blood and lymphatic 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
	Common	Gingival bleeding
Skin and subcutaneous tissue disorders	Very common	Telangiectasia[1] Rash
	Common	Erythema
General disorders and administration site conditions	Common	Injection site pruritus
Investigations	Common	Increased blood pressure[1,3]

[1] See description of selected adverse reactions

[2] Includes 'thrombocytopenia' and 'platelet count decreased'

[3] Includes 'hypertension', 'blood pressure diastolic increased' and 'blood pressure increased'

Other reasons for considering the risk not important for the RMP:

- **Impaired fertility**

The potential risk of Impaired fertility is based on non-clinical studies.

- **Serious bleeding**

In clinical studies, as noted in the SmPC, serious bleeding events (including gastrointestinal haemorrhage, intracranial haemorrhage) have been observed in 4.3% of patients taking sotatercept. Patients with serious bleeding events were more likely to be on prostacyclin background therapy and/or antithrombotic agents, have low platelet count, or be > 65 years of age.

- **Unintended underdose by HCP-trained lay user leading to lack of efficacy**

Unintended underdose by HCP-trained lay user leading to lack of efficacy is a potential risk based on the human factors studies.

These potential risks are adequately labelled in the SmPC and PL. No additional risk minimisation measures or additional pharmacovigilance activities are warranted. Additionally, with respect to unintended underdose, lack of efficacy and medication errors are routinely reviewed in the PSUR.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table SVII.1.2.1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety concern	Benefit risk impact
Important Identified Risk	
Erythrocytosis	Erythrocytosis may be asymptomatic or may be associated with vague symptoms such as headache, dizziness, myalgia, but may also predispose to potentially serious adverse consequences including hyperviscosity syndrome, hypertension, and thromboembolic events. In STELLAR, elevations in Hgb (>2 g/dL above ULN) occurred in 20 (12.3%) patients on sotatercept. No severe elevations (≥4 g/dL above ULN) were observed. Increases in Hgb were manageable by dose delays, dose reductions, or both. Periodic monitoring of hemoglobin is recommended, and dose modification guidance is provided in the product labeling. Because erythrocytosis can lead to serious adverse consequences, erythrocytosis is considered an important identified risk.
Important Potential Risks	
Severe thrombocytopenia	Severe thrombocytopenia may lead to serious or life-threatening hemorrhage. In STELLAR, reductions in platelet count <50,000/mm^3 (<50.0 x 10^9/L) occurred in 1.8% of patients on sotatercept. It is contraindicated to initiate treatment if the platelet count is consistently less than 50,000/mm^3 (50.0 x 10^9/L). Periodic monitoring of platelet counts is recommended, and dose modification guidance is provided in the product labeling. While severe thrombocytopenia may increase the risk of serious bleeding, a causal relationship between severe thrombocytopenia and sotatercept has not been established. Therefore, severe thrombocytopenia is considered an important potential risk.
Embryo-foetal toxicity	Based on findings in pregnant rats and rabbits, sotatercept may cause fetal harm if administered to pregnant women. As of the data cutoff, there was 1 pregnancy reported in the placebo group during the DBPC period of STELLAR. Treatment was withdrawn and the pregnancy was terminated electively by therapeutic abortion. Women of child-bearing potential (WOCBP) should use effective contraception during treatment and for at least 4 months after the last dose if treatment is discontinued. In view of the lack of clinical data, embryo-foetal toxicity is considered an important potential risk.
Missing Information	
Long-term safety	Long-term follow-up in the PAH clinical development programme is limited. Further data will be collected during the Company-sponsored long-term follow-up study (SOTERIA). Available data are presented in section SVII.3. The anticipated long-term use of sotatercept makes long-term safety relevant for inclusion in the RMP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

This section is not applicable as there are no new safety concerns identified for sotatercept.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Details on the important risks of sotatercept in the PAH population are presented in three formats: safety data from the pivotal STELLAR study, safety data from the Phase 3 studies, ZENITH and HYPERION, and cumulative safety data from SPECTRA, PULSAR, STELLAR, ZENITH, HYPERION, and SOTERIA.

STELLAR was a pivotal, multicenter, randomized, double-blind, placebo-controlled study in participants with PAH WHO FC II or III. In the 6-month DBPC period, participants were randomized to placebo or sotatercept as a single initial dose of 0.3 mg/kg, followed by 0.7 mg/kg for the remainder of the study. The extension period, beyond the 6-month DBPC period until the last participant completed the DBPC period, is referred to as the LTDB period.

ZENITH was a Phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group study in participants with PAH WHO FC III or FC IV who were at high risk of mortality. The study was divided into a Screening Period (up to 4 weeks), a DBPC Treatment Period (up to approximately 40 months), and a Follow-up Period (up to 8 weeks). Participants were randomized to placebo or sotatercept at a starting dose of 0.3 mg/kg, followed by 0.7 mg/kg for the remainder of the study.

HYPERION was a Phase 3, randomized, double-blind, placebo-controlled study to evaluate sotatercept in newly diagnosed intermediate- and high-risk PAH patients. The trial was event-driven based on clinical worsening and could last up to 47 months. Participants were randomized 1:1 to receive either placebo plus background PAH therapy or sotatercept plus background PAH therapy (starting dose 0.3 mg/kg, target dose 0.7 mg/kg).

Cumulative safety data from the 2 Phase 2 studies in PAH WHO FC II or III (SPECTRA and PULSAR), 3 Phase 3 studies in PAH WHO FC II or III (STELLAR, HYPERION and SOTERIA), and 1 Phase 3 study in PAH FC III or IV (ZENITH) are also provided for supportive safety analysis. This dataset is referred to as Cumulative Sotatercept Treatment in the tables in this section.

SPECTRA was an open-label study in participants with PAH WHO FC III. Participants in SPECTRA received an initial dose of 0.3 mg/kg, followed by 0.7 mg/kg for the remainder of the study.

PULSAR was a randomized placebo-controlled study in participants with PAH WHO FC II or III. Participants were randomized to placebo, sotatercept 0.3 mg/kg, or sotatercept 0.7 mg/kg in the 24-week placebo-controlled period. Participants in the placebo group were re-randomized to treatment with either sotatercept 0.3 or 0.7 mg/kg in the 30-month open-label extension period. Participants initially randomized to sotatercept continued the same

dose in the open-label extension period. After analyses of the primary endpoint, investigators were unblinded and permitted to uptitrate participants to the 0.7 mg/kg dose of sotatercept.

SOTERIA is an ongoing, open-label, follow-up study to assess long-term safety, tolerability and efficacy in participants who complete the Phase 2/3 PAH studies in the sotatercept programme. In SOTERIA, all participants from STELLAR received a single initial dose of sotatercept of 0.3 mg/kg, subsequently followed by 0.7 mg/kg, and will continue the 0.7 mg/kg dose for the remainder of the study. Participants from the clinical worsening event-driven studies, ZENITH and HYPERION, were eligible to roll over into SOTERIA if they met the rollover criteria specified in each study protocol or when the study ended. Participants from PULSAR and SPECTRA continued the same dose from their parent study (with an option to titrate to 0.7 mg/kg if on <0.7 mg/kg). All participants in SOTERIA have the option of choosing self-administration after HCP training with the kits.

For cumulative tables, data from SOTERIA are included under the respective parent study. In addition, there is no pooled placebo group in this dataset because participants randomized to placebo in the DBPC period of PULSAR crossed over to sotatercept treatment in the extension period, and SPECTRA was a single-arm uncontrolled study.

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Erythrocytosis
Potential Mechanisms Sotatercept functions as a ligand trap by binding to select TGF-β superfamily ligands. Sotatercept is thought to increase RBC counts, hemoglobin and hematocrit by trapping GDF-11 and other ligands that bind to ActRIIA and impede terminal erythroid maturation [Ref. 5.4: 084N7D] [Ref. 5.4: 084N7K]. As a result, increased erythroid maturation and increased erythropoiesis occur.
Evidence Source(s) and Strength of Evidence Mechanism of action: strong evidence Animal studies: moderate evidence Clinical studies: strong evidence
Characterization of the Risk Refer to Table SII.1 for key safety findings associated with erythrocytosis in animal studies. As of the data cutoff for this RMP, no new information from post-marketing experience has been identified that necessitates an update to this safety concern. **Frequency with 95% CI** Erythrocytosis occurred more frequently in participants taking sotatercept than in the placebo group in STELLAR, ZENITH and HYPERION.

STELLAR [a]		
Erythrocytosis [b]	**Placebo (N=160)**	**Sotatercept (N=306)**
Participants with ≥ 1 SAE, n (%)	0 (0.0)	0 (0.0)
Incidence (%) of Participants with ≥ 1 AE	1 (0.6)	44 (14.4)
TAR-EAIR/100 PYAR [c] (95% CI)	0.8 (0.0, 4.5)	7.1 (5.1, 9.5)

[a] Participants from STELLAR treated with placebo, but treated with sotatercept after the rollover to SOTERIA, are included in both placebo (while participating in STELLAR) and sotatercept (while participating in SOTERIA) groups. SOTERIA with data cut as of 15-Aug-2024.

[b] MedDRA search strategy includes PTs Red blood cell count increased, Full blood count increased, Haematocrit increased, Haemoglobin increased, Haemoglobin abnormal, Polycythaemia, Stress polycythaemia

[c] TAR-EAIR is determined for participants with ≥ 1 AE and is defined as: (Number of participants with event / total person-years at risk) * 100 where the person-years for participants at risk with the event is calculated as (Start date of the first event – first dose date +1)/365.25. For participants that did not experience the event, the person-years for participants at risk with the event is calculated as (end date of treatment-emergent period – first dose date +1)/365.25. The total person-years at risk is the sum of the person-years at risk for all participants within the treatment group.

ZENITH [a]		
Erythrocytosis [b]	**Placebo (N=86)**	**Sotatercept (N=113)**
Participants with ≥ 1 SAE, n (%)	0 (0.0)	0 (0.0)
Incidence (%) of Participants with ≥ 1 AE	1 (1.2)	15 (13.3)
TAR-EAIR/100 PYAR [c] (95% CI)	1.8 (0.0, 10.1)	16.9 (9.5, 27.9)

[a] Participants from ZENITH treated with placebo, but treated with sotatercept after the rollover to SOTERIA, are included in both placebo (while participating in ZENITH) and sotatercept (while participating in SOTERIA) groups. SOTERIA with data cut as of 15-Aug-2024.

[b] MedDRA search strategy includes PTs Red blood cell count increased, Full blood count increased, Haematocrit increased, Haemoglobin increased, Haemoglobin abnormal, Polycythaemia, Stress polycythaemia.

[c] TAR-EAIR is determined for participants with ≥ 1 AE and is defined as: (Number of participants with event / total person-years at risk) * 100 where the person-years for participants at risk with the event is calculated as (Start date of the first event – first dose date +1)/365.25. For participants who did not experience the event, the person-years for participants at risk with the event is calculated as (end date of treatment-emergent period – first dose date +1)/365.25. The total person-years at risk is the sum of the person-years at risk for all participants within the treatment group.

HYPERION [a]		
Erythrocytosis [b]	**Placebo (N=160)**	**Sotatercept (N=198)**
Participants with ≥ 1 SAE, n (%)	0 (0.0)	0 (0.0)
Incidence (%) of Participants with ≥ 1 AE	2 (1.3)	19 (9.6)
TAR-EAIR/100 PYAR [c] (95% CI)	1.8 (0.2, 6.4)	12.7 (7.6, 19.8)

[a] Participants from HYPERION treated with placebo, but treated with sotatercept after the rollover to SOTERIA, are included in both placebo (while participating in HYPERION) and sotatercept (while participating in SOTERIA) groups. SOTERIA with data cut as of 15-Aug-2024.

[b] MedDRA search strategy includes PTs Red blood cell count increased, Full blood count increased, Haematocrit increased, Haemoglobin increased, Haemoglobin abnormal, Polycythaemia, Stress polycythaemia.

[c] TAR-EAIR is determined for participants with ≥ 1 AE and is defined as: (Number of participants with event / total person-years at risk) * 100 where the person-years for participants at risk with the event is calculated as (Start date of the first event – first dose date +1)/365.25. For participants who did not experience the event, the person-years for participants at risk with the event is calculated as (end date of treatment-emergent period – first dose date +1)/365.25. The total person-years at risk is the sum of the person-years at risk for all participants within the treatment group.

Cumulative Sotatercept Treatment [a]	
Erythrocytosis [b]	**Sotatercept (N=742)**
Participants with ≥ 1 SAE, n (%)	1 (0.1)
Incidence (%) of Participants with ≥ 1 AE	157 (21.2)
TAR-EAIR/100 PYAR[c] (95% CI)	12.5 (10.7, 14.7)

[a] Includes data from PULSAR, SPECTRA, STELLAR, ZENITH, HYPERION as of the data cutoff. SOTERIA with data cut as of 15-Aug-2024.

[b] MedDRA search strategy includes PTs Red blood cell count increased, Full blood count increased, Haematocrit increased, Haemoglobin increased, Haemoglobin abnormal, Polycythaemia, Stress polycythaemia.

[c] TAR-EAIR is determined for participants with ≥ 1 AE and is defined as: (Number of participants with event / total person-years at risk) * 100 where the person-years for participants at risk with the event is calculated as (Start date of the first event – first dose date +1)/365.25. For participants who did not experience the event, the person-years for participants at risk with the event is calculated as (end date of treatment-emergent period – first dose date +1)/365.25. The total person-years at risk is the sum of the person-years at risk for all participants within the treatment group.

Seriousness/Outcomes

Cumulatively, there was 1 treatment-related SAE (red blood cell count increased) that occurred in 1 participant.

The outcomes of AEs of erythrocytosis in the PAH clinical development programme are summarized.

Sotatercept Treatment [a, b, c, d]				
Outcome	**STELLAR** [a] **[N=306 (%)]**	**ZENITH** [a] **[N=113 (%)]**	**HYPERION** [a] **[N=198 (%)]**	**Cumulative** [b] **[N=742 (%)]**
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not Resolved	18 (5.9)	3 (2.7)	7 (3.5)	52 (7.0)
Resolved	26 (8.5)	14 (16.3)	14 (7.1)	110 (14.8)
Resolving	9 (2.9)	1 (0.9)	1 (0.5)	23 (3.1)
Sequelae	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total Participants	44 (14.4)	15 (13.3)	19 (9.6)	157 (21.2)

[a] Participants from STELLAR, ZENITH, and HYPERION treated with placebo, but treated with sotatercept after the rollover to SOTERIA, are included in both placebo (while participating in STELLAR, ZENITH or HYPERION) and sotatercept (while participating in SOTERIA) groups.

[b] Cumulative sotatercept treatment includes data from PULSAR, SPECTRA, STELLAR, ZENITH, and HYPERION as of the data cutoff. SOTERIA with data cut as of 15-Aug-2024.

[c] MedDRA search strategy includes PTs Red blood cell count increased, Full blood count increased, Haematocrit increased, Haemoglobin increased, Haemoglobin abnormal, Polycythaemia, Stress polycythaemia.

[d] A participant may be counted more than once on each applicable row if experiencing more than 1 AE.

Severity and Nature of Risk

All but 1 case in the PAH clinical trial programme were mild to moderate.

Sotatercept Treatment [a]				
Severity [c]	**STELLAR** [a] **[N =306 (%)]**	**ZENITH** [a] **[N=113 (%)]**	**HYPERION** [a] **[N=198 (%)]**	**Cumulative** [b] **[N=742 (%)]**
Mild	29 (9.5)	8 (7.1)	11 (5.6)	110 (14.8)
Moderate	15 (4.9)	7 (6.2)	8 (4.0)	46 (6.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

[a] Participants from STELLAR, ZENITH and HYPERION treated with placebo, but treated with sotatercept after the rollover to SOTERIA, are included in both placebo (while participating in STELLAR, ZENITH or HYPERION) and sotatercept (while participating in SOTERIA) groups.

[b] Cumulative sotatercept treatment includes data from PULSAR, SPECTRA, STELLAR, ZENITH, and HYPERION as of the data cutoff. SOTERIA with data cut as of 15-Aug-2024.

[c] Participants with > 1 event for any given row label category are counted a single time for that category. If a subject experiences an AE with the same SOC and PT more than once with a different severity, then the preferred term with the highest severity will be used.

Risk Factors and Risk Groups

PAH is associated with a hypercoagulable state [Ref. 5.4: 084N70], and thromboembolism is a comorbidity of PAH. Thromboembolic events occurred in 8% of the PAH population (n= 4,445) in the COMPERA registry [Ref. 5.4: 0888S7]. Patients with a history of thromboembolism may be at increased risk of erythrocytosis-associated thromboembolic events [Ref. 5.4: 084P4K, 0885QC, 0885QB].

Preventability

Ongoing monitoring of hemoglobin is recommended to minimise risk. Dose modification recommendations are included in labeling to manage increases in hemoglobin. Patients with a history of thromboembolism should be on appropriate medical prophylaxis (eg, antiplatelet agents, anticoagulants).

Impact on the Risk-Benefit Balance of the Product

Increases in hemoglobin are inherent to the mechanism of action and are not necessarily adverse in patients with PAH if hemoglobin remains within the normal range.

Clinically significant erythrocytosis, if not appropriately managed, may lead to complications including thromboembolic events, increased blood pressure, and hyperviscosity syndrome.

The risk is manageable and, given the significant morbidity and mortality associated with PAH, the impact of erythrocytosis on benefit-risk is expected to be low. Therefore, routine PV activities and risk minimisation measures are considered sufficient.

Public Health Impact

This risk has no public health impact outside its effects on individual patients.

Important Potential Risk: Severe thrombocytopenia

Potential Mechanisms

Not known.

Evidence Source(s) and Strength of Evidence

Animal studies: weak evidence

Clinical studies: moderate evidence

Characterization of the Risk

In non-clinical studies, sotatercept administration caused decreases in platelet volume or number in rats that were of minimal toxicological significance, and slight decreases in platelet number in monkeys with no correlative change in coagulation parameters. In both species, platelet effects were non-adverse and reversible.

As of the data cutoff for this RMP, no new information from post-marketing experience has been identified that necessitates an update to this safety concern.

Frequency with 95% CI

Severe thrombocytopenia occurred at low rates in participants taking sotatercept and in the placebo group in STELLAR and ZENITH. No cases of severe thrombocytopenia were reported in HYPERION. The cumulative incidence of severe thrombocytopenia (TAR-EAIR) for sotatercept was similar to the incidence from STELLAR and ZENITH.

STELLAR [a]		
Severe thrombocytopenia [b]	**Placebo (N=160)**	**Sotatercept (N=306)**
Participants with ≥ 1 SAE, n (%)	0 (0.0)	1 (0.3)
Incidence (%) of Participants with ≥ 1 AE	0 (0.0)	3 (1.0)
TAR-EAIR/100 PYAR [c] (95% CI)	0 (NE, NE)	0.5 (0.1, 1.3)

NE=not estimable

[a] Participants from STELLAR treated with placebo, but treated with sotatercept after the rollover to SOTERIA, are included in both placebo (while participating in STELLAR) and sotatercept (while participating in SOTERIA) groups. SOTERIA with data cut as of 15-Aug-2024.

[b] Includes any PT within MedDRA SMQ Haematopoietic thrombocytopenia (narrow) which met ≥ Grade 3 or 'Severe' severity criteria.

[c] TAR-EAIR is determined for participants with ≥ 1 AE and is defined as: (Number of participants with event / total person-years at risk) * 100 where the person-years for participants at risk with the event is calculated as (Start date of the first event – first dose date +1)/365.25. For participants that did not experience the event, the person-years for participants at risk with the event is calculated as (end date of treatment-emergent period – first dose date +1)/365.25. The total person-years at risk is the sum of the person-years at risk for all participants within the treatment group.

ZENITH [a]		
Severe thrombocytopenia [b]	**Placebo (N=86)**	**Sotatercept (N=113)**
Participants with ≥ 1 SAE, n (%)	0 (0.0)	0 (0.0)
Incidence (%) of Participants with ≥ 1 AE	1 (1.2)	1 (0.9)
TAR-EAIR/100 PYAR [c] (95% CI)	1.8 (0.0, 10.2)	1.0 (0.0, 5.8)

[a] Participants from ZENITH treated with placebo, but treated with sotatercept after the rollover to SOTERIA, are included in both placebo (while participating in ZENITH) and sotatercept (while participating in SOTERIA) groups. SOTERIA with data cut as of 15-Aug-2024.

[b] Includes any PT within MedDRA SMQ Haematopoietic thrombocytopenia (narrow) which met ≥ Grade 3 or 'Severe' severity criteria.

[c] TAR-EAIR is determined for participants with ≥ 1 AE and is defined as: (Number of participants with event / total person-years at risk) * 100 where the person-years for participants at risk with the event is calculated as (Start date of the first event – first dose date +1)/365.25. For participants that did not experience the event, the person-years for participants at risk with the event is calculated as (end date of treatment-emergent period – first dose date +1)/365.25. The total person-years at risk is the sum of the person-years at risk for all participants within the treatment group.

HYPERION [a]		
Severe thrombocytopenia [b]	**Placebo (N=160)**	**Sotatercept (N=198)**
Participants with ≥ 1 SAE, n (%)	0 (0.0)	0 (0.0)
Incidence (%) of Participants with ≥ 1 AE	0 (0.0)	0 (0.0)
TAR-EAIR/100 PYAR [c] (95% CI)	0 (NE, NE)	0 (NE, NE)

NE=not estimable

[a] Participants from HYPERION treated with placebo, but treated with sotatercept after the rollover to SOTERIA, are included in both placebo (while participating in HYPERION) and sotatercept (while participating in SOTERIA) groups. SOTERIA with data cut as of 15-Aug-2024.

[b] Includes any PT within MedDRA SMQ Haematopoietic thrombocytopenia (narrow) which met ≥ Grade 3 or 'Severe' severity criteria.

[c] TAR-EAIR is determined for participants with ≥ 1 AE and is defined as: (Number of participants with event / total person-years at risk) * 100 where the person-years for participants at risk with the event is calculated as (Start date of the first event – first dose date +1)/365.25. For participants that did not experience the event, the person-years for participants at risk with the event is calculated as (end date of treatment-emergent period – first dose date +1)/365.25. The total person-years at risk is the sum of the person-years at risk for all participants within the treatment group.

Cumulative Sotatercept Treatment [a]	
Severe thrombocytopenia [b]	**Sotatercept (N=742)**
Participants with ≥ 1 SAE, n (%)	4 (0.5)
Incidence (%) of Participants with ≥ 1 AE	11 (1.5)
TAR-EAIR/100 PYAR [c] (95% CI)	0.8 (0.4, 1.4)

[a] Includes data from PULSAR, SPECTRA, STELLAR, ZENITH and HYPERION as of the data cutoff. SOTERIA with data cut as of 15-Aug-2024.

[b] Includes any PT within MedDRA SMQ Haematopoietic thrombocytopenia (narrow) which met ≥ Grade 3 or 'Severe' severity criteria.

[c] TAR-EAIR is determined for participants with ≥ 1 AE and is defined as: (Number of participants with event / total person-years at risk) * 100 where the person-years for participants at risk with the event is calculated as (Start date of the first event – first dose date +1)/365.25. For participants that did not experience the event, the person-years for participants at risk with the event is calculated as (end date of treatment-emergent period – first dose date +1)/365.25. The total person-years at risk is the sum of the person-years at risk for all participants within the pooled treatment group.

Seriousness/Outcomes

Participants with SAEs of severe thrombocytopenia had alternative explanations for the events.

The outcomes of AEs associated with severe thrombocytopenia in the PAH clinical development programme are summarized.

Sotatercept Treatment [a, b, c, d]				
Outcome	**STELLAR** [a] **[N=306 (%)]**	**ZENITH** [a] **[N=113 (%)]**	**HYPERION** [a] **[N=198 (%)]**	**Cumulative** [b] **[N=742 (%)]**
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not Resolved	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Resolved	3 (1.0)	1 (0.9)	0 (0.0)	9 (1.2)
Resolving	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Sequelae	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total Participants	3 (1.0)	1 (0.9)	0 (0.0)	11 (1.5)

[a] Participants from STELLAR, ZENITH and HYPERION studies treated with placebo, but treated with sotatercept after the rollover to SOTERIA, are included in both placebo (while participating in STELLAR, ZENITH or HYPERION) and sotatercept (while participating in SOTERIA) groups.

[b] Includes data from PULSAR, SPECTRA, STELLAR, ZENITH, and HYPERION as of the data cutoff. SOTERIA with data cut as of 15-Aug-2024.

[c] Includes any PT within MedDRA SMQ Haematopoietic thrombocytopenia (narrow) that met ≥ Grade 3 or 'Severe' severity criteria.

[d] A participant may be counted more than once on each applicable row if experiencing more than 1 AE.

Severity and Nature of Risk

In STELLAR and ZENITH, 3/306 (1.0%) and 1/113 (0.9%) of participants experienced AE(s) of severe thrombocytopenia, respectively. No events of severe thrombocytopenia were reported in HYPERION. Cumulatively, 11/742 (1.5%) participants in the PAH clinical development programme experienced AEs of severe thrombocytopenia. No consistent temporal association of severe thrombocytopenia with bleeding events was observed.

Risk Factors and Risk Groups

A study of the prevalence of thrombocytopenia in patients with IPAH showed that men (34%) were more likely to have thrombocytopenia than women (15%) [Ref. 5.4: 084PMK].

Thrombocytopenia is also associated with the use of prostacyclin analogues. Published studies show that thrombocytopenia (platelet count < 150,000/mL) was observed in 34% of PAH patients treated with epoprostenol compared with 15% of patients receiving oral therapy with bosentan, ambrisentan, or sildenafil, seen over a 12-month period. The dose of epoprostenol was associated with the severity of thrombocytopenia [Ref. 5.4: 0844LG]. While most patients had mild thrombocytopenia with no obvious clinical consequences, some patients had significant morbidity related to thrombocytopenia.

During STELLAR (DBPC+LTDB), thrombocytopenia was reported more frequently in participants also receiving prostacyclin infusion (21.5%) compared to participants not receiving prostacyclin infusion (3.1%). In ZENITH, thrombocytopenia was reported frequently in participants in the sotatercept group also receiving prostacyclin infusion (24.5%) compared to participants in the sotatercept group not receiving prostacyclin infusion (0%). In HYPERION, thrombocytopenia was reported in 4.4% of patients taking sotatercept. No severe reduction in platelet count < 50 x 10^9/L occurred in patients taking sotatercept. Thrombocytopenia was reported more frequently in patients also receiving prostacyclin infusion (7.7%) compared to patients not receiving prostacyclin infusion (3.7%).

Preventability

Dose modification recommendations are included in product labeling. The patient's platelet count should be monitored prior to the first dose and periodically thereafter to determine whether dose adjustments are required. It is contraindicated to initiate treatment if the platelet count is consistently < 50,000/mm^3 (50.0 x 10^9/L).

Impact on the Risk-Benefit Balance of the Product

Severe thrombocytopenia may be associated with bleeding that could be life-threatening. The risk is manageable and, given the significant morbidity and mortality associated with PAH, the impact on benefit-risk is expected to be low. Therefore, routine risk minimisation (product labeling) and routine PV/safety monitoring via ongoing clinical trials are considered sufficient risk management measures.

Public Health Impact

This risk has no public health impact outside its effects on individual patients.

Important Potential Risk: Embryo-foetal toxicity

Potential Mechanisms

By virtue of sotatercept's mechanism of action, increases in postimplantation loss and effects on fetal growth and development may occur.

Evidence Source(s) and Strength of Evidence

Animal studies: strong evidence

Characterization of the Risk

Refer to Table SII.1 for key safety findings associated with embryo-foetal toxicity in animals.

As of the data cutoff, in the clinical experience, 3 pregnancies were reported. One pregnancy was reported in the placebo group during the DBPC period of STELLAR. Treatment was withdrawn and the pregnancy was terminated electively by therapeutic abortion. A second pregnancy was reported in SOTERIA and was also terminated. The third pregnancy, also reported in SOTERIA, reported delivery of a premature baby and foetal exposure during pregnancy. This report mentioned confounding factors of high-risk pregnancy due to the underlying maternal heritable pulmonary hypertension with worsening oxygenation and lactatemia, that prompted caesarean section prior to the estimated date of delivery. No fetal malformations were reported.

As of the data cutoff for this RMP, no new information from post-marketing experience has been identified that necessitates an update to this safety concern.

Risk Factors and Risk Groups

WOCBP who do not adhere to using effective contraception.

Preventability

Sotatercept is not recommended during pregnancy and in WOCBP not using contraception. Pregnancy testing is recommended for WOCBP before starting treatment. WOCBP should use effective contraception during treatment and for at least 4 months after the last dose if treatment is discontinued. Pregnancy and pregnancy outcome should be reported per routine pharmacovigilance.

Impact on the Risk-Benefit Balance of the Product

With appropriate use of pregnancy testing and adherence to use of effective contraception, the impact on the benefit-risk of sotatercept is expected to be minimal.

Public Health Impact

With effective contraception in WOCBP, there is no anticipated public health impact.

Because limited information is available, an accurate estimate of the incidence and prevalence of adverse pregnancy outcomes in the PAH population cannot be provided. Women with PAH are advised not to become pregnant because of the risk of PAH worsening, therefore pregnancy rates are low.

SVII.3.2 Presentation of the Missing Information

Long-term safety
Evidence Source: Long-term safety data are available from STELLAR, ZENITH, HYPERION, PULSAR, and SPECTRA participants exposed to sotatercept for ≥ 12 months (565/742 [76.1%]; 1468.90 person-years). **Populations in Need of Further Characterization:** SOTERIA was implemented to evaluate long-term safety and efficacy in patients on sotatercept. Participants from all other ongoing and future sotatercept PAH studies may also roll over into SOTERIA and will facilitate accrual of long-term safety data.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Erythrocytosis
Important potential risks	Severe thrombocytopenia
	Embryo-foetal toxicity
Missing information	Long-term safety

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Specific Adverse Reaction Follow-Up Questionnaire for Embryo-foetal toxicity:

The Company will use a sotatercept-specific adverse reaction follow-up questionnaire to obtain structured information on reported exposure during pregnancy and potential adverse pregnancy outcomes in the post marketing setting. The questionnaire will be distributed to health care professionals and authors for any spontaneous reports received and reports from the literature, respectively, of pregnancies and/or potential adverse pregnancy outcomes. The information collected via the follow-up questionnaire will enhance the assessment of post marketing reports in order to further understand potential adverse pregnancy outcomes in women treated with sotatercept while pregnant.

This questionnaire is provided in Annex 4.

Other Forms of Routine Pharmacovigilance Activities:

Not applicable.

III.2 Additional Pharmacovigilance Activities

One clinical trial is being conducted to address missing information: MK-7962-004 (SOTERIA) will provide information on long-term safety.

Details of SOTERIA are provided here as well as in Annex 2.

Study Short Name and Title:

An Open-label Long-term Follow-up Study to Evaluate the Effects of Sotatercept When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy for the Treatment of PAH (SOTERIA).

Rationale and Study Objectives:

Rationale:

This Phase 3 study is being conducted to assess the long-term safety, tolerability, and efficacy of sotatercept in PAH in participants who completed a Phase 2 or Phase 3 study.

Primary Objective:

The primary objective of this open-label, LTFU study is to evaluate the long-term safety and tolerability of sotatercept when added to background PAH therapy in adult participants with PAH.

Secondary Objective:

The secondary objective is to follow participants from parent sotatercept studies who were treated with sotatercept or placebo and assess continued efficacy.

Study Design:

This open-label, LTFU study will evaluate the safety, tolerability, and efficacy of sotatercept in participants with PAH previously treated with sotatercept or placebo.

Safety assessments will include adverse events of interest. Erythrocytosis (increased hemoglobin) and severe thrombocytopenia are adverse events of interest. Laboratory values, including haemoglobin levels and platelet counts, will be monitored at least quarterly. The summary of these laboratory values will be included in the annual update reports for SOTERIA.

Study Population:

Participants eligible to enroll in the study will have participated in and completed the relevant study requirements of the parent PAH sotatercept clinical studies.

Milestones:

Annual updates: Progress reports on results of safety analyses will be provided yearly.

Protocol MK-7962-004 Final Clinical Study Report submission: 30-NOV-2028.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table III.3.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
A Long-term Follow-up Study of Sotatercept for PAH Treatment SOTERIA Ongoing	Primary: - To evaluate the long-term safety and tolerability of sotatercept when added to background PAH therapy in adult participants with PAH. Secondary: - To follow participants from parent sotatercept studies who were treated with sotatercept or placebo and assess continued efficacy.	- Erythrocytosis - Severe thrombocytopenia - Long-term safety (including long-term safety in HCP-trained lay users)	Annual updates Final study report submission	Progress reports on results of safety analyses will be provided yearly. 30-NOV-2028

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no ongoing or proposed PAES for sotatercept.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Erythrocytosis	**Routine risk communication:** SmPC Sections 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects. Package leaflet Section 2 What you need to know before you use Winrevair and Section 4 Possible side effects. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Sections 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use. Package leaflet Section 2 What you need to know before you use Winrevair. **Other routine risk minimisation measures beyond product labeling:** None.
Severe thrombocytopenia	**Routine risk communication:** SmPC Sections 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects. Package leaflet Section 2 What you need to know before you use Winrevair and Section 4 Possible side effects. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Sections 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use. Package leaflet Section 2 What you need to know before you use Winrevair. **Other routine risk minimisation measures beyond product labeling:** None.
Embryo-foetal toxicity	**Routine risk communication:** SmPC Section 4.6 Fertility, pregnancy and lactation. Package leaflet Section 2 What you need to know before you use Winrevair. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.6 Fertility, pregnancy and lactation. **Other routine risk minimisation measures beyond product labeling:** None.

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Long-term safety	**Routine risk communication:** SmPC Section 4.8 Undesirable effects. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond product labeling:** None.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Erythrocytosis	**Routine risk minimisation measures:** SmPC Sections 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects. Package leaflet Section 2 What you need to know before you use Winrevair and Section 4 Possible side effects. **Additional risk minimisation measures:** None.	Routine pharmacovigilance activities. **Additional pharmacovigilance activities:** SOTERIA.
Severe thrombocytopenia	**Routine risk minimisation measures:** SmPC Sections 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects. Package leaflet Section 2 What you need to know before you use Winrevair and Section 4 Possible side effects. **Additional risk minimisation measures:** None.	Routine pharmacovigilance activities. **Additional pharmacovigilance activities:** SOTERIA.
Embryo-foetal toxicity	**Routine risk minimisation measures:** SmPC Section 4.6 Fertility, pregnancy and lactation. Package leaflet Section 2 What you need to know before you use Winrevair. **Additional risk minimisation measures:** None.	Routine pharmacovigilance activities. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Sotatercept Pregnancy Questionnaire (attached in Annex 4) **Additional pharmacovigilance activities:** None.
Long-term safety	**Routine risk minimisation measures:** SmPC Section 4.8 Undesirable effects. **Additional risk minimisation measures:** None.	Routine pharmacovigilance activities. **Additional pharmacovigilance activities:** SOTERIA.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for Winrevair (sotatercept)

This is a summary of the risk management plan (RMP) for Winrevair. The RMP details important risks of Winrevair, how these risks can be minimised, and how more information will be obtained about risks and uncertainties (missing information) of Winrevair.

Winrevair's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Winrevair should be used.

This summary of the RMP for Winrevair should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Winrevair's RMP.

I. The Medicine and What it is Used for

Winrevair is authorised for the treatment of pulmonary arterial hypertension (PAH) in adults. It is used with other therapies to treat PAH in adults. PAH is a type of high blood pressure in the arteries of your lungs. In PAH, these arteries get narrower, which makes it harder for the heart to pump blood through these vessels, and leads to symptoms like fatigue, dizziness, and difficulty breathing (see SmPC for the full indication). It contains sotatercept as the active substance, and it is given subcutaneously (as an injection just under the skin).

Winrevair acts on the causes of PAH responsible for the narrowing of the arteries of your lungs, which makes it easier for the heart to pump blood to your lungs and slows down the progression of your disease. It can relieve your symptoms of PAH, help you live longer and lower your need for a lung transplant or hospitalisation for PAH.

Further information about the evaluation of Winrevair's benefits can be found in Winrevair's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/winrevair).

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterize the Risks

Important risks of Winrevair, together with measures to minimise such risks and the proposed studies for learning more about risks of Winrevair, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Winrevair is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Winrevair are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Winrevair. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Erythrocytosis
Important potential risks	Severe thrombocytopenia
	Embryo-foetal toxicity
Missing information	Long-term safety

II.B Summary of Important Risks

The safety information in the product labeling is aligned to the reference medicinal product.

Table II.B.1: Important Identified Risk: Erythrocytosis

Evidence for linking the risk to the medicine	Mechanism of action: strong evidence Animal studies: moderate evidence Clinical studies: strong evidence
Risk factors and risk groups	Increased hemoglobin (a molecule in the blood that carries oxygen) can cause the blood to become thicker than usual, which could lead to blood clotting in the blood vessels. Therefore, patients with increased hemoglobin and a history of blood clots may be at increased risk for developing blood clots that could break off and block another blood vessel.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects. Package leaflet Section 2 What you need to know before you use Winrevair and Section 4 Possible side effects. **Additional risk minimisation measures:** None.

Table II.B.2: Important Potential Risk: Severe Thrombocytopenia

Evidence for linking the risk to the medicine	Animal studies: weak evidence Clinical studies: moderate evidence
Risk factors and risk groups	From published research, men with idiopathic PAH (PAH of unknown cause) are more likely than women to have thrombocytopenia (a decrease in platelet count [cells involved in forming blood clots]). Thrombocytopenia is associated with the use of prostacyclin analogues, medications used to treat PAH.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects. Package leaflet Section 2 What you need to know before you use Winrevair and Section 4 Possible side effects. **Additional risk minimisation measures:** None.

Table II.B.3: Important Potential Risk: Embryo-foetal Toxicity

Evidence for linking the risk to the medicine	Animal studies: strong evidence
Risk factors and risk groups	Women of child-bearing potential who do not adhere to using effective contraception.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.6 Fertility, pregnancy and lactation. Package leaflet Section 2 What you need to know before you use Winrevair. **Additional risk minimisation measures:** None.

Table II.B.4: Missing Information: Long-term Safety

Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.8 Undesirable effects. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** SOTERIA.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Winrevair.

II.C.2 Other Studies in Post-Authorisation Development Plan

One clinical trial is being conducted to address missing information.

1) SOTERIA

Purpose of the study:

SOTERIA is being conducted to assess the long-term safety, tolerability, and efficacy of sotatercept in PAH.

The primary objective of this long-term follow-up study is to evaluate the long-term safety and tolerability of sotatercept when added to background PAH therapy in adult participants with PAH. The secondary objective is to follow participants from parent sotatercept studies that were treated with sotatercept or placebo and assess continued efficacy.

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ANNEXES

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

WINREVAIR® (sotatercept) – PREGNANCY QUESTIONNAIRE

DRAFT

Initial Pregnancy Questionnaire

Merck Sharp & Dohme LLC, Rahway, NJ, USA is committed to the CONFIDENTIAL collection of patient information. In order to allow for the collection of pregnancy outcome data, minimize duplicate reporting, and prevent loss to follow-up, please COMPLETE ALL SECTIONS below. Please correct any inaccurate pre-filled information.

Healthcare Provider (HCP) Information (Enter 'N/A' or 'Unknown' as appropriate)

Name	Address	Phone	Fax	Office Contact
OB/GYN/Midwife				

Patient (Mother's) Information:

Office Chart Number: _____ Date of Birth: _____

Date of receipt of mother's information: _____

Patient name (Last, First, Middle): _____

Address: _____

City: _____ State: _____ Zip Code: _____

Race/ethnicity: ☐ Caucasian ☐ Black ☐ Asian ☐ Hispanic ☐ Native American ☐ Multiracial

Height: _____ Weight (lbs. or kg): _____

Occupation: _____ Body Mass Index: _____

Education level: _____ Place of delivery/address: _____

Maternal Medical History/Concurrent Conditions and Risk Factors:			
Chronic and/or autoimmune disease	☐ Yes	☐ No	If yes, specify:
Infections	☐ Yes	☐ No	If yes, specify:
Thyroid disorder	☐ Yes	☐ No	If yes, specify:
Depression or other psychiatric disorders	☐ Yes	☐ No	If yes, specify:
Hypertension	☐ Yes	☐ No	If yes, specify:
Diabetes	☐ Yes	☐ No	If yes, specify:
Seizure disorder	☐ Yes	☐ No	If yes, specify:
Smoking	☐ Yes	☐ No	If yes, how many packs per day:
Alcohol use	☐ Yes	☐ No	If yes, amount and frequency:
Recreational drug use	☐ Yes	☐ No	If yes, what, amount and frequency:
Family history of birth defect and/or psychomotor retardation	☐ Yes	☐ No	If yes, ☐ Maternal or ☐ Paternal If yes, degree of relationship
Exposure to environmental toxins or radiation	☐ Yes	☐ No	If yes, specify:
List any other concurrent conditions, illnesses, or medical problems (include dates):			

WINREVAIR® (sotatercept) – PREGNANCY QUESTIONNAIRE

DRAFT

WINREVAIR® (sotatercept) Use Prior to LMP or During This Pregnancy:

Strength	Start date	Stop date
0.3 mg/kg		
0.7 mg/kg		

Other Medication Use During this Pregnancy (Medical prescriptions, OTC products, Pregnancy supplements):

Drug name and strength (mg)	Indication	Start date	Stop date	Total daily dosage

Current Pregnancy:

Method of contraception use: _____

Was adherence to contraception as recommended followed? ☐ Yes ☐ No

If no, was this a deliberate choice at the discretion of patient/HCP ☐ Yes

Estimated date of conception (if known): _____

Date of last menstrual period (LMP): _____

Gestational age (based on ☐ Ultrasound or ☐ LMP): _____

Gestational age at the time of exposure to WINREVAIR® (sotatercept) : _____

Estimated delivery date: _____

Number of fetuses: ☐ 1 ☐ 2 ☐ 3 ☐ Other: _____

Concurrent conditions: ☐ Pre-eclampsia ☐ Eclampsia ☐ Gestational diabetes

Pregnancy confirmed: ☐ Yes ☐ No

If yes: ☐ Pregnancy test (HCG) ☐ Ultrasound ☐ Other (Specify: _____)

Total weight gain with current pregnancy (lbs. or kg): _____

Prenatal testing	Date(s) of test	Results of test	Reason for test	Comments
Ultrasound				
Amniocentesis				
MSAFP				
ABO/Rh				
Glucose				
B-Strep				
CVS				
Other _____				

WINREVAIR® (sotatercept) – PREGNANCY QUESTIONNAIRE

DRAFT

Obstetric History:

List all previous pregnancies, including spontaneous abortions and elective terminations:

Delivery date	Weeks from LMP	Sex of neonate	Neonate Weight (lbs. oz., or kg)	Pregnancy Outcome (ie, full-term delivery, pre-term delivery, ectopic pregnancy, molar pregnancy, spontaneous abortion/miscarriage, elective termination, fetal death [stillbirth])

Did a birth defect occur in any previous pregnancy? ☐ Yes ☐ No ☐ Unknown

If yes, specify: _____

Did a stillbirth or miscarriage occur in any previous pregnancy? ☐ Yes ☐ No ☐ Unknown

If yes, in what week of pregnancy did the stillbirth or miscarriage occur? _____

Is there a history of previous maternal pregnancy complications? ☐ Yes ☐ No ☐ Unknown

If yes, please specify: _____

Is there a personal or family history of genetic disorders? ☐ Yes ☐ No ☐ Unknown

If yes, is it ☐ Maternal or ☐ Paternal

If yes, what type of genetic disorder(s)? _____

Is this a history of subfertility? ☐ Yes ☐ No ☐ Unknown

Questionnaire was completed by:_____ **Date:**_____

Pregnancy Outcome Questionnaire

Merck Sharp & Dohme LLC, Rahway, NJ, USA is committed to the CONFIDENTIAL collection of patient information. In order to allow for the collection of pregnancy outcome data, minimize duplicate reporting, and prevent loss to follow-up, please COMPLETE ALL SECTIONS below. Please correct any inaccurate pre-filled information.

Patient name: _____

Pregnancy Outcome (**If multiple birth**, please photocopy and complete a form for each infant)

☐ Live birth (if yes, please complete below neonate information)
- ☐ Preterm birth (delivery prior to 37th completed week)
- ☐ Very pre-term (delivery prior to 32nd completed week)
- ☐ Small for gestational age

Method of delivery

☐ Vaginal delivery ☐ Assisted vaginal delivery ☐ Cesarean birth ☐ Assisted vaginal delivery after Cesarean

	Birthdate	Gender	Weight (specify unit)	Length (specify unit)	Head Circumference (specify unit)	Weeks from LMP
Neonate details						

APGAR Score 1 minute: _____ 5 minute: _____10 minute: _____

Neonate/infant name (if known): _____

☐ ☐

Were there congenital anomalies? ☐ Yes ☐ No If yes, describe: _____

Were there other complications (eg, illness, hospitalization, drug therapies) or abnormalities? If so, describe: _____

_____

Pregnancy order (if multiple)? ☐ First ☐ Second ☐ Third ☐ Other (Specify:_____)

Other Pregnancy Outcomes

☐ Elective termination ☐ Spontaneous abortion (< 20 weeks) ☐ Fetal death/stillbirth (≥ 20 weeks)

☐ Ectopic pregnancy If yes to one of the above pregnancy outcomes: Date: _____

Weeks from LMP:_____

For reports of fetal death/stillbirth (> 20 weeks):

Were the products of conception visually examined? ☐ Yes ☐ No ☐ Unknown

Was the fetus normal upon visual examination? ☐ Yes ☐ No ☐ Unknown

If no, describe: _____

Was there a fetal autopsy performed? ☐ Yes ☐ No ☐ Unknown

If yes, were there abnormalities identified? ☐ Yes ☐ No ☐ Unknown

If yes, describe: _____

Obstetric Information

Type of delivery: ☐ Vaginal ☐ Cesarean section

☐ Yes ☐ No Complication during pregnancy, specify: _____

☐ Yes ☐ No Complication during labor/delivery, specify: _____

☐ Yes ☐ No Diagnostic tests during pregnancy.

If yes, dates and test results: _____

☐ Yes ☐ No Infections or illnesses during pregnancy, specify: _____

☐ Yes ☐ No Concurrent medical conditions, specify: _____

_____

WINREVAIR® Use Prior to LMP or During This Pregnancy:

Strength	Start date	Stop date
0.3 mg/kg		
0.7 mg/kg		

Other Medication Use During this Pregnancy:

Drug name and strength (mg)	Indication	Start date	Stop date	Total daily dosage

Describe any additional information that might help in interpreting the outcome of this pregnancy:

_____

_____

_____

Pediatrician/ Family HCP Name	Address	Phone	Fax	Office contact

Questionnaire was completed by:_____ **Date:** _____

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.