11 December 2025
EMADOC-1700519818-2692691
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Winrevair

International non-proprietary name: sotatercept

Procedure No. EMA/VR/0000278021

Marketing Authorisation Holder (MAH): Merck Sharp & Dohme B.V.

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
6MWD	6-minute walk distance
ActRIIA	activin receptor type IIA
ADA	antidrug antibody
AE	adverse event
AEOI	adverse event of interest
AESI	adverse event of special interest
APaT	all participants as treated
BMPRII	bone morphogenetic protein receptor type II
CI	confidence interval
CO	cardiac output
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	connective tissue disease
DBP	diastolic blood pressure
DBPC	Double-Blind Placebo-controlled
DMC	data monitoring committee
EMA	European Medicines Agency
EOS	end of study
ERA	endothelin receptor antagonists
ESC/ERS	European Society of Cardiology/European Respiratory Society
EU	European Union
FAS	full analysis set
FC	functional class
FDA	Food and Drug Administration (US)
HR	hazard ratio
IA	interim analysis
mPAP	mean pulmonary arterial pressure
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OS	overall survival

PAH	pulmonary arterial hypertension
PDE5	phosphodiesterase 5
PH	pulmonary hypertension
PPA	prostacyclin pathway agent
PRIME	Priority MEdicine
PT	preferred term
PVR	pulmonary vascular resistance
REVEAL	Registry to Evaluate Early and Long-term PAH Disease Management
RV	right ventricular
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
sGC	soluble guanylate cyclase
Smad	Small Mothers Against Decapentaplegic
ULN	upper level normal
US	United States
VSMCs	vascular smooth muscle cells
WHO	World Health Organization

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 02 June 2025 an application for a variation. The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include in combination with other pulmonary arterial hypertension (PAH) therapies treatment of adult patients with PAH World Health Organisation Functional Class IV for WINREVAIR, based on interim results from study ZENITH (also referred as MK-7962-006 and A011-14); this is a phase 3, randomized, double-blind, placebo-controlled study to evaluate sotatercept when added to maximum tolerated background therapy in participants with pulmonary arterial hypertension (PAH) World Health Organization (WHO) Functional Class (FC) III or FC IV at high risk of mortality; As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH removed the first PSUR commitment following 6 months post authorisation as it has already been fulfilled. As part of the application, the MAH is requesting a 1-year extension of the market protection.

Information relating to orphan designation

Winrevair was designated as an orphan medicinal product EU/1/24/1850 on 27 August 2024. Winrevair was designated as an orphan medicinal product in the following indication: Treatment of pulmonary arterial hypertension.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0414/2022 on the agreement of a paediatric investigation plan (PIP).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on (EMA/SA/0000050772) The Scientific Advice pertained to clinical aspects.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: n/a

Timetable	Actual dates
Submission date	02 June 2025
Start of procedure:	21 June 2025
CHMP Rapporteur's preliminary assessment report circulated on:	14 August 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	18 September 2025
MAH's responses submitted to the CHMP on:	09 October 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	18 November 2025
CHMP opinion:	11 December 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Pulmonary arterial hypertension (PAH) is a rare (15 to ~60 people per million), chronic, progressive, and fatal disease that can present at any age, causing limitations in physical activity and quality of life despite treatment with approved therapies.

State the claimed the therapeutic indication

The Applicant aims to change the current indication of:
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 to III, to improve exercise capacity (see section 5.1).
To:
Winrevair, in combination with other pulmonary arterial hypertension (PAH) therapies, is indicated for the ~~long-term~~ treatment of PAH in adult patients with WHO Functional Class (FC) II, III, and IV (see section 5.1).

Biologic features, aetiology and pathogenesis

The pathophysiology of PAH involves pulmonary endothelial dysfunction, resulting in impaired production of endogenous vasodilators (e.g. nitric oxide and prostacyclin), overexpression of vasoconstrictors (e.g. endothelin-1), and the abnormal proliferation of pulmonary VSMCs in pulmonary arterioles, which results in progressive pulmonary vascular remodeling, increased PVR, and eventually right sided heart failure. The hemodynamic definition of PAH was updated in 2019 at the 6th World

Symposium on Pulmonary Hypertension (WSPH) (Simonneau, Montani et al. 2019). Precapillary pulmonary artery hypertension is defined hemodynamically by the presence of a mean pulmonary artery pressure (mPAP) ≥ 20 mmHg at rest, PAWP ≤15 mmHg and a PVR ≥3 WU. PAH (WHO Group 1) is classified into the following subtypes based on aetiology: idiopathic, heritable, drug and toxin-induced, connective tissue disorders, and post-shunt correction. Literature on PAH implicates defects in the BMPR2 signal pathway as an important factor contributing to the pathophysiology of PAH. While genetic mutations in BMPR2 are associated with the majority of familial PAH and approximately 25% of idiopathic, downregulation of BMPR2 expression has been associated with development of PAH regardless of mutational status. This information strongly suggests a key role of TGF-β family members in the pathogenesis of PAH.

Clinical presentation, diagnosis and stage/prognosis

Despite the availability of several approved therapies, 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.

Management

Current PAH therapies improve exercise capacity and prolong time to clinical worsening but have not shown an effect on overall mortality. Approved therapies act via the prostacyclin, endothelin, or nitric oxide pathways, believed to primarily mediate their effects through pulmonary vasodilation. Current PAH therapies include agents such as ERAs, PDE5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists, in addition to general supportive care agents (e.g. anticoagulants, diuretics, digoxin). Sotatercept itself is now also approved and marketed.

2.1.2. About the product

Sotatercept is an activin signaling inhibitor with high selectivity for activin A. Sotatercept consists of a recombinant homodimeric ActRIIA-Fc fusion protein that acts as a ligand trap that scavenges excess activin A and other ligands for ActRIIA to inhibit activin signaling. As a result, sotatercept rebalances the pro-proliferative (ActRIIA/Smad2/3-mediated) and antiproliferative (BMPRII/Smad1/5/8-mediated) signaling to modulate vascular proliferation.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

For the current type II variation, the focus is on the results from the ZENITH trial (interim analysis), supported by data from the open-label long-term follow-up study SOTERIA. The prespecified IA of the primary efficacy endpoint occurred when approximately 50% of the required number of primary endpoint events had accrued (26-JUL-2024) and median participant time on study was at least 6 months. The independent DMC met on 14-NOV-2024 and recommended stopping the study early based on predefined efficacy criteria specified on the SAP. The Sponsor's Executive Oversight Committee followed the DMC's recommendation considering sotatercept's effect on major morbidity and mortality, and the loss of clinical equipoise, making continuation of placebo treatment unethical. Early termination of ZENITH was communicated to sites on 25-NOV-2024 and all participants on treatment were offered enrolment in the open-label, long-term follow-up study, SOTERIA.

For the ZENITH trial, a scientific advice was received (EMA/SA/0000050772) pertaining to the sufficiency of the ZENITH study (A011-14) to show a reduction in mortality in participants with PAH,

including the primary composite endpoint, patient population, key secondary endpoints, an event-driven duration and statistical considerations.

With respect to the primary endpoint of time to all-cause death or PAH-related hospitalization of ≥24 hours, the CHMP considered this composite primary endpoint robust, clinically meaningful and therefore acceptable. Furthermore, in addition to the proposed key secondary endpoint of overall survival, PAH-related hospitalization of ≥24 hours should also be evaluated as secondary endpoint to ensure that the effect of one component of the composite endpoint is not negating the effect of another.

A PIP was agreed on 08-JUN-2021 (P/0227/2021) and has been subsequently modified. The current decision P/0414/2022 of 29-SEP-2022 was used to obtain a positive outcome for a PIP compliance check, which was received on 26-APR-2023 (EMEA-C1-002756-PIP01-19-M01). No deferred measures have been completed at the time of this variation application submission. Consequently, the PIP compliance check dated 26-APR-2023 is referenced to meet the paediatric requirements.

The paediatric coordinator confirms that the Study 2 (Open-label, 24-week study to assess PK, safety and pharmacodynamic effects of sotatercept as add-on therapy to standard-of care in children from 1 to less than 18 years of age) is compliant with the latest PIP as set out in the above stated Agency's Decision.

2.1.4. General comments on compliance with GCP

The clinical study was conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such studies including the archiving of essential documents. The study was conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed.

Clinical trials carried out outside of the European Union meet the ethical requirements of Directive 2001/20/EC or Regulation (EU) No 536/2014.

2.2. Non-clinical aspects

No new non-clinical data has been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

As a recombinant fusion protein, consisting entirely of naturally occurring amino acids, sotatercept is not anticipated to pose a risk to the environment. Evaluation of environmental risk is not needed, in line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMA 2006). The justification for not submitting an environmental risk assessment according to the current ERA guideline (CPMP/SWP/4447/00) has been found acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Applicant states that the ZENITH trial was conducted in accordance with local and/or national regulations (including all applicable data protection laws and regulations), ICH GCP and with the ethical principles that have their origin in the Declaration of Helsinki regarding IEC review, informed consent, and the protection of human participants in biomedical research (Ethics and Responsibilities).

Overview of clinical studies:

Table 1: Overview of clinical studies

Study Number (Status) [CTD Location]	Design	Number of Participants by Intervention Group	Study Population (N)	Primary Endpoint(s)
MK-7962-006/ A011-14/ZENITH (ongoing) [Ref. 5.3.5.1: P006V01MK7962]	Randomized, double-blind, placebo-controlled, multicenter, parallel-group study in participants aged ≥18 years with PAH (WHO FC III or IV)	Placebo SC Q3W Sotatercept starting dose of 0.3 mg/kg SC Q3W with a target dose of 0.7 mg/kg SC Q3W.	Males and females Age: 18 to 75 years, inclusive Indication: PAH (Group 1 PH) WHO FC III or IV at high risk of mortality	Time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours

FC=functional class; PAH=pulmonary arterial hypertension; PH=pulmonary hypertension; Q3W=every 3 weeks; SC=subcutaneous; WHO=World Health Organization.

2.3.2. Pharmacokinetics

In the original marketing application, the results from 2 Phase 1 studies in healthy participants (P009/A011-01 and P010/A011-02), results from an integrated popPK analysis including data from the above 2 Phase 1 studies and additional 2 Phase 2 studies (PULSAR, SPECTRA), as well as 1 Phase 3 study (STELLAR) in participants with pulmonary arterial hypertension (PAH), world health organization (WHO) functional class (FC) II or III are presented. In the current extension of variation additional PK data is generated in study ZENITH.

Bioanalytical methods

Pharmacokinetics

The concentrations of sotatercept in human serum for ZENITH were determined with the same validated competitive ELISA method used for PAH Phase 2 and Phase 3 studies submitted in the original marketing application. The calibration ranges were 40 to 2000 ng/mL.

The interim sample analysis report (A011-14) was provided. The longest time transpired between collection date and analysis was 835 days. Long-term stability for 1360 days at -70°C was confirmed. In total 1727 samples were received frozen on dry ice (including 1 back-up sample), consisting of 822 placebos and 902 analysed samples. 3 samples were not reported due to 'received ambient'. A total number of 35 of 902 (3.9%) samples were reanalysed, 9x due to BQL with dilution, 12x due to replicate BQL, 13x due to not reportable (NR, %CV > 20%), 1x due to AQL, and 1x as client requested reassay. 93 samples were included in the ISR, 90 out 93 samples (96.8%) were within ±30% difference. Of all measured samples, 28 samples experienced temperature excursions at the central lab, though the excursions did not exceed established stability parameters determined in the validation, and were therefore analysed and their data reported, and 1 sample was received in an expired tube.

Immunogenicity

The multi-tiered testing strategy and validated assays that were applied to assess sotatercept immunogenicity in ZENITH are the same as those used in the studies PULSAR, SPECTRA, and STELLAR. The sensitivity of the assay in serum is approximately 5 ng/mL of the antibody positive control (ACE-011).

Pharmacokinetic data analysis

The original integrated popPK model was used to estimate sotatercept exposure in participants with PAH enrolled in ZENITH. All exploratory data analyses and presentations of data were performed using R Version 3.5.3. Population modelling was performed using NONMEM, Version 7.4.

Evaluation and qualification of models

PopPK modelling

Objective

The objective of the popPK analysis were to compare the pharmacokinetics (PK) of sotatercept between participants with PAH class II and III and participants with PAH class III and IV populations. In the original marketing application, the results from an integrated popPK model and exposure-response models in participants with PAH who participated in SPECTRA, PULSAR, and STELLAR were submitted. With this submission, the results from the popPK analysis of ZENITH study data are presented and compared with the initial model.

Data

ZENITH is a double-blind, randomized, placebo-controlled, Phase 3 study in participants with PAH, WHO FC III or IV at high risk of mortality who are on maximum tolerated background therapy. A total of 173 participants were randomized in a 1:1 ratio to receive either placebo or sotatercept SC every 21 days plus background PAH therapy (86 in the sotatercept group, 87 in the placebo group). One subject was immediately discontinued due to an error in randomization. As of the data cutoff (26-07-2024) in the sotatercept group, 86 were randomized, 86 were treated, 6 completed treatment, 4 completed study, 12 discontinued treatment, 12 discontinued study, 68 ongoing on treatment, 70 ongoing in the study. Participants were considered as having completed the study if they had an event of PAH worsening-related hospitalization of ≥24 hours or lung transplantation.

The sotatercept group was 70.9% female, had a median age of 58 years (range: 19 – 75 years), and was primarily white (84.9%). The median body mass index (BMI) was 24.4 kg/m^2 (range: 16.3-49.5 kg/m^2). The most prevalent PAH WHO FC was Class III 74.4% and the remain subjects had PAH WHO FC Class IV. Half of the population had idiopathic PAH (50%), whereas in 27.9% of the population the PAH was associated with connective tissue diseases (CTD), 10.5% had heritable PAH, 6.4% had drug/toxin-induced PAH, and 5.2% had PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair. The median value of the estimated glomerular filtration rate (estimated by MDRD) was 62.0 mL/min/1.73 m^2 (range: 25-136 mL/min/1.73 m^2).

The starting dose of sotatercept was 0.3 mg/kg SC at Visit 1, followed by the target dose of 0.7 mg/kg SC for the remainder of the study see table below (Table 2 Starting dose and target dose), unless dose modifications were required.

Table 1: Starting dose and target dose

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use
Placebo (Arm 1)	Placebo	0 mg	0 mg Q3W	SC	V1 to EOT/EOS	Placebo
Sotatercept (Arm 2)	Sotatercept	60 mg/vial	0.3 mg/kg Q3W	SC	V1	Test Product
Sotatercept (Arm 2)	Sotatercept	60 mg/vial	0.7 mg/kg Q3W	SC	V2 to EOT/EOS	Test Product

EOS=end of study; EOT=end of treatment; Q3W=every 3 weeks; SC=subcutaneous; V=Visit.
Sotatercept dose reductions (from 0.7 to 0.3 mg/kg) due to a safety event are described in the study protocol.
Sotatercept dose re-escalation may occur according to the study protocol.

Sparse blood samples were collected Day 1, predose and at 1 to 2, 2 to 4, and 4 to 8 hours postdose and on other visits (Visit 2-5, 9 and 13), samples for PK were collected prior to study drug administration. Sample concentrations that were calculated below 40.0 ng/mL are reported as below

quantifiable limit (BQL). The disposition of BLQ samples by study and PK sampling time are provided in the table below (Table 2 Disposition of BLQ samples by study and PK sampling time).

Table 3: Disposition of BLQ samples by study and PK sampling time

Study	Initial dose	Visit	Number of BLQ samples	Total samples	% BLQ
PULSAR	0.3 mg/kg SC	Day 1 0 to 4 hours postdose	45	46	97.8%
		Post Day 1	0	912	0.0%
	0.7 mg/kg SC	Day 1 0 to 4 hours postdose	47	53	88.7%
		Post Day 1	1	1014	0.1%
SPECTRA	0.3 mg/kg SC	Post Day 1	1	101	1.0%
STELLAR	0.3 mg/kg SC	Post Day 1	3	839	0.4%
ZENITH	**0.3 mg/kg SC**	**Day 1 1 to 2 hours postdose**	**77**	**86**	**89.5%**
		Day 1 2 to 4 hours postdose	**56**	**86**	**65.1%**
		Day 1 4 to 8 hours postdose	**24**	**81**	**29.6%**
		Post Day 1	**0**	**553**	**0.0%**

A total of 656 sotatercept serum concentrations obtained from 86 participants available at the interim analysis (IA) data cutoff date (26-JUL-2024) were included in the popPK analysis. Initially, one participant was excluded in NONMEM analysis with a NAN error. However, upon further review by the applicant, it was noted that inadvertently all samples of the participant were excluded instead of only one observation which had a negative time since first dose. Therefore, an updated value is included in Table 3.

Method

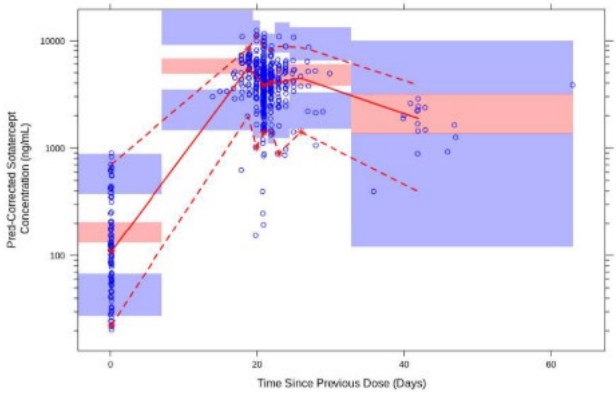
The Phase 2/3 popPK model developed in the initial application was used to describe ZENITH PK data (MAXEVAL = 0). All exploratory data analyses and presentations of data were performed using R Version 3.5.3. Population modelling was performed using NONMEM®, Version 7.4.

The previously developed population PK model consists of a two-compartment model with linear elimination and first-order absorption for the SC route of administration. The effects of time varying body weight on CL and VC, and baseline albumin on CL were identified as significant covariates. The base PK model included a separate log residual error model for patients with PAH. The previous population pharmacokinetic model was validated using prediction-corrected visual predictive checks and goodness of fit plots.

External validation

The performance of the previously developed population pharmacokinetic model for the ZENITH study is graphically displayed in Figure 1 and Figure 2. Figure 3 provides the separate VPC plots for each study accounting for all BLQ samples. Model parameters were not re-estimated based on the full dataset.

Figure 1: Prediction Corrected Visual Predictive Check of the Existing PopPK model in Predicting ZENITH PK with MAXEVAL=0



Blue dots are observed data (ZENITH study), dotted red line is 5th and 95th percentile of the observed percentiles and blue shaded area percentile 90% confidence interval of the observed percentiles. Solid red line is the median and the red shaded is 90% CI interval around the median.

Figure 2: Observed vs Individual Predicted Sotatercept Concentrations of ZENITH with MAXEVAL=0

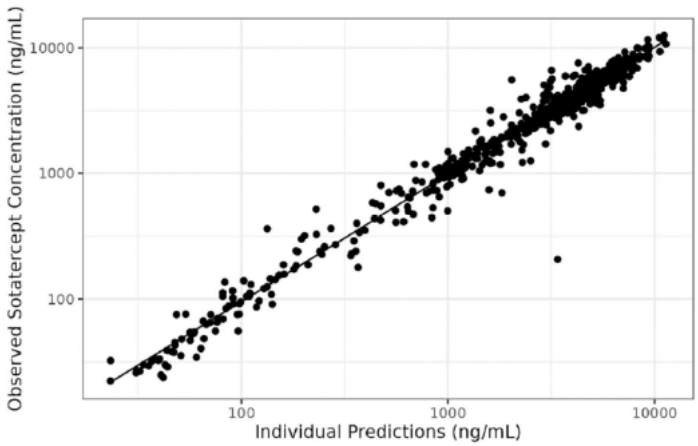
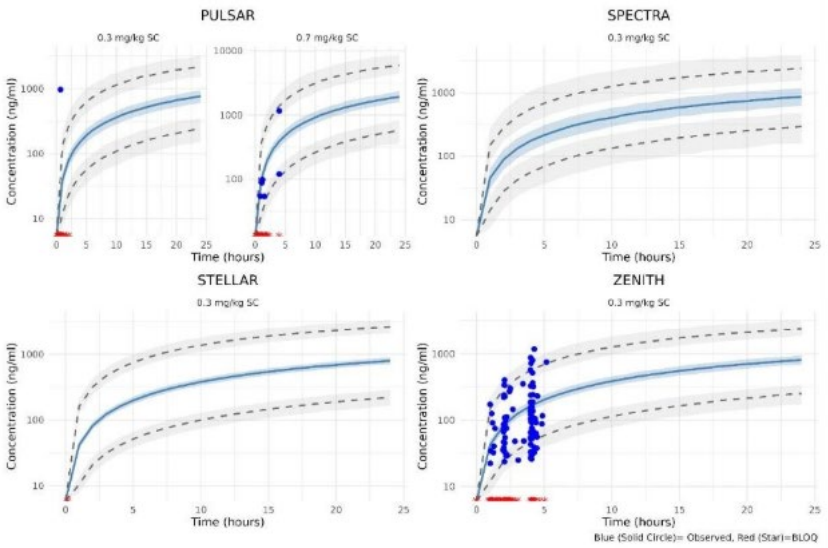


Figure 3: VPC Plots for Day 1 PK from PULSAR (0.3 mg/kg, 0.7 mg/kg), SPECTRA (0.3 mg/kg), STELLAR (0.3 mg/kg) and ZENITH (0.3 mg/kg)



Pharmacokinetics in target populations

As the previous pharmacokinetic model was considered externally validated with the new dataset, individual exposure (Cavg,ss) following 0.7 mg/kg Q3W was calculated using empirical bayes estimates (EBE)-based parameter estimates for each participant treated with sotatercept in ZENITH, and was compared with the distribution of Cavg,ss of participants treated with sotatercept in the Phase 2 and 3 studies (PULSAR, SPECTRA, and STELLAR) (086H0S) (Figure 4 and Table 4).

Figure 4: Distribution of steady-state Average Concentration (Cavg,ss) following 0.7mg/kg Q3W dosing between ZENITH vs Phase 2/3 population

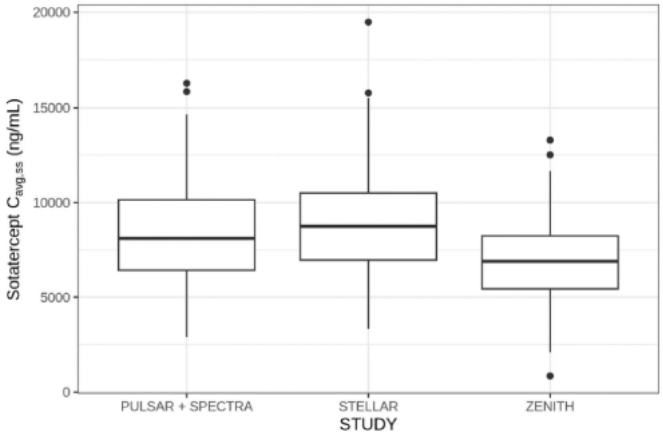


Table 4: Comparison of steady-state Cavg,ss following 0.7mg/kg Q3W dosing between ZENITH vs Phase 2/3 population

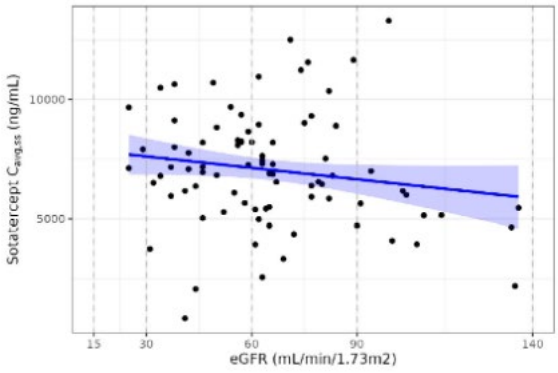
	Steady-state Sotatercept Cavg (ng/mL)			
	PULSAR + SPECTRA (n = 124)	STELLAR (n = 162)	**ZENITH [updated] (n = 86)**	ZENITH [original]* (n = 85)
Median (5th - 95th percentile)	8104 (4076 - 13188)	8749 (5013 - 12981)	**6752 (3429 - 11128)**	6900 (3429 - 11175)
Geo Mean (90% CI)	7779 (7382 - 8197)	8456 (8124 - 8802)	**6483 (6016 - 7049)**	6538 (6065 - 7049)

Cavg,ss = average concentration at steady state, CI = confidence interval.

* Source: [Ref. 5.3.5.3: 08SQ07]

The impact of baseline renal function (eGFR estimated using MDRD equation) on the exposure of sotatercept in ZENITH participants was explored. The result showed that mild to severe renal impairment (eGFR 15 to <60 mL/min/1.73m^2) had no impact on the Sotatercept exposure (Figure 5).

Figure 5: Scatter plot of steady-state Cavg,ss following 0.7mg/kg Q3W dosing in ZENITH vs eGFR (estimated by MDRD)

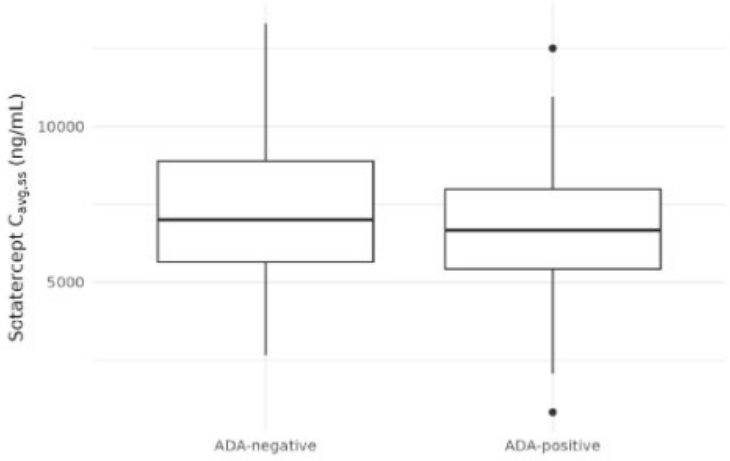


Plot of eGFR vs sotatercept Cavs ss, black dots represent Cavg ss for each individual, blue solid line, and shaded area represent regression line and 90% confidence interval, calculated p-value is 0.14. Vertical dashed lines represent eGFR cutouts.

Immunogenicity

See section 'Pharmacodynamics – Secondary pharmacology' for additional immunology data. Cavg,ss was compared between the ADA-negative and ADA-positive participants in the ZENITH study. The result showed that ADA status had minimal impact on the Sotatercept exposure in the ZENITH population(Table 5).

Figure 6: Comparison of sotatercept Cavg at steady-state between ADA-negative vs ADA-positive participants in ZENITH



Cavg,ss = average concentration at steady state.

Table 5: Comparison of Cavg,ss following 0.7mg/kg Q3W dosing between ADA-negative vs ADA-positive participants in the ZENITH study

	Cavg,ss (ng/mL) by ADA status	
	ADA-negative (n=51)	ADA-positive (n=34)
Geo Mean (90%CI)	6867 (6344-7432)	6089 (5271-7034)

2.3.3. Pharmacodynamics

No new clinical pharmacology or biopharmaceutic studies are included in this supplemental application.

Mechanism of action

No new studies on the mechanism of action were performed. In the MAA, the following mechanism was proposed by the Applicant: Sotatercept is an activin signaling inhibitor with high selectivity for Activin-A, a dimeric glycoprotein which belongs to the TGF-β superfamily of ligands. Activin A binds to ActRIIregulating key signaling for inflammation, cell proliferation, apoptosis, and tissue homeostasis. Activin A levels are increased in PAH patients. Activin binding to ActRIIpromotes proliferative signaling while there is a decrease in anti-proliferative BMPR-II signaling. The imbalance of ActRII-BMPRII signaling underlying PAH results in vascular cell hyperproliferation causing pathological remodeling of the pulmonary arterial wall, narrowing the arterial lumen, increasing pulmonary vascular resistance, and leads to increased pulmonary artery pressure and right ventricular dysfunction. Sotatercept consists of a recombinant homodimeric activin receptor type IIA-Fc (ActRIIA Fc) fusion protein which acts as a ligand trap that scavenges excess activin A and other ligands for ActRII to inhibit activin signaling. As a result, sotatercept rebalances the pro-proliferative (ActRII/Smad2/3- mediated) and anti-proliferative (BMPRII/Smad1/5/8 mediated) signaling to modulate vascular proliferation.

Primary pharmacology

No new primary pharmacology data has been presented.

Secondary pharmacology

The Applicant has included an analysis of Assessment of Immunogenicity in ZENITH.

The immunogenicity assessment for ZENITH used the same multi-tiered testing strategy and the same assays that were utilized for STELLAR. Serum samples were evaluated initially by a sensitive and drug-tolerant ADA assay that included both screening and confirmation. Confirmed ADA-positive samples subsequently underwent additional characterization for ADA titer and neutralizing antibody activity. The immunogenicity assessment strategy and bioanalytical methodology are described in detail in the original marketing application. To assess ADA response to sotatercept in ZENITH, serum samples at multiple time points across the treatment were collected, and parallel PK samples were collected to assess the potential impact of ADA on drug exposure.

The median duration of exposure to sotatercept through the data cutoff was 322.0 days. Of the 84 evaluable participants from ZENITH at the data cutoff, 33 (39.3%) developed an ADA response to sotatercept: 32 were treatment-induced positive participants and 1 was a treatment-boosted positive participant. Two additional participants were non–treatment-emergent positive. Of the 33 participants who developed an ADA response, 17 (51.5%) were neutralizing antibody negative and 16 (48.5%) were neutralizing antibody positive.

Of the 33 participants who developed an ADA response (treatment-induced and treatment-boosted positive), the median (Q1, Q3) ADA onset time was 8.4 weeks (3.1 weeks, 12.3 weeks) after first sotatercept treatment, and the median (Q1, Q3) ADA duration was 14.7 weeks (6.0 weeks, 28.7 weeks).

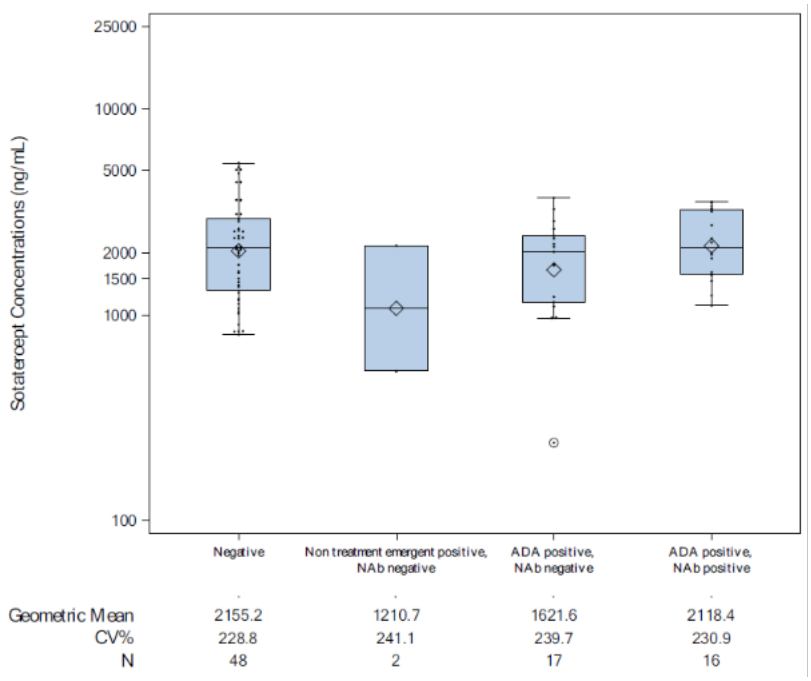
Overall, there were no notable differences in sotatercept serum concentrations when analyzed by ADA status, see Table 6 and Figure 7.

Table 6: Serum Concentration by ADA Status

Serum concentration (ng/mL) overall[b]	Negative	Non-treatment emergent positive			ADA Positive[a]		
		NAb negative	NAb positive	Total	NAb negative	NAb positive	Total
Geometic Mean (CV%)	2155.2 (228.8)	1210.7 (241.1)	NA (NA)	1210.7 (241.1)	1621.6 (239.7)	2118.4 (230.9)	1847.7 (236.8)
90% CI	1920.4, 2418.8	673.4, 2176.7	NA, NA	673.4, 2176.7	1327.7, 1980.6	1732.1, 2590.9	1603.4, 2129.1

[a]ADA positive includes both Treatment induced positive and Treatment boosted positive.
[b]Overall refers to all post-baseline values.
ADA= anti-drug antibodies; CI = confidence interval; CV = coefficient of variation; NAb = neutralizing antibody.
Database cutoff date: 26JUL2024

Figure 7: Serum Concentration by ADA Status



There were no differences in the proportions of participants who had a primary endpoint event, see Table 7. Among ADA negative sotatercept treated patients, there were 7 events (14.6%) and among ADA positive there were 5 events (15.2%). In Nab negative patients there were 3 events (17.6%) and in Nab positive patients there were 2 events (12.5%). Although the number of events is still low, no trend is visible that ADA or NAb affected the risk of an event in ZENITH.

Table 7: Frequency of Protocol-Specified Events of All-cause Death, Lung Transplantation, or PAH Worsening-related Hospitalization

	Placebo	Negative	Non-treatment emergent positive						ADA Positive[a]					
			NAb negative		NAb positive		Total		NAb negative		NAb positive		Total	
	n (%)	n (%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	86	48	2		0		2		17		16		33	
Number of Events (%)	47 (54.7)	7 (14.6)	1	(50.0)	0	(0.0)	1	(50.0)	3	(17.6)	2	(12.5)	5	(15.2)

[a]ADA positive includes both Treatment induced positive and Treatment boosted positive.
ADA= anti-drug antibodies; NAb = neutralizing antibody
Database cutoff date: 26JUL2024

There were also no notable differences in the number of patients experiencing an AEs or AESI/AEOIs, see Table 8 and Table 9 The incidence of renal toxicity and increased hemoglobin was numerically higher in those with ADA, but the absolute numbers are too low to conclude on this. Overall, no difference needing further investigating were found according to ADA status. There was one serious AESI/AEOI in the category immunogenicity, but this was in the placebo arm.

Table 8: Adverse Events Summary by ADA Status

	Placebo	Negative	Non-treatment emergent positive						ADA Positive[a]					
			NAb negative		NAb positive		Total		NAb negative		NAb positive		Total	
	n (%)	n (%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	86	48	2		0		2		17		16		33	
with one or more adverse events	83 (96.5)	48 (100.0)	2	(100.0)	0	(0.0)	2	(100.0)	16	(94.1)	16	(100.0)	32	(97.0)
with no adverse event	3 (3.5)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)	0	(0.0)	1	(3.0)
with drug-related[b] adverse events	28 (32.6)	35 (72.9)	1	(50.0)	0	(0.0)	1	(50.0)	10	(58.8)	9	(56.3)	19	(57.6)
with non-serious adverse events	82 (95.3)	48 (100.0)	2	(100.0)	0	(0.0)	2	(100.0)	16	(94.1)	16	(100.0)	32	(97.0)
with serious adverse events	55 (64.0)	25 (52.1)	2	(100.0)	0	(0.0)	2	(100.0)	9	(52.9)	8	(50.0)	17	(51.5)
With serious drug-related[b] adverse events	2 (2.3)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(12.5)	2	(6.1)
who died	12 (14.0)	2 (4.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)	0	(0.0)	1	(3.0)
who died due to a drug-related[b] adverse event	0 (0.0)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	4 (4.7)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related[b] adverse event	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	4 (4.7)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related[b] adverse event	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a]ADA positive includes both Treatment induced positive and Treatment boosted positive.
[b]Relatedness to study drug was determined by the investigator as suspected related.
This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days.
MedDRA version 27.0 was used in the reporting of this study.
ADA= anti-drug antibodies; NAb = neutralizing antibody.
Database cutoff date: 26JUL2024

Table 9: Participants with AESI by ADA status

	Placebo	Negative	Non-treatment emergent positive						ADA Positive[a]					
			NAb negative		NAb positive		Total		NAb negative		NAb positive		Total	
	n (%)	n (%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	86	48	2		0		2		17		16		33	
with one or more selected adverse events	59 (68.6)	44 (91.7)	2	(100.0)	0	(0.0)	2	(100.0)	14	(82.4)	12	(75.0)	26	(78.8)
with no adverse events	27 (31.4)	4 (8.3)	0	(0.0)	0	(0.0)	0	(0.0)	3	(17.6)	4	(25.0)	7	(21.2)
Bleeding events	**30 (34.9)**	**30 (62.5)**	**2**	**(100.0)**	**0**	**(0.0)**	**2**	**(100.0)**	**10**	**(58.8)**	**11**	**(68.8)**	**21**	**(63.6)**
Cardiac events	**26 (30.2)**	**7 (14.6)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(17.6)**	**2**	**(12.5)**	**5**	**(15.2)**
Cardiac failure	10 (11.6)	2 (4.2)	0	(0.0)	0	(0.0)	0	(0.0)	2	(11.8)	2	(12.5)	4	(12.1)
Cardiac failure acute	1 (1.2)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac tamponade	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiogenic shock	2 (2.3)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiorenal syndrome	0 (0.0)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Coronary artery disease	0 (0.0)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pericardial effusion	2 (2.3)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Right ventricular failure	12 (14.0)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)	0	(0.0)	1	(3.0)
Hepatic toxicity	**5 (5.8)**	**2 (4.2)**	**1**	**(50.0)**	**0**	**(0.0)**	**1**	**(50.0)**	**2**	**(11.8)**	**0**	**(0.0)**	**2**	**(6.1)**
Immunogenicity	**8 (9.3)**	**10 (20.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(23.5)**	**3**	**(18.8)**	**7**	**(21.2)**
Dermatitis	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)	0	(0.0)	1	(3.0)
Dermatitis contact	0 (0.0)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)	1	(3.0)
Drug eruption	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eczema	0 (0.0)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)	1	(6.3)	2	(6.1)
Eye swelling	0 (0.0)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)	0	(0.0)	1	(3.0)
Eyelid oedema	0 (0.0)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Face oedema	0 (0.0)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypersensitivity	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus allergic	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Rash	1 (1.2)	4 (8.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)	1	(3.0)
Rash pustular	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Rhinitis allergic	1 (1.2)	2 (4.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)	0	(0.0)	1	(3.0)
Shock	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Swelling face	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Swelling of eyelid	0 (0.0)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	0 (0.0)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)	1	(3.0)
Increased blood pressure/hypertension	**1 (1.2)**	**0 (0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Hypertension	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Increased hemoglobin (increased hematocrit, increased RBC count)	**1 (1.2)**	**5 (10.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(17.6)**	**3**	**(18.8)**	**6**	**(18.2)**
Renal toxicity	**11 (12.8)**	**3 (6.3)**	**1**	**(50.0)**	**0**	**(0.0)**	**1**	**(50.0)**	**3**	**(17.6)**	**2**	**(12.5)**	**5**	**(15.2)**
Acute kidney injury	6 (7.0)	2 (4.2)	1	(50.0)	0	(0.0)	1	(50.0)	1	(5.9)	0	(0.0)	1	(3.0)
Chronic kidney disease	0 (0.0)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)	2	(12.5)	3	(9.1)
Proteinuria	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Renal failure	1 (1.2)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Renal impairment	3 (3.5)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)	0	(0.0)	1	(3.0)
Telangiectasia	**3 (3.5)**	**16 (33.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(17.6)**	**3**	**(18.8)**	**6**	**(18.2)**
Telangiectasia	3 (3.5)	16 (33.3)	0	(0.0)	0	(0.0)	0	(0.0)	3	(17.6)	3	(18.8)	6	(18.2)
Thrombo-embolic events	**3 (3.5)**	**1 (2.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(5.9)**	**1**	**(6.3)**	**2**	**(6.1)**
Cerebral congestion	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)	1	(3.0)
Device occlusion	1 (1.2)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary embolism	0 (0.0)	0 (0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)	0	(0.0)	1	(3.0)
Vascular device occlusion	1 (1.2)	1 (2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Thrombocytopenia	**7 (8.1)**	**7 (14.6)**	**2**	**(100.0)**	**0**	**(0.0)**	**2**	**(100.0)**	**2**	**(11.8)**	**1**	**(6.3)**	**3**	**(9.1)**

2.3.4. Discussion on clinical pharmacology

PopPK modelling

A previously developed and validated popPK model was used and external validation was performed using the data from the ZENITH study. Model parameters were not re-estimated based on the full

dataset. The pcVPCs and GOF indicate adequate predictive performance of the model for the ZENITH study data.

Since the population PK model is not fitted to the new data, the BQL samples cannot be handled in any other way than in the original analysis, i.e. they are excluded from the analysis. A difference in percentage of data below LLOQ in the original and current analyses is observed (i.e., 5% with the original application and around 27% with the current application). More post-dose PK samples were taken on day 1 in the ZENITH study (i.e., between 1-2, 2-4, and 4-8 hours), compared to none on day 1 in the SPECTRA and STELLAR study, and one post-dose day 1 moment in the PULSAR study (i.e., between 0-4 hours). The percentages BLQ between the PULSAR and the ZENITH study day 1 post-dose samples are comparable. Figure 3 shows the separate VPC plots for each study accounting for all BLQ samples. The predicted plasma concentration profile matches the measurable PK samples well in the ZENITH study. It would have been more informative to show VPCs per study stratified by samples being above or below the lower limit of quantification, in which samples above the limit of quantification are displayed as prediction-corrected observed and predicted concentrations and samples below the lower limit of quantification as the percentage or fraction of observed and predicted samples below the quantification limit. Nevertheless, samples above quantification level at trough were similar, which seems to suggest that the observed pharmacokinetic profiles are equivalent.

Pharmacokinetics in target populations
The popPK analysis consisted of an external validation of a previously developed population pharmacokinetic model on the new dataset, resulting in adequate predictive performance with no re-estimation of model parameters. From this it can be concluded that there is no clinically relevant difference in PK in patients with PAH WHOF FC III and IV compared to patients with PAH WHOF FC II and III. However, the requested comparison of below LLOQ samples between the currently approved indication and the proposed indication, as well as the pcVPC accounting for data below LLOQ should provide further information on the assessment of the PK in the target population and, hence, the assessment of the proposed update of section 5.2.

Pharmacodynamics and immunogenicity
Regarding pharmacodynamics, no new studies were conducted. Overall, the clinical pharmacology has already been assessed in detail in the original MAA. ADA data from the ZENITH trial was presented. Antibodies to sotatercept were detected in 33 (39.3%) of 84 evaluable participants. Neutralizing antibodies were detected in 16 (48.5%) of the 33 participants who developed an ADA response. This is a higher response compared to the ADA responses in the PULSAR and SPECTRA combined (13 of 125 (10.4%) ADA positive and 0.8% tested positive for neutralizing antibodies), and STELLAR study (42 of 162 (5.9%) ADA positive and 6.8% tested positive for neutralizing antibodies). Nevertheless, there was no meaningful impact on the exposure to sotatercept or the efficacy and safety found with sotatercept ADA response in ZENITH participants.

2.3.5. Conclusions on clinical pharmacology

Regarding pharmacokinetics, the popPK analysis consisted of an external validation of a previously developed population pharmacokinetic model on the new dataset, resulting in adequate predictive performance with no re-estimation of model parameters. Therefore, there is no clinically relevant difference in PK in patients with PAH WHO FC III and IV compared to patients with PAH WHO FC II and III.

Regarding pharmacodynamics, no new studies were conducted. ADA data from the ZENITH trial was presented. Antibodies to sotatercept were detected in 33 (39.3%) of 84 evaluable participants.

Neutralizing antibodies were detected in 16 (48.5%) of the 33 participants who developed an ADA response. There was no meaningful impact on the exposure to sotatercept or the efficacy and safety found with sotatercept ADA response in ZENITH participants.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose response studies were performed for the current variation. In the original MAA, the data from the PULSAR and STELLAR trial were the basis for justifying a starting dose of 0.3 mg/kg subcutaneously (SC) with a target dose of 0.7 mg/kg administered SC) every 21 days.

2.4.2. Main study(ies)

ZENITH (A011-14)

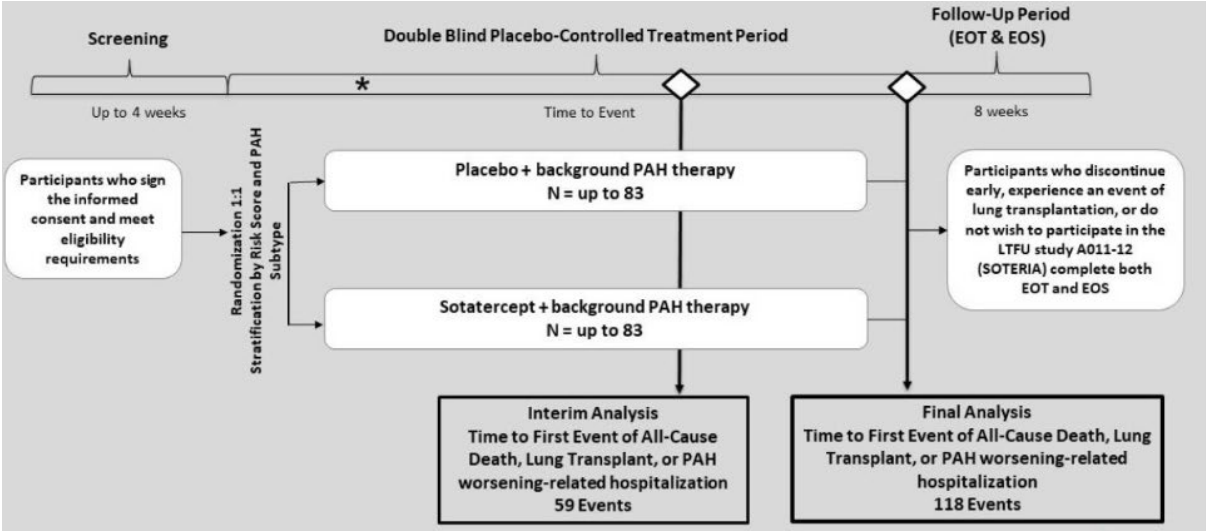
Methods

ZENITH is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate sotatercept when added to maximum tolerated background PAH therapy in participants with PAH WHO FC III or FC IV who are at high risk of mortality. The study consists of 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 who met all eligibility criteria were randomized in a 1:1 ratio to receive either placebo or sotatercept SC every 21 days plus background PAH therapy. The starting dose of sotatercept was 0.3 mg/kg SC at Visit 1, followed by the target dose of 0.7 mg/kg SC for the remainder of the study, unless dose modifications were required. Randomization was stratified by REVEAL Lite 2 risk score and PAH subtype.

Participants who did not experience a primary endpoint event (first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours) remained in the DBPC Treatment Period. Participants who experienced an event of PAH worsening-related hospitalization of ≥24 hours completed an EOT Visit and were eligible to enroll into the open-label, LTFU study SOTERIA (NCT04796337). Participants who elected not to continue into SOTERIA, experienced an event of lung transplantation, or discontinued from the study early without experiencing a primary endpoint event completed the Follow-up Period, including both the EOT and EOS Visits.

An IA of the primary efficacy endpoint occurred when the required number of participants experienced a primary endpoint event and median participant time on study was at least 6 months. The study was stopped early for efficacy following the IA per the DMC recommendation. An overview of the global design is shown in Figure 8.

Figure 8: Study Design ZENITH



Study participants

Male and female participants 18 to 75 years of age, inclusive, with documented diagnostic RHC and confirmed diagnosis of WHO PAH Group 1 in the subtype of idiopathic PAH, heritable PAH, drug/toxin-induced PAH, PAH associated with CTD, or PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair, and who met the following key inclusion criteria were eligible to participate in the study:

- Symptomatic PAH classified as WHO FC III or IV
- REVEAL Lite 2 risk score of ≥9
- RHC performed during screening, documenting a PVR of ≥5 WU and a pulmonary capillary wedge pressure or left ventricular end-diastolic pressure of ≤15 mm Hg
- Clinically stable and on stable doses of maximum tolerated double or triple background PAH therapies for at least 30 days prior to screening

Participants were excluded if they met the following exclusion criteria:

- Diagnosis of PH WHO Groups 2, 3, 4, or 5
- Diagnosis of the following PAH Group 1 subtypes: HIV-associated PAH and PAH associated with portal hypertension
- Diagnosis of pulmonary veno-occlusive diseases or pulmonary capillary hemangiomatosis or overt signs of capillary and/or venous involvement
- Hemoglobin at screening above gender-specific ULN, per local laboratory test
- Baseline platelet count <50,000/mm3 (<50.0 × 10^9/L) at screening
- Baseline SBP <85 mm Hg at screening

Overall, these inclusion criteria indicate that compared to STELLAR (used for the MAA), ZENITH is investigating a more severely impaired patient population, at high risk of clinical events of worsening.

Treatments

Each eligible participant will be randomly assigned in a 1:1 ratio to one of the following 2 treatment arms (see Table 10):

• Arm 1: Placebo administered SC every 21 days plus background PAH therapy
• Arm 2: Sotatercept at a starting dose of 0.3 mg/kg, with a target dose of 0.7 mg/kg, administered SC every 21 days plus background PAH therapy

Prior to administration, the lyophilized sotatercept drug product (60 mg/vial) or matching placebo will be reconstituted with 1.3 mL of sterile water for injection. Reconstituted sotatercept yields a 50 mg/mL solution of sotatercept.

All participants will begin treatment at a starting dose of 0.3 mg/kg at Visit 1. At Visit 2, the dose will be escalated to the target dose of 0.7 mg/kg and remain at 0.7 mg/kg for the duration of the treatment period, unless dose reduction criteria are met. However, if at Visit 2 Hgb increases by more than 2.0 g/dL from the previous dosing visit and this value is above the gender-specific ULN per local laboratory test, dosing should be delayed.

Dose Modifications Due to Hemoglobin Increase

From Visit 3 onward, if Hgb level increases by more than 2 g/dL from the previous dosing visit and this value is above the gender-specific ULN per local laboratory test, then a maximum of 3 consecutive dose delays are allowed during the DBPC Treatment Period. After the third dose delay, if Hgb level persists at more than 2 g/dL above the previous dosing visit and this value is above the gender-specific ULN per local laboratory test, then the dose should be reduced to 0.3 mg/kg. If the participant is already at a dose of 0.3 mg/kg, the study Medical Monitor should be consulted, and study drug discontinuation should be considered. If Hgb level increases more than 4 g/dL above the participant's baseline value, the study Medical Monitor should be consulted, and study drug discontinuation should be considered.

Dose Modifications Due to Low Platelet Count

From Visit 3 onwards, if platelet count is less than 50,000/mm3, dose delay is allowed for up to 3 visits. If platelet count remains less than 50,000/mm3 after 3 consecutive dose delays, then study treatment should be discontinued/not restarted. At the visit following each dose delay, if platelet count is more than 50,000/mm3, then the dose should be reduced to 0.3 mg/kg and study treatment should be restarted. If the participant is already at a dose of 0.3 mg/kg, study treatment should be restarted at 0.3 mg/kg.

Other Dose Modifications

The 3rd general revision of the protocol (STUDY A011-14, AMENDMENT 03, VERSION 4.0), there were also dose modifications based on telangiectasia and serious bleeding events:

In cases of the identification of new events of telangiectasia that are of moderate or greater severity/intensity or for the progression of a telangiectasia event from mild to moderate, the dose of study drug should be delayed for 1 visit if the participant was receiving 0.7 mg/kg study drug, or for 3 visits if the participant was receiving 0.3 mg/kg at the time of the event. If, following the dose hold(s), there has been no progression in the severity of the event of telangiectasia, dosing of study drug may be resumed at a dose level of 0.3 mg/kg. If the event of telangiectasia progresses during the time in which study drug dosing has been delayed, the investigator should consult the Medical Monitor and consider discontinuation from study drug.

In cases of serious active bleeding, the dose of study intervention should be delayed until the event resolves. If more than one dose delay due to a serious bleeding event occurs, then the Medical Monitor should be consulted.

Dose Re-escalation Following Dose Reduction

In cases of dose reduction due to an AE not related to study drug, the dose can be re-escalated when the AE is resolved. In cases of dose reduction due to increases in Hgb, the dose will be re-escalated to

0.7 mg/kg after 2 consecutive visits at which Hgb values are stable and equal to or lower than the ULN. Similarly, in cases of dose reduction due to decrease in platelet count, the dose will be re-escalated to 0.7 mg/kg after 2 consecutive visits at which platelet counts are stable and more than 50,000/mm3, with no association with AEs of bleeding.

The general dosing strategy is the same as applied in the pivotal phase 3 trial STELLAR, used to grant a MAA for sotatercept.

Table 10: Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Placebo (Arm 1)	Placebo Comparator	Placebo	Placebo	Injection, Powder, Lyophilized, For Solution	0 mg	0 mg Q3W	SC	V1 to EOT/EOS	Placebo	IMP	Central
Sotatercept (Arm 2)	Experimental	Sotatercept	Biological/Vaccine	Injection, Powder, Lyophilized, For Solution	60 mg/vial	0.3 mg/kg Q3W	SC	V1	Test Product	IMP	Central
Sotatercept (Arm 2)	Experimental	Sotatercept	Biological/Vaccine	Injection, Powder, Lyophilized, For Solution	60 mg/vial	0.7 mg/kg Q3W	SC	V2 to EOT/EOS	Test Product	IMP	Central

EOS=end of study; EOT=end of treatment; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q3W=every 3 weeks; SC=subcutaneous; V=Visit.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.
Sotatercept dose reductions (from 0.7 to 0.3 mg/kg) due to a safety event are described in the study protocol [16.1.1]. Sotatercept dose re-escalation may occur according to the study protocol [16.1.1].

Objectives

The objective of this study was to evaluate the effects of sotatercept treatment (plus maximum tolerated background PAH therapy) versus placebo (plus maximum tolerated background PAH therapy) on time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours, in participants with WHO FC III and FC IV PAH at high risk of mortality.

Outcomes/endpoints

The primary efficacy endpoint was the time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours.

The secondary efficacy endpoints were ranked as follows:

1. Overall survival
2. Transplant-free survival
3. Proportion of participants who experienced a mortality event at EOS
4. Change from baseline in REVEAL Lite 2 risk score at Week 24
5. Proportion of participants achieving a low or intermediate (≤7) REVEAL Lite 2 risk score at Week 24
6. Change from baseline in NT-proBNP levels at Week 24
7. Change from baseline in mPAP at Week 24
8. Change from baseline in PVR at Week 24
9. Proportion of participants who improve in WHO FC at the end of the DBPC Treatment Period
10. Change from baseline in 6MWD at Week 24
11. Change from baseline in CO at Week 24

Sample size

The sample size determination is based on the primary efficacy endpoint of time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours using EAST® version 6.4. In STELLAR, the hazard ratio (HR) in the sotatercept group compared with the placebo group was 0.16 (95% CI: 0.08 to 0.35) [Hoeper, M. M., et al 2023]. Given the differences in the populations and definitions of endpoints between STELLAR and this study, the HR is assumed to be 0.55 in this study.

Assuming a HR of 0.55, a 1:1 randomization, a 1-sided 0.025 Type 1 error rate, 90% power, and with a planned IA at approximately 50% of the required number of events with the option to stop the study for futility, approximately 118 events will be required based on the log-rank test.

Given that approximately 166 participants are planned to be enrolled in this study, the accrual period is approximately 26 months, assuming an accrual rate of approximately 6.5 participants per month. In addition, assuming a dropout hazard rate of 0.04% per month (0.5% per year), and the probability of observing an event for placebo is 0.45 for the first year, 0.60 for the second year, and 0.90 for the third year and later, the projected time of the IA will occur around 26 months. If the study continues after IA, the final analysis will happen around 40 months. Median participant time on study must be at least 6 months in order for analyses following the occurrence of the required number of events.

Randomisation

The randomization schedule is stratified by REVEAL Lite 2.0 risk score (9 to 10 or ≥ 11) and PAH subtype (CTD-associated or not CTD-associated) at screening. This risk score utilizes six non-invasive variables: functional class, systolic blood pressure, heart rate, 6-minute walk distance, N-terminal prohormone of brain natriuretic peptide, and renal insufficiency.

Participants who have signed the informed consent and meet all eligibility criteria will be stratified by REVEAL Lite 2.0 risk score and PAH subtype and then randomized in a 1:1 ratio to receive placebo plus maximum tolerated background PAH therapy or sotatercept plus maximum tolerated background PAH therapy. Randomization assignments will be generated through a computerized system, provided by an Interactive Response Technology (IRT).

Blinding (masking)

Both the investigators and the participants will be blinded throughout the study. Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

An independent blinded adjudication committee will adjudicate clinical events up to the end of the study, including death, to determine whether these events are due to PAH.

In the event of a medical emergency for an individual participant, where knowledge of the study drug is critical to the participant's medical management, the investigator may break the blind for that participant via the IRT (see the IRT Manual for further instruction). If the nature of the emergency does not permit consultation with the Medical Monitor prior to breaking the blind, the investigator must inform the Medical Monitor that the blind has been broken at the earliest opportunity. In non-urgent situations, the investigator is recommended to discuss the issue with the study Medical Monitor prior to breaking the blind. Only if knowledge of the participant's treatment assignment is necessary for the medical management of that participant should the blind be broken.

If the blind is broken, the participant will be discontinued from the study and will not be eligible to enroll into the LTFU study, A011-12 (SOTERIA). The investigator should not inform the participant of their treatment assignment under any circumstances.

Statistical methods

The estimands of this study were constructed in accordance with the ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.

The treatment policy for the primary endpoint.

Treatment: The treatment conditions of interest are sotatercept on top of background PAH therapy compared with placebo on top of background PAH therapy.

Population: Participants in the FAS, which includes all randomized participants irrespective of the background PAH therapy.

Variable (or endpoint): Time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥ 24 hours.

Intercurrent events: The following intercurrent events will be considered and the "treatment policy strategy" will be followed:

1. If a participant discontinues treatment, the "treatment policy strategy" is followed, and the data after the occurrence of event is used.
2. If a participant is lost to follow-up, the participant is censored at that point. For this event, the "while on treatment and/or followed" strategy is used.
3. If a participant dies, the event occurred by definition following "composite estimand strategy."

Population-level summary: The difference between treatment groups for the time-to-event variable (hazard ratio).

Loss to follow-up was intentionally not defined as an ICE because study follow-up is not relevant to the quantity to be estimated (the estimand). Following ICH E9(R1), discontinuation from treatment was defined as an ICE, using a treatment policy strategy. Loss to follow-up was considered an important data limitation to be addressed in the analysis methodology. Sensitivity analyses following two approaches were implemented to investigate the robustness of the primary results to missing follow-up: multiple imputation using the jump-to-reference method and tipping point.

Estimands for the secondary endpoints

The handling of intercurrent events for the secondary endpoints is shown Table 11.

Table 11: Handling of intercurrent events for secondary endpoints.

Intercurrent event	Strategy
Time-to-event endpoints	
Changes in treatment[a]	Treatment policy
Continuous longitudinal endpoints	
Changes in treatment	Treatment policy
Death	Composite (death = worst rank outcome)
Binary endpoints	
Changes in treatment	Treatment policy
Death[b]	Composite (death = failure)

[a] Dose reduction, dose delay, discontinuation from sotatercept or placebo, or changes to background PAH therapy.
[b] Applicable only for endpoints where death was not already part of the endpoint.

Missing data were handled as follows:

- Time-to-event endpoints: The primary approach was the same as for the primary endpoint, and a sensitivity analysis using the jump-to-reference method (also the same as for the primary endpoint) was performed.

- Continuous longitudinal endpoints: Non-existent Week 24 data because of death were assigned a value corresponding to the worst rank. Missing Week 24 data following non-fatal morbidity events were assigned a value corresponding to the next-worst rank. Missing Week 24 data due to other reasons were imputed using multiple imputation 1) following the distributions of the corresponding treatment arm (primary) and 2) following the distribution of the placebo arm (sensitivity analyses).

- Binary endpoints: All missing Week 24 data were imputed as failures.

In total 118 events were needed for showing a HR of 0.55 with an alpha of 0.05 and power of 90%. In total approximately 166 participants are needed considering the event rate expectations of 40%, 60 and 90% in the first 3 years respectively. The subjects were randomised to sotatercept and placebo arms using a 1:1 ratio stratified by REVEAL Lite 2.0 risk score (9 to 10 or ≥ 11) and PAH subtype (CTD-associated or not CTD-associated) at screening.

Stratified log rank test will be used for the primary endpoint. Cox proportional hazards model (stratified by randomisation factors) will be used to estimate the HR and its 95% confidence interval.

Sensitivity analysis are planned for the primary endpoint:

1. by excluding the deaths after study discontinuation and excluding the post study follow-up time
2. by imputing missing follow up time and events using the retrieved dropout method
3. by imputing missing follow up time and events using the jump to reference methods
4. by imputing missing follow-up time and events using the tipping point method.

Analyses approach for the primary endpoint is endorsed.

Interim analysis

One interim analysis of the primary efficacy endpoint is planned to occur when approximately 59 participants have experienced an event for primary endpoint, roughly at 50% of the total required number of events. The efficacy boundary is derived using a Lan-DeMets spending function

approximating O'Brien- Fleming bounds and futility boundary is derived using a gamma family spending function approximating Hwang-Shi-Decani bounds with gamma=-7.

If the efficacy boundary is crossed for the primary endpoint at the IA, then analyses of secondary endpoints will be performed using a gatekeeping method. The 1-sided type 1 error rate for the evaluation of secondary endpoints will be the same as that used for the primary hypothesis at the IA.

Interim analysis rules for futility and the efficacy bounds are considered acceptable.

Results

Participant flow

A total of 255 participants were screened and 173 were randomized. One participant was randomized in error and immediately discontinued by the site. This participant, who was randomized to the placebo group, did not receive study intervention and was excluded from the efficacy and safety analysis populations. All 82 nonrandomized participants did not meet entry criteria and were screen failures. A total of 18 participants originally screen-failed, were rescreened, and were later randomized. The most common reason for screen failure was not meeting the REVEAL Lite 2 risk score criteria.

Of the 172 randomized patients, 86 were randomized to sotatercept and 86 to placebo. As of the data cutoff date, 108 participants remained in the study and 102 participants were still receiving study intervention. The proportion of participants who had Visit 9 (Week 24) or a subsequent visit was greater in the sotatercept group (83.7%) than in the placebo group (64.0%) and was due to higher numbers of participants in the placebo group who experienced clinical events before Visit 9 (Week 24) and either discontinued or completed the study early. The proportion of participants who completed the study was lower in the sotatercept group (4.7%) than in the placebo group (34.9%) due to the higher numbers of participants in the placebo group who had a PAH worsening-related hospitalization of ≥24 hours or lung transplantation. These participants were considered as having completed the study.

The proportion of participants who discontinued study intervention was lower in the sotatercept group (14.0%) than in the placebo group (22.1%). The most common primary reason for discontinuation of study intervention and study discontinuation in both intervention groups was death, which occurred less frequently in the sotatercept group (5 [5.8%]) than in the placebo group (10 [11.6%]). The median duration of follow-up was longer for the sotatercept group (10.6 months) compared with the placebo group (7.1 months)

Recruitment

Clinical investigator study sites were located in 12 countries: Australia, Belgium, Canada, France, Germany, Israel, Italy, Mexico, Netherlands, Spain, United Kingdom, and United States. The participant first visit was 01-DEC-2021 and the date of the current interim analyses was 26-JUL-2024. A total of 255 participants were screened and 173 were randomized across 53 study sites.

Conduct of the study

Changes in the conduct of the study implemented by protocol amendment are summarized below in Table 12.

Table 12: Summary of Protocol Amendments

Document	Country	Date of Issue	Overall Rationale
P006-01	Global	16-JUN-2022	This amendment was primarily created to: • Update inclusion and exclusion criteria to allow inclusion of additional high-risk patients. • Update AESIs based on review of safety data from the PULSAR study.
P006-02	France	16-DEC-2021	The key changes for this amendment were as follows: • Added telangiectasia as an AESI and provided monitoring parameters. • Added dose modifications required for AEs of telangiectasia.
P006-03	UK	22-OCT-2021	This amendment was primarily created to address a health authority request to clarify that in non-urgent situations where knowledge of the study drug is critical to the participant's medical management, the investigator is recommended to discuss the issue with the study Medical Monitor prior to breaking the blind.
P006-04	UK	03-NOV-2021	This amendment was primarily created to address a health authority request to clarify that in the event of a medical emergency and in non-urgent situations, the investigator may break the blind for a participant via IRT.
P006-06	Global	29-JUN-2023	The primary reasons for this amendment were as follows: • Modified the protocol to allow participants who experience a confirmed event of PAH worsening-related hospitalization of ≥24 hours to enter the open-label, long-term follow-up study (A011-12, SOTERIA) following an End-of-Treatment Visit. • Modified the assumed hazard ratio, required number of primary endpoint events to trigger the interim and final analyses, and the interim analysis timepoint.
P006-07	Global	23-APR-2024	This protocol amendment was created primarily to add dose modification instructions due to serious bleeding events, add event adjudication language, and update the risk/benefit section.

No confirmed events of premature unblinding were reported for this study.

Protocol deviations were defined, identified, captured, and categorized by Acceleron.

Important protocol deviations were reported for 56 participants, see Table 13 The most common important protocol deviation category (≥10% in either group) was study treatment administration/dispensation. The proportion of participants with important protocol deviations related to entry criteria was comparable in both groups. All participants with entry criteria deviations were assessed by the investigator and the Sponsor and deemed acceptable to continue in the study. These important protocol deviations were distributed across study sites and retraining was conducted at these sites. No participant's data were excluded from analysis due to a protocol deviation.

Table 13: Summary of Important Deviations

	Sotatercept		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	86		86		172	
with one or more important deviations	58	(67.4)	48	(55.8)	106	(61.6)
with no important deviations	28	(32.6)	38	(44.2)	66	(38.4)
ICH/GCP Deviation	**47**	**(54.7)**	**39**	**(45.3)**	**86**	**(50.0)**
Data Privacy	14	(16.3)	9	(10.5)	23	(13.4)
ICF Process/Timing	16	(18.6)	12	(14.0)	28	(16.3)
Inv Oversight	6	(7.0)	5	(5.8)	11	(6.4)
Inv Qualifications/Agreements	2	(2.3)	3	(3.5)	5	(2.9)
Inv Record Keeping CRF	2	(2.3)	1	(1.2)	3	(1.7)
Inv Record Keeping Esntl Docs	1	(1.2)	0	(0.0)	1	(0.6)
Inv Record Keeping Source Docs	3	(3.5)	4	(4.7)	7	(4.1)
Inv Safety Reporting (CRF)	24	(27.9)	19	(22.1)	43	(25.0)
Inv Safety Rptg (Reg/Sponsor)	0	(0.0)	1	(1.2)	1	(0.6)
Study Trtmt Supplies/Control	1	(1.2)	0	(0.0)	1	(0.6)
Protocol Deviation	**33**	**(38.4)**	**23**	**(26.7)**	**56**	**(32.6)**
Exclusion Criteria	2	(2.3)	0	(0.0)	2	(1.2)
Inclusion Criteria	3	(3.5)	4	(4.7)	7	(4.1)
Missing Endpoint Assessments	0	(0.0)	2	(2.3)	2	(1.2)
Other Protocol Deviation	3	(3.5)	3	(3.5)	6	(3.5)
Study Procedures/Assessments	0	(0.0)	2	(2.3)	2	(1.2)
Protocol Deviation	**33**	**(38.4)**	**23**	**(26.7)**	**56**	**(32.6)**
Study Treatment Admin/Dispense	25	(29.1)	11	(12.8)	36	(20.9)
Study Treatment Randomization	6	(7.0)	6	(7.0)	12	(7.0)
Visit Scheduling	4	(4.7)	0	(0.0)	4	(2.3)
Withdrawal/Term Criteria	1	(1.2)	0	(0.0)	1	(0.6)

Every participant is counted a single time for each applicable row and column.
Important deviations are defined as the significant deviations per study deviation rules.
Database cutoff date: 26JUL2024

Numbers analysed

Efficacy analyses were performed in the FAS population, which included 172 of the 173 randomized participants (excluding 1 participant who was randomized in error and immediately discontinued by the site). This participant did not receive study intervention.

Baseline data

Demographics and baseline disease characteristics were generally comparable between the sotatercept and placebo groups, see Table 14 The sotatercept had slightly more males, elderly, patients on triple therapy and patients with lower kidney function, although the differences with the placebo group were small. Overall, the majority of participants were female (76.7%), the most common race was white (86.6%), and the most common ethnicity was not Hispanic or Latino (87.8%). The median age was 57.5 years (range: 18 to 75 years). The 3 most common PAH (Group 1 PH) subtypes were idiopathic PAH (50.0%), PAH associated with CTD (27.9%), and heritable PAH (10.5%). The mean time since PAH diagnosis was 7.68 years. There were more participants on background PAH triple therapy (72.1%) compared with double therapy (27.9%). More than half of participants were on prostacyclin infusion therapy (59.3%). There were more participants in WHO FC III (74.4%) compared with WHO FC IV (25.6%). The REVEAL Lite 2 risk score was <9 for 2.3% of participants, 9 to 10 for 67.4% of participants, and ≥11 for 30.2% of participants. The population represents a severe PAH patients at high risk of events of clinical worsening.

Table 14: Baseline table part 1

	Sotatercept		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	86		86		172	
Sex						
Male	25	(29.1)	15	(17.4)	40	(23.3)
Female	61	(70.9)	71	(82.6)	132	(76.7)
Age (Years)						
18 to <45	21	(24.4)	21	(24.4)	42	(24.4)
45 to <65	35	(40.7)	45	(52.3)	80	(46.5)
65 to ≤75	30	(34.9)	20	(23.3)	50	(29.1)
>75	0	(0.0)	0	(0.0)	0	(0.0)
Mean	55.3		53.5		54.4	
SD	14.3		14.3		14.3	
Median	58.0		57.0		57.5	
Range	19 to 75		18 to 75		18 to 75	
Race						
American Indian Or Alaska Native	0	(0.0)	1	(1.2)	1	(0.6)
Asian	4	(4.7)	3	(3.5)	7	(4.1)
Black Or African American	5	(5.8)	4	(4.7)	9	(5.2)
Other	3	(3.5)	2	(2.3)	5	(2.9)
White	73	(84.9)	76	(88.4)	149	(86.6)
Missing	1	(1.2)	0	(0.0)	1	(0.6)
Ethnicity						
Hispanic Or Latino	6	(7.0)	12	(14.0)	18	(10.5)
Not Hispanic Or Latino	78	(90.7)	73	(84.9)	151	(87.8)
Not Reported	1	(1.2)	1	(1.2)	2	(1.2)
Unknown	1	(1.2)	0	(0.0)	1	(0.6)
Region[a]						
North America	36	(41.9)	45	(52.3)	81	(47.1)
Europe	47	(54.7)	40	(46.5)	87	(50.6)
Asia/Pacific	3	(3.5)	1	(1.2)	4	(2.3)
BMI (kg/m^2)						
Participants with data	86		86		172	
Mean	25.2		25.8		25.5	
SD	5.77		5.90		5.83	
Median	24.4		24.6		24.5	
Range	16.3 to 49.5		16.8 to 41.9		16.3 to 49.5	
REVEAL Lite 2.0 Risk Score						
<9	1	(1.2)	3	(3.5)	4	(2.3)
9 to 10	59	(68.6)	57	(66.3)	116	(67.4)
≥11	26	(30.2)	26	(30.2)	52	(30.2)
WHO Diagnostic Pulmonary Hypertension Group I, PAH						
Idiopathic PAH	42	(48.8)	44	(51.2)	86	(50.0)
Heritable PAH	11	(12.8)	7	(8.1)	18	(10.5)
Drug or toxin-induced PAH	6	(7.0)	5	(5.8)	11	(6.4)
PAH associated with connective tissue disease	22	(25.6)	26	(30.2)	48	(27.9)
PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following shunt repair	5	(5.8)	4	(4.7)	9	(5.2)
6 Minute Walk Distance (m)						
Participants with data	86		86		172	
Mean	270.3		270.7		270.5	
SD	104.8		99.9		102.1	
Median	292.6		282.5		290.7	
Range	11.0 to 501.0		44.2 to 493.0		11.0 to 501.0	
WHO Function Class						
III	66	(76.7)	62	(72.1)	128	(74.4)
IV	20	(23.3)	24	(27.9)	44	(25.6)
Combination Therapy						
	Sotatercept		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Double Therapy	21	(24.4)	27	(31.4)	48	(27.9)
Triple Therapy	65	(75.6)	59	(68.6)	124	(72.1)

Table 14 Baseline table part 2

	Sotatercept		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Prostacyclin Infusion Therapy						
Prostacyclin Infusion Therapy	53	(61.6)	49	(57.0)	102	(59.3)
Non- Prostacyclin Infusion Therapy	33	(38.4)	37	(43.0)	70	(40.7)
PVR (dynes*sec/cm5)						
Participants with data	86		85		171	
Mean	883.2		874.7		879.0	
SD	410.93		344.23		378.15	
Median	792.0		792.0		792.0	
Range	328.0 to 2464.0		360.0 to 1928.0		328.0 to 2464.0	
Cardiac Output (L/min)						
Participants with data	86		86		172	
Mean	4.7		4.5		4.6	
SD	1.22		1.41		1.32	
Median	4.5		4.4		4.5	
Range	2.2 to 8.0		2.2 to 9.6		2.2 to 9.6	
Cardiac Index (L/min/m2)						
Participants with data	86		86		172	
Mean	2.6		2.6		2.6	
SD	0.62		0.76		0.69	
Median	2.5		2.3		2.5	
Range	1.4 to 4.1		1.4 to 4.4		1.4 to 4.4	
eGFR (ml/min/1.73m2)						
Participants with data	85		86		171	
Mean	65.1		73.5		69.3	
SD	24.57		29.65		27.49	
Median	62.0		69.0		64.0	
Range	25 to 136		23 to 181		23 to 181	
NT-proBNP (pg/mL)						
Participants with data	86		86		172	
Mean	3603.1		2687.3		3145.2	
SD	4101.20		2771.24		3519.81	
Median	1969.0		2123.5		2078.5	
Range	184 to 22752		19 to 19519		19 to 22752	

SD=Standard deviation.
[a] Region is defined based on the physical geography of the countries.
All the measurements were taken during the screening.
BMI = body mass index; eGFR = estimated glomerular filtration rate; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; REVEAL = registry to evaluate early and long-term PAH disease management; WHO = world health organization.
Database cutoff date: 26JUL2024.

The median duration of exposure to study intervention through the data cutoff was substantially longer in the sotatercept group (322.0 days) than in the placebo group (215.5 days). Dose escalation occurred in 84 participants in the sotatercept group and 84 in the placebo group. The median time to first escalation for these participants was 22.0 days in both groups.

A total of 16 (18.6%) participants in the sotatercept group and 3 (3.5%) participants in the placebo group experienced a dose reduction through the IA data cuttoff. The median time to dose reduction was 201.0 days in the sotatercept group and 108.0 days in the placebo group. Experiencing an AE was the most common reason for a dose reduction in both groups.

A total of 31 (36.0%) participants in the sotatercept group and 23 (26.7%) participants in the placebo group experienced at least 1 dose delay through the IA data cutoff. The median time to dose delay was 164.0 days in the sotatercept group and 85.0 days in the placebo group. The most common reasons for dose delays were per protocol dose delay guidelines (particularly due to increased hemoglobin) and/or other AEs in the sotatercept group and other AEs in the placebo groups.

A tabulated overview of dose modification is shown in Table 15

Table 15: Overview of dose modifications.

	Sotatercept n (%)	Placebo n (%)	Total n (%)
Participants in population	86 (100.0)	86 (100.0)	172 (100.0)
Number of dose reductions per participant			
0	70 (81.4)	83 (96.5)	153 (89.0)
1	16 (18.6)	3 (3.5)	19 (11.0)
Time to first reduction (days)			
n	16	3	19
Mean (SD)	257.7 (171.2)	102.3 (12.5)	233.2 (166.8)
Median	201.0	108.0	149.0
Range	49.0 to 505.0	88.0 to 111.0	49.0 to 505.0
Reasons for dose reduction [a]			
Adverse Event	11	2	13
Per protocol dose modification guidelines due to hemoglobin increase	1	0	1
Per protocol dose modification guidelines due to low platelet count	2	1	3
Other	2	0	2
Number of dose delays per participant			
0	55 (64.0)	63 (73.3)	118 (68.6)
1	18 (20.9)	15 (17.4)	33 (19.2)
2	6 (7.0)	7 (8.1)	13 (7.6)
3	5 (5.8)	1 (1.2)	6 (3.5)
5	2 (2.3)	0 (0.0)	2 (1.2)
Time to first delay (days)			
n	31	23	54
Mean (SD)	192.1 (153.3)	128.2 (104.5)	164.9 (137.3)
Median	164.0	85.0	127.5
Range	21.0 to 505.0	22.0 to 406.0	21.0 to 505.0
Reasons for dose delay [a]			
Adverse Event	16	12	28
Investigator request	2	2	4
Patient request	1	3	4
Per protocol dose delay guidelines due to hemoglobin increase	19	1	20
Per protocol dose delay guidelines due to low platelet count	8	2	10
Per protocol dose delay guidelines due to AESI of telangiectasia	2	1	3
Visit was not done	6	6	12
Other	1	5	6

[a] Participants with multiple reductions or delays are counted once toward each unique reason.
Database cutoff date: '26JUL2024'.

Outcomes and estimation

Primary endpoint:
The time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours was significantly longer in the sotatercept group than in the placebo group. Fewer participants in the sotatercept group (15 [17.4%]) than in the placebo group (47 [54.7%]) had a primary endpoint event as of the data cutoff, see Table 16

The risk of a first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours was 76% lower in the sotatercept group compared with the placebo group (HR: 0.24; 95% CI: 0.13, 0.43; p<0.0001). The median time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours was not reached (due to too few events to allow estimation) in the sotatercept group compared with 9.6 months (95% CI: 6.2,

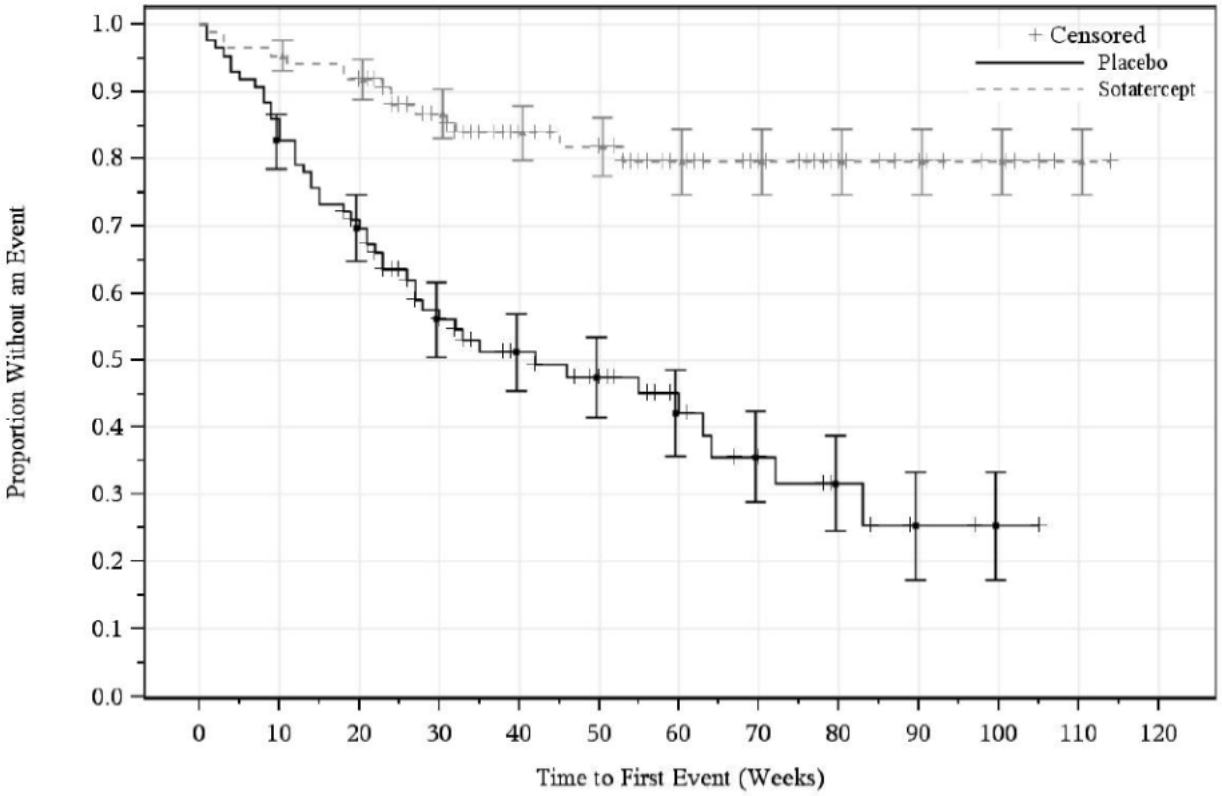
14.8) in the placebo group. Kaplan-Meier curves showed separation beginning at approximately Week 5 and increasing for the remainder of the study.

Table 16: Analysis of Time to First Event of All-cause Death, Lung Transplantation, or PAH Worsening-related Hospitalization of ≥ 24 Hours

	Sotatercept (N=86)	Placebo (N=86)
Number of Participants with ≥1 Event (%)	15 (17.4)	47 (54.7)
All-cause death	6 (7.0)	3 (3.5)
Lung transplantation	1 (1.2)	1 (1.2)
PAH worsening-related hospitalization of ≥24 hours	8 (9.3)	43 (50.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	9.6 (6.2, 14.8)
[Q1, Q3]	[NR, NR]	[3.4, NR]
Person-months	974.8	671.3
Incidence Rate / 100 Person-months	1.5	7.0
vs Placebo		
Hazard Ratio (95% CI)[b]	0.24 (0.13, 0.43)	
p-value[c]	<0.0001	

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by the randomization stratification factors.
[c] One-sided p-value based on log-rank test stratified by the randomization stratification factors.
NR = Not reached.
This table includes the first event of adjudication-confirmed PAH worsening-related hospitalization ≥24 hours, lung transplantation, or all-cause death prior to the cutoff date. All pre-cutoff deaths are included, regardless of adjudication and regardless of whether they occurred during or post ZENITH.
The statistical criterion of superiority of Sotatercept to placebo at the interim analysis is based on the 1-sided p-value <0.0021.
CI = confidence interval; PAH = pulmonary arterial hypertension
Database Cutoff Date: 26JUL2024.

Figure 9: Kaplan-Meier Plot of Time to First Event of All-cause Death, Lung Transplantation, or PAH Worsening-related Hospitalization of ≥ 24 Hours



Number of participants at risk

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

Number of events inside period

Placebo	12	13	10	4	2	1	3	1	1	0	0	0	0
Sotatercept	4	3	4	2	1	1	0	0	0	0	0	0	0

Summary of Each Component of the Primary Endpoint

The indented rows for the components of the composite primary endpoint in Table 17 reflect only those events that were counted as first events (i.e. that contributed to the counts in the first row of the table). The analysis of the primary composite endpoint from Table 17 is repeated in the first row of Table 18. The subsequent rows in Table 18 show each component of the composite as a standalone outcome. Any participant who had more than one component of the composite endpoint counts toward each applicable row. The number of additional events in Table 18 was 5 lung transplantations (all in the placebo group) and 11 deaths (10 in the placebo group and 1 in the sotatercept group). When considering the components as standalone outcomes, each was directionally consistent with the composite primary endpoint.

Table 17: Summary of the Components of the Primary Endpoint

	Sotatercept (N=86) n (%)	Placebo (N=86) n (%)	Hazard Ratio (95% CI) p-value
Number (%) of participants with ≥ 1 primary event during or post ZENITH	15 (17.4)	47 (54.7)	0.24 (0.13, 0.43) <0.0001
Components of primary endpoint events[a]			
All-cause death[b]	7 (8.1)	13 (15.1)	
Lung transplantation	1 (1.2)	6 (7.0)	
PAH worsening-related hospitalization of ≥ 24 hours	8 (9.3)	43 (50.0)	

[a]A participant is included in more than one row if multiple events meeting primary endpoint definition were observed.
[b]Include all deaths up to the data cutoff date, except for those occurring after lung transplantation or enrollment in SOTERIA.
CI = confidence interval.
Database cutoff date: 26JUL2024

An overview of the IE events other than death per treatment group is shown in Table 18.

Table 18: Overview of intercurrent events of changes in treatment

	Sotatercept n (%)	Placebo n (%)	Total n (%)
Participants in population	86 (100.0)	86 (100.0)	172 (100.0)
Number of dose reductions per participant			
0	70 (81.4)	83 (96.5)	153 (89.0)
1	16 (18.6)	3 (3.5)	19 (11.0)
Number of dose delays per participant			
0	55 (64.0)	63 (73.3)	118 (68.6)
1	18 (20.9)	15 (17.4)	33 (19.2)
2	6 (7.0)	7 (8.1)	13 (7.6)
3	5 (5.8)	1 (1.2)	6 (3.5)
5	2 (2.3)	0 (0.0)	2 (1.2)
Number of dose escalations per participant			
0	2 (2.3)	2 (2.3)	4 (2.3)
1	80 (93.0)	81 (94.2)	161 (93.6)
2	4 (4.7)	3 (3.5)	7 (4.1)
Status for the study medication			
Discontinued	12 (14.0)	19 (22.1)	31 (18.0)
Changes in PAH Background Therapy			
Discontinued PAH Therapy	7 (8.1)	4 (4.7)	11 (6.4)
Initiated New PAH Therapy	5 (5.8)	12 (14.0)	17 (10.0)
Altered Dosage of PAH Therapy	24 (27.9)	24 (27.9)	48 (27.9)
Database cutoff date: 26JUL2024			

Sensitivity analyses of the primary endpoint

Results from the sensitivity analysis excluding post-study deaths (ie, including only adjudicated events) were consistent with results from the primary analysis, see Table 19.

Table 19: Sensitivity analyses of the primary endpoint using only mortality during the study

	Sotatercept (N=86)	Placebo (N=86)
Number of Events (%)	14 (16.3)	46 (53.5)
All-cause death	5 (5.8)	2 (2.3)
Lung transplantation	1 (1.2)	1 (1.2)
PAH worsening-related hospitalization of ≥24 hours	8 (9.3)	43 (50.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	10.7 (6.2, 14.8)
[Q1, Q3]	[NR, NR]	[3.4, NR]
Person-months	973.9	669.0
Event Rate / 100 Person-months	1.4	6.9
vs Placebo		
Hazard Ratio (95% CI)[b]	0.23 (0.12, 0.42)	
p-value[c]	<0.0001	

For the primary endpoint, any participant who did not have a reported event prior to the data cutoff date and who discontinued the study prior to the cutoff date was considered as lost to follow-up. There were 4 participants in each arm considered as lost to follow-up for the primary endpoint. Results from the sensitivity analysis using the jump to reference imputation method for missing follow-up were consistent with results from the primary analysis, see Table 20.

Table 20: Sensitivity Analysis - Multiple Imputation using Jump to Reference Method

	Sotatercept (N=86)	Placebo (N=86)
Number (%) of observed first events	15 (17.4)	47 (54.7)
All-cause death	6 (7.0)	3 (3.5)
Lung transplantation	1 (1.2)	1 (1.2)
PAH worsening-related hospitalization of >=24 hours	8 (9.3)	43 (50.0)
Number (%) of participants missing follow-up time[a]	4 (4.7)	4 (4.7)
Total missing follow-up time[b] (months)	19.2	9.0
Comparison vs. Placebo		
Hazard Ratio (95% CI)[c]	0.24 (0.13, 0.43)	
p-value[d]	<.0001	

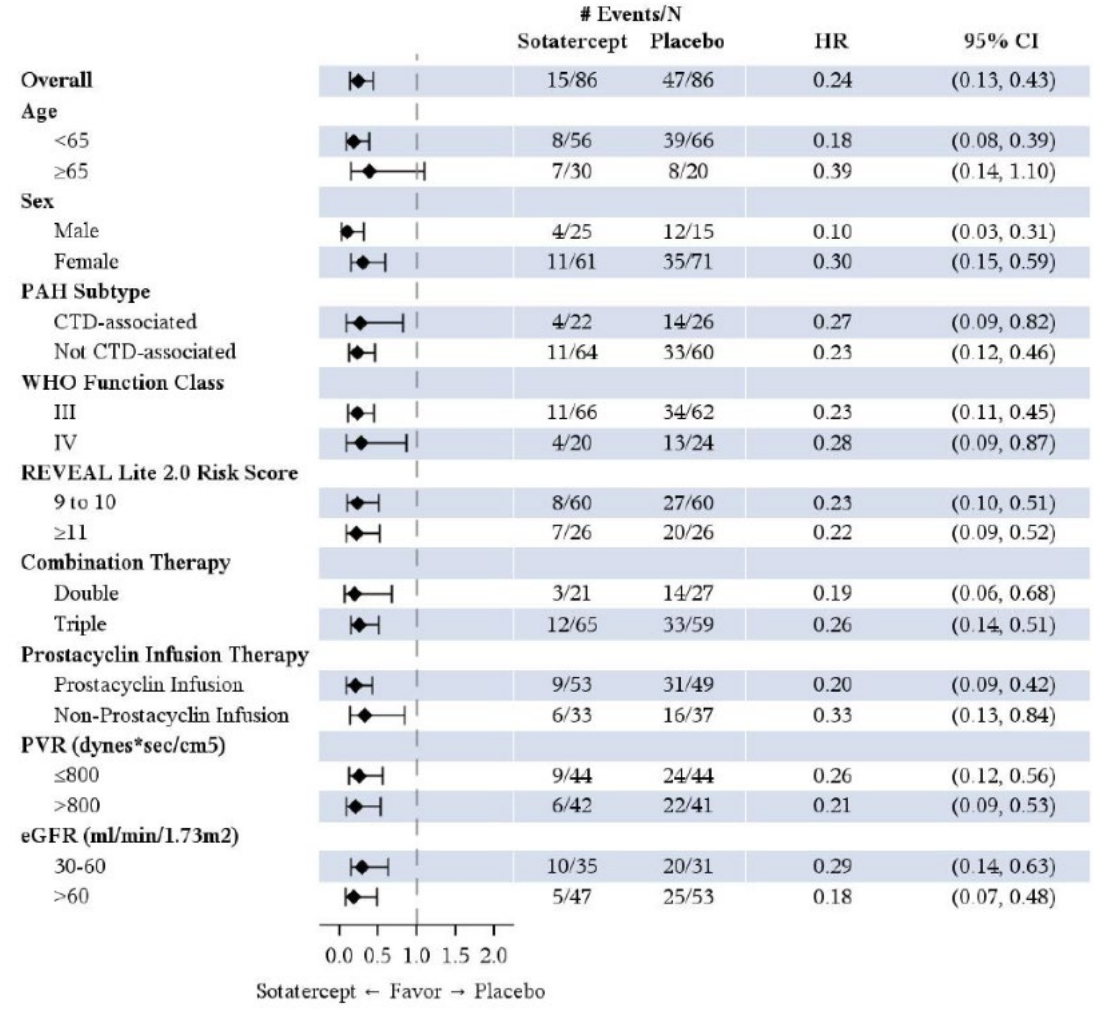
[a]Any participant who did not have a reported event prior to the database cutoff date and discontinued the study prior to the cutoff date will be considered as having missing follow-up.
[b]Lost follow-up time will be calculated as the time from the last visit with full assessment of efficacy endpoints to the data cutoff date.
[c]Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by the randomization stratification factors.
[d]One-sided p-value based on the log-rank test stratified by randomization factors.
This table includes the same events as the primary analysis.
CI = confidence interval; PAH = pulmonary arterial hypertension
Database cutoff date: 26JUL2024

The sensitivity analysis using the tipping point method showed that the tipping point was not estimable, this was due to the low number of participants in the sotatercept group with missing follow-up time and the low HR.

Subgroup analyses of the primary endpoint

The treatment effect of sotatercept on the time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours was consistent across the prespecified subgroups, as shown in the Forest plot in Figure 10. Of note, the effect of the primary endpoint was also present in the subgroup of WHO FC IV, as well as in patients at higher risk of events (REVEAL score >=11).

Figure 10: Forest plot of subgroup analyses of the primary endpoint



	# Events/N Sotatercept	Placebo	HR	95% CI
Overall	15/86	47/86	0.24	(0.13, 0.43)
Age				
<65	8/56	39/66	0.18	(0.08, 0.39)
≥65	7/30	8/20	0.39	(0.14, 1.10)
Sex				
Male	4/25	12/15	0.10	(0.03, 0.31)
Female	11/61	35/71	0.30	(0.15, 0.59)
PAH Subtype				
CTD-associated	4/22	14/26	0.27	(0.09, 0.82)
Not CTD-associated	11/64	33/60	0.23	(0.12, 0.46)
WHO Function Class				
III	11/66	34/62	0.23	(0.11, 0.45)
IV	4/20	13/24	0.28	(0.09, 0.87)
REVEAL Lite 2.0 Risk Score				
9 to 10	8/60	27/60	0.23	(0.10, 0.51)
≥11	7/26	20/26	0.22	(0.09, 0.52)
Combination Therapy				
Double	3/21	14/27	0.19	(0.06, 0.68)
Triple	12/65	33/59	0.26	(0.14, 0.51)
Prostacyclin Infusion Therapy				
Prostacyclin Infusion	9/53	31/49	0.20	(0.09, 0.42)
Non-Prostacyclin Infusion	6/33	16/37	0.33	(0.13, 0.84)
PVR (dynes*sec/cm5)				
≤800	9/44	24/44	0.26	(0.12, 0.56)
>800	6/42	22/41	0.21	(0.09, 0.53)
eGFR (ml/min/1.73m2)				
30-60	10/35	20/31	0.29	(0.14, 0.63)
>60	5/47	25/53	0.18	(0.07, 0.48)

Secondary endpoints

Overall survival

The primary analysis of overall survival (OS) included all deaths up to the data cutoff date, except for those occurring after lung transplantation or enrollment in SOTERIA. The point estimate for the OS HR favored the sotatercept group over the placebo group (HR: 0.42; 95% CI: 0.17, 1.07; p=0.0313). However, only 20 events were observed (7 events in the sotatercept group and 13 events in the placebo group), and the boundary for statistical significance was not crossed. For the overall survival and mortality event endpoints, participants with unknown vital status as of the data cutoff date were considered as loss to follow-up. There was 1 participant in the sotatercept group and 2 participants in the placebo group satisfying this criterion. Results from the sensitivity analysis including all deaths up to the data cutoff date, even those occurring after lung transplantation or enrollment in SOTERIA, were consistent with results from the primary analysis (8 death in sotatercept, 18 in placebo; HR: 0.40 (0.17, 0.93); P=0.0134).

The first ranked secondary endpoint of OS was tested at the IA, and the boundary for statistical significance (prespecified 1-sided alpha of 0.0021) was not crossed. The subsequent secondary endpoints were not eligible to be tested due to the hierarchical testing strategy. All p-values for the subsequent secondary endpoints are not controlled for multiplicity and have not been used to draw

inference about the efficacy of sotatercept. Only confidence intervals are therefore provided and the results only summarized shortly in this report.

Transplant-free Survival

The primary analysis of transplant-free survival included all lung transplantations and all deaths up to the data cutoff date, except for those occurring after enrollment in SOTERIA. A total of 8 events were observed in the sotatercept group compared with 19 in the placebo group. For transplant-free survival, any participant who discontinued the study prior to the data cutoff date and did not have a reported lung transplantation or death prior to the data cutoff was considered as having missing follow-up. There were 7 participants in the sotatercept group and 26 participants in the placebo group satisfying this criterion. The point estimate for the transplant-free survival HR favored the sotatercept group over the placebo group (HR: 0.34; 95% CI: 0.15, 0.78). A similar result was found in a sensitivity analysis using multiple imputations with jump to reference method.

Proportion of participants who experienced a mortality event at end of study

The proportion of participants who had a mortality event at EOS favoured the sotatercept group (8.1%) over the placebo group (15.1%).

Change from baseline in REVEAL Lite 2 risk score at Week 24

The analysis of change from baseline in REVEAL Lite 2 risk score at Week 24 favored the sotatercept group over the placebo group. The median treatment difference between the sotatercept and placebo groups at Week 24 was -3.1 (95% CI: -4.25, -1.88) (Hodges-Lehmann Location shift).

Proportion who achieved a low or intermediate REVEAL Lite 2 risk score at Week 24

The proportion of participants with a REVEAL Lite 2 risk score >7 at baseline who achieved a low or intermediate (≤ 7) REVEAL Lite 2 risk score at Week 24 favored the sotatercept group (49.3%) over the placebo group (15.3%).

Change from baseline in NT-proBNP levels at Week 24

The analysis of change from baseline in NT-proBNP at Week 24 favored the sotatercept group over the placebo group. The median treatment difference between the sotatercept and placebo groups at Week 24 was -2339.1 pg/mL (95% CI: -3378.74; -1299.44) (Hodges-Lehmann Location shift).

Change from baseline in mPAP at Week 24

The analysis of change from baseline in mPAP at Week 24 favored the sotatercept group over the placebo group. The median treatment difference between the sotatercept and placebo groups at Week 24 was -21.2 mm Hg (95% CI: -27.78; -14.59) (Hodges-Lehmann Location shift).

Change from baseline in PVR at Week 24

The analysis of change from baseline in PVR at Week 24 favored the sotatercept group over the placebo group. The median treatment difference between the sotatercept and placebo groups at Week 24 was -339.6 dynes*sec/cm5 (95% CI: -511.09; -168.06) (Hodges-Lehmann Location shift).

Proportion of participants who improved in WHO FC at the end of the DBPC treatment period

The proportion of participants with improvement in WHO FC at the end of the DBPC Treatment Period favoured the sotatercept group (n=48; 55.8%) over the placebo group (n=24; 27.9%).

Change from baseline in 6MWD at Week 24

The analysis of change from baseline in 6MWD at Week 24 favored the sotatercept group over the placebo group. The median treatment difference between the sotatercept and placebo groups at Week 24 was 63.0 meters (95% CI: 23.22; 102.73) (Hodges-Lehmann Location shift).

Change from baseline in cardiac output at Week 24

There was no notable difference in the change from baseline in cardiac output (CO) at Week 24 in the sotatercept group compared with the placebo group. In the sotatercept group, there was a CO decrease of 0.10 L/min and in the placebo group, there was a CO decrease of 0.38 L/min. The median treatment difference between the sotatercept and placebo groups at Week 24 was 0.5 L/min (95% CI: -0.18, 1.16) (Hodges-Lehmann Location shift).

Change from baseline in EQ-5D-5L *at Week 24*

Only descriptive statistics within each intervention group are provided for change from baseline in EQ-5D-5L at Week 24 because the compliance rate was <50%. The low compliance rate limits the interpretation of these results.

Ancillary analyses

To further support the proposed changes in the indication of sotatercept, notably including WHO FC IV, the Applicant has provided post-hoc analyses on the secondary endpoints stratified according to WHO FC III or FC IV. For the primary endpoint, these analyses are already presented above, demonstrating that the HR for the primary endpoint was comparable in WHO FC III (HR: 0.23 (0.11; 0.45)) and WHO FC IV (HR: 0.28 (0.09; 0.87)).

These post hoc subgroup analyses of secondary efficacy by WHO FC are shown in Table 21, and are not adjusted for multiplicity and in some cases are based on very small sample sizes and therefore should be interpreted with caution

Table 21: Post-hoc analyses of secondary endpoints stratified for WHO functional class

Endpoint	WHO FC = III		WHO FC = IV	
	Sotatercept N = 66	Placebo N = 62	Sotatercept N = 20	Placebo N = 24
Overall Survival				
Number of Participants with Events (%)	5 (7.6)	10 (16.1)	2 (10.0)	3 (12.5)
Hazard Ratio (95% CI)[a]	0.37 (0.13, 1.10)		0.61 (0.10, 3.87)	
Transplant-Free Survival				
Number of Participants with Events (%)	5 (7.6)	14 (22.6)	3 (15.0)	5 (20.8)
Hazard Ratio (95% CI)[a]	0.27 (0.10, 0.76)		0.59 (0.14, 2.54)	
Proportion of Participants with Mortality Event				
Number of Deaths (%)	5 (7.6)	10 (16.1)	2 (10.0)	3 (12.5)
Difference in Proportion (95% CI)[b]	-8.55 (-20.76, 2.82)		-2.50 (-23.30, 19.96)	
Change from Baseline in REVEAL Lite 2.0 Risk Score at Week 24[c]				
Median (min, max)	-2.0 (-2, -2)	0.0 (0, 0)	-4.0 (-5, -4)	0.0 (0, 0)
Hodges-Lehmann Location Shift (95% CI)[d]	-3 (-5, -2)		-4 (-6, -2)	
Proportion of Participants Achieving a Low or Intermediate REVEAL Lite 2.0 Risk Score at Week 24[c]				
Participants with Improvement/Participants with REVEAL Lite 2.0 Risk Score >7 at Baseline (%)	24/53 (45.3)	6/52 (11.5)	10/16 (62.5)	5/20 (25.0)
Difference in Proportion (95% CI)[b]	33.74 (17.07, 49.04)		37.50 (4.64, 63.39)	
Change from Baseline in NT-proBNP (pg/mL) at Week 24[c]				
Median (min, max)	-1215.5 (-1216, -1216)	311.1 (253, 324)	-1233.0 (-1233, -1233)	76.0 (76, 76)
Hodges-Lehmann Location Shift (95% CI)[d]	-1978.2 (-2926.00, -1030.37)		-4283.0 (-8906.00, -1151.00)	
Change from Baseline in mPAP (mmHg) at Week 24[c]				
Median (min, max)	-13.0 (-13, -13)	5.3 (5, 6)	-18.0 (-18, -18)	6.0 (6, 6)
Hodges-Lehmann Location Shift (95% CI)[d]	-18.2 (-24.72, -11.77)		-24.0 (-34.00, -14.00)	
Change from Baseline in PVR (dynes*sec/cm^5) at Week 24[c]				
Median (min, max)	-154.3 (-156, -152)	15.6 (0, 40)	-192.0 (-192, -192)	152.0 (152, 152)
Hodges-Lehmann Location Shift (95% CI)[d]	-263.9 (-455.50, -72.25)		-416.0 (-776.00, -200.00)	
Proportion of Participants Improving in WHO FC				
Number of Participants with Improvement (%)	30 (45.5)	11 (17.7)	18 (90.0)	13 (54.2)
Difference in Proportion (95% CI)[b]	27.71 (11.78, 42.39)		35.83 (9.23, 57.78)	
Change from Baseline in 6MWD (m) at Week 24[c]				
Median (min, max)	43.09 (41.6, 44.0)	-7.71 (-10.0, -2.0)	100.00 (92.0, 102.0)	6.00 (6.0, 6.0)
Hodges-Lehmann Location Shift (95% CI)[d]	52.9 (5.51, 100.19)		117.1 (20.43, 213.87)	
Change from Baseline in CO (L/min) at Week 24[c]				
Median (min, max)	-0.12 (-0.1, -0.1)	-0.21 (-0.4, 0.1)	0.01 (0.0, 0.0)	-0.83 (-0.8, -0.8)
Hodges-Lehmann Location Shift (95% CI)[d]	0.2 (-0.46, 0.89)		0.4 (-0.66, 1.33)	

[a] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[b] Based on Miettinen and Nurminen method.
[c] For endpoints associated with Week 24, only randomized participants on the study more than 24 weeks before the database cutoff were included: 60 received sotatercept and 55 received placebo in the WHO FC III subgroup, while 17 received sotatercept and 23 received placebo in the WHO FC IV subgroup.
[d] Based on aligned rank Wilcoxon test.
N = number of participants in the treatment group.
6MWD = 6-minute walking distance; CI = confidence interval; CO = cardiac output; NT-proBNP = N-terminal pro-B-type natriuretic peptide; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance. REVEAL= Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; WHO FC = World Health Organization functional class.
Database cutoff date: 26JUL2024

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22: Summary of efficacy results from the main supporting studies

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Sotatercept When Added to Maximum Tolerated Background Therapy in Participants With Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Functional Class (FC) III or FC IV at High Risk of Mortality			
Study identifier	Acceleron Study: A011-14 IND: 136150 NCT: 04896008 EudraCT: 2021-001498-21 Other Code: ZENITH (also referred to as MK-7962-006 and A011-14)		
Design	Phase 3, multicenter, efficacy, safety, parallel-assignment, double-blind, placebo-controlled intervention study		
	Screening: Double-blind Placebo-controlled (DBPC) Treatment Period: Follow-up Period:		Up to 4 weeks The DBPC treatment period ends when one of the following occurs first: 1) at least 118 participants experience a primary endpoint event for the final analysis or 2) the study is stopped early at the interim analysis for either efficacy or safety. Up to 8 weeks
Hypothesis	Superiority		
Treatments groups	Sotatercept		Starting dose 0.3 mg/kg followed by 0.7 mg/kg for the remainder of the study, unless dose modifications were required; N=86 randomized. The median duration of study intervention through the data cutoff was 322.0 days.
	Placebo		Placebo for the duration of the study; N=86 randomized. The median duration of study intervention through the data cutoff was 215.5 days.
Endpoints and definitions	Primary endpoint	Time to first event of all-cause death, lung transplantation, or pulmonary arterial hypertension (PAH) worsening-related hospitalization of ≥24 hours	Time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours
	Secondary endpoints	Overall survival	Overall survival
		Transplant-free survival	Transplant-free survival
		Proportion who experience a mortality event	Proportion of participants who experienced a mortality event at end of study

		REVEAL Lite 2 risk score	Change from baseline in REVEAL Lite 2 risk score at Week 24
		Proportion who achieved a low or intermediate (≤7) REVEAL Lite 2 risk score	Proportion of participants achieving a low or intermediate (≤7) REVEAL Lite 2 risk score at Week 24
		N-terminal prohormone B-type natriuretic peptide (NT-proBNP)	Change from baseline in NT-proBNP (pg/mL) levels at Week 24
		Mean pulmonary artery pressure (mPAP)	Change from baseline in mPAP (mmHg) at Week 24
		Pulmonary vascular resistance (PVR)	Change from baseline in PVR (dynes*sec/cm5) at Week 24
		Proportion who improved in World Health Organization functional class (WHO FC)	Proportion of participants who improved in WHO FC at the end of the DBPC treatment period
		6-minute walk distance (6MWD)	Change from baseline in 6MWD (m) at Week 24
		Cardiac output	Change from baseline in cardiac output (L/min) at Week 24
Database lock	18-OCT-2024		

Results and Analysis	
Analysis description	**Primary Analysis**

Analysis population and time point description	Final efficacy analyses based on data generated through the data cutoff of 26-JUL-2024 were performed in the full analysis set (FAS) population, which included 172 of the 173 randomized participants (excluding 1 participant who was randomized in error and immediately discontinued by the site; this participant did not receive study intervention). The primary endpoint, a composite of time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours was analysed as time to event. The secondary endpoints were analysed as follows, by hierarchical testing order: ○ Overall survival analysed as time to event ○ Transplant-free survival analysed as time to event ○ Proportion of participants who experienced a mortality event at end of study ○ Change from baseline in REVEAL Lite 2 risk score at Week 24 ○ Proportion who achieved a low or intermediate REVEAL Lite 2 risk score at Week 24 ○ Change from baseline in NT-proBNP levels at Week 24 ○ Change from baseline in mPAP at Week 24 ○ Change from baseline in PVR at Week 24 ○ Proportion of participants who improved in WHO FC at the end of the DBPC treatment period ○ Change from baseline in 6MWD at Week 24 ○ Change from baseline in cardiac output at Week 24		
Descriptive statistics and estimate variability	Treatment group	Sotatercept	Placebo
	Number of participants	86	86
	Primary Endpoint: Time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours No. of participants with ≥1 event (%)	15 (17.4)	47 (54.7)
	Secondary endpoint: Overall survival No. of events (%)	7 (8.1)	13 (15.1)
	Secondary endpoint: Transplant-free survival No. of events (%)	8 (9.3)	19 (22.1)
	Secondary endpoint: Mortality event No. of participants deceased at end of study (%)	7 (8.1)	13 (15.1)

	Secondary endpoint: REVEAL Lite 2 risk score No. of participants randomized more than 24 weeks Median change from baseline (min, max)	77 -3.0 (-3.2, -2)	78 0.0 (0,0)
	Secondary endpoint: Proportion who achieved		

	a low/intermediate (≤7) REVEAL Lite 2 risk score No. of participants with REVEAL Lite 2 >7 at baseline and randomized for more than 24 weeks No. of participants who achieved a low/intermediate (≤7) REVEAL Lite 2 risk score (%)	69 34 (49.3)	72 11 (15.3)
	Secondary endpoint: NT-proBNP (pg/mL) No. of participants randomized more than 24 weeks Median change from baseline (min, max)	77 -1233.0 (-1233, -1233)	78 255.4 (211, 263)
	Secondary endpoint: mPAP (mmHg) No. of participants randomized more than 24 weeks Median change from baseline (min, max)	77 -13.6 (-14, -13)	78 5.5 (5, 6)
	Secondary endpoint: PVR (dynes*sec/cm5) No. of participants randomized more than 24 weeks Median change from baseline (min, max)	77 -156.6 (-160, -152)	78 46.6 (36, 104)
	Secondary endpoint: WHO FC improvement No. of participants No. of participants with WHO FC improvement	86 48 (55.8)	86 24 (27.9)
	Secondary endpoint: Exercise capacity 6MWD (m) No. of participants randomized more than 24 weeks Median change from baseline (min, max)	77 45.39 (45.0, 46.0)	78 -5.36 (-9.5, -1.0)
	Secondary endpoint: Cardiac output (L/min) No. of participants randomized more than 24 weeks Median change from baseline (min, max)	77 -0.10 (-0.1, -0.1)	78 -0.38 (-0.4, -0.4)
Effect estimate per comparison	Primary Endpoint: Time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours	Comparison Groups	Sotatercept vs Placebo
		Hazard ratio (95% CI) Cox regression model	0.24 (0.13, 0.43)
		p-value	<.0001

		One-sided *p*-value based on log-rank test	
	Secondary endpoint: Overall survival	Comparison Groups	Sotatercept vs Placebo
		Hazard ratio (95% CI) Cox regression model	0.42 (0.17, 1.07)
		p-value [a] One-sided *p*-value based on log-rank test	0.0313
	Secondary endpoint: Transplant-free survival	Comparison Groups	Sotatercept vs Placebo
		Hazard ratio (95% CI) Cox regression model	0.34 (0.15, 0.78)
		p-value [a] One-sided *p*-value based on log-rank test	0.0039

	Secondary endpoint: Mortality event	Comparison Groups	Sotatercept vs Placebo
		Estimate (95% CI) based on Miettinen and Nurminen method	-7.29 (-17.65, 2.41)
		p-value [a] Two-sided *p*-value based on Cochran-Mantel-Haenszel method	0.135
	Secondary endpoint: REVEAL Lite 2 risk score	Comparison Groups	Sotatercept vs Placebo
		Hodges-Lehmann location shift (95% CI) based on aligned rank stratified Wilcoxon test	-3.1 (-4.25, -1.88)
		p-value [a] Two-sided *p*-value based on aligned rank stratified Wilcoxon test	<.001
	Secondary endpoint: Proportion who achieved a low/intermediate (≤7) REVEAL Lite 2 risk score	Comparison Groups	Sotatercept vs Placebo
		Estimate (95% CI) based on M&N method	33.05 (18.41, 46.98)
		p-value [a] Two-sided *p*-value is based on Cochran-Mantel-Haenszel method	<.001
	Secondary endpoint: NT-proBNP (pg/mL)	Comparison Groups	Sotatercept vs Placebo
		Hodges-Lehmann location shift (95% CI) Based on aligned rank stratified Wilcoxon test	-2339.1 (-3378.74, -1299.44)
		p-value [a] Two-sided *p*-value based on aligned	<.001

		rank stratified Wilcoxon test	

	Secondary endpoint: mPAP (mmHg)	Comparison Groups	Sotatercept vs Placebo
		Hodges-Lehmann location shift (95% CI) Hodges-Lehmann location shift using aligned rank stratified Wilcoxon test	-21.2 (-27.78, -14.59)
		p-value [a] Two-sided *p*-value based on aligned rank stratified Wilcoxon test	<.001
	Secondary endpoint: PVR (dynes*sec/cm5)	Comparison Groups	Sotatercept vs Placebo
		Hodges-Lehmann location shift (95% CI) Hodges-Lehmann location shift using aligned rank stratified Wilcoxon test	-339.6 (-511.09, -168.06)
		p-value [a] Two-sided *p*-value based on aligned rank stratified Wilcoxon test	<.001
	Secondary endpoint: WHO FC improvement	Comparison Groups	Sotatercept vs Placebo
		Estimate (95% CI) Based on Miettinen and Nurminen method	27.41 (12.85, 40.98)
		p-value [a] Two-sided *p*-value based on Cochran-Mantel-Haenszel method	<.001

	Secondary endpoint: Exercise capacity 6MWD (m)	Comparison Groups	Sotatercept vs Placebo
		Hodges-Lehmann location shift (95% CI) Hodges-Lehmann location shift using aligned rank stratified Wilcoxon test	63.0 (23.22, 102.73)
		p-value based on aligned rank stratified Wilcoxon test	0.001
	Secondary endpoint: Cardiac output (L/min)	Comparison Groups	Sotatercept vs Placebo
		Hodges-Lehmann location shift (95% CI) Hodges-Lehmann location shift using aligned rank stratified Wilcoxon test	0.5 (-0.18, 1.16)
		p-value [a] Two-sided *p*-value based on aligned rank stratified Wilcoxon test	0.119
Notes	[a] The first ranked secondary endpoint of overall survival was tested at the IA, and the boundary for statistical significance (prespecified 1-sided alpha of 0.0021) was not crossed. The subsequent secondary endpoints were not eligible to be tested due to the hierarchical testing strategy. All *p*-values for the subsequent 11 secondary endpoints are not controlled for multiplicity and have not been used to draw inference about the efficacy of sotatercept.		

Analysis performed across trials (pooled analyses and meta-analysis)

This section is not applicable because the current application presents efficacy results from a single study (ZENITH, MK-7962-006).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The demonstration of efficacy for the current type II variation was based on the interim analyses results from the phase 3 trial ZENITH. This event-driven, randomized, double-blind, placebo-controlled, multicenter trial evaluated the efficacy of sotatercept when added to maximum tolerated background PAH therapy in participants with PAH at high risk of mortality. Key inclusion criteria were male and female participants aged 18 to 75 years with documented WHO PAH group 1 with WHO FC III or IV, with a REVEAL Lite 2 risk score ≥9 and clinically stable on maximum tolerated double or triple background PAH therapy for at least 30 days. The REVEAL Lite 2 score utilizes six non-invasive variables to assess the risk of mortality, using functional class, systolic blood pressure, heart rate, 6-minute walk distance, N-terminal prohormone of brain natriuretic peptide, and renal insufficiency. By focusing on WHO FC III and IV, as well using a high risk score of the REVEAL Lite 2, the study has selected a population at high risk of adverse events, suitable for an event-driven study on hard outcomes. Key exclusion criteria were HIV-associated PAH, PAH associated with portal hypertension, PAH of groups 2,3,4 and 5, hemoglobin above the upper limit of normal, platelet counts <50.000/m^3 and baseline systolic blood pressure below 85mmHg. The exclusion criteria are in line with the STELLAR study and are endorsed. Eligible patients were randomized 1:1 to either the placebo arm or the sotatercept arm, both of which received treatment subcutaneously every 21 days, on top of background PAH therapy. The randomization schedule was stratified by REVEAL Lite 2.0 risk score (9 to 10 or ≥ 11) and PAH subtype (CTD-associated or not CTD-associated) at screening, and both patients and study investigators were blinded throughout the study.

Patients in the sotatercept arm started at a dose of 0.3 mg/kg and were up titrated to a target dose of 0.7 mg/kg at the second visit. Similar to what was done in the STELLAR study (basis of the MAA), up titration did not take place if patients experienced hemoglobin increase >2 g/dL with values above upper limit of normal. At further visits, dose delays were implemented if platelets were <50.000/mm^3 or hemoglobin increased (> 2.0 g/dL AND Hgb above gender specific ULN). Overall, the dose modification rules were similar to STELLAR, based on which the SmPC posology was accepted. Therefore, the dose modifications rules are considered reasonable and acceptable.

The primary efficacy endpoint was the time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours. This endpoint differs from both the STELLAR and EMA guidance definition of Time to Clinical Worsening (TTCW). Because ZENITH was purposefully designed to evaluate the effects on major morbidity and mortality events, the study population and the components of the primary endpoint in ZENITH differed from the study population and the TTCW components in STELLAR which enrolled a less severely affected patient population (WHO FC II and III). For instance, the 3rd component of the EMA recommended TTCW endpoint (Time to PAH-related deterioration identified by at least one of the following parameters: i. increase in WHO FC; ii. deterioration in exercise testing; iii. signs or symptoms of right-sided heart failure) would not be applicable to a high-risk FC III and IV PAH population, given the impossibility to increase from WHO FC IV and inability of many patients in WHO FC IV to perform exercise testing. Furthermore, while STELLAR used listing for lung and/or heart transplant as a component of TTCW, ZENITH selected lung transplantation, as it is a definitive, objective event that is less influenced by local listing practices and

centre-specific variability. Further, while STELLAR included the component for rescue therapy (need to initiate rescue therapy with an approved background PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more) and the component for atrial septostomy, these components were not relevant for ZENITH as enrolled participants were already receiving maximum tolerated PAH therapies. The differences between the used endpoint in ZENITH and the endpoints in the EMA guidance and STELLAR are well justified and endorsed. Overall, the primary efficacy endpoint of time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours, is considered a robust, clinically meaningful and acceptable, as was also concluded in the Scientific advice on the ZENITH trial (EMA/SA/0000050772). Intercurrent events such as treatment discontinuation are handled using the treatment policy strategy, death is treated as an event (composite strategy), and loss to follow-up leads to censoring (while-on-treatment-and/or-followed strategy) and the treatment effect is expressed as a hazard ratio.

Individual components of the primary endpoint were included as sensitivity analyses, which is endorsed. Secondary endpoints included overall survival, transplant-free survival, change in REVEAL score, change in NT-proBNP, mPAP, PVR, 6-MWD and cardiac output. These secondary endpoints are considered relevant and provide further insights on the effects of sotatercept.

For the IA, the p-value of <0.0021 is used as threshold to show efficacy for the primary endpoint. In the SAP, the value of the alpha for showing efficacy at the IA was specified as 0.0015. The Applicant has explained that according to the SAP, the alpha spending at the IA would be based on the information fraction, calculated as the actual number of events at IA over the target number of events at final analysis. There were 62 events in the IA and the target number was 0.118. The p-value boundary was therefore relaxed from 0.0015 to 0.0021 because the interim analysis occurred with slightly more information (62 vs 59 events), meaning a larger fraction of the total type I error could be "spent,". More accumulated data allows a slightly higher nominal p-value under the same alpha-spending function, which is acceptable.

Efficacy data and additional analyses

A total of 255 participants were screened and 173 were randomized. One participant was randomized in error and immediately discontinued by the site. Of the 172 randomized patients, 86 were randomized to sotatercept and 86 to placebo. The sotatercept had slightly more males, elderly, patients on triple therapy and patients with lower kidney function, although the differences with the placebo group were small.

Overall, the majority of participants were female (76.7%), the most common race was white (86.6%), and the most common ethnicity was not Hispanic or Latino (87.8%). The median age was 57.5 years (range: 18 to 75 years). The 3 most common PAH (Group 1 PH) subtypes were idiopathic PAH (50.0%), PAH associated with CTD (27.9%), and heritable PAH (10.5%). The mean time since PAH diagnosis was 7.68 years. There were more participants on background PAH triple therapy (72.1%) compared with double therapy (27.9%). More than half of participants were on prostacyclin infusion therapy (59.3%). There were more participants in WHO FC III (74.4%) compared with WHO FC IV (25.6%). The REVEAL Lite 2 risk score was <9 for 2.3% of participants, 9 to 10 for 67.4% of participants, and ≥11 for 30.2% of participants. The population represents severe PAH patients at high risk of events of clinical worsening. The median duration of exposure to study intervention through the data cutoff was substantially longer in the sotatercept group (322.0 days) than in the placebo group (215.5 days), due to more patients reaching the endpoint of clinical worsening in the placebo group. Dose delays occurred in 31 participants in the sotatercept group and 23 in the placebo group. Dose reductions occurred in 16 participants in the sotatercept group and 3 in the placebo group. The reasons were mostly due to adverse events.

The primary endpoint time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours was significantly longer in the sotatercept group than in the placebo group. Fewer participants in the sotatercept group (15 [17.4%]) than in the placebo group (47 [54.7%]) had a primary endpoint event. The risk of a first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours was 76% lower in the sotatercept group compared with the placebo group (HR: 0.24; 95% CI: 0.13, 0.43; p<0.0001). Given the clinical relevance of the endpoint and the substantial effect size observed, the primary outcome underscores the benefit of sotatercept in patients with PAH. The effect on the primary endpoint was primarily driven by PAH related hospitalization ≥24 hours, which occurred in half of the placebo patients as the first event. And at first glance, the slightly higher number of all-cause mortality events in the sotatercept group may suggest worse overall survival. However, when looking at the total number of mono-components (secondary endpoints), the number of events was lower for each component, including all-cause death, in the sotatercept group as compared to the placebo group.

Sensitivity analyses excluding post-study deaths and sensitivity analyses using jump to reference imputation were both consistent with the primary analysis. Robustness was further demonstrated in subgroup analyses, where the effects on the primary endpoint were consistent across all prespecified subgroups. Of specific interest, the effect size was comparable in those with WHO FC III (HR: 0.23 (95%CI: 0.11; 0.45) and WHO FC IV (HR: 0.28 (95% CI: 0.09; 0.87), supporting the proposed extension of the indication to include WHO FC IV. The 2022 ESC/ERS PAH treatment guidelines includes that initial triple combination therapy including including an i.v./s.c. prostacyclin analogue may be considered in patients presenting at intermediate risk but severe haemodynamic impairment (e.g. RAP ⩾20 mmHg, CI. It is therefore of interest that the effect of sotatercept was consistent in both those on double (HR: 0.19 (95% CI: 0.06; 0.68)) and triple background therapy (HR: 0.26 (95% CI: 0.13; 0.84)). Specifically, the only PAH drug with an indication for WHO FC IV is the intravenous prostacyclin epoprostenol. It is therefore of interest that the effect of sotatercept on the primary endpoint was present in both patients using prostacyclin infusion (HR: 0.20 (95% CI: 0.09; 0.42) and those not using prostacyclin infusion (HR: 0.33 (95% CI: 0.13; 0.84)). Overall, these data support that sotatercept is also beneficial in adult PAH patients with WHO FC IV.

For the first tested secondary endpoint of overall survival, the hazard ratio favored the sotatercept group over the placebo group (HR: 0.42; 95% CI: 0.17, 1.07; p=0.0313). However, only 20 events were observed (7 events in the sotatercept group and 13 events in the placebo group), and the boundary for statistical significance was not crossed (prespecified 1-sided alpha of 0.0021). The other secondary endpoints were therefore not eligible to hierarchical testing. However, beneficial trends were demonstrated in the secondary endpoints of transplant free survival, proportion of participants who experienced a mortality event at end of study, change from baseline in REVEAL Lite 2 risk score, proportion who achieved a low or intermediate REVEAL Lite 2 risk score, change from baseline in NT-proBNP, mean pulmonary arterial pressure, pulmonary vascular resistance and 6-minute walking distance. Overall, the results of the secondary endpoints support the primary endpoint and provide additional support for the benefits of sotatercept. To further support the proposed changes in the indication of sotatercept, notably including WHO FC IV, the Applicant has provided post-hoc analyses on the secondary endpoints stratified according to WHO FC III or FC IV. These analyses, although not adjusted for multiplicity and in some cases based on very small sample sizes, demonstrated beneficial trends in both WHO FC III and FC IV, further supporting the results of the subgroup analyses of the primary endpoint.

Alignment with STELLAR

During the initial MAA, time to clinical worsening was included as a secondary endpoint in the STELLAR trial, which included patients with WHO FC II and III. Sotatercept resulted in a significant improvement in the 5th secondary endpoint time to clinical worsening (TTCW) compared with placebo (5.5% vs 26.3%; p< 0.01), which were mainly driven by fewer patients with a need to initiate rescue therapy (1.2% vs. 10.6%) and patients with deterioration of PAH (3.1% vs. 9.4%). This resulted in an 84% lower risk in the sotatercept group compared with the placebo group (HR: 0.163; 95% CI, 0.076, 0.347; Logrank test p-value < 0.001). In a post-hoc analyses aligning more with the EMA guidance definition of TTCW, treatment with sotatercept resulted in a significant improvement in TTCW compared with placebo (5.5% vs 18.1%; p< 0.01), resulting in a risk reduction of 73% compared with the placebo group (HR: 0.274; 95% CI, 0.129, 0.582; P<0.001). At the time of MAA, the TTCW endpoint in STELLAR was considered preliminary due to the relatively low number of events, which led to an indication restricted to improving exercise capacity. Despite the differences in the definition of the endpoints (as discussed above), both these results from ZENITH and STELLAR reflect the time to clinical worsening and in both studies sotatercept demonstrated significant, substantial and comparable effect. Taken together, these results support inclusion of "WHO FC IV" to the indication and removal 'to improve exercise capacity' from the indication for adult PAH patients WHO FC II, III, and IV.

2.4.4. Conclusions on the clinical efficacy

The ZENITH trial demonstrated that among high-risk adults with PAH who were receiving the maximum tolerated dose of background therapy, treatment with sotatercept resulted in a lower risk of a composite of death from any cause, lung transplantation, or hospitalization (≥24 hours) for worsening pulmonary arterial hypertension than placebo. The results were robust and consistent across subgroup analyses, including WHO FC IV. Taken together with the results from the previously assessed STELLAR trial, the presented data supports extension of the indication to include WHO FC IV and to remove 'to improve exercise capacity' from the indication.

2.5. Clinical safety

Introduction

In the initial MAA, evaluation of the safety was based on data from 4 studies of sotatercept in PAH, including 2 phase 2 studies (P001/A011-09/PULSAR and P002/A011-10/SPECTRA), 1 pivotal phase 3 study (P003/A011-11/STELLAR), and the open-label phase 3 study SOTERIA (P004/A011-12/SOTERIA), which are hereafter referred to as PULSAR, SPECTRA, STELLAR, and SOTERIA. Based on this data, it was concluded that sotatercept was generally well-tolerated, however, associated with increased haemoglobin and thrombocytopenia, both of which are considered manageable by dose modification. Further higher incidences of telangiectasia, bleeding events (mostly epistaxis), and increased blood pressure were observed in participants treated with sotatercept compared with those treated with placebo. Although the safety exposure was considered sufficient, the safety data package did not fulfil the requirements of the "reflection paper on assessment of cardiovascular safety profile of medicinal products" (EMA/CHMP/50549/2015) which will be addressed post-marketing.

The safety data in this submission are based on the final CSR (data final DBL 06-Jun-2025) of ZENITH (MK-7962-006), which evaluated the efficacy and safety of sotatercept in adults with PAH (Group 1 PH) on maximum tolerated background PAH therapy.

Data presentations for AEs with 95% CIs for differences between the sotatercept and placebo groups are provided as a review tool to identify potential imbalances needing further evaluation, and not as a demonstration of association with study intervention. If the 95% CI for the between-group difference

excludes 0 for a given intervention group, the proportion of participants with the AE is described as "higher" or "lower" in that group compared with the other group. The occurrence of an AE may be described as "more common" or "less common" if the 95% CI includes 0.

Patient exposure

A total of 172 participants (86 in the sotatercept group and 86 in the placebo group) were treated with at least 1 dose of study intervention and included in the FAS population. The median duration of exposure to study intervention through the data cutoff was substantially longer in the sotatercept group (434.5 days) than in the placebo group (267.5 days) (Table 23). The imbalance is largely due to the higher numbers of participants in the placebo group who were classified as completing the study after a PAH worsening-related hospitalization of ≥24 hours or lung transplantation, as well as the higher number of participants in the placebo group who discontinued study intervention due to death or an AE (Table 24).

Table 23: Summary of follow-up duration (Full Analysis Set)

	Sotatercept	Placebo	Total
Follow-up duration (month)a	(N=86)	(N=86)	(N=172)
0 to 6 months	7 (8.1)	25 (29.1)	32 (18.6)
>6 to 12 months	23 (26.7)	30 (34.9)	53 (30.8)
>12 to 24 months	46 (53.5)	29 (33.7)	75 (43.6)
>24 months	10 (11.6)	2 (2.3)	12 (7.0)
Median (Range)	14.6 (0.3 - 30.4)	8.9 (0.7 - 29.0)	12.1 (0.3 - 30.4)
Mean (SD)	15.0 (6.98)	10.5 (6.37)	12.8 (7.04)
	[a]Follow-up duration is defined as the time from randomized date to the date of death, the study withdrawal date, or the database cutoff date, whichever comes earliest. Database cutoff date: 06JUN2025		

Table 24: Disposition of Participants

	Sotatercept		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	86		86		172	
Status for Trial						
Completed	69	(80.2)	60	(69.8)	129	(75.0)
Discontinued	17	(19.8)	26	(30.2)	43	(25.0)
Adverse Event	1	(1.2)	2	(2.3)	3	(1.7)
Death	7	(8.1)	11	(12.8)	18	(10.5)
More Than 3 Dose Delays Required Per Dose Adjustment Guidelines	1	(1.2)	0	(0.0)	1	(0.6)
QTcF Above 500 ms	0	(0.0)	1	(1.2)	1	(0.6)
Unwillingness Or Inability To Comply With Protocol	1	(1.2)	1	(1.2)	2	(1.2)
Withdrawal By Subject	2	(2.3)	6	(7.0)	8	(4.7)
Other	5	(5.8)	5	(5.8)	10	(5.8)
Status for Study Medication in Trial						
Started	86		86		172	

Completed	6	(7.0)	37	(43.0)	43	(25.0)
Discontinued	80	(93.0)	49	(57.0)	129	(75.0)
Adverse Event	1	(1.2)	2	(2.3)	3	(1.7)
Death	7	(8.1)	11	(12.8)	18	(10.5)
More Than 3 Dose Delays Required Per Dose Adjustment Guidelines	1	(1.2)	0	(0.0)	1	(0.6)
Status for Study Medication in Trial						
QTcF > 500 ms During The	0	(0.0)	1	(1.2)	1	(0.6)
Study Terminated By Sponsor	63	(73.3)	23	(26.7)	86	(50.0)
Unwillingness Or Inability To Comply With Protocol	1	(1.2)	1	(1.2)	2	(1.2)
Withdrawal By Subject	2	(2.3)	6	(7.0)	8	(4.7)
Other	5	(5.8)	5	(5.8)	10	(5.8)

Each participant is counted once for Trial Disposition based on the latest corresponding disposition record.
Participants are considered to have completed the study if they experienced an event of PAH worsening-related hospitalization of ≥ 24 hours or lung transplantation, or they discontinued the study treatment due to "study terminated by sponsor".
Other reasons include starting commercial drug and PI discretion.
Database cutoff date: 06JUN2025.

Adverse events

Overall summary of adverse events (AEs)

The proportion of participants with treatment emergent AEs (TEAEs) was comparable between the sotatercept and the placebo group (Table 25). Severe AEs, SAEs, and AEs leading to death occurred less commonly for participants in the sotatercept group than in the placebo group. Additionally, the proportions of participants with AEs leading to discontinuation of study intervention and SAEs leading to discontinuation of study intervention were lower in the sotatercept group than in the placebo group. Only one participant in the sotatercept group discontinued study intervention due to an AE compared to 4 participants in the placebo group. Nine participants had AEs leading to death in the sotatercept group compared with 13 in the placebo group; none were considered related to study intervention by the investigator.

Table 25: Analysis of Adverse Event Summary (All Participants as Treated)

	Sotatercept		Placebo		Difference in % (Sotatercept – Placebo) Estimate (95% CI)[a]
	n	(%)	n	(%)	
Participants in population	86		86		
with one or more adverse events	85	(98.8)	85	(98.8)	0.0 (-5.3, 5.3)
with no adverse event	1	(1.2)	1	(1.2)	0.0 (-5.3, 5.3)
with drug-related[b] adverse events	58	(67.4)	29	(33.7)	33.7 (19.0, 47.0)
with non-serious adverse events	84	(97.7)	83	(96.5)	1.2 (-5.0, 7.8)
with serious adverse events	52	(60.5)	64	(74.4)	-14.0 (-27.5, 0.1)
with serious drug-related[b] adverse events	4	(4.7)	2	(2.3)	2.3 (-4.0, 9.4)
who died	9	(10.5)	13	(15.1)	-4.7 (-15.1, 5.6)
who died due to a drug-related[b] adverse event	0	(0.0)	0	(0.0)	0.0 (-4.3, 4.3)
discontinued drug due to an adverse event	1	(1.2)	4	(4.7)	-3.5 (-10.4, 2.2)
discontinued drug due to a drug-related[b] adverse event	0	(0.0)	1	(1.2)	-1.2 (-6.3, 3.2)
discontinued drug due to a serious adverse event	1	(1.2)	4	(4.7)	-3.5 (-10.4, 2.2)
discontinued drug due to a serious drug-related[b] adverse event	0	(0.0)	1	(1.2)	-1.2 (-6.3, 3.2)

[a] Based on Miettinen & Nurminen method.
[b] Relatedness to study drug was determined by the investigator as suspected related.
This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days .
Estimated differences and CIs were provided in accordance with the statistical analysis plan.
CI=confidence interval.
Database cutoff date: 06JUN2025.

Common Adverse events

The proportions of participants with AEs by PT were generally similar in the 2 groups (Table 26). The most common reported AEs (incidence ≥10%) that occurred in a higher proportion of participants in the sotatercept group than in the placebo group (≥5.0 percentage point difference) were palpitations, diarrhoea, vomiting, pneumonia, haemoglobin increased, back pain, epistaxis, telangiectasia, and erythema.

Table 26: Analysis of Participants With Adverse Events (Incidence≥ 4 Participants in One or More Treatment Groups) (All Participants as Treated)

					Difference in %
	Sotatercept		Placebo		(Sotatercept – Placebo)
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	86		86		
with one or more adverse events	85	(98.8)	85	(98.8)	0.0 (-5.3, 5.3)
with no adverse events	1	(1.2)	1	(1.2)	0.0 (-5.3, 5.3)
Blood and lymphatic system disorders	**24**	**(27.9)**	**24**	**(27.9)**	**0.0 (-13.4, 13.4)**
Thrombocytopenia	12	(14.0)	8	(9.3)	4.7 (-5.2, 14.8)
Anaemia	10	(11.6)	8	(9.3)	2.3 (-7.3, 12.1)
Polycythaemia	4	(4.7)	0	(0.0)	4.7 (0.3, 11.4)
Iron deficiency anaemia	3	(3.5)	4	(4.7)	-1.2 (-8.4, 5.7)
Cardiac disorders	**39**	**(45.3)**	**44**	**(51.2)**	**-5.8 (-20.5, 9.1)**
Palpitations	10	(11.6)	5	(5.8)	5.8 (-2.9, 15.1)
Atrial fibrillation	8	(9.3)	2	(2.3)	7.0 (-0.0, 15.3)
Cardiac failure	5	(5.8)	9	(10.5)	-4.7 (-13.7, 3.9)
Right ventricular failure	4	(4.7)	18	(20.9)	-16.3 (-26.7, -6.7)
Supraventricular tachycardia	4	(4.7)	2	(2.3)	2.3 (-4.0, 9.4)
Tachycardia	4	(4.7)	3	(3.5)	1.2 (-5.7, 8.4)
Ear and labyrinth disorders	**10**	**(11.6)**	**6**	**(7.0)**	**4.7 (-4.4, 14.1)**
Vertigo	5	(5.8)	2	(2.3)	3.5 (-3.0, 10.9)
Eye disorders	**17**	**(19.8)**	**5**	**(5.8)**	**14.0 (4.2, 24.4)**
Cataract	4	(4.7)	2	(2.3)	2.3 (-4.0, 9.4)
Gastrointestinal disorders	**51**	**(59.3)**	**45**	**(52.3)**	**7.0 (-7.9, 21.5)**
Diarrhoea	22	(25.6)	15	(17.4)	8.1 (-4.3, 20.5)
Nausea	16	(18.6)	15	(17.4)	1.2 (-10.6, 12.9)
Vomiting	12	(14.0)	7	(8.1)	5.8 (-3.8, 15.8)
Gingival bleeding	9	(10.5)	2	(2.3)	8.1 (0.9, 16.7)
Abdominal pain	7	(8.1)	3	(3.5)	4.7 (-2.7, 12.9)
Gastrooesophageal reflux disease	5	(5.8)	1	(1.2)	4.7 (-1.1, 11.9)
Abdominal pain upper	4	(4.7)	5	(5.8)	-1.2 (-8.9, 6.4)
Haematochezia	4	(4.7)	0	(0.0)	4.7 (0.3, 11.4)
Constipation	3	(3.5)	4	(4.7)	-1.2 (-8.4, 5.7)
General disorders and administration site conditions	**50**	**(58.1)**	**53**	**(61.6)**	**-3.5 (-18.0, 11.1)**
Fatigue	13	(15.1)	14	(16.3)	-1.2 (-12.4, 10.0)
Oedema peripheral	13	(15.1)	20	(23.3)	-8.1 (-20.1, 3.8)
Influenza like illness	8	(9.3)	2	(2.3)	7.0 (-0.0, 15.3)
Pyrexia	7	(8.1)	5	(5.8)	2.3 (-5.9, 10.9)
Non-cardiac chest pain	6	(7.0)	3	(3.5)	3.5 (-3.7, 11.4)
Chest discomfort	5	(5.8)	4	(4.7)	1.2 (-6.4, 8.9)
Asthenia	3	(3.5)	4	(4.7)	-1.2 (-8.4, 5.7)
Hepatobiliary disorders	**4**	**(4.7)**	**4**	**(4.7)**	**0.0 (-7.4, 7.4)**

Infections and infestations	**68**	**(79.1)**	**51**	**(59.3)**	**19.8 (6.0, 32.9)**
COVID-19	17	(19.8)	15	(17.4)	2.3 (-9.5, 14.2)
Nasopharyngitis	13	(15.1)	11	(12.8)	2.3 (-8.4, 13.1)
Pneumonia	11	(12.8)	5	(5.8)	7.0 (-1.9, 16.5)
Urinary tract infection	7	(8.1)	2	(2.3)	5.8 (-1.0, 13.9)
Influenza	5	(5.8)	1	(1.2)	4.7 (-1.1, 11.9)
Sinusitis	5	(5.8)	4	(4.7)	1.2 (-6.4, 8.9)
Bronchitis	4	(4.7)	1	(1.2)	3.5 (-2.2, 10.4)
Cellulitis	4	(4.7)	1	(1.2)	3.5 (-2.2, 10.4)
Respiratory tract infection	4	(4.7)	5	(5.8)	-1.2 (-8.9, 6.4)
Sepsis	4	(4.7)	1	(1.2)	3.5 (-2.2, 10.4)
Upper respiratory tract infection	4	(4.7)	6	(7.0)	-2.3 (-10.4, 5.4)
Injury, poisoning and procedural complications	**20**	**(23.3)**	**15**	**(17.4)**	**5.8 (-6.4, 18.0)**
Fall	7	(8.1)	3	(3.5)	4.7 (-2.7, 12.9)
Contusion	5	(5.8)	3	(3.5)	2.3 (-4.7, 9.9)
Investigations	**24**	**(27.9)**	**23**	**(26.7)**	**1.2 (-12.2, 14.5)**
Haemoglobin increased	9	(10.5)	1	(1.2)	9.3 (2.8, 17.7)
C-reactive protein increased	4	(4.7)	3	(3.5)	1.2 (-5.7, 8.4)
Weight decreased	1	(1.2)	4	(4.7)	-3.5 (-10.4, 2.2)
Metabolism and nutrition disorders	**44**	**(51.2)**	**38**	**(44.2)**	**7.0 (-7.9, 21.6)**
Hypokalaemia	17	(19.8)	15	(17.4)	2.3 (-9.5, 14.2)
Iron deficiency	11	(12.8)	8	(9.3)	3.5 (-6.3, 13.5)
Hypocalcaemia	5	(5.8)	0	(0.0)	5.8 (1.4, 12.9)
Hypomagnesaemia	5	(5.8)	1	(1.2)	4.7 (-1.1, 11.9)
Decreased appetite	4	(4.7)	6	(7.0)	-2.3 (-10.4, 5.4)
Gout	4	(4.7)	0	(0.0)	4.7 (0.3, 11.4)
Hyperkalaemia	4	(4.7)	3	(3.5)	1.2 (-5.7, 8.4)
Hypervolaemia	4	(4.7)	2	(2.3)	2.3 (-4.0, 9.4)
Hyponatraemia	4	(4.7)	4	(4.7)	0.0 (-7.4, 7.4)
Musculoskeletal and connective tissue disorders	**38**	**(44.2)**	**25**	**(29.1)**	**15.1 (0.7, 29.0)**
Back pain	12	(14.0)	4	(4.7)	9.3 (0.7, 18.8)
Arthralgia	11	(12.8)	7	(8.1)	4.7 (-4.8, 14.5)
Pain in extremity	4	(4.7)	4	(4.7)	0.0 (-7.4, 7.4)
Muscle spasms	2	(2.3)	6	(7.0)	-4.7 (-12.4, 2.0)
Myalgia	2	(2.3)	5	(5.8)	-3.5 (-10.9, 3.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**8**	**(9.3)**	**4**	**(4.7)**	**4.7 (-3.4, 13.3)**
Nervous system disorders	**43**	**(50.0)**	**34**	**(39.5)**	**10.5 (-4.4, 24.9)**
Headache	23	(26.7)	22	(25.6)	1.2 (-12.0, 14.3)
Dizziness	9	(10.5)	10	(11.6)	-1.2 (-11.1, 8.7)
Paraesthesia	4	(4.7)	0	(0.0)	4.7 (0.3, 11.4)
Syncope	4	(4.7)	2	(2.3)	2.3 (-4.0, 9.4)
Presyncope	1	(1.2)	4	(4.7)	-3.5 (-10.4, 2.2)
Product issues	**3**	**(3.5)**	**5**	**(5.8)**	**-2.3 (-9.9, 4.7)**

Psychiatric disorders	**17**	**(19.8)**	**8**	**(9.3)**	**10.5 (-0.1, 21.4)**
Insomnia	6	(7.0)	4	(4.7)	2.3 (-5.4, 10.4)
Renal and urinary disorders	**14**	**(16.3)**	**16**	**(18.6)**	**-2.3 (-13.9, 9.2)**
Acute kidney injury	4	(4.7)	6	(7.0)	-2.3 (-10.4, 5.4)
Chronic kidney disease	4	(4.7)	1	(1.2)	3.5 (-2.2, 10.4)
Reproductive system and breast disorders	**4**	**(4.7)**	**4**	**(4.7)**	**0.0 (-7.4, 7.4)**
Respiratory, thoracic and mediastinal disorders	**56**	**(65.1)**	**61**	**(70.9)**	**-5.8 (-19.6, 8.2)**
Epistaxis	39	(45.3)	8	(9.3)	36.0 (23.5, 47.9)
Dyspnoea	13	(15.1)	21	(24.4)	-9.3 (-21.3, 2.7)
Cough	8	(9.3)	6	(7.0)	2.3 (-6.4, 11.3)
Acute respiratory failure	4	(4.7)	3	(3.5)	1.2 (-5.7, 8.4)
Hypoxia	4	(4.7)	2	(2.3)	2.3 (-4.0, 9.4)
Pulmonary arterial hypertension	4	(4.7)	27	(31.4)	-26.7 (-37.9, -16.1)
Rhinitis allergic	4	(4.7)	1	(1.2)	3.5 (-2.2, 10.4)
Haemoptysis	1	(1.2)	5	(5.8)	-4.7 (-11.9, 1.1)
Pulmonary hypertension	0	(0.0)	7	(8.1)	-8.1 (-15.9, -3.7)
Skin and subcutaneous tissue disorders	**39**	**(45.3)**	**14**	**(16.3)**	**29.1 (15.6, 41.7)**
Telangiectasia	22	(25.6)	3	(3.5)	22.1 (12.4, 32.7)
Pruritus	7	(8.1)	2	(2.3)	5.8 (-1.0, 13.9)
Erythema	6	(7.0)	0	(0.0)	7.0 (2.5, 14.4)
Rash	5	(5.8)	1	(1.2)	4.7 (-1.1, 11.9)
Vascular disorders	**20**	**(23.3)**	**20**	**(23.3)**	**0.0 (-12.7, 12.7)**
Click or tap here to enter text.Hypotension	12	(14.0)	10	(11.6)	2.3 (-8.0, 12.8)

[a] Based on Miettinen & Nurminen method.
Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Medical Dictionary for Regulatory Activities 27.1 was used in the reporting of this study.
This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days .
Preferred terms are sorted by descending frequency in the Sotartercept group within the system organ class.
CI = confidence interval.
Database cutoff date: 06JUN2025

Treatment related adverse events

The proportion of participants with AEs considered related to study intervention by the investigator was higher in the sotatercept group than in the placebo group (Table 27). AEs considered related to study intervention that occurred more commonly (≥5.0 percentage point difference) in the sotatercept group than in the placebo group were epistaxis (30.2% vs 4.7%), telangiectasia (22.1% vs 3.5%), hemoglobin increased (10.5% vs 0.0%), and gingival bleeding (8.1% vs 1.2%).

Table 27: Participants With Drug-Related Adverse Events (Incidence > 0% in One or More Treatment Groups) (All Participants as Treated)

	Sotatercept		Placebo	
	n	(%)	n	(%)

Participants in population	86		86	
with one or more drug-related adverse events	58	(67.4)	29	(33.7)
with no drug-related adverse events	28	(32.6)	57	(66.3)
Blood and lymphatic system disorders	**10**	**(11.6)**	**6**	**(7.0)**
Anaemia	0	(0.0)	1	(1.2)
Increased tendency to bruise	0	(0.0)	1	(1.2)
Iron deficiency anaemia	1	(1.2)	0	(0.0)
Polycythaemia	4	(4.7)	0	(0.0)
Thrombocytopenia	7	(8.1)	4	(4.7)
Ear and labyrinth disorders	**3**	**(3.5)**	**0**	**(0.0)**
Vertigo	3	(3.5)	0	(0.0)
Eye disorders	**1**	**(1.2)**	**0**	**(0.0)**
Vision blurred	1	(1.2)	0	(0.0)
Gastrointestinal disorders	**17**	**(19.8)**	**5**	**(5.8)**
Abdominal pain	2	(2.3)	0	(0.0)
Colitis ulcerative	1	(1.2)	0	(0.0)
Colonic angioectasia	1	(1.2)	0	(0.0)
Diarrhoea	2	(2.3)	1	(1.2)
Diarrhoea haemorrhagic	1	(1.2)	0	(0.0)
Dyspepsia	1	(1.2)	0	(0.0)
Gastritis haemorrhagic	1	(1.2)	0	(0.0)
Gingival bleeding	7	(8.1)	1	(1.2)
Haematemesis	1	(1.2)	0	(0.0)
Haematochezia	1	(1.2)	0	(0.0)
Nausea	5	(5.8)	3	(3.5)
Tooth socket haemorrhage	1	(1.2)	0	(0.0)
Vomiting	3	(3.5)	0	(0.0)
General disorders and administration site conditions	**10**	**(11.6)**	**5**	**(5.8)**
Chest discomfort	1	(1.2)	0	(0.0)
Fatigue	4	(4.7)	1	(1.2)
Influenza like illness	1	(1.2)	0	(0.0)
Injection site bruising	1	(1.2)	0	(0.0)
Injection site haemorrhage	0	(0.0)	1	(1.2)
Injection site pain	2	(2.3)	3	(3.5)
Pain	1	(1.2)	0	(0.0)
Injury, poisoning and procedural complications	**2**	**(2.3)**	**0**	**(0.0)**
Contusion	1	(1.2)	0	(0.0)
Post procedural haemorrhage	1	(1.2)	0	(0.0)
Investigations	**11**	**(12.8)**	**0**	**(0.0)**
Blood iron decreased	1	(1.2)	0	(0.0)
Haematocrit increased	1	(1.2)	0	(0.0)
Haemoglobin increased	9	(10.5)	0	(0.0)
Red blood cell count increased	2	(2.3)	0	(0.0)
White blood cell count decreased	1	(1.2)	0	(0.0)

Metabolism and nutrition disorders	**0**	**(0.0)**	**3**	**(3.5)**
Decreased appetite	0	(0.0)	2	(2.3)
Iron deficiency	0	(0.0)	1	(1.2)
Musculoskeletal and connective tissue disorders	**2**	**(2.3)**	**1**	**(1.2)**
Arthralgia	1	(1.2)	0	(0.0)
Musculoskeletal chest pain	1	(1.2)	0	(0.0)
Pain in jaw	0	(0.0)	1	(1.2)
Nervous system disorders	**9**	**(10.5)**	**10**	**(11.6)**
Dizziness	1	(1.2)	0	(0.0)
Headache	7	(8.1)	7	(8.1)
Hypoaesthesia	0	(0.0)	1	(1.2)
Migraine	0	(0.0)	2	(2.3)
Paraesthesia	2	(2.3)	0	(0.0)
Reproductive system and breast disorders	**1**	**(1.2)**	**1**	**(1.2)**
Gynaecomastia	1	(1.2)	0	(0.0)
Heavy menstrual bleeding	0	(0.0)	1	(1.2)
Dyspnoea	1	(1.2)	0	(0.0)
Epistaxis	26	(30.2)	4	(4.7)
Haemoptysis	0	(0.0)	2	(2.3)
Nasal congestion	1	(1.2)	0	(0.0)
Rhinorrhoea	1	(1.2)	0	(0.0)
Skin and subcutaneous tissue disorders	**25**	**(29.1)**	**5**	**(5.8)**
Ecchymosis	0	(0.0)	1	(1.2)
Erythema	1	(1.2)	0	(0.0)
Pruritus	2	(2.3)	1	(1.2)
Rash	4	(4.7)	0	(0.0)
Rash erythematous	1	(1.2)	0	(0.0)
Rosacea	1	(1.2)	0	(0.0)
Telangiectasia	19	(22.1)	3	(3.5)
Urticaria	1	(1.2)	0	(0.0)
Vascular disorders	**0**	**(0.0)**	**2**	**(2.3)**
Flushing	0	(0.0)	1	(1.2)
Hypertension	0	(0.0)	1	(1.2)

Every participant is counted a single time for each applicable row and column.
Relatedness to study drug was determined by the investigator as suspected related.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days.
MedDRA version 27.1 was used in the reporting of this study.
Database cutoff date: 06JUN2025

Adverse events of special interest (AESI) and events of interest (AEOIs)

The overall proportion of participants with AESI (telangiectasia) and AEOIs (selected medical concepts based on mechanism of action, nonclinical findings, and previous clinical study findings) was higher in the sotatercept group than in the placebo group (Table 28). AESI/AEOIs considered serious were less commonly reported for participants in the sotatercept group than in the placebo group (20.9% vs. 40.7%, respectively). AESI/AEOIs considered related to study intervention by the investigator were

more commonly reported for participants in the sotatercept group than in the placebo group (61.6% vs. 17.4%, respectively).

Results for the AESI (telangiectasia) and AEOIs (e.g. increased hemoglobin, bleeding events, thrombocytopenia, increase BP) with imbalances (95% CI for the between-group difference excluding 0) in the sotatercept versus placebo group are summarized below. Although the 95% CI for the AEOIs increased blood pressure and thrombocytopenia did not exclude 0, discussion of the results is included, as changes from baseline in blood pressure and platelet counts were observed in the sotatercept group.

Table 28: Analysis of Participants With AESI/AEOI (All Participants As Treated)

					Difference in %
	Sotatercept		Placebo		(Sotatercept – Placebo)
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	86		86		
with one or more AESI adverse events	76	(88.4)	63	(73.3)	15.1 (3.4, 26.9)
with no AESI adverse events	10	(11.6)	23	(26.7)	-15.1 (-26.9, -3.4)
Bleeding events	**56**	**(65.1)**	**31**	**(36.0)**	**29.1 (14.2, 42.6)**
Epistaxis	39	(45.3)	8	(9.3)	36.0 (23.5, 47.9)
Anaemia	10	(11.6)	8	(9.3)	2.3 (-7.3, 12.1)
Gingival bleeding	9	(10.5)	2	(2.3)	8.1 (0.9, 16.7)
Contusion	5	(5.8)	3	(3.5)	2.3 (-4.7, 9.9)
Haematochezia	4	(4.7)	0	(0.0)	4.7 (0.3, 11.4)
Gastritis haemorrhagic	2	(2.3)	0	(0.0)	2.3 (-2.0, 8.1)
Gastrointestinal haemorrhage	2	(2.3)	0	(0.0)	2.3 (-2.0, 8.1)
Haematemesis	2	(2.3)	0	(0.0)	2.3 (-2.0, 8.1)
Petechiae	2	(2.3)	1	(1.2)	1.2 (-4.2, 7.1)
Retinal haemorrhage	2	(2.3)	0	(0.0)	2.3 (-2.0, 8.1)
Anal haemorrhage	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Bleeding varicose vein	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Catheter site bruise	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Cerebral haemorrhage	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Conjunctival haemorrhage	1	(1.2)	2	(2.3)	-1.2 (-7.1, 4.2)
Diarrhoea haemorrhagic	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Haematoma	1	(1.2)	2	(2.3)	-1.2 (-7.1, 4.2)
Haematuria	1	(1.2)	1	(1.2)	0.0 (-5.3, 5.3)
Haemoptysis	1	(1.2)	5	(5.8)	-4.7 (-11.9, 1.1)
Haemorrhage	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Haemorrhagic ovarian cyst	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Haemorrhoidal haemorrhage	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Injection site bruising	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Injection site haematoma	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Oesophageal haemorrhage	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Post procedural haemorrhage	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Purpura	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)

Rectal haemorrhage	1	(1.2)	0	(0.0)		1.2 (-3.2, 6.3)
Retroperitoneal haematoma	1	(1.2)	0	(0.0)		1.2 (-3.2, 6.3)
Subdural haematoma	1	(1.2)	0	(0.0)		1.2 (-3.2, 6.3)
Tooth socket haemorrhage	1	(1.2)	0	(0.0)		1.2 (-3.2, 6.3)
Vaginal haemorrhage	1	(1.2)	1	(1.2)		0.0 (-5.3, 5.3)
Vitreous haemorrhage	1	(1.2)	0	(0.0)		1.2 (-3.2, 6.3)
Blood urine present	0	(0.0)	1	(1.2)		-1.2 (-6.3, 3.2)
Ear haemorrhage	0	(0.0)	1	(1.2)		-1.2 (-6.3, 3.2)
Ecchymosis	0	(0.0)	2	(2.3)		-2.3 (-8.1, 2.0)
Haemoperitoneum	0	(0.0)	1	(1.2)		-1.2 (-6.3, 3.2)
Haemothorax	0	(0.0)	1	(1.2)		-1.2 (-6.3, 3.2)
Heavy menstrual bleeding	0	(0.0)	1	(1.2)		-1.2 (-6.3, 3.2)
Increased tendency to bruise	0	(0.0)	1	(1.2)		-1.2 (-6.3, 3.2)
Injection site haemorrhage	0	(0.0)	1	(1.2)		-1.2 (-6.3, 3.2)
Spontaneous haematoma	0	(0.0)	1	(1.2)		-1.2 (-6.3, 3.2)
Cardiac events	**14**	**(16.3)**	**31**	**(36.0)**		**-19.8 (-32.4, -6.7)**
Cardiac failure	5	(5.8)	9	(10.5)		-4.7 (-13.7, 3.9)
Right ventricular failure	4	(4.7)	18	(20.9)		-16.3 (-26.7, -6.7)
Pericardial effusion	3	(3.5)	2	(2.3)		1.2 (-5.0, 7.8)
Cardiac failure acute	1	(1.2)	1	(1.2)		0.0 (-5.3, 5.3)
Cardiorenal syndrome	1	(1.2)	0	(0.0)		1.2 (-3.2, 6.3)
Coronary artery disease	1	(1.2)	0	(0.0)		1.2 (-3.2, 6.3)
Angina pectoris	0	(0.0)	1	(1.2)		-1.2 (-6.3, 3.2)
Cardiac tamponade	0	(0.0)	1	(1.2)		-1.2 (-6.3, 3.2)
Cardiogenic shock	0	(0.0)	2	(2.3)		-2.3 (-8.1, 2.0)
Hepatic toxicity	**7**	**(8.1)**	**5**	**(5.8)**		**2.3 (-5.9, 10.9)**
Hepatic enzyme increased	2	(2.3)	1	(1.2)		1.2 (-4.2, 7.1)
Ascites	1	(1.2)	1	(1.2)		0.0 (-5.3, 5.3)
Focal nodular hyperplasia	1	(1.2)	0	(0.0)		1.2 (-3.2, 6.3)
Hepatobiliary disease	1	(1.2)	0	(0.0)		1.2 (-3.2, 6.3)
Hepatomegaly	1	(1.2)	0	(0.0)		1.2 (-3.2, 6.3)
International normalised ratio increased	1	(1.2)	1	(1.2)		0.0 (-5.3, 5.3)
Portal hypertensive gastropathy	1	(1.2)	0	(0.0)		1.2 (-3.2, 6.3)
Hepatic cirrhosis	0	(0.0)	1	(1.2)		-1.2 (-6.3, 3.2)
Hepatic cyst	0	(0.0)	1	(1.2)		-1.2 (-6.3, 3.2)
Hepatic failure	0	(0.0)	1	(1.2)		-1.2 (-6.3, 3.2)
Immunogenicity	**18**	**(20.9)**	**8**	**(9.3)**		**11.6 (0.9, 22.6)**
Rash	5	(5.8)	1	(1.2)		4.7 (-1.1, 11.9)
Rhinitis allergic	4	(4.7)	1	(1.2)		3.5 (-2.2, 10.4)
Eczema	3	(3.5)	0	(0.0)		3.5 (-0.9, 9.8)
Dermatitis contact	2	(2.3)	0	(0.0)		2.3 (-2.0, 8.1)
Urticaria	2	(2.3)	0	(0.0)		2.3 (-2.0, 8.1)
Dermatitis	1	(1.2)	1	(1.2)		0.0 (-5.3, 5.3)
Eye swelling	1	(1.2)	0	(0.0)		1.2 (-3.2, 6.3)

Eyelid oedema	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Face oedema	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Rash erythematous	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Swelling of eyelid	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Catheter site rash	0	(0.0)	1	(1.2)	-1.2 (-6.3, 3.2)
Drug eruption	0	(0.0)	1	(1.2)	-1.2 (-6.3, 3.2)
Hypersensitivity	0	(0.0)	1	(1.2)	-1.2 (-6.3, 3.2)
Pruritus allergic	0	(0.0)	1	(1.2)	-1.2 (-6.3, 3.2)
Rash pustular	0	(0.0)	1	(1.2)	-1.2 (-6.3, 3.2)
Shock	0	(0.0)	1	(1.2)	-1.2 (-6.3, 3.2)
Swelling face	0	(0.0)	1	(1.2)	-1.2 (-6.3, 3.2)
Increased blood pressure/hypertension	**2**	**(2.3)**	**1**	**(1.2)**	**1.2 (-4.2, 7.1)**
Hypertension	2	(2.3)	1	(1.2)	1.2 (-4.2, 7.1)
Increased hemoglobin (increased hematocrit, increased RBC count)	**13**	**(15.1)**	**1**	**(1.2)**	**14.0 (6.7, 23.2)**
Haemoglobin increased	9	(10.5)	1	(1.2)	9.3 (2.8, 17.7)
Polycythaemia	4	(4.7)	0	(0.0)	4.7 (0.3, 11.4)
Haematocrit increased	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Renal toxicity	**10**	**(11.6)**	**13**	**(15.1)**	**-3.5 (-14.1, 7.0)**
Acute kidney injury	4	(4.7)	6	(7.0)	-2.3 (-10.4, 5.4)
Chronic kidney disease	4	(4.7)	1	(1.2)	3.5 (-2.2, 10.4)
Renal failure	1	(1.2)	2	(2.3)	-1.2 (-7.1, 4.2)
Renal impairment	1	(1.2)	3	(3.5)	-2.3 (-8.8, 3.2)
Proteinuria	0	(0.0)	1	(1.2)	-1.2 (-6.3, 3.2)
Telangiectasia	**22**	**(25.6)**	**3**	**(3.5)**	**22.1 (12.4, 32.7)**
Telangiectasia	22	(25.6)	3	(3.5)	22.1 (12.4, 32.7)
Thrombo-embolic events	**4**	**(4.7)**	**3**	**(3.5)**	**1.2 (-5.7, 8.4)**
Cardiac ventricular thrombosis	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Deep vein thrombosis	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Pulmonary embolism	1	(1.2)	0	(0.0)	1.2 (-3.2, 6.3)
Vascular device occlusion	1	(1.2)	2	(2.3)	-1.2 (-7.1, 4.2)
Cerebral congestion	0	(0.0)	1	(1.2)	-1.2 (-6.3, 3.2)
Thrombocytopenia	**13**	**(15.1)**	**9**	**(10.5)**	**4.7 (-5.6, 15.1)**
Thrombocytopenia	12	(14.0)	8	(9.3)	4.7 (-5.2, 14.8)
Platelet count decreased	1	(1.2)	1	(1.2)	0.0 (-5.3, 5.3)

[a] Based on Miettinen & Nurminen method.
Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days .
Medical Dictionary for Regulatory Activities (MedDRA) 27.1 was used in the reporting of this study.
AEOI = adverse event of interest; AESI = adverse event of special interest; CI = confidence interval.
Database cutoff date: 06JUN2025

AESI Telangiectasia

Telangiectasia was reported for a higher proportion of participants in the sotatercept group (22 [25.6%]) compared with the placebo group (3 [3.5%]). No participant had an event that was considered to be serious or severe by the investigator, and none led to discontinuation of study intervention. Of the 22 participants with the AESI telangiectasia in the sotatercept group, 11 also had events of epistaxis, and 2 had serious AEOI bleeding events (subdural hematoma and gastritis hemorrhagic).

AEOI Increased Hemoglobin

The proportion of participants with the AEOI increased hemoglobin was higher in the sotatercept group (13 [15.1%]) than in the placebo group (1 [1.2%]). None of these events were considered to be serious or severe by the investigator, and none led to discontinuation of study intervention. Of the 13 participants with the AEOI increased hemoglobin in the sotatercept group, none had an AEOI thromboembolic event. Hemoglobin increased led to the interruption of study intervention, per protocol, for 8 participants in the sotatercept group compared with 1 participant in the placebo group.

Hemoglobin laboratory results are presented below.

AEOI Bleeding Events

The proportion of participants with AEOI bleeding events was higher in the sotatercept group (56 [65.1%]) than in the placebo group (31 [36.0%]). Within the AEOI bleeding events, the most commonly reported AEs in the sotatercept group were epistaxis (39 [45.3%]) followed by gingival bleeding (9 [10.5%]). Participants with epistaxis, and to a lesser extent gingival bleeding, accounted almost entirely for the imbalance between the sotatercept and placebo groups. In the sotatercept group, 1 participant had an event of epistaxis that was serious and another participant had a nonserious event that was severe. In the placebo group, 2 participants had events of epistaxis that were serious. None of the gingival bleeding events were serious or severe. No participant in the sotatercept group discontinued study intervention due to an AEOI bleeding event compared with 1 participant in the placebo group.

Serious AEOI Bleeding Events

Serious AEOI bleeding events were reported for 6 participants in each group (Table 29). Two participants in the sotatercept group had serious events of gastritis hemorrhagic; no other serious AEOI bleeding event was reported for >1 participant in the sotatercept group. One participant died in the sotatercept group due to a cerebral hemorrhage considered not related to study intervention by the investigator compared with none in the placebo group. Three participants in the sotatercept group had serious AEOI bleeding events (epistaxis, gastritis hermorrhagic, and hematemesis) that were considered related to study intervention by the investigator compared with 2 participants in the placebo group (epistaxis and hemoptysis). No participant in the sotatercept group discontinued study intervention due to a serious AEOI bleeding event compared with 1 participant in the placebo group.

Table 29: Participants With Serious AESI/AEOI Adverse Events (Incidence > 0% in One or More Treatment Groups) (All Participants as Treated)

	Sotatercept		Placebo	
	n	(%)	n	(%)
Participants in population	86		86	
with one or more serious AESI/AEOI	18	(20.9)	35	(40.7)
with no serious AESI/AEOI	68	(79.1)	51	(59.3)
Bleeding events	**6**	**(7.0)**	**6**	**(7.0)**
Anaemia	0	(0.0)	2	(2.3)
Cerebral haemorrhage	1	(1.2)	0	(0.0)
Epistaxis	1	(1.2)	2	(2.3)
Gastritis haemorrhagic	2	(2.3)	0	(0.0)
Gastrointestinal haemorrhage	1	(1.2)	0	(0.0)
Haematemesis	1	(1.2)	0	(0.0)
Haemoperitoneum	0	(0.0)	1	(1.2)
Haemoptysis	0	(0.0)	1	(1.2)
Subdural haematoma	1	(1.2)	0	(0.0)

AEOI Increased Blood Pressure

The AEOI increased blood pressure was reported for 2 participants in the sotatercept group and 1 participant in the placebo group. Neither of these events was serious or severe, nor led to discontinuation of study intervention.

Changes from baseline in SBP and DBP are presented below.

AEOI Thrombocytopenia

The AEOI thrombocytopenia was reported more commonly for participants in the sotatercept group (13 [15.1%]) than in the placebo group (9 [10.5%]). In the sotatercept group, 1 participant had 2 events of thrombocytopenia that were serious and another participant had a nonserious event that was severe. One of the SAEs and the severe AE led to the interruption of study intervention. In the placebo group, 1 participant had 3 nonserious events of thrombocytopenia that were severe and led to the interruption of study intervention. No participant discontinued study intervention due to the AEOI thrombocytopenia. All participants in the sotatercept group with the AEOI thrombocytopenia were receiving prostacyclin infusion therapy at baseline. Of the 13 participants in the sotatercept group with the AEOI thrombocytopenia, 6 also had events of epistaxis; none of the 13 participants with AEOI thrombocytopenia had a serious bleeding event. The AEOI thrombocytopenia led to the interruption of study intervention or dose reduction, per protocol, in 9 participants in the sotatercept group compared with 1 in the placebo group.

Resolution status of dose modifications due to adverse events

In participants receiving sotatercept in ZENITH, most occurrences of AESI telangiectasia, AEOI increased hemoglobin, and AEOI thrombocytopenia that led to dose modification (most frequently, dose delay) resulted in resolution of the event (Table 30. Of 6 AESI telangiectasia events leading to dose delay, 5 resolved. Of 22 AEOI increased hemoglobin events leading to dose delay, 20 resolved. Of 8 AEOI thrombocytopenia events leading to dose delay, 5 resolved. For each of the 3 categories, all events leading to dose reduction were resolved, and there were no events that led to discontinuation of sotatercept.

Table 30: Resolution Status of events leading to dose delay, dose reduction, or treatment discontinuation for adverse events of special interest and select adverse events of interest-Safety Set (MK-7962-006 ZENITH)

	Sotatercept N=86	Placebo N=86	Total N=172
AESI: Telangiectasia			
Number of events	36	5	41
Resolved	19	2	21
Not resolved	17	3	20
Number of events leading to dose delay	6	1	7
Resolved	5	1	6
Not resolved	1	0	1
Number of events leading to dose reduction	3	0	3
Resolved	3	0	3
Not resolved	0	0	0
Number of events leading to treatment discontinuation	0	0	0
Resolved	0	0	0
Not resolved	0	0	0
AEOI: Increased hemoglobin (increased hematocrit, increased RBC count)			
Number of events	29	1	30
Resolved	27	1	28
Not resolved	2	0	2
Number of events leading to dose delay	22	1	23
Resolved	20	1	21
Not resolved	2	0	2
Number of events leading to dose reduction	1	0	1
Resolved	1	0	1
Not resolved	0	0	0
Number of events leading to treatment discontinuation	0	0	0
Resolved	0	0	0
Not resolved	0	0	0

	Sotatercept N=86	Placebo N=86	Total N=172
AEOI: Thrombocytopenia			
Number of events	17	11	28
Resolved	12	10	22
Not resolved	5	1	6
Number of events leading to dose delay	8	2	10
Resolved	5	2	7
Not resolved	3	0	3
Number of events leading to dose reduction	1	0	1
Resolved	1	0	1
Not resolved	0	0	0

Number of events leading to treatment discontinuation	0	0	0
Resolved	0	0	0
Not resolved	0	0	0

N = number of subjects in the treatment group or overall.
Note: The AESI/AEOI outcomes of "Recovered/Resolved", "Recovered/Resolved with Sequelae", "Recovering/Resolving" were mapped to "Resolved" while outcomes of "Fatal", "Not Recovered/Not Resolved", and "Unknown" were mapped to "Not resolved".
Note: The number of events leading to dose delay, dose reduction, and treatment discontinuation do not necessarily sum to the total number of events.
A treatment-emergent adverse event is an event that has a start date on or after the first dose of treatment and up to 8 weeks after the last dose of treatment. Adverse Events were coded using MedDRA Version 27.1.

Serious adverse event/deaths/other significant events

Serious adverse events

SAEs were reported less commonly in the sotatercept group than in the placebo group. The proportion of participants with SAEs that led to discontinuation of study intervention was lower in the sotatercept group than in the placebo group (Table 31).

In the sotatercept group, the most commonly reported (incidence ≥4 participants) SAEs were pneumonia, atrial fibrillation, cardiac failure, and PAH (denoting a worsening of PAH). SAEs associated with PAH disease progression (e.g. PAH, right ventricular failure, cardiac failure, PH, and dyspnea) were more commonly reported for participants in the placebo group than in the sotatercept group (Table 31.

SAEs considered related to study intervention by the investigator were reported for 4 participants in the sotatercept group (colitis ulcerative (n=1), epistaxis (n=1), gastritis hemorrhagic (n=1), and hematemesis (n=1)) and 2 participants in the placebo group (epistaxis and iron deficiency in 1 participant and hemoptysis in 1 participant). No individual SAE by PT was reported for >1 participant in either group. No participant in the sotatercept group and 1 in the placebo group discontinued study intervention due to an intervention-related SAE (epistaxis) (Table 31).

Table 31: Participants With Serious Adverse Events (Incidence ≥ 4 participants with an Adverse Event in One or More Treatment Groups) (All Participants as Treated)

	Sotatercept		Placebo	
	n	(%)	n	(%)
Participants in population	86		86	
with one or more serious adverse events	52	(60.5)	64	(74.4)
with no serious adverse events	34	(39.5)	22	(25.6)
Cardiac disorders	**16**	**(18.6)**	**30**	**(34.9)**
Atrial fibrillation	5	(5.8)	0	(0.0)
Cardiac failure	4	(4.7)	8	(9.3)
Right ventricular failure	2	(2.3)	17	(19.8)
Gastrointestinal disorders	**5**	**(5.8)**	**4**	**(4.7)**
General disorders and administration site conditions	**5**	**(5.8)**	**7**	**(8.1)**
Infections and infestations	**25**	**(29.1)**	**14**	**(16.3)**
Pneumonia	8	(9.3)	4	(4.7)
Injury, poisoning and procedural complications	**4**	**(4.7)**	**4**	**(4.7)**
Metabolism and nutrition disorders	**9**	**(10.5)**	**5**	**(5.8)**

Musculoskeletal and connective tissue disorders	**3**	**(3.5)**	**4**	**(4.7)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4**	**(4.7)**	**2**	**(2.3)**
Product issues	**2**	**(2.3)**	**4**	**(4.7)**
Respiratory, thoracic and mediastinal disorders	**11**	**(12.8)**	**36**	**(41.9)**
Dyspnoea	0	(0.0)	4	(4.7)
Pulmonary arterial hypertension	4	(4.7)	24	(27.9)
Pulmonary hypertension	0	(0.0)	6	(7.0)
	Sotatercept	Placebo		
Vascular disorders	**2**	**(2.3)**	**4**	**(4.7)**

Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if it meets the criterion in the report title.
Medical Dictionary for Regulatory Activities (MedDRA) version 27.1 was used in the reporting of this study.
This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days.
Database cutoff date: 06JUN2025

Deaths

Nine participants had AEs leading to death in the sotatercept group compared with 13 in the placebo group (Table 32). No individual PT leading to death was reported for >1 participant in the sotatercept group. In the placebo group, the most commonly reported AEs leading to death were PAH for 4 participants, cardiac failure for 2 participants; no other AE leading to death was reported for >1 participant in this group. None of the AEs leading to death were considered related to study intervention by the investigator.

Table 32: Participants With Adverse Events Leading to Death (Incidence > 0% in One or More Treatment Groups)(All Participants as Treated)

	Sotatercept		Placebo	
	n	(%)	n	(%)
Participants in population	86		86	
with one or more adverse events	9	(10.5)	13	(15.1)
with no adverse events	77	(89.5)	73	(84.9)
Cardiac disorders	**2**	**(2.3)**	**5**	**(5.8)**
Cardiac failure	0	(0.0)	2	(2.3)
Cardio-respiratory arrest	1	(1.2)	1	(1.2)
Cardiogenic shock	0	(0.0)	1	(1.2)
Right ventricular failure	1	(1.2)	1	(1.2)
General disorders and administration site conditions	**0**	**(0.0)**	**2**	**(2.3)**
Multiple organ dysfunction syndrome	0	(0.0)	1	(1.2)
Sudden death	0	(0.0)	1	(1.2)
Hepatobiliary disorders	**0**	**(0.0)**	**1**	**(1.2)**
Hepatic failure	0	(0.0)	1	(1.2)
Infections and infestations	**5**	**(5.8)**	**1**	**(1.2)**
Brain abscess	1	(1.2)	0	(0.0)
Pneumonia	1	(1.2)	0	(0.0)
Pneumonia parainfluenzae viral	1	(1.2)	0	(0.0)
Sepsis	1	(1.2)	0	(0.0)

Septic shock	1	(1.2)	1	(1.2)
Investigations	**0**	**(0.0)**	**1**	**(1.2)**
Cardiac output decreased	0	(0.0)	1	(1.2)
Nervous system disorders	**1**	**(1.2)**	**0**	**(0.0)**
Cerebral haemorrhage	1	(1.2)	0	(0.0)
Renal and urinary disorders	**0**	**(0.0)**	**1**	**(1.2)**
Renal failure	0	(0.0)	1	(1.2)
Respiratory, thoracic and mediastinal disorders	**1**	**(1.2)**	**5**	**(5.8)**
Pulmonary arterial hypertension	1	(1.2)	4	(4.7)
Pulmonary hypertension	0	(0.0)	1	(1.2)
Vascular disorders	**0**	**(0.0)**	**2**	**(2.3)**
Artery dissection	0	(0.0)	1	(1.2)
Reperfusion injury	0	(0.0)	1	(1.2)

Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Medical Dictionary for Regulatory Activities (MedDRA) 27.1 was used in the reporting of this study.
This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days.
Database cutoff date: 06JUN2025

Laboratory findings

No new safety concerns based on laboratory abnormalities were observed in the sotatercept group and results were consistent with those observed in previous sotatercept studies.

Hematology

A mean increase from baseline in hemoglobin was observed in the sotatercept group (1.48 g/dL at Week 24) compared with no notable change from baseline in the placebo group over time. No participants in either group had increases in hemoglobin to greater than 4 g/dL above the ULN (CTCAE Grade 3).

Mean increases from baseline in hematocrit and erythrocytes were observed in the sotatercept group compared with no notable changes from baseline in the placebo group over time. In the sotatercept group, mean increases from baseline at Week 24 were 4.39% for hematocrit and 0.43 × 10^{12}/L for erythrocytes; similar results were also observed after Week 24.

Mean decreases from baseline in platelet counts were observed at Week 24 in the sotatercept and placebo groups (-15.19 × 10^9/L and -8.94 × 10^9/L, respectively). A shift to a more severe CTCAE category (worst postbaseline grade) for a decrease from baseline in platelet counts occurred more commonly in participants in the sotatercept group than in the placebo group. Four (4.8%) participants in the sotatercept group had shifts to platelet counts <50 × 10^9/L (CTCAE Grade 3) compared with 2 (2.4%) in the placebo group. One (1.2%) participant in the sotatercept group had a shift to platelet counts <25 × 10^9/L (CTCAE Grade 4) compared with none in the placebo group. Each of the 5 participants in the sotatercept group who had worst post-baseline grades of 3 or 4 were receiving prostacyclin as a prior and concomitant medication.

Chemistry

There were no notable differences in mean changes from baseline over time in chemistry parameters between the 2 groups. Shifts in selected laboratory parameters based on CTCAE criteria (worst postbaseline grade), including alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, and eGFR were not notably different between the sotatercept and placebo groups.

Vital Signs

Small mean increases from baseline in blood pressure were observed in the sotatercept group (3.10 mm Hg in SBP and 5.06 mm Hg in DBP at Week 24) compared with minimal changes from baseline in the placebo group. The proportions of participants who met predetermined criteria for increases from baseline in systolic and diastolic blood pressure over time were low and generally similar in both groups. A shift toward a more severe CTCAE category (worst post-baseline grade) from baseline for hypertension occurred more commonly for participants in the sotatercept group than in the placebo group, with 5 (6.0%) participants on sotatercept shifting to a worst post-baseline of Grade 3 (SBP ≥160 mm Hg or DBP ≥100 mm Hg) compared with no participants on placebo.

Immunogenicity

Of the 84 evaluable participants at the data cutoff, 36 (42.9%) developed an ADA response to sotatercept: 35 of the 36 were treatment-induced positive participants and 1 was a treatment-boosted positive participant (Table 33). Two additional participants were non–treatment-emergent positive. The median maximum post-dose titer was 10 (range: 10 to 320). Of the 36 participants who developed an ADA response, 16 (44.4%) were neutralizing antibody negative and 20 (55.6%) were neutralizing antibody positive. Of the 36 participants who developed an ADA response (treatment-induced and treatment-boosted positive), the median (Q1, Q3) ADA onset time was 9.0 weeks (3.1 weeks, 24.1 weeks) after first sotatercept treatment. Thirteen (36.1%) participants demonstrated transient ADA responses (lasting <16 weeks), and 20 (55.6%) participants had a persistent ADA response (≥16 weeks).

There were no notable differences in the proportions of participants who had a primary endpoint event or the proportions of participants with AEs or AESIs/AEOIs when analyzed by ADA status. There were no clinically meaningful safety findings attributable to immunogenicity and no SAEs attributable to immunogenicity in sotatercept treated participants.

Table 33: Incidence of Immunogenicity Status Over Time (All Participants as Treated)

	Sotatercept n (%)
Participants in population	86
Unevaluable participants	2
Evaluable participants[a]	84
Immunogenicity Status	
Negative	46 (54.8)
Inconclusive[b]	0 (0.0)
Non-treatment emergent positive[c]	2 (2.4)
Treatment-emergent ADA positive to Sotatercept	36 (42.9)
Treatment induced positive[d]	35 (41.7)
Treatment boosted positive[e]	1 (1.2)
Maximum post dose Titer	
Median (Min, Max)	10 (10, 320)
Neutralizing Antibody Results in Participants with a Positive ADA Response	
Non-treatment emergent	2
Neutralizing negative	2 (100.0)
Neutralizing positive	0 (0.0)
Treatment-emergent ADA positive to Sotatercept[f]	36
Neutralizing negative	16 (44.4)
Neutralizing positive	20 (55.6)

[a] Participants with at least one ADA assay result after treatment with Sotatercept. The number of participants evaluable is the denominator of the percentages in the table except for neutralizing antibody results.
[b] Participants with a drug concentration in the last sample (or prior timepoint if last visit drug concentration was missing) that exceeded the DTL (20,000 ng/ml)
[c] Participants positive at baseline were considered non-treatment emergent positive if only positive at baseline or if post dose titer increased by less than 2-fold relative to the baseline titer.
[d] Participants who were negative at baseline and positive post dose were considered treatment induced.
[e] Participants positive at baseline were considered treatment boosted if post dose titer increased by greater than or equal to 2-fold relative to the baseline titer.
[f] The number of Treatment-emergent ADA positive participants is the denominator of the percentages for neutralizing antibody results.
ADA = anti-drug antibody; DTL = drug tolerance level; NAb = neutralizing antibody.
Database cutoff date: 06JUN2025

Safety in special populations

Age

The proportions of participants with AEs in the sotatercept and placebo groups were generally consistent between age subgroups (<65 and ≥65 years of age) (Table 34). SAEs were less commonly reported in the sotatercept group compared with the placebo group for both age categories of participants <65 years of age and participants ≥65 years of age. Similarly, AEs leading to deaths were less commonly reported in the sotatercept group than in the placebo group for both age categories.

Table 34: Adverse Events Summary by Age Group at Baseline (All Participants as Treated)

	<65 years				≥65 years			
	Sotatercept		Placebo		Sotatercept		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	56		66		30		20	
with one or more adverse events	55	(98.2)	65	(98.5)	30	(100.0)	20	(100.0)
with no adverse event	1	(1.8)	1	(1.5)	0	(0.0)	0	(0.0)
with drug-related[a] adverse events	40	(71.4)	22	(33.3)	18	(60.0)	7	(35.0)
with non-serious adverse events	55	(98.2)	63	(95.5)	29	(96.7)	20	(100.0)
with serious adverse events	33	(58.9)	49	(74.2)	19	(63.3)	15	(75.0)
with serious drug-related[a] adverse events	3	(5.4)	1	(1.5)	1	(3.3)	1	(5.0)
who died	5	(8.9)	10	(15.2)	4	(13.3)	3	(15.0)
who died due to a drug-related[a] adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	1	(1.8)	3	(4.5)	0	(0.0)	1	(5.0)
discontinued drug due to a drug-related[a] adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.0)
discontinued drug due to a serious adverse event	1	(1.8)	3	(4.5)	0	(0.0)	1	(5.0)
discontinued drug due to a serious drug-related[a] adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.0)

[a]Relatedness to study drug was determined by the investigator as suspected related.
This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days.
MedDRA version 27.1 was used in the reporting of this study.
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WHO FC III or IV

The AE summaries were generally consistent across subgroups for WHO FC III and IV through the final analysis (Table 35). In both WHO FC III and FC IV subgroups, proportions of participants with SAEs were lower in the sotatercept groups compared with the placebo groups

There were no meaningful differences in AESI/AEOI based on subgroup analysis, taking into consideration the relatively low numbers of WHO FC IV participants (Table 36). In both WHO FC subgroups, the proportions of participants with AEOI cardiac events were lower in the sotatercept group when compared with the placebo group. The imbalance between the sotatercept and placebo groups for AEOI bleeding events was greater in WHO FC IV when compared with the imbalance in WHO FC III, however this appears to be attributable to a lower rate in the placebo group and the proportions of participants in the sotatercept group with bleeding events were similar between WHO FC III and WHO FC IV. The imbalance between sotatercept and placebo for AEOI immunogenicity was greater in WHO FC IV when compared with the imbalance in WHO FC III, however there were few participants in the sotatercept group with immunogenicity events, and the imbalance was mostly due to rashes, and not to systemic events associated with hypersensitivity.

Table 35: Adverse Events Summary by WHO Function Class at Baseline (All Participants as Treated)

	Class III				Class IV			
	Sotatercept		Placebo		Sotatercept		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	66		62		20		24	
with one or more adverse events	66	(100.0)	62	(100.0)	19	(95.0)	23	(95.8)
with no adverse event	0	(0.0)	0	(0.0)	1	(5.0)	1	(4.2)
with drug-related[a] adverse events	43	(65.2)	23	(37.1)	15	(75.0)	6	(25.0)
with non-serious adverse events	65	(98.5)	62	(100.0)	19	(95.0)	21	(87.5)
with serious adverse events	40	(60.6)	47	(75.8)	12	(60.0)	17	(70.8)
with serious drug-related[a] adverse events	3	(4.5)	2	(3.2)	1	(5.0)	0	(0.0)
who died	8	(12.1)	10	(16.1)	1	(5.0)	3	(12.5)
who died due to a drug-related[a] adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	1	(1.5)	3	(4.8)	0	(0.0)	1	(4.2)
discontinued drug due to a drug-related[a] adverse event	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	1	(1.5)	3	(4.8)	0	(0.0)	1	(4.2)
discontinued drug due to a serious drug-related[a] adverse event	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)

[a]Relatedness to study drug was determined by the investigator as suspected related.

This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days.

MedDRA version 27.1 was used in the reporting of this study.

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Table 36: Participants With AESI/AEOI Adverse Events by WHO Function Class at Baseline (Incidence > 0% in any Column)(All Participants as Treated)

	Class III				Class IV			
	Sotatercept		Placebo		Sotatercept		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	66		62		20		24	
with one or more adverse events	58	(87.9)	47	(75.8)	18	(90.0)	16	(66.7)
with no adverse events	8	(12.1)	15	(24.2)	2	(10.0)	8	(33.3)
Bleeding events	**44**	**(66.7)**	**25**	**(40.3)**	**12**	**(60.0)**	**6**	**(25.0)**
Anaemia	8	(12.1)	7	(11.3)	2	(10.0)	1	(4.2)
Anal haemorrhage	0	(0.0)	0	(0.0)	1	(5.0)	0	(0.0)
Bleeding varicose vein	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Blood urine present	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Catheter site bruise	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Cerebral haemorrhage	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Conjunctival haemorrhage	0	(0.0)	2	(3.2)	1	(5.0)	0	(0.0)
Contusion	2	(3.0)	3	(4.8)	3	(15.0)	0	(0.0)
Diarrhoea haemorrhagic	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Ear haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)
Ecchymosis	0	(0.0)	2	(3.2)	0	(0.0)	0	(0.0)
Epistaxis	32	(48.5)	7	(11.3)	7	(35.0)	1	(4.2)
Gastritis haemorrhagic	2	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal haemorrhage	1	(1.5)	0	(0.0)	1	(5.0)	0	(0.0)
Gingival bleeding	8	(12.1)	2	(3.2)	1	(5.0)	0	(0.0)
Haematemesis	0	(0.0)	0	(0.0)	2	(10.0)	0	(0.0)
Haematochezia	2	(3.0)	0	(0.0)	2	(10.0)	0	(0.0)

Haematoma	0	(0.0)	2	(3.2)	1	(5.0)	0	(0.0)
Haematuria	1	(1.5)	0	(0.0)	0	(0.0)	1	(4.2)
Haemoperitoneum	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)
Haemoptysis	1	(1.5)	5	(8.1)	0	(0.0)	0	(0.0)
Haemorrhage	0	(0.0)	0	(0.0)	1	(5.0)	0	(0.0)
Haemorrhagic ovarian cyst	0	(0.0)	0	(0.0)	1	(5.0)	0	(0.0)
Haemorrhoidal haemorrhage	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Haemothorax	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Heavy menstrual bleeding	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Increased tendency to bruise	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)
Injection site bruising	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Injection site haematoma	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Injection site haemorrhage	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Oesophageal haemorrhage	0	(0.0)	0	(0.0)	1	(5.0)	0	(0.0)
Petechiae	2	(3.0)	1	(1.6)	0	(0.0)	0	(0.0)
Post procedural haemorrhage	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Purpura	0	(0.0)	0	(0.0)	1	(5.0)	0	(0.0)
Rectal haemorrhage	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Retinal haemorrhage	1	(1.5)	0	(0.0)	1	(5.0)	0	(0.0)
Retroperitoneal haematoma	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Spontaneous haematoma	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)
Subdural haematoma	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Tooth socket haemorrhage	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Vaginal haemorrhage	1	(1.5)	0	(0.0)	0	(0.0)	1	(4.2)
Vitreous haemorrhage	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac events	**12**	**(18.2)**	**21**	**(33.9)**	**2**	**(10.0)**	**10**	**(41.7)**
Angina pectoris	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)

Cardiac failure	5	(7.6)	6	(9.7)	0	(0.0)	3	(12.5)
Cardiac failure acute	1	(1.5)	1	(1.6)	0	(0.0)	0	(0.0)
Cardiac tamponade	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)
Cardiogenic shock	0	(0.0)	1	(1.6)	0	(0.0)	1	(4.2)
Cardiorenal syndrome	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Coronary artery disease	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Pericardial effusion	2	(3.0)	1	(1.6)	1	(5.0)	1	(4.2)
Right ventricular failure	2	(3.0)	13	(21.0)	2	(10.0)	5	(20.8)
Hepatic toxicity	**6**	**(9.1)**	**5**	**(8.1)**	**1**	**(5.0)**	**0**	**(0.0)**
Ascites	1	(1.5)	1	(1.6)	0	(0.0)	0	(0.0)
Focal nodular hyperplasia	0	(0.0)	0	(0.0)	1	(5.0)	0	(0.0)
Hepatic cirrhosis	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Hepatic cyst	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Hepatic enzyme increased	1	(1.5)	1	(1.6)	1	(5.0)	0	(0.0)
Hepatic failure	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Hepatobiliary disease	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatomegaly	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
International normalised ratio increased	1	(1.5)	1	(1.6)	0	(0.0)	0	(0.0)
Portal hypertensive gastropathy	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Immunogenicity	**11**	**(16.7)**	**6**	**(9.7)**	**7**	**(35.0)**	**2**	**(8.3)**
Catheter site rash	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Dermatitis	1	(1.5)	1	(1.6)	0	(0.0)	0	(0.0)
Dermatitis contact	2	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)
Drug eruption	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Eczema	1	(1.5)	0	(0.0)	2	(10.0)	0	(0.0)
Eye swelling	0	(0.0)	0	(0.0)	1	(5.0)	0	(0.0)
Eyelid oedema	0	(0.0)	0	(0.0)	1	(5.0)	0	(0.0)

Face oedema	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Hypersensitivity	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Pruritus allergic	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Rash	3	(4.5)	0	(0.0)	2	(10.0)	1	(4.2)
Rash erythematous	0	(0.0)	0	(0.0)	1	(5.0)	0	(0.0)
Rash pustular	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Rhinitis allergic	3	(4.5)	1	(1.6)	1	(5.0)	0	(0.0)
Shock	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)
Swelling face	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Swelling of eyelid	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	2	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)
Increased blood pressure/hypertension	**2**	**(3.0)**	**1**	**(1.6)**	**0**	**(0.0)**	**0**	**(0.0)**
Hypertension	2	(3.0)	1	(1.6)	0	(0.0)	0	(0.0)
Increased hemoglobin (increased hematocrit, increased RBC count)	**9**	**(13.6)**	**0**	**(0.0)**	**4**	**(20.0)**	**1**	**(4.2)**
Haematocrit increased	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Haemoglobin increased	7	(10.6)	0	(0.0)	2	(10.0)	1	(4.2)
Polycythaemia	2	(3.0)	0	(0.0)	2	(10.0)	0	(0.0)
Renal toxicity	**8**	**(12.1)**	**9**	**(14.5)**	**2**	**(10.0)**	**4**	**(16.7)**
Acute kidney injury	4	(6.1)	4	(6.5)	0	(0.0)	2	(8.3)
Chronic kidney disease	2	(3.0)	1	(1.6)	2	(10.0)	0	(0.0)
Proteinuria	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Renal failure	1	(1.5)	1	(1.6)	0	(0.0)	1	(4.2)
Renal impairment	1	(1.5)	2	(3.2)	0	(0.0)	1	(4.2)
Telangiectasia	**17**	**(25.8)**	**2**	**(3.2)**	**5**	**(25.0)**	**1**	**(4.2)**
Telangiectasia	17	(25.8)	2	(3.2)	5	(25.0)	1	(4.2)

Thrombo-embolic events	**4**	**(6.1)**	**3**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**
Cardiac ventricular thrombosis	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Cerebral congestion	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)
Deep vein thrombosis	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary embolism	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular device occlusion	1	(1.5)	2	(3.2)	0	(0.0)	0	(0.0)
Thrombocytopenia	**10**	**(15.2)**	**6**	**(9.7)**	**3**	**(15.0)**	**3**	**(12.5)**
Platelet count decreased	1	(1.5)	0	(0.0)	0	(0.0)	1	(4.2)
Thrombocytopenia	9	(13.6)	6	(9.7)	3	(15.0)	2	(8.3)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days.

MedDRA version 27.1 was used in the reporting of this study.

Database cutoff date: 06JUN2025

Hepatic impairment

Patients with hepatic impairment were not eligible for enrollment per the ZENITH eligibility criteria, which required participants to have ALT, AST, and total bilirubin levels ≤ 3.0 x ULN. As a result, the Applicant has insufficient data to describe the safety profile of sotatercept in participants with hepatic impairment.

Severe renal impairment

Median baseline eGFR in ZENITH participants was 64.0 ml/min/1.73m^2. No meaningful differences in the AE summary tables (final DBL 06-JUN-2025), were observed between sotatercept-treated participants with renal impairment (baseline eGFR <60 ml/min/1.73m^2; n=37) and sotatercept-treated participants with normal renal function or mild renal impairment (baseline eGFR ≥60 ml/min/1.73m^2; n=48) (Table 37. In both sotatercept and placebo groups, there were higher proportions of participants in the renal impairment subgroup with SAEs compared with the normal renal function subgroup, however the differences between sotatercept and placebo groups were similar in both subgroups. All participants who discontinued study intervention due to an AE were in the renal impairment subgroup (n=1 in the sotatercept group and n=4 in the placebo group).

Through the final analysis, in both the sotatercept and placebo groups, AEOI renal toxicity was reported in higher proportions of participants with renal impairment compared with those with normal renal function or mild renal impairment, however the proportion of participants with AEOI renal toxicity was lower in the sotatercept group when compared with placebo in the impaired renal function subgroup (Table 38). No consistent patterns emerged between the sotatercept and placebo groups on subgroup analysis by renal function for AEOI with one exception. In the sotatercept group, there was a higher proportion of participants with AEOI increased hemoglobin in participants with renal impairment (21.6%) compared to those with normal renal function (10.4%), with a single report on placebo.

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Table 37: Adverse Events Summary by eGFR Category at Baseline

	<60				≥60			
	Sotatercept		Placebo		Sotatercept		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	37		33		48		53	
with one or more adverse events	36	(97.3)	33	(100.0)	48	(100.0)	52	(98.1)
with no adverse event	1	(2.7)	0	(0.0)	0	(0.0)	1	(1.9)
with drug-related[a] adverse events	23	(62.2)	11	(33.3)	34	(70.8)	18	(34.0)
with non-serious adverse events	36	(97.3)	32	(97.0)	47	(97.9)	51	(96.2)
with serious adverse events	25	(67.6)	28	(84.8)	26	(54.2)	36	(67.9)
with serious drug-related[a] adverse events	2	(5.4)	1	(3.0)	2	(4.2)	1	(1.9)
who died	4	(10.8)	6	(18.2)	5	(10.4)	7	(13.2)
who died due to a drug-related[a] adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	1	(2.7)	4	(12.1)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related[a] adverse event	0	(0.0)	1	(3.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	1	(2.7)	4	(12.1)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related[a] adverse event	0	(0.0)	1	(3.0)	0	(0.0)	0	(0.0)

[a]Relatedness to study drug was determined by the investigator as suspected related.

This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days.

MedDRA version 27.1 was used in the reporting of this study.

Database cutoff date: 06JUN2025

Table 38: Participants With AESI/AEOI Adverse Events by eGFR at Baseline (Incidence > 0% in Any Column) (All Participants as Treated)

	<60				≥60			
	Sotatercept		Placebo		Sotatercept		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	37		33		48		53	
with one or more adverse events	33	(89.2)	24	(72.7)	42	(87.5)	39	(73.6)
with no adverse events	4	(10.8)	9	(27.3)	6	(12.5)	14	(26.4)
Bleeding events	**24**	**(64.9)**	**10**	**(30.3)**	**31**	**(64.6)**	**21**	**(39.6)**
Anaemia	7	(18.9)	1	(3.0)	2	(4.2)	7	(13.2)
Anal haemorrhage	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Bleeding varicose vein	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Blood urine present	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Catheter site bruise	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Cerebral haemorrhage	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Conjunctival haemorrhage	0	(0.0)	1	(3.0)	1	(2.1)	1	(1.9)
Contusion	3	(8.1)	1	(3.0)	2	(4.2)	2	(3.8)
Diarrhoea haemorrhagic	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Ear haemorrhage	0	(0.0)	1	(3.0)	0	(0.0)	0	(0.0)
Ecchymosis	0	(0.0)	1	(3.0)	0	(0.0)	1	(1.9)
Epistaxis	19	(51.4)	4	(12.1)	20	(41.7)	4	(7.5)
Gastritis haemorrhagic	1	(2.7)	0	(0.0)	1	(2.1)	0	(0.0)
Gastrointestinal haemorrhage	1	(2.7)	0	(0.0)	1	(2.1)	0	(0.0)
Gingival bleeding	3	(8.1)	0	(0.0)	6	(12.5)	2	(3.8)
Haematemesis	0	(0.0)	0	(0.0)	2	(4.2)	0	(0.0)
Haematochezia	3	(8.1)	0	(0.0)	1	(2.1)	0	(0.0)
Haematoma	0	(0.0)	1	(3.0)	1	(2.1)	1	(1.9)

Haematuria	1	(2.7)	0	(0.0)	0	(0.0)	1	(1.9)
Haemoperitoneum	0	(0.0)	1	(3.0)	0	(0.0)	0	(0.0)
Haemoptysis	0	(0.0)	1	(3.0)	1	(2.1)	4	(7.5)
Haemorrhage	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Haemorrhagic ovarian cyst	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Haemorrhoidal haemorrhage	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Haemothorax	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Heavy menstrual bleeding	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Increased tendency to bruise	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Injection site bruising	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Injection site haematoma	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Injection site haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Oesophageal haemorrhage	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Petechiae	1	(2.7)	0	(0.0)	1	(2.1)	1	(1.9)
Post procedural haemorrhage	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Purpura	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Rectal haemorrhage	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Retinal haemorrhage	0	(0.0)	0	(0.0)	2	(4.2)	0	(0.0)
Retroperitoneal haematoma	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Spontaneous haematoma	0	(0.0)	1	(3.0)	0	(0.0)	0	(0.0)
Subdural haematoma	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Tooth socket haemorrhage	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Vaginal haemorrhage	0	(0.0)	0	(0.0)	1	(2.1)	1	(1.9)
Vitreous haemorrhage	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac events	**8**	**(21.6)**	**13**	**(39.4)**	**6**	**(12.5)**	**18**	**(34.0)**
Angina pectoris	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Cardiac failure	3	(8.1)	6	(18.2)	2	(4.2)	3	(5.7)

Cardiac failure acute	0	(0.0)	1	(3.0)	1	(2.1)	0	(0.0)
Cardiac tamponade	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Cardiogenic shock	0	(0.0)	0	(0.0)	0	(0.0)	2	(3.8)
Cardiorenal syndrome	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Coronary artery disease	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Pericardial effusion	1	(2.7)	1	(3.0)	2	(4.2)	1	(1.9)
Right ventricular failure	2	(5.4)	6	(18.2)	2	(4.2)	12	(22.6)
Hepatic toxicity	**4**	**(10.8)**	**2**	**(6.1)**	**3**	**(6.3)**	**3**	**(5.7)**
Ascites	1	(2.7)	0	(0.0)	0	(0.0)	1	(1.9)
Focal nodular hyperplasia	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatic cirrhosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Hepatic cyst	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Hepatic enzyme increased	1	(2.7)	1	(3.0)	1	(2.1)	0	(0.0)
Hepatic failure	0	(0.0)	1	(3.0)	0	(0.0)	0	(0.0)
Hepatobiliary disease	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Hepatomegaly	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
International normalised ratio increased	1	(2.7)	0	(0.0)	0	(0.0)	1	(1.9)
Portal hypertensive gastropathy	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Immunogenicity	**6**	**(16.2)**	**2**	**(6.1)**	**12**	**(25.0)**	**6**	**(11.3)**
Catheter site rash	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Dermatitis	1	(2.7)	1	(3.0)	0	(0.0)	0	(0.0)
Dermatitis contact	0	(0.0)	0	(0.0)	2	(4.2)	0	(0.0)
Drug eruption	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Eczema	1	(2.7)	0	(0.0)	2	(4.2)	0	(0.0)
Eye swelling	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Eyelid oedema	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Face oedema	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)

Hypersensitivity	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Pruritus allergic	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Rash	1	(2.7)	0	(0.0)	4	(8.3)	1	(1.9)
Rash erythematous	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Rash pustular	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Rhinitis allergic	3	(8.1)	1	(3.0)	1	(2.1)	0	(0.0)
Shock	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Swelling face	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Swelling of eyelid	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Urticaria	0	(0.0)	0	(0.0)	2	(4.2)	0	(0.0)
Increased blood pressure/hypertension	**0**	**(0.0)**	**1**	**(3.0)**	**2**	**(4.2)**	**0**	**(0.0)**
Hypertension	0	(0.0)	1	(3.0)	2	(4.2)	0	(0.0)
Increased hemoglobin (increased hematocrit, increased RBC count)	**8**	**(21.6)**	**0**	**(0.0)**	**5**	**(10.4)**	**1**	**(1.9)**
Haematocrit increased	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Haemoglobin increased	6	(16.2)	0	(0.0)	3	(6.3)	1	(1.9)
Polycythaemia	2	(5.4)	0	(0.0)	2	(4.2)	0	(0.0)
Renal toxicity	**6**	**(16.2)**	**9**	**(27.3)**	**4**	**(8.3)**	**4**	**(7.5)**
Acute kidney injury	2	(5.4)	3	(9.1)	2	(4.2)	3	(5.7)
Chronic kidney disease	4	(10.8)	1	(3.0)	0	(0.0)	0	(0.0)
Proteinuria	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Renal failure	0	(0.0)	2	(6.1)	1	(2.1)	0	(0.0)
Renal impairment	0	(0.0)	3	(9.1)	1	(2.1)	0	(0.0)
Telangiectasia	**11**	**(29.7)**	**0**	**(0.0)**	**11**	**(22.9)**	**3**	**(5.7)**
Telangiectasia	11	(29.7)	0	(0.0)	11	(22.9)	3	(5.7)
Thrombo-embolic events	**2**	**(5.4)**	**1**	**(3.0)**	**2**	**(4.2)**	**2**	**(3.8)**

Cardiac ventricular thrombosis	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Cerebral congestion	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Deep vein thrombosis	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary embolism	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular device occlusion	0	(0.0)	1	(3.0)	1	(2.1)	1	(1.9)
Thrombocytopenia	**7**	**(18.9)**	**4**	**(12.1)**	**6**	**(12.5)**	**5**	**(9.4)**
Platelet count decreased	0	(0.0)	0	(0.0)	1	(2.1)	1	(1.9)
Thrombocytopenia	7	(18.9)	4	(12.1)	5	(10.4)	4	(7.5)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days.

MedDRA version 27.1 was used in the reporting of this study.

Database cutoff date: 06JUN2025

Safety related to drug-drug interactions and other interactions

TEAEs by background PAH therapy

The proportions of participants with AEs in the sotatercept and placebo groups were generally consistent between background PAH therapy subgroups (double and triple therapy) (Table 39).

Table 39: Adverse Events Summary by Background PAH Therapy at Baseline (All Participants as Treated)

	Double Combination				Triple Combination			
	Sotatercept		Placebo		Sotatercept		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	21		27		65		59	
with one or more adverse events	21	(100.0)	27	(100.0)	64	(98.5)	58	(98.3)
with no adverse event	0	(0.0)	0	(0.0)	1	(1.5)	1	(1.7)
with drug-related[a] adverse events	13	(61.9)	10	(37.0)	45	(69.2)	19	(32.2)
with non-serious adverse events	21	(100.0)	27	(100.0)	63	(96.9)	56	(94.9)
with serious adverse events	14	(66.7)	19	(70.4)	38	(58.5)	45	(76.3)
with serious drug-related[a] adverse events	2	(9.5)	1	(3.7)	2	(3.1)	1	(1.7)
who died	2	(9.5)	4	(14.8)	7	(10.8)	9	(15.3)
who died due to a drug-related[a] adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	1	(3.7)	1	(1.5)	3	(5.1)
discontinued drug due to a drug-related[a] adverse event	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	1	(3.7)	1	(1.5)	3	(5.1)
discontinued drug due to a serious drug-related[a] adverse event	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)

[a]Relatedness to study drug was determined by the investigator as suspected related.
This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days.
MedDRA version 27.1 was used in the reporting of this study.
Database cutoff date: 06JUN2025

TEAEs by prostacyclin infusion

The proportions of participants with AEs in the sotatercept and placebo groups were generally consistent between prostacyclin infusion therapy subgroups (users and non-users) (Table 40). SAEs were less commonly reported in the sotatercept group than in the placebo group for participants receiving prostacyclin infusion therapy as well as for participants who were not receiving prostacyclin infusion therapy.

The AEOI thrombocytopenia was only reported for participants who had been receiving prostacyclin infusion therapy at baseline (24.5% vs 16.3% for sotatercept and placebo in the prostacyclin infusion therapy subgroup and 0% vs 2.7%, respectively, in the non-prostacyclin infusion therapy subgroup).

Table 40: Adverse Events Summary by Prostacyclin Infusion Therapy Used at Baseline (All Participants as Treated)

	Prostacyclin Infusion Therapy				Non-Prostacyclin Infusion Therapy			
	Sotatercept		Placebo		Sotatercept		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	53		49		33		37	
with one or more adverse events	53	(100.0)	48	(98.0)	32	(97.0)	37	(100.0)
with no adverse event	0	(0.0)	1	(2.0)	1	(3.0)	0	(0.0)
with drug-related[a] adverse events	36	(67.9)	16	(32.7)	22	(66.7)	13	(35.1)
with non-serious adverse events	52	(98.1)	46	(93.9)	32	(97.0)	37	(100.0)
with serious adverse events	36	(67.9)	42	(85.7)	16	(48.5)	22	(59.5)
with serious drug-related[a] adverse events	3	(5.7)	2	(4.1)	1	(3.0)	0	(0.0)
who died	7	(13.2)	7	(14.3)	2	(6.1)	6	(16.2)
who died due to a drug-related[a] adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	1	(1.9)	4	(8.2)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related[a] adverse event	0	(0.0)	1	(2.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	1	(1.9)	4	(8.2)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related[a] adverse event	0	(0.0)	1	(2.0)	0	(0.0)	0	(0.0)

[a]Relatedness to study drug was determined by the investigator as suspected related.
This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days.
MedDRA version 27.1 was used in the reporting of this study.
Database cutoff date: 06JUN2025

Discontinuation due to adverse events

One participant discontinued study intervention due to an AE in the sotatercept group compared with 4 in the placebo group (Table 41).

AEs that led to study discontinuation were less commonly reported for participants in the sotatercept group than in the placebo group (Table 41). This imbalance was primarily due to fatal AEs that occurred more commonly in the placebo group. No AE leading to study discontinuation was reported for >1 participant in the sotatercept group.

Table 41: Participants With Adverse Events Resulting in Study Withdrawal (Incidence > 0% in One or More Treatment Groups) (All Participants as Treated)

	Sotatercept		Placebo	
	n	(%)	n	(%)
Participants in population	86		86	
with one or more adverse events resulting in discontinuation of study	7	(8.1)	13	(15.1)
with no adverse events resulting in discontinuation of study	79	(91.9)	73	(84.9)
Cardiac disorders	**2**	**(2.3)**	**3**	**(3.5)**
Cardiac failure	0	(0.0)	2	(2.3)
Cardio-respiratory arrest	1	(1.2)	1	(1.2)
Pericardial effusion	1	(1.2)	0	(0.0)
Right ventricular failure	1	(1.2)	0	(0.0)
General disorders and administration site conditions	**0**	**(0.0)**	**1**	**(1.2)**
Sudden death	0	(0.0)	1	(1.2)
Hepatobiliary disorders	**0**	**(0.0)**	**1**	**(1.2)**
Hepatic failure	0	(0.0)	1	(1.2)
Infections and infestations	**4**	**(4.7)**	**1**	**(1.2)**
Brain abscess	1	(1.2)	0	(0.0)
COVID-19 pneumonia	1	(1.2)	0	(0.0)
Pneumonia	1	(1.2)	0	(0.0)
Pneumonia parainfluenzae viral	1	(1.2)	0	(0.0)
Sepsis	1	(1.2)	0	(0.0)
Septic shock	0	(0.0)	1	(1.2)
Investigations	**0**	**(0.0)**	**2**	**(2.3)**
Cardiac output decreased	0	(0.0)	1	(1.2)
Electrocardiogram QT prolonged	0	(0.0)	1	(1.2)
Metabolism and nutrition disorders	**0**	**(0.0)**	**1**	**(1.2)**
Iron deficiency	0	(0.0)	1	(1.2)
Nervous system disorders	**1**	**(1.2)**	**0**	**(0.0)**

Cerebral haemorrhage	1	(1.2)	0	(0.0)
Renal and urinary disorders	**0**	**(0.0)**	**1**	**(1.2)**
Renal failure	0	(0.0)	1	(1.2)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**6**	**(7.0)**
Epistaxis	0	(0.0)	1	(1.2)
Pulmonary arterial hypertension	0	(0.0)	4	(4.7)
Pulmonary hypertension	0	(0.0)	1	(1.2)
Vascular disorders	**0**	**(0.0)**	**1**	**(1.2)**
Artery dissection	0	(0.0)	1	(1.2)

Every participant is counted a single time for each applicable row and column.

Medical Dictionary for Regulatory Activities (MedDRA) version 27.1 was used in the reporting of this study.

This table includes on-treatment adverse events that occurred from Day 1 through the last dose date + 56 days.

Database cutoff date: 06JUN2025

Post marketing experience

The safety profile of sotatercept was summarized in the Periodic Safety Update Report covering the period 26-MAR-2024 through 25-SEP-2024.

2.5.1. Discussion on clinical safety

The safety data in this extension of indication submission are based on the final CSR (final DBL 06-Jun-2025) of the randomized double-blind placebo-controlled phase 3 ZENITH study (MK-7962-006), which evaluated the efficacy and safety of sotatercept in adults with PAH (Group 1 PH) with WHO FC III and IV on maximum tolerated background PAH therapy. In agreement with the EMA, the study was stopped early for efficacy and the IA data was submitted to support use of sotatercept in reducing the risk of major mortality and morbidity events in adult patients with PAH.

In early 2025, the Applicant's intent to stop the study early for efficacy as per DMC recommendation and file an application based upon ZENITH IA data was discussed with EMA. In general, the Agencies agreed with the Applicant's plan to stop the study early and were supportive of an application based on IA data to support use of sotatercept in reducing the risk of major mortality and morbidity events in adult patients with PAH. The Applicant chose not to pool the data of ZENITH with the data of the randomized double-blind placebo-controlled phase 3 study STELLAR, since the ZENITH study represents a population at high risk. The approach to not pool the safety data was accepted by the CHMP provided that the results of the study with highest frequency in ADRs are included in section 4.8 of the SmPC.

Patient exposure. In ZENITH, a total of 172 patients with PAH (n=86 each in the sotatercept and placebo group) were treated with at least one dose of study intervention. The median duration of exposure was higher in the sotatercept group compared with the control group (435 vs. 268 days, respectively), which can be explained by the higher number of patients in the placebo group who were classified as completing the study after a time to clinical worsening event (TTCW) as well as the higher

number of subjects in the placebo group who discontinued the study due to death or a (serious) AE. The imbalance in the duration of exposure, which allowed for a longer duration to observe safety events in the sotatercept group compared with the placebo group, should be considered when interpreting the results of the safety analyses. Further, a total of 56 patients was exposed to sotatercept for at least one year. During the initial MAA, a total of 343 patients had at least 52 weeks of exposure to sotatercept (Pool B) at the data cut-off of 08-Nov-2023, which was acceptable in terms of short-term safety (up to 1 year). With regard to long-term safety, the median duration of exposure of 431 patients in the overall sotatercept group was 657 days and the median number of doses received was 30, which was considered acceptable. Moreover, additional long-term safety data will be collected from the ongoing open-label study SOTERIA of which the estimated duration of enrollment for each subject is approximately 4 years. Nevertheless, the cardiovascular safety remains unclear (see also below).

Adverse events. In ZENITH, treatment-emergent adverse events (TEAEs) were frequently reported; however, the percentage of patients with TEAEs was similar between the sotatercept and the placebo group (99% each). The most frequent AEs (≥ 5.0% patients) with a higher incidence (≥ 3.0% difference) in the sotatercept group compared with the placebo group were epistaxis (45.3% vs. 9.3%), telangiectasia (25.6% vs. 3.5%), diarrhoea (25.6% vs. 17.4%), thrombocytopenia (14.0% vs. 9.3%), back pain (14.0% vs. 4.7%), vomiting (14.0% vs. 8.1%), arthralgia (12.8% vs. 8.1%), gingival bleeding (10.5% vs. 2.3%), pneunomia (12.8% vs. 5.8%), palpitations (11.6% vs. 5.8), hemoglobin increased (10.5% vs. 1.2%), atrial fibrillation (9.3% vs. 2.3%), urinary tract infection (8.1% vs. 2.3%), abdominal pain (8.1% vs. 3.5%), influenza like illness (9.3% vs. 2.3%), pruritis (8.1% vs. 2.3%), erythema (7.0% vs. 0%), vertigo (5.8% vs. 2.3%), gastroesophageal reflex (5.8% vs. 1.2%), hypocalcaemia (5.8% vs. 0%), hypomagnesaemia (5.8% vs. 1.2%), and rash (5.8% vs. 1.2%).

Additionally, less frequent TEAEs with a higher incidence (≥ 3.0% difference) in the sotatercept group compared with the placebo group were polycythaemia (4.7% vs. 0%), haematochezia (4.7% vs. 0%), cellulitis (4.7% vs. 1.2%), bronchitis (4.7% vs. 1.2%), sepsis (4.7% vs. 1.2%), paraethesia (4.7% vs. 0%), chronic kidney disease (4.7% vs. 1.2%), gout (3.5% vs. 0%) and feeling cold (3.5% vs. 0%).

The incidence of TEAEs considered related to study drug was higher in the sotatercept group (67.4%) compared with the placebo group (33.7%). The most frequent drug-related AEs (≥ 5.0% patients) with a higher incidence in sotatercept compared with placebo (≥3.0% difference) were epistaxis (30.2% vs. 4.7%), telangiectasia (22.1% vs. 3.5%), haemoglobin increased (10.5% vs. 0%), gingival bleeding (8.1% vs 1.2%), thrombocytopenia (8.1% vs 4.7%). Additionally, less frequent TEAEs considered related to study drug with a higher incidence (≥ 3.0% difference) in the sotatercept group compared with the placebo group were polycythaemia (4.7% vs. 0%), vertigo (3.5% vs. 0), vomiting (3.5% vs. 0), fatigue (4.7% vs 1.2%), rash (4.7% vs. 0%). These common and less common TEAEs considered related to study drug are all known ADRs, which are currently already included in section 4.8 of the SmPC, with the exception of vomiting and fatigue for which there is insufficient evidence to demonstrate a causal relationship.

The approach for determining new ADRs for inclusion in the labelling was similar to the one used in the original MAA. More specifically, candidate ADRs were identified from ZENITH as PTs, regardless of relationship, with a rate of occurrence in the sotatercept group greater than 5% and at least 5 percentage points greater than placebo, where the lower bound of the 95% CI around the point estimates excluded 0. Further, due to the differences in median duration of exposure to study intervention between sotatercept (434.5 days) and placebo (267.5) groups, also exposure-adjusted rates (EAER and EAIR) were considered. Additionally, concordance of findings with prior placebo-controlled PAH studies was also taken into consideration based on results from STELLAR and PULSAR. In this respect, the imbalances in frequencies in TEAEs (≥ 3.0% more in the sotatercept group and

regardless of considered related to study drug yes/no), including the TEAEs of vomiting, pneumonia, back pain, palpitations, atrial fibrillation, urinary tract infection, abdominal pain, influenza like illness, gastroesophageal reflux disease, haematochezia, hypocalcaemia, hypomagnesaemia, bronchitis, sepsis, gout, paraesthesia, chronic kidney disease, feeling cold were evaluated by the applicant. Based on ADR analysis, urinary tract infection and back pain are included in the labelling as ADRs. For the other AEs for which an imbalance is observed there is insufficient evidence to include these as ADRs in the labelling.

Based on the results of ZENITH, there are no signs of increased risk for the AE of intrapulmonary shunt. However, there is currently a Type II variation application for sotatercept ongoing to evaluate whether section 4.8 of the SmPC needs to be updated to include "intrapulmonary shunt" based on results from the OLE SOTERIA, post-marketing data, and scientific literature (EMA/VR/0000272214).

AEs of (special) interest. The percentage of subjects with adverse events of special interest (AESI) and adverse event of interest (AEOIs) was higher in the sotatercept group (88.4%) compared with the placebo group (73.3%). The incidence of the AESI telangiectasia was higher in the sotatercept group than in the placebo group (25.6% vs. 3.5%). The frequency was somewhat higher as observed in the pivotal trial STELLAR submitted during the initial MAA (16.6% vs. 4.4%), which can be explained by the more advanced disease state of the population studied in ZENITH. Nevertheless, no event was considered a serious adverse event (SAE) and none led to discontinuation of study drug, which is reassuring

The incidence of the AEOI increased haemoglobin was higher in the sotatercept group than in the placebo group (15.1% vs 1.2%), of which no event was considered to be serious and none led to discontinuation of study drug. Of the 13 subjects with the AEOI increased haemoglobin in the sotatercept group, none had an AEOI thromboembolic event, which is reassuring. The mean increase from baseline at Week 24 was 1.48 g/dL in the sotatercept group compared with no notable changes in the placebo group. Similarly, hematocrit increased by 4.4% and erythrocytes by 0.43*1012/L.

The incidence of the AEOI of bleeding events was higher in the sotatercept group than in the placebo group (65.1% vs 36.0%, respectively), which was mainly driven by higher percentages of subjects with epistaxis (45.3% vs. 9.3%) and gingival bleeding (10.5% vs. 2.3%) in the sotatercept group compared with the placebo group. The incidences in bleeding events were higher than observed in the STELLAR study (35.0% vs. 15.6%), which can be explained by the more advanced disease state of the population studied in ZENITH. Nevertheless, none of the subjects discontinued the study drug, which is reassuring. In the sotatercept group, 6 serious AEOI bleeding events of cerebral haemorrhagic, epistaxis, gastritis haemorrhagic, haematemesis, and subdural haematoma were reported of which epistaxis, gastritis haemorrhagic and haematemesis were considered related to study drug by the investigator. To reflect this, the warning "In clinical studies, serious bleeding events (including gastrointestinal, intracranial haemorrhage) have been observed in 4.3% of patients during treatment with sotatercept (see section 4.8)" has previously already been included in section 4.4 of the SmPC.

The AEOI of thrombocytopenia was more commonly reported in the sotatercept group compared with the placebo group (15.1% vs. 10.5%). In the sotatercept group, 1 subject had 2 events of thrombocytopenia that were serious and another subject had a nonserious event that was severe. One of the SAEs and the severe AE led to the interruption of study intervention, but no subject discontinued study drug due to thrombocytopenia. Furthermore, similar as observed during the initial MAA, all subjects with the AEOI thrombocytopenia were receiving prostacyclin infusion therapy at baseline. The underlying mechanism and risk factors for thrombocytopenia are still not fully known. None of the 13 subjects with the AEOI thrombocytopenia had a serious bleeding event, which is reassuring. Mean decreases from baseline in platelet counts were observed at week 24 both treatment groups, however, these decreased were higher in the sotatercept group compared with the placebo group (-15.19 ×

10^9/L and -8.94 × 10^9/L, respectively). A shift to a more severe CTCAE category (worst postbaseline grade) for a decrease from baseline in platelet counts occurred more commonly in subjects in the sotatercept group compared with the placebo group. Four (4.8%) subjects in the sotatercept group had shifts to platelet counts <50 × 10^9/L (CTCAE Grade 3) compared with 2 (2.4%) in the placebo group. One (1.2%) subject in the sotatercept group had a shift to platelet counts <25 × 10^9/L (CTCAE Grade 4) compared with none in the placebo group.

The AESI of telangiectasia and AEOI increased hemoglobin and thrombocytopenia were manageable, as the majority of events resolved after dose modification (dose delay or dose reduction). Nevertheless, data of dose delay showed that not all cases resolved (telangiectasia n=1/6, increased hemoglobin 2/22, thrombocytopenia 3/8). In the study protocol is stated that in case an event does not resolve, study drug discontinuation should be considered, but none of the events led to discontinuation of sotatercept. Nevertheless, since the SmPC contains clear dose recommendations in case of Hgb increases or thrombocytopenia, this issue is not further pursued.

The incidence of the AEOI of immunogenicity was higher in the sotatercept group than in the placebo group (20.9% vs. 9.3% respectively), which was mainly driven by higher percentages of subjects with rash in the sotatercept group compared with the placebo group (5.8% vs. 1.2%).

In ZENITH, no differences were observed in the incidence of the AEOIs of increased blood pressure (2.4% vs. 1.2%), whereas this was somewhat higher in the sotatercept group compared with placebo in the pivotal study STELLAR submitted during the initial MAA (4.3% vs. 0.6%). However, small increases in blood pressure were observed in the sotatercept (3.10 mmHg in SBP and 5.06 mmHg in DBP at Week 24) compared with minimal changes in the placebo group. Nevertheless, as already previously concluded, it is reasonable to assume that the beneficial effects outweigh the potential harm of higher blood pressure, given the severity of the disease. Moreover, since "increased blood pressure" is already stated as an ADR in section 4.8 and all events in the clinical program were nonserious, a warning in section 4.4 is not deemed necessary.

No differences were observed in the frequencies of the AEOIs of cardiac events (16.3% vs. 36.0% for the sotatercept and placebo group, respectively), hepatic toxicity (8.1% vs. 5.8%), renal toxicity (11.6% vs 15.1%), and thrombo-embolic events (4.7% vs. 3.5%).

Overall, the AESI of telangiectasia and the AEOIs of increased haemoglobin, bleeding events in terms of epistaxis and gingival bleeding, increased blood pressure, thrombocytopenia, and immunogenicity in terms of rash were associated with the use of sotatercept and were previously identified as ADRs and consequently already included in section 4.8 of the SmPC. The incidences of these AESIs/AEOIs observed in the ZENITH study were higher than those observed in the STELLAR study, which can be explained by the more advanced disease state of the population studied.

MACE events. As already indicated during the initial MAA, it is unknown whether the combined risk of increased haemoglobin, decreased platelet counts, bleeding events, and hypertension adversely affects long-term cardiovascular safety. Previously, MACE and MACE+ analyses were requested from the STELLAR, PULSAR and SPECTRA studies to exclude such long-term adverse events on cardiovascular safety, as the dossier did not fulfil the requirements of the "reflection paper on assessment of cardiovascular safety profile of medicinal products". The provided MACE(+) analyses MACE and additional data on exposure adjusted rates of events in the Cardiac disorders SOC from these studies did not indicate that there is an increased risk for MACE over time, however, the number of events were too low to draw firm conclusions. Therefore, the Applicant has made a commitment during the initial MAA to perform a meta-analysis on cardiovascular safety once data from the other clinical trials are available. In the current application, MACE(+) analyses based on data of the ZENITH study have

not been provided. Considering that the incidence in deaths is lower in the sotatercept group compared with the placebo group (10.5% vs. 15.1%) and the results on MACE are anticipated to be limited, this issue is not pursued, but the results on the meta-analyses on cardiovascular safety are awaited.

Serious AEs. SAEs were frequently reported, however, the percentage of subjects with SAEs (60.5% vs. 74.4%) and SAEs leading to discontinuation of study drug (1.2% vs. 4.7%) were lower in the sotatercept group compared with the placebo group, which is reassuring. The most frequent SAEs (≥ 4 patients) with a higher incidence (≥ 3.0% difference) in the sotatercept group compared with the placebo group were pneumonia (9.3% vs. 4.7%), atrial fibrillation (5.8% vs. 0%), for which there is insufficient evidence to demonstrate a causal relationship (see above). For the other SAEs, no notable pattern was observed in the sotatercept group compared with the placebo group. SAEs considered related to study intervention by the investigator were reported for 3 subjects in the sotatercept group (colitis ulcerative, epistaxis, and hematemesis). The events of epistaxis and hematemesis have been discussed above.

Deaths. The incidence in death was lower in the sotatercept group compared with the placebo group (10.5% vs. 15.1%). In the sotatercept group, no individual PT leading to death was reported for >1 subject and none of the AEs leading to death were considered related to study drug by the investigator. Overall, the lower number of deaths on sotatercept is reassuring and reflects the efficacy, most of the deaths in the placebo group were cardiac and PAH related.

Laboratory findings. For discussion on hematology, please see above**.** Further, no notable differences in mean changes from baseline over time in chemistry parameters have been observed.

Immunogenicity. In ZENITH, 36 (42.9%) patients tested positive for sotatercept ADAs, which comprised 1 (1.2%) treatment boosted positive and 35 (40.7%) treatment-emergent positive patients. Of these 36 subjects, 16 (44.4%) were neutralizing antibody negative and 20 (55.6%) were neutralizing antibody positive. This is a higher response compared to the ADA responses in the PULSAR and SPECTRA combined (13 of 125 (10.4%) ADA positive and 0.8% tested positive for neutralizing antibodies), and STELLAR study (42 of 162 (5.9%) ADA positive and 6.8% tested positive for neutralizing antibodies). Nevertheless, there were no clinically meaningful safety findings attributable to ADA, which is reassuring.

Safety in special populations.

Regarding age, the proportions of subjects with AEs in the sotatercept and placebo groups were generally consistent between age subgroups (<65 and ≥65 years of age).

Further, patients with hepatic impairment were not eligible for enrollment per the ZENITH eligibility criteria.

Regarding patients with renal impairment, the results did not show any meaningful differences in safety profile between sotatercept-treated participants with renal impairment (baseline eGFR <60 ml/min/1.73m^2; n=37) and sotatercept-treated participants with normal renal function or mild renal impairment (baseline eGFR ≥60 ml/min/1.73m^2; n=48).

Safety related to drug-drug interactions and other interactions.

In ZENITH, in the sotatercept group, epistaxis (49.2% vs. 33.3%) and gingival bleeding (12.3% vs. 4.8%), and thrombocytopenia (18.5% vs. 4.8%) were more commonly reported in subjects on triple PAH background therapy than on double therapy. When evaluating the TEAEs by prostacyclin infusion therapy, only an imbalance in thrombocytopenia for prostacyclin infusion therapy (22.6% vs 16.3% for sotatercept and placebo, respectively) compared with non-prostacyclin infusion therapy (0% in each treatment group) was observed, suggestive of a pharmacodynamic interaction of prostacyclin infusion

therapy and sotatercept. Currently a warning on the increased risk for thrombocytopenia and bleeding events in patients also receiving prostacyclin infusion therapy is already present in section 4.4 of the SmPC.

Discontinuations due to AEs. One subject discontinued study intervention due to an AE in the sotatercept group compared with 4 in the placebo group. Additionally, the percentage of subjects which discontinued the study due to AEs were lower in the sotatercept group compared with the placebo group (8.1% vs 15.1%), which is reassuring. This imbalance was primarily due to fatal AEs that occurred more commonly in the placebo group.

2.5.2. Conclusions on clinical safety

Sotatercept was generally well-tolerated and had a manageable safety profile in participants with PAH (WHO Group 1, FC III or IV). Treatment with sotatercept was associated with increased haemoglobin and thrombocytopenia, both of which were manageable by dose modification. Similar as observed during the initial MAA, the incidences of telangiectasia and bleeding events (mostly epistaxis and gingival bleeding), were higher in subjects treated with sotatercept than in those treated with placebo. The incidences of these AESIs/AEOIs observed in the ZENITH study were higher than those observed in the STELLAR study, which can be explained by the more advanced disease state of the population studied. Further, fewer deaths occurred in subjects treated with sotatercept than in those treated with placebo in ZENITH.

Overall, the safety results of ZENITH were consistent with the findings in STELLAR.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version. Part I of the RMP has been updated to reflect the new indication and the results of the ZENITH trial are added to Part II. There was no change of the Safety concerns, Pharmacovigilance plan and Risk Minimisation Measures. The PRAC considered that the risk management plan version 2.0 is acceptable.

Safety concerns

Table 42: 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

Pharmacovigilance plan

Table 43: Table of 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

Risk minimisation measures

Table 44: 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.

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
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: • WINREVAIR (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.

The CHMP considers that the risk management plan version 2.0 is acceptable

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC have been updated. Annex II is updated and the Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Pulmonary Arterial Hypertension (PAH) is a chronic and progressive disease of the small pulmonary arteries that is characterised by vascular proliferation and remodeling. It results in increased pulmonary artery pressure and pulmonary vascular resistance and, ultimately, right ventricular heart failure and death. Although the pathogenesis of PAH is not completely understood, it likely involves an imbalance in the normal relationships between vasodilators and vasoconstrictors, growth inhibitors and mitogenic factors, and antithrombotic and prothrombotic determinants that are probably consequences of pulmonary endothelial cell dysfunction and/or injury.

Sotatercept is an activin signalling inhibitor with high selectivity for Activin-A, a dimeric glycoprotein which belongs to the TGF-β superfamily of ligands. Activin A binds to ActRIIA regulating key signalling for inflammation, cell proliferation, apoptosis, and tissue homeostasis. The proposed indication of sotatercept is:

*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 ~~to,~~ III, **and IV** ~~to improve exercise capacity~~ (see section 5.1)*

3.1.2. Available therapies and unmet medical need

In the European Union (EU), multiple drugs have gained approval for PAH treatment. These drugs predominantly focus on pathways that either directly or indirectly enhance blood flow through the pulmonary vasculature, primarily acting as vasodilators. The main pathways targeted by these drugs are endothelin-1 pathway, nitric oxide pathway modulators (which operate via cGMP signalling), and prostacyclins and prostacyclin receptor agonists (which function through cAMP signalling). The intent behind these drugs, whether administered as monotherapy or in combination, is to ameliorate vascular tone by addressing the underlying dysregulated processes that lead to pulmonary vasoconstriction.

Endothelin-1 pathway. Endothelin-1 (ET-1), a hormone with vasoactive properties produced by endothelial cells, functions as a vasoconstrictor. In the context of PAH, dysregulated ET-1 production contributes to heightened pulmonary vascular resistance. ET-1 engages cell surface receptors known as Endothelin-A (ETA) and Endothelin-B (ETB), expressed on vascular smooth muscle cells (VSMCs) and endothelial cells respectively. Blocking these endothelin receptors has demonstrated the ability to counteract the vasoconstrictive effects of ET-1. Several approved drugs, including bosentan, ambrisentan, and macitentan, fall into the category of endothelin receptor antagonists (ERAs) and function by inhibiting one or both of these receptors. Clinical studies have attested to their capacity to decrease pulmonary vascular resistance and enhance exercise capacity. However, the use of ERAs require monitoring of the liver function.

Nitric oxide pathway modulators. Phosphodiesterase type-5 inhibitors (PDE5i) represent a class of compounds extensively used in PAH treatment. Proper functioning of vascular smooth muscle cells (VSMCs) to maintain vascular tone relies on adequate levels of cyclic guanosine monophosphate (cGMP) and nitric oxide (NO). PDE5, highly expressed in the VSMCs of pulmonary vasculature and upregulated in PAH, contributes to cGMP breakdown, resulting in vasoconstriction. PDE5 inhibitors, such as sildenafil and tadalafil, intervene by preventing the degradation of cGMP, thereby maintaining its levels and promoting vasodilation.

Riociguat, distinct from PDE5 inhibitors, operates as a stimulator of soluble guanylate cyclase. This enzyme is responsible for converting guanosine triphosphate (GTP) into cGMP. Clinical trials involving riociguat and PDE5 inhibitors have evidenced improvements in disease symptoms and exercise tolerance.

Prostacyclins and prostacyclin receptor agonists. Prostacyclins, potent vasodilatory hormones primarily released by endothelial cells, have played a pivotal role in the development of targeted PAH therapy. Epoprostenol, the initial therapy of this kind, is typically reserved for class III and IV patients due to its continuous intravenous infusion requirement, necessitating a permanent catheter. While newer-generation prostacyclins, such as treprostinil, offer improved physiochemical properties, they too demand continuous infusion, meticulous dose titration, and safety monitoring. Notably, inhaled and oral prostacyclins have mitigated some challenges associated with continuous infusion. Selexipag, an oral prostacyclin receptor agonist, has emerged as a recent option, exhibiting the ability to slow PAH disease progression when added to existing treatments. However, for adult PAH patients with WHO FC IV, only epoprostenol has a registered indication in the EU.

Recent PAH treatment guidelines recommend that most PAH patients be managed with a risk-adapted treatment strategy, including use of combination drug therapy. Despite the availability of several approved therapies, 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. Thus, there is a clear, high unmet medical need for novel therapies that specifically target the underlying cause of PAH by restoring vascular wall homeostasis.

3.1.3. Main clinical studies

The demonstration of efficacy and safety for the current type II variation was based on the interim analyses results from the phase 3 trial ZENITH. This event-driven, randomized, double-blind, placebo-controlled, multicenter trial evaluated the efficacy and safety of sotatercept when added to maximum tolerated background PAH therapy in participants with PAH at high risk of mortality. Key inclusion criteria were male and female participants 18 to 75 years with documented WHO PAH group 1 with WHO FC III or IV, with a REVEAL Lite 2 risk score ≥9 and clinically stable on maximum tolerated double or triple background therapy for at least 30 days. Eligible patients were randomized 1:1 to either the placebo arm or the sotatercept arm, both of which received treatment subcutaneously every 21 days, on top of background PAH therapy. The randomization schedule was stratified by REVEAL Lite 2.0 risk score (9 to 10 or ≥ 11) and PAH subtype (CTD-associated or not CTD-associated) at screening, and both patients and study investigators were blinded throughout the study.

Patients in the sotatercept arm started at a dose of 0.3 mg/kg and were up titrated to a target dose of 0.7 mg/kg at the second visit. Up titration did not take place if patients experienced hemoglobin increase >2 g/dL with values above upper limit of normal. At further visits, dose delays were implemented if platelets were <50.000/mm^3 or hemoglobin increased (> 2.0 g/dL AND Hgb above gender specific ULN). The primary efficacy endpoint was the time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours. Secondary endpoints included overall survival, transplant-free survival, change in REVEAL score, change in NT-proBNP, mPAP, PVR, 6-MWD and cardiac output.

3.2. Favourable effects

Primary endpoint

Fewer participants in the sotatercept group (15 [17.4%]) than in the placebo group (47 [54.7%]) reached the primary endpoint of a first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours. The risk of a first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours was 76% lower in the sotatercept group compared with the placebo group (HR: 0.24; 95% CI: 0.13, 0.43; p<0.0001). The results of the primary endpoint were similar in sensitivity analyses excluding post-study deaths as well as sensitivity analysis using jump to reference imputation. The results of the primary endpoint were consistent in all prespecified subgroup analyses, including the WHO FC III (HR: 0.23 (95% CI: 0.11; 0.45) and WHO FC IV (HR: 0.28 (95% CI: 0.09; 0.87) subgroups.

3.3. Uncertainties and limitations about favourable effects

Mechanism of action

The mechanism of action of sotatercept remains not fully elucidated. Biological processes of activin-A other than vascular remodelling may contribute to the beneficial effect of sotatercept in patients with PAH, including effects on cardiac structure and function, skeletal muscle wasting, and vascular wall calcification.

Primary endpoint

The effect on the primary endpoint was mostly driven by PAH related hospitalization ≥24 hours, which occurred in half of the placebo patients as the first event (9.3% vs. 50.0% for sotatercept and placebo, respectively). And at first glance, the higher number of all-cause mortality events in the sotatercept group may suggest worse overall survival (7.0% vs. 3.5% for sotatercept and placebo, respectively). However, when considering the total number of mono-component events, it becomes clear that this difference reflects patients experiencing hospitalization prior to death, rather than excess mortality per se. In fact, when looking at the total number of mono-components, the number of events was lower for each individual component in the sotatercept group as compared to the placebo group (8.1% vs 15.1%).

Secondary endpoints

For the first tested secondary endpoint of overall survival, the hazard ratio favored the sotatercept group over the placebo group (HR: 0.42; 95% CI: 0.17, 1.07; p=0.0313). However, only 20 events were observed (7 events in the sotatercept group and 13 events in the placebo group), and the boundary for statistical significance was not crossed (prespecified 1-sided alpha of 0.0021). The descriptive data on the secondary endpoints demonstrated beneficial trends of sotatercept on transplant free survival, proportion of participants who experienced a mortality event at end of study, change from baseline in REVEAL Lite 2 risk score, proportion who achieved a low or intermediate REVEAL Lite 2 risk score, change from baseline in NT-proBNP, mean pulmonary arterial pressure, pulmonary vascular resistance and 6-minute walking distance. However, these secondary endpoints were not eligible to hierarchical testing. As a result, their findings should be considered exploratory and interpreted with caution.

3.4. Unfavourable effects

Deaths. The incidence in death was lower in the sotatercept group compared with the placebo group (10.5% vs. 15.1%). No individual PT leading to death was reported for >1 subject and none of the AEs leading to death were considered related to study drug by the investigator. Overall, the lower number of deaths on sotatercept reflects the efficacy, most of the deaths in the placebo group were cardiac and PAH related.

Serious AEs. SAEs were frequently reported, however, the percentage of subjects with SAEs (60.5% vs. 74.4%) and SAEs leading to discontinuation of study drug (1.2% vs. 4.7%) were lower in the sotatercept group compared with the placebo group.

AESI/AEOI. The AESI of telangiectasia and the AEOIs of increased haemoglobin, bleeding events in terms of epistaxis and gingival bleeding, increased blood pressure, thrombocytopenia, and immunogenicity in terms of rash were associated with the use of sotatercept and were previously identified as ADRs and consequently already included in section 4.8 of the SmPC

Bleeding events. The incidence of the AEOI of bleeding events was higher in the sotatercept group than in the placebo group (65.1% vs 36.0%, respectively), which was mainly driven by higher percentages of subjects with epistaxis (45.3% vs. 9.3%) and gingival bleeding (10.5% vs. 2.3%) in the sotatercept group compared with the placebo group. In the sotatercept group, 6 serious AEOI bleeding events and none discontinued treatment due to bleeding events.

Thrombocytopenia. The AEOI of thrombocytopenia was more commonly reported in the sotatercept group compared with the placebo group (15.1% vs. 10.5%). In the sotatercept group, 1 subject had 2 events of thrombocytopenia that were serious and another subject had a nonserious event that was severe. One of the SAEs and the severe AE led to the interruption of study intervention, but no subject discontinued study drug due to thrombocytopenia. Similar as observed during the initial MAA, all subjects with the AEOI thrombocytopenia were receiving prostacyclin infusion therapy at baseline. None of the 13 subjects with the AEOI thrombocytopenia had a serious bleeding event

Telangiectasia. The incidence of the AESI telangiectasia was high in the sotatercept group than in the placebo group (25.6% vs. 3.5%), of which no event was considered a serious adverse event (SAE) and none led to discontinuation of study drug

Increased haemoglobin. The incidence of the AEOI increased haemoglobin was higher in the sotatercept group than in the placebo group (15.1% vs 1.2%), of which no event was considered to be serious and none led to discontinuation of study drug. Of the 13 subjects with the AEOI increased haemoglobin in the sotatercept group, none had an AEOI thromboembolic event. The mean increase from baseline at Week 24 was 1.48 g/dL in the sotatercept group compared with no notable changes in the placebo group. Similarly, hematocrit increased by 4.4% and erythrocytes by $0.43*10^{12}$/L.

3.5. Uncertainties and limitations about unfavourable effects

Cardiovascular safety In the initial application the MACE (+) analyses did not indicate that there is an increased risk for MACE over time, however, the number of events were too low to draw firm conclusions. In the current application, MACE(+) analyses based on data of the ZENITH study have not been provided. But considering that the incidence in deaths is lower in the sotatercept group compared with the placebo group (10.5% vs. 15.1%) and the results on MACE are anticipated to be limited, this is reassuring.

Serious bleeding events. The underlying mechanism and risk factors for serious bleeding events are not fully known. Most patients with a serious bleeding events were on both anticoagulants and prostacyclin analogs.

Thrombocytopenia. The underlying mechanism and risk factors for thrombocytopenia are not fully known. Thrombocytopenia occurred more often in patients on simultaneous prostacyclin analogue infusion therapy.

3.6. Effects Table

Table 45: Effects Table for Sotatercept based on ZENITH trial

Effect	Short description	Unit	Treatment Sotatercept (n=86)	Control (n=86)	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint	First event of TTCW - all-cause death - lung transplantation - PAH worsening-related hospitalization of ≥24 hours	N (%)	15 (17.4%) 6 (7.0%) 1 (1.2%) 8 (9.3%)	47 (54.7%) 3 (3.5%) 1 (1.2%) 43 (50%)	Hazard ratio: 0.24 (95% CI: 0.13; 0.43); P<0.0001 **SoE:** Consistent results in all subgroup analyses (including WHO FC IV, use of prostacyclin infusion and triple background therapy). Effect size comparable to TTCW endpoint in STELLAR	ZENITH
Unfavourable Effects						
AEOI	Bleeding events (mostly epistaxis and gingival bleeding)	[n (%)]	56 (65.1%)	31 (36.0%)	**SoE**: Consistent but higher incidences compared with STELLAR (35% vs. 15.6%)	ZENITH
AEOI	Thrombocytopenia	[n (%)]	13 (15.1%)	9 (10.5%)	**SoE:** Consistent but somewhat higher incidences compared with STELLAR (10.0% vs. 3.1%)	
AESI	Telangiectasia (dilated blood vessels under skin)	[n (%)]	22 (25.6%)	3 (3.5%)	**SoE:** Consistent but somewhat higher incidences compared with STELLAR (16.6% vs. 4.4%)	
AEOI	Increased haemoglobin	[n (%)]	13 (15.1%)	1 (1.2%)	**SoE:** Consistent but somewhat higher incidences compared with STELLAR (8.6% vs. 0.6%)	

Abbreviations: AEOI: adverse event of interest; AESI: adverse event of special interest; WHO: world health organization; FC: functional class; TTCW; time to clinical worsening

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

PAH is a chronic, progressive disease of the small pulmonary arteries that is characterised by vascular proliferation and remodeling. It results in increased pulmonary artery pressure and pulmonary vascular resistance and, ultimately, right ventricular heart failure and death. Despite the combined use of

several available therapies, a substantial number of patients with PAH remain at high risk of mortality. Patients categorized as high risk based on the 2015 7-variable ESC/ERS guidelines have a particularly poor prognosis, with a 5-year survival of only 32.4%. Thus, there is a clear, high unmet medical need for novel therapies with a mechanism of action other than pulmonary vasodilation for patients with PAH WHO FC IV to delay time to major morbidity-mortality events and improve survival in patients with PAH.

Efficacy results from the ZENITH trial conducted in patients with PAH WHO FC III and IV demonstrate a 76% reduction in the risk of the first event of mortality, lung transplantation or PAH hospitalization ≥24 hours, which is considered a robust, clinically meaningful and acceptable. The effect on the primary endpoint was primarily driven by PAH related hospitalization ≥24 hours, which occurred in half of the placebo patients as the first event (9.3% vs. 50.0% for sotatercept and placebo, respectively). And at first glance, the slightly higher number of all-cause mortality events in the sotatercept group may suggest worse overall survival (7.0% vs. 3.5% for sotatercept and placebo, respectively). However, when looking at the total number of mono-components, the number of events was lower for each component in the sotatercept group as compared to the placebo group (8.1% vs 15.1%). The robustness is supported by the subgroup analyses where the effect was consistent across all prespecified subgroups. Most notably, subgroup analyses in subgroup FC IV demonstrated a similar effect as in FC III, supporting the extension of the indication proposed by the Applicant.

Nonetheless, the used primary endpoint in ZENITH differs from both the STELLAR and EMA guidance definition of Time to Clinical Worsening (TTCW). The third component of the EMA recommended TTCW endpoint (i.e. *time to PAH-related deterioration identified by at least one of the following parameters: i. increase in WHO FC; ii. deterioration in exercise testing; iii. signs or symptoms of right-sided heart failure*) would however not be applicable to a high-risk PAH WHO FC III and IV population, given the impossibility to increase from WHO FC IV and inability of many patients in WHO FC IV to perform exercise testing. Furthermore, while STELLAR used listing for lung and/or heart transplant as a component of TTCW, ZENITH selected lung transplantation due to its relative independence from differences in local practice. The differences between the used endpoint in ZENITH and the endpoints in the EMA guidance and STELLAR are sufficiently justified and endorsed. Despite the differences in the definition of the endpoints (as discussed above), both these results from ZENITH and STELLAR reflect the time to clinical worsening and in both studies sotatercept demonstrated significant, substantial and comparable effect. Taken together, these results support an overall treatment indication, rather than an indication limited to improving exercise capacity, for adult PAH patients from WHO FC II, III, and IV.

Sotatercept was generally well-tolerated and had a manageable safety profile in participants with PAH (WHO Group 1, FC III or IV). Treatment with sotatercept was associated with increased haemoglobin and thrombocytopenia, both of which were manageable by dose modification. Similar as observed during the initial MAA, the incidences of telangiectasia, bleeding events (mostly epistaxis and gingival bleeding), and increased blood pressure were higher in subjects treated with sotatercept than in those treated with placebo. The incidences of these AESIs/AEOIs observed in the ZENITH study were higher than those observed in the STELLAR study, which can be explained by the more advanced disease state of the population studied.

As already indicated during the initial MAA, it is unknown whether the combined risk of increased haemoglobin, decreased platelet counts, bleeding events, and hypertension adversely affects long-term cardiovascular safety. The MACE(+) analyses and rates of events in the Cardiac disorders SOC submitted during the initial MAA did not indicate that there is an increased risk for MACE over time, however, the number of events were too low to draw firm conclusions. Therefore, the Applicant has made a commitment during the initial MAA to perform a meta-analysis on cardiovascular safety once

data from the other clinical trials are available. In the current application, MACE(+) analyses based on data of the ZENITH study have not been provided. Considering that the incidence in deaths is lower in the sotatercept group compared with the placebo group (10.5% vs. 15.1%) and the results on MACE are anticipated to be limited, this issue is not pursued, but the results on the meta-analyses on cardiovascular safety are awaited as a Recommendation.

Overall, the safety results of ZENITH were consistent with the findings in STELLAR.

3.7.2. Balance of benefits and risks

The benefits of sotatercept in terms of preventing events of mortality, lung transplantation and PAH related hospitalization compared to placebo are accompanied by manageable and well known risks. Notwithstanding these results, the benefit/risk balance is positive.

Currently available safety data does not yet fulfil the requirements of the "*reflection paper on assessment of cardiovascular safety profile of medicinal products*". Nevertheless, the Applicant has previously already made the commitment to conduct a meta-analysis post-marketing in line with the EMA reflection paper on cardiovascular safety in order to further address this issue.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of sotatercept in the proposed indication is considered positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I, II, IIIB

Extension of indication to include in combination with other pulmonary arterial hypertension (PAH) therapies treatment of adult patients with PAH World Health Organisation Functional Class IV for WINREVAIR, based on interim results from study ZENITH (also referred as MK-7962-006 and A011-14); this is a phase 3, randomized, double-blind, placebo-controlled study to evaluate sotatercept when added to maximum tolerated background therapy in participants with pulmonary arterial hypertension (PAH) World Health Organization (WHO) Functional Class (FC) III or FC IV at high risk of mortality; As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH removed the first PSUR commitment following 6 months post authorisation as it has already been fulfilled. As part of the application, the MAH is requesting a 1-year extension of the market protection.

Amendments to the marketing authorisation

In view of the data submitted with the variation amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

The following obligation has been fulfilled, and therefore it is recommended that is be deleted from the Annex II:

The MAH removed the first PSUR commitment following 6 months post authorisation as it has already been fulfilled

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

• At the request of the European Medicines Agency;

• Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix).