27 June 2024
EMA/330301/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Winrevair

International non-proprietary name: sotatercept

Procedure No. EMEA/H/C/005647/0000

Note

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

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List of abbreviations

6MWD	6-minute walk distance
ACE-011	sotatercept
ActRIIA	activin receptor type IIA
ADA	antidrug antibody
AE	adverse event
AEOI	adverse event of interest
AESI	adverse event of special interest
AS	active substance
AUC	area under the curve
BLA	biologics license application
BMP	bone morphogenetic protein
BMI	body mass index
BMPR2	bone morphogenetic protein receptor type II
CAPA	corrective and preventive action
Cave	average concentration
CE-SDS	capillary electrophoresis with sodium dodecyl sulfate
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	confidence interval
CL	clearance
CL/F	apparent clearance
Cmax	maximum concentration
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease of 2019
CPP	critical process parameter
CQA	critical quality attribute
CSR	clinical study report
CTD	connective tissue disease
CYP	cytochrome P450
DBPC	Double-Blind Placebo-controlled
DDI	drug-drug interaction
DP	drug product
DS	drug substance
ECD	extracellular domain
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMEA	Europe, Middle East, and Africa
EOP	end of period
EOT	end of treatment
EQ-5D-5L	EuroQoL-5 dimensions index
E-R	exposure-response
ERA	endothelin receptor antagonists
ESKD	end-stage kidney disease
FAS	full analysis set
FC	functional class
FMEA	failure mode effect analysis
FP	finished product
FSH	follicle stimulating hormone
GDF	growth and differentiation factor

GLP	Good laboratory practice
GSPR	general safety and performance requirements
HCP	healthcare provider
HCP	Host cell protein
HDPE	High-density polyethylene
hERG	Human Ether-a-go-go Related Gene
HILIC	hydrophilic interaction liquid chromatography
HR	hazard ratio
HRQoL	health-related quality of life
HMW	High molecular weight
IC50	half maximal inhibitory concentration
ICH	International Council for Harmonisation
iCIEF	imaged capillary isoelectric focusing
iCPET	invasive cardiopulmonary exercise test
IFU	Instructions for use
IgG1	Immunoglobulin G1
iSAP	integrated statistical analysis plan
ISO	International Organization for Standardization
IV	intravenous
ka	absorption rate constant
LMW	low molecular weight
LS	least-squares
LTDB	Long-Term Double-Blind
MCB	master cell bank
MCI	multi-component improvement
MCS	mental component score
MedDRA	Medical Dictionary for Regulatory Activities
MMV	Murine minute virus
mPAP	mean pulmonary arterial pressure
MRI	magnetic resonance imaging
MSD	Merck Sharpe & Dohme
NAb	neutralizing antibody
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PACMP	Post Approval Change Management Protocol
PAH	pulmonary arterial hypertension
PAH SYMPACT®	Pulmonary Arterial Hypertension Symptoms and Impact Questionnaire
PAR	Proven Acceptable Range
PBS	phosphate-buffered saline
PCS	physical component score
PD	pharmacodynamic
PDE5	phosphodiesterase 5
PETG	polyethylene terephthalate glycol
PFS	pre-filled syringe
PH	pulmonary hypertension
PK	pharmacokinetic
PLCSL	slope for placebo effect
PMW	postmenopausal women
popPK	population pharmacokinetics
PPCB	Post-production cell bank
PPQ	Process performance qualification
PPRA	Process parameter risk assessment
PQA	Product quality attribute
PRO	patient reported outcome
PRV	pseudorabies virus

PT	preferred term
PVR	pulmonary vascular resistance
Q3W	every 3 weeks
Q4W	every 4 weeks
QoL	quality of life
qPCR	quantitative polymerase chain reaction
RBC	red blood cell
RET	reticulocyte
RHC	right heart catheterization
RV	right ventricular
RV SV	right ventricular stroke volume
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SDS PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SE	standard error
SEC-HPLC	Size-exclusion chromatography
SF-36	36-item Short Form Health Survey
Smad	Small Mothers Against Decapentaplegic
SmPC	Summary of product characteristics
SMQ	standardized MedDRA query
SOC	standard of care
sWFI	sterile water for injection
t1/2	half-life
TAPSE	tricuspid annular plane systolic excursion
TAR-EAIR	time at risk - exposure adjusted incidence rate
TEAE	treatment-emergent adverse event
TGF	transforming growth factor
Tmax	maximum concentration
TRTPOW	power function of E-R relationship of Cavg and 6MWD
UF/DF	Ultrafiltration/Diafiltration
ULN	upper limit of normal
US FDA	United States Food and Drug Administration
USA	United States of America
UV	ultraviolet
VO2 max	peak O2 uptake
VSMC	vascular smooth muscle cell
WCB	Working cell bank
WHO	World Health Organization
XmulV	Xenotropic murine leukaemia virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme B.V. submitted on 4 October 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Winrevair, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

Winrevair, was designated as an orphan medicinal product EU/3/20/2369 on 9 December 2020 in the following condition: Treatment of pulmonary arterial hypertension.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Winrevair as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Winrevair

The applicant applied for the following indication:

> *"Winrevair is indicated for the treatment of pulmonary arterial hypertension (PAH) in adult patients on standard of care with WHO Functional Class (FC) II to III, to improve exercise capacity, provide clinical improvement, improve WHO FC and delay disease progression, including to reduce the risk of death and hospitalisation for PAH.*
>
> *Efficacy has been shown in a PAH population including aetiologies of idiopathic and heritable PAH, PAH associated with connective tissue disease, drug or toxin-induced PAH, or PAH associated with congenital heart disease with repaired shunts (see section 5.1)."*

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 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).

At the time of submission of the application, the PIP P/0414/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised

orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance Sotatercept contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. PRIME

Winrevair was granted eligibility to PRIME on 30 April 2020 in the following indication: treatment of pulmonary arterial hypertension (PAH).

Eligibility to PRIME was granted at the time in view of the following:

- Despite recent advances in the treatment of pulmonary arterial hypertension, PAH ultimately remains a progressive disorder leading to mortality in severe cases. Therefore, the unmet medical need is agreed for a product that would bring a major therapeutic advantage over existing therapies.
- Sotatercept presents a new mechanism of action targeting the SMAD signalling dysregulation which appears to be involved in normal vasculature function. Activity is observed in rat hypoxia prevention models and compared with existing therapies however no experiment is provided on top of existing therapies.
- The clinical data presented from PULSAR, Phase 2, double blind, randomized, placebo-controlled, parallel-group study of sotatercept plus standard of care (SOC) versus placebo plus SOC showed promising activity in patients with PAH on top of standard of care (triple, double or monotherapy). It is therefore concluded that sotatercept has the potential to address the above-mentioned unmet medical need.

Upon granting of eligibility to PRIME, Johann Lodewijk (Hans) Hillege was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 30 September 2020. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

- CMC development and approach;
- Nonclinical justification for not performing carcinogenicity testing;
- Nonclinical changes in heart weight;
- Clinical development plan, to clarify that 6MWD is considered for initial application but comprehensive clinical data on TTCW will be gathered from longer running studies with an intent to show disease modification;
- Justification of dose selection;
- To incorporate appropriate hazard ratio in analysis of 6MWD to exclude detrimental effect;

separate effect of 6MWD from change in haemoglobin;
- To consider subset of PULSAR patients on maximal background PAH therapy with no other alternatives as an interesting group to show sotatercept addressing unmet medical need for a CMA.

1.7. Scientific advice

The applicant received the following CHMP Scientific Advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
23 July 2020	EMEA/H/SA/4497/1/2020/SME/PR/II	Clemens Mittmann, Peter Mol
25 February 2021	EMA/SA/0000050772	Peter Mol, Fernando de Andres-Trelles
25 March 2021	EMA/SA/0000052162	Peter Mol, Andreas Kirisits

The Scientific Advice pertained to the following quality and clinical aspects:

Quality aspects

- Critical quality attributes;
- Control strategy for the commercial drug substance (DS) and drug product (DP);
- DS PPQ strategy intended to verify process performance and support registration of the sotatercept DS manufacturing process;
- DP PPQ bracketing strategy;
- DS and DP stability programs;
- Non-integral drug device combination kit.

Clinical aspects

- Adequacy of the design of and preliminary efficacy/safety results from the PULSAR study, complemented by data from the SPECTRA study, in support of a conditional marketing authorisation;
- Design of the proposed Phase 3 study A011-11, including the population, study entry criteria and stratification factors, a novel multi-component primary endpoint (improvement in 6MWD, NT-proBNP levels and PVR), secondary endpoints, a starting dose of 0.7 mg/kg with an intrasubject dose modification plan, safety monitoring plan, and whether the overall safety database once data from the Phase 3 study are available would be adequate to support full approval;
- Design of the proposed SOTERIA study (A011-12) for long-term follow-up;
- Adequacy of patient population, primary endpoint, and statistical methods in the HYPERION study (A011-13) to demonstrate disease modification for participants newly diagnosed with symptomatic PAH;
- 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.

1.8. Steps taken for the assessment of the product

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

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Antonio Gomez-Outes

The application was received by the EMA on	4 October 2023
Accelerated Assessment procedure was agreed-upon by CHMP on	20 July 2023
The procedure started on	26 October 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 December 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 January 2024
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 January 2024
CVS Working Party experts were convened to address questions raised by the CHMP on The CHMP considered the views of the CVS Working Party as presented in the minutes of this meeting.	1 February 20224
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 February 2024
The procedure was reverted to a standard assessment timetable on	26 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	02 April 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 April 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 June 2024

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Winrevair on	27 June 2024
The CHMP adopted a report on similarity of Winrevair with Opsumit on (see Appendix on similarity)	27 June 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	27 June 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. 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.

2.1.2. 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.

2.1.3. 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.

2.1.4. 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).

2.2. About the product

Winrevair contains sotatercept, which 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 ActRII

(both ActRIIA and ActRIIB) regulating key signaling for inflammation, cell proliferation, apoptosis, and tissue homeostasis.

Activin-A levels are increased in PAH patients. Activin binding to ActRII promotes 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 (ActRIISmad2/3-mediated) and anti-proliferative (BMPRII/Smad1/5/8 mediated) signaling to modulate vascular proliferation.

The proposed indication is treatment of PAH, in combination with other PAH therapies, in adult patients with WHO Functional Class (FC) II to III, to improve exercise capacity.

It is available as a powder for solution for injection in vials containing 45 mg or 60 mg, and is administered once every 3 weeks as a single subcutaneous injection according to patient weight.

2.3. Type of application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the fact that presented data suggested a statistically compelling and clinically substantial improvement in the primary endpoint of 6MWT following sotatercept treatment compared with placebo on top of optimized, stable background therapy, and which seemed to be accompanied by manageable risks. In this respect, sotatercept therapy, as a novel mechanism of action, could potentially provide a major improvement in the currently available therapies and a valuable addition to the existing treatment armamentarium for PAH.

However, during the procedure the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as among others, two clinical major objections were raised in the CHMP Day 90 LoQ for which extensive responses were requested, and which could not be adequately addressed by the applicant within the timetable for accelerated assessment. As a result the procedure was reverted to a standard assessment timetable.

2.4. Questions to be posed to additional experts

During the procedure, the CHMP agreed to consult the CVS WP about the question whether a multicomponent responder endpoint, defined as the proportion of participants achieving all of the following at week 24 relative to baseline: 1) improvement in 6MWD (increase ≥ 30m); 2) improvement in NT-proBNP (decrease in NT-proBNP ≥ 30%) or maintenance/achievement of NT-proBNP level <300 ng/L; 3) improvement in WHO FC or maintenance of WHO FC II, and the PRO PAH-SYMPACT questioinnaire, could be clinically relevant.

The CVS WP discussed during its meeting on 1 February 2024 the List of Questions from the CHMP.

Multicomponent responder endpoint

The Group expressed that all three components of the endpoint could be considered to be clinically relevant. Therefore, the value of each component of this multicomponent endpoint could be considered

on its own. It could also be agreed that a patient improving in all these three dimensions (conjunction **AND**) is better off than a patient not showing such improvements. This endpoint could be considered an efficacy endpoint opposite of Time To Clinical Worsening. Because it is a responder-endpoint, interpretation should be familiar to HCP.

However, this endpoint is not established in the field and its prognostic and/or regulatory value are not established. Importantly, similar components have not been considered acceptable in the context of a multicomponent endpoint to establish a win-ratio (conjunction (hierarchical) **OR**). Combining functional endpoints and laboratory endpoints was not seen as appropriate for regulatory decision making. The opinion of the majority but not all members was that inclusion of this multicomponent endpoint in section 5.1 of the SmPC might give a wrong message and could be misunderstood as support for using multicomponent endpoints in future developments.

Thus, the endpoint can be considered clinically relevant and informative to both the potential prescriber and the patient, but not suitable for regulatory decision making.

PRO PAH-SYMPACT

Regarding the PRO PAH-SYMPACT questionnaire it was noted during the discussion that it is a PRO instrument developed and validated in accordance with the FDA. It was supported as well by the qualification procedure in the past and Letter of support for the development of the PAH-SYMACT Instrument for use in PAH trials was issued (30 March 2023; EMADOC-1700519818-1054252). The letter states that the overall validation strategy is reasonable, the validation exercise is at an advanced stage and the information provided is promising. Additional analyses are welcomed to assess:

- Prospective validation of meaningful change thresholds (MCT);
- Responsiveness over a range of patients at different stages of severity of the disease;
- Analyses on correlations with disease progression and deterioration;
- The impact of missing data.

Provided additional supportive analyses are presented, PRO endpoints reflective of the symptom and impact domains of the PAH-SYMPACT can be considered for regulatory decisions and included in the EU Product Information for medicinal products for the treatment of PAH.

Currently, no further data have been presented for PAH SYMPACT, nor its domains.

2.5. Quality aspects

2.5.1. Introduction

The finished product is presented as a powder and solvent for solution for injection containing 45 or 60 mg of sotatercept as active substance. Other ingredients are: citric acid monohydrate (E330), sodium citrate (E331), polysorbate 80 (E433) and sucrose.

The product is available in 2 mL capacity, type I glass vial sealed with a bromobutyl rubber stopper with polymer coating and aluminium seal with polypropylene flip-off cap. The flip-off cap of the 45 mg/vial strength presentation is of lime colour; whilst the flip-off cap of the 60 mg/vial strength presentation is of burgundy colour.

Both strengths are available either as a vial only presentation, or as a kit co-packaged with: 1 x 1.5 mL syringe filled with 1.0 mL water for injection (sWFI) as solvent (for the 45 mg/vial strength) or with 1.3 mL sWFI (for the 60 mg/vial strength); 1 x 3.0 mL dosing syringe with 0.1 mL graduations, 1 vial

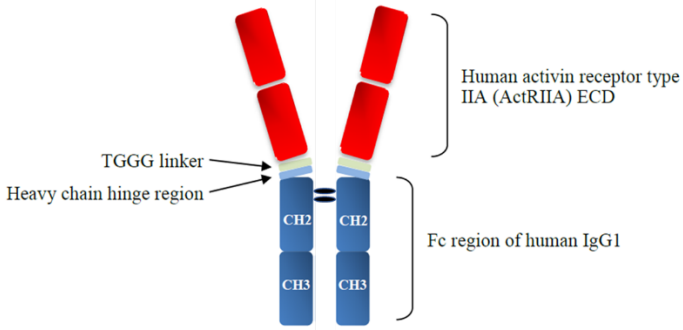
adaptor (13 mm), 1 needle for injection and 4 alcohol wipes. All the presentations come with the option of one or two vials.

2.5.2. Active substance

General information

Sotatercept is a recombinant human homodimeric fusion protein consisting of the extracellular domain (ECD) of human activin receptor type IIA (ActRIIA) linked to Fc domain of human IgG1. Each monomer consists of 344 amino acids. Sotatercept contains a total of 16 disulfide bonds and three N-glycosylation sites. A schematic representation is provided in Figure 1.

Figure 1. Schematic Representation of Sotatercept Structure



Abbreviations: CH2(3)= heavy chain constant region domain 2(3); ECD= extracellular domain; Fc= fragment crystallizable; TGGG= threonine-glycine-glycine-glycine

Sotatercept is an activin signalling inhibitor with high selectivity for Activin-A which binds to the activin receptor type II (ActRII) regulating key signalling for inflammation, cell proliferation, apoptosis, and tissue homeostasis. Sotatercept acts as a ligand trap that scavenges excess activin A and other ligands for ActRII to inhibit activin signalling. As a result, sotatercept rebalances the pro-proliferative (ActRII/Smad2/3- mediated) and anti-proliferative (BMPRII/Smad1/5/8-mediated) signalling to modulate vascular proliferation.

Manufacture, process controls and characterisation

The active substance (AS), also referred to as drug substance (DS), is manufactured at AbbVie Bioresearch Center, Worcester, MA, USA.

Sotatercept finished product (FP), also referred to as drug product (DP), is released from MSD in Haarlem, the Netherlands.

Description of manufacturing process and process controls

Sotartecept AS manufacturing process has been adequately described. Sotatercept is expressed in a CHO cell line using a fed-batch process. The commercial sotatercept manufacturing process follows a standard process for monoclonal antibodies production. In summary, the AS is derived from the sotatercept working cell bank (WCB), processed through a single production bioreactor, purified through the downstream process, and filled. A comprehensive description has been provided for each step of the sotatercept AS manufacturing process. Culture media and composition of buffers used during purifications are described. Proven Acceptable Ranges (PARs) are given for both critical and non-critical process parameter. The performance of the process is adequately checked by in-process

controls. Process description is updated to include adequate details. An appropriate lower PAR limit for inactivation hold pH has been included.

The AS control strategy is a planned set of controls derived from current product and process understanding that assures consistency in process performance and product quality. At the time of process characterisation, the final CQAs were not known. Hence, all product quality attributes (PQAs) were considered in the initial assessment. A product quality attribute assessment was performed to determine the overall risk of PQAs to impact patient safety and efficacy. Based on both risk assessment and technical judgment, selected PQAs were studied in process characterisation.

A process parameter risk assessment (PPRA) was performed to identify process parameters to be included in sotatercept process characterisation studies based on their anticipated risk or impact to relevant output attributes. Following completion of the PPRA, selected parameters were evaluated during the process characterisation studies using a combination of one-factor-at-a-time (univariate) and design of experiment (multivariate) methodologies. Parameters with high normal operating impact ratios on PQAs were categorized as critical process parameters (CPPs), while medium and low impact parameters were categorized as PPs. Proven Acceptable Ranges (PARs) were established for all process parameters based on the level of risk identified during the risk assessment and/or the level of impact demonstrated during process characterisation studies.

The approach of the company to identify parameters to be included in sotatercept process qualification studies (process parameter risk assessment), the outlined design and evaluation of the process characterisation studies and assignment of critical process parameters is supported. For development of the integrated control strategy reference is made to the finished medicinal product section of this report.

The container closure system is sufficiently described and its suitability is sufficiently demonstrated by long-term stability studies and data on extractable/leachables.

Control of materials

Sufficient information on raw materials used in the AS manufacturing process has been submitted; namely on the development genetics, host cell line, generation and isolation of clone, preparation of two Research cell banks and preparations of the master cell bank (MCB). A two-tiered cell banking system is used and sufficient information is provided regarding testing of the MCB, WCB, and two post-production cell banks, which were tested in accordance with ICH guidelines Q5A (viral safety), Q5B (Analysis of the Expression Construct) and Q5D (derivation and characterisation of cell substrates). Tests performed at Cell Banks are described and the choice of the tests meets current guidelines. All testing results met the acceptance criteria and confirmed the absence of adventitious agents and infectious retroviruses. As can be expected for CHO cells, retrovirus-like type A and C particles were observed in the cell banks and one of the post-production cell banks (PPCBs) tested positive for reverse transcriptase activity. These retrovirus-like particles in CHO cells have been studied extensively and are defective for replication. The down-stream manufacturing process of sotatercept has been validated to provide adequate retrovirus clearance (see adventitious agents section).

A satisfactory protocol has been presented for preparation and qualification of future WCBs in order to introduce new WCB without prior approval of the health authorities. Based on a risk assessment and in line with current guidelines and 3Rs principles, *in vivo* testing for adventitious agents was removed from the panel of control tests to be performed on future cell banks.

The quality of raw materials is presented as compendial (USP-NF, Ph.Eur.) with the exception of raw materials used in the upstream manufacturing process. The qualitative composition of cell culture media has been added to the dossier.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the sotartecept AS manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the AS manufacturing process with regard to critical, as well as non-critical operational parameters, in-process tests hold times of intermediates, adventitious agent testing on unprocessed bulk, upstream contamination checks and downstream bioburden and endotoxins tests. The testing regime is adequate to control contamination. Actions taken if limits are exceeded are specified.

Process validation

The process performance qualification (PPQ) of the commercial manufacturing process was performed on three full scale consecutive process validation lots. This number is considered sufficient for this type of product. The PPQ validation lots were manufactured using normal processing parameter set points and conditions. Results of critical and non-critical process parameters, in process controls, microbial controls and performance attributes are provided. In addition, product-related impurities and % monomers were determined at relevant stages of the down-stream process. The data provided are satisfactory and consistent between batches and indicates that each step has been appropriately designed and controlled. All AS testing results met the prospective process validation acceptance criteria with the exception of two deviations. For both deviations it is agreed that there was no adverse impact to the PPQ lot and product quality or overall campaign. It can be concluded that the process verification studies confirm that the full-scale commercial process performs effectively and is able to produce an AS meeting its predetermined controls and acceptance criteria.

Small scale studies using process intermediates from the PPQ batches supports the proposed hold times. Preliminary life-times of the resins used in the three chromatographic purification operations have been properly validated at laboratory scale using qualified scale-down models. Clear protocols for confirmation of the proposed life-times at production scale have been provided. Validation of the UF/DF membrane life-time, filter validation, AS shipping and reprocessing have been adequately performed and do not give rise to any concerns.

Manufacturing process development

The AS manufacturing process for sotatercept was developed through several stages. The FP used in the phase 3 clinical study (STELLAR) was manufactured from Process IIIa AS. AS process IIIa is the same process as the proposed commercial process. FP used in the phase 2 studies (PULSAR and SPECTRA) was manufactured from process IIIa and process III AS. An analytical comparability study has been performed, consisting of meeting acceptance criteria for release (with similar range of results), evaluation of stability data trends, degradation profile, and characterisation testing using a range of techniques.

Major changes were introduced during development while analytical testing of these batches was limited. The totality of evidence substantiates that is sufficiently representative for the current material taking into account the scope of the studies in which this material was used.

A section describing the analytical method history has been included. For compendial methods and some methods which were highly similar in their evolution, bridging was not performed. In some cases, bridging of the data was conducted to ensure that the methods are fit for purpose for commercial use. Bridging between methods has been provided for potency, purity, residual host cell protein. This is deemed acceptable.

Characterisation

Sotatercept primary structure, post-translational modifications, carbohydrate structure, disulphide structure, secondary/tertiary structure and quaternary structure have been thoroughly characterized using state of the art methods. A representative AS lot using the final commercial Process IIIa, was used for in-depth characterisation. This AS lot is qualified as the primary reference standard. Three PPQ of the commercial manufacturing process were also characterized to demonstrate consistency of product quality.

The complete amino acid sequence of sotatercept was confirmed by peptide mapping. The full N-terminal peptide of sotatercept was identified as 100% unmodified. As can be expected, the C-terminal showed some heterogeneity.

Several sequence variants have been observed at low levels in sotatercept. These sequence variants are considered as product-related impurities.

Sotatercept functions as a soluble form of ActRIIA that traps TGF-β superfamily ligands that normally bind to ActRIIA and ActRIIB. The proposed cell-based potency assay in the cell line mimics the supposed mechanism of action and could be acceptable as a functional assay.

The Fc portion of sotatercept was characterized for Fc functional activity. Literature data provides evidence for limited cell-surface availability of TGFβ superfamily receptor-bound ligands and that sotatercept only binds to soluble ligands and cannot bind appreciably to TGFβ superfamily ligands already engaged with endogenous type II receptors in the cell membrane.

Structure-function studies of sotatercept were performed to understand the degradation pathways and to assess the criticality of structural changes. Structural changes were introduced by forced degradation and evaluated by structural and functional characterisation. In addition, functional impact of structural changes were evaluated.

Specification

The commercial release and stability specifications to confirm the identity, strength, quality, potency, and purity of AS are provided. The release specification includes tests for: description (appearance, colour, clarity and degree of opalescence, all Ph. Eur.); identification (peptide mapping, in house); potency (functional cell-based assay, in-house); strength (protein concentration by UV spectroscopy); purity/product related impurities (charge distribution by desialylated iCIEF; size heterogeneity by SEC-HPLC; intact (major peak) and minor peak (LMW species) by CE-SDS; intact (major peak) and minor peak (LMW species) by CE-SDS; N-glycan profile by rapifluor HILIC-UPLC); process related impurities (residual host cell DNA by qPCR; residual host cell by ELISA; proteins and residual protein A by ELISA), physico-chemical attributes (pH, Ph. Eur.), microbiological quality (bacterial endotoxin and bioburden, Ph. Eur.).

Tests included in the specifications were selected based on understanding of the critical quality attributes (CQAs). Overall, the tests and test methods included in the specification are in line with those of monoclonal antibodies and other Fc fusion proteins. The applicant is recommended to including a release specification for total sialic acid content as sialic acid plays a critical role in circulatory half-life of glycoproteins (REC). In regard to purity, considering the sequence variants found as impurities, as mentioned in characterisation section, the applicant was requested to include a test for them in the specification table, with a total limit for the sum of them. In response the Applicant provided data that indicates that sequence variants are present at consistently low levels in line with other commercially available recombinant antibodies manufactured in a CHO platform. The applicant also committed to characterise the levels of sequence variants for the following commercial sotatercept AS batches, post approval. If low level is demonstrated, level of sequence variants in the AS release

batch specifications would be deemed unnecessary (REC). A more detailed glycosylation profile was requested. The applicant is also recommended to re-evaluate these limits when more batch data are available (REC). Since impurities are present at low level, no tox studies were deemed necessary. Acceptance criteria for qualitative measurements attributes (appearance, peptide mapping) were established based on batch release data. Acceptance criteria for microbial safety tests (bioburden and endotoxin) are based on regulatory guidelines and FP safety, and acceptance criteria for process-related impurities (residual HCP, residual DNA and residual Protein A) on manufacturing and FP safety. These acceptance criteria are acceptable, with the exception of residual HCP as the substantiation that the limit is safe because it is within the industry best practice $\leqslant$100 ng/mg was not agreed. The applicant tightened the limit of residual HCP and is recommended to re-evaluate the acceptance criteria based on commercial batches post approval. (REC) Also the limit for residual Protein A has been reconsidered as requested.

Acceptance criteria for SEC, CE-SDS, cIEF, N-glycan profiling and potency are based on the statistical analysis of the available release data and stability data, potential impact of product-related variants on potency, pharmacokinetics and immunogenicity/safety, and clinical experience. Acceptance criteria for some of these tests were tightened during the procedure.

Analytical methods

Test methods, system suitability criteria and sample acceptance criteria have been described in sufficient detail to allow assessment. A number of concerns were identified during the procedure for specific methods which were solved by improving the method descriptions. The applicant is recommended to update the analytical method description of the iCIEF, SEC-HPLC and CE-SDS (reduced and non-reduced) with additional context regarding acceptance criteria. (REC). Compendial methods have been acceptably verified. Non-compendial methods were validated in line with ICH "Validation of Analytical Procedures: Text and Methodology" Q2(R1) guidelines. However, it is recommended to perform supplemental intermediate precision validations for the protein concentration, iCIEF, SEC, and CE-SDS methods (REC). The HCP assay was properly developed and validated.

Batch analysis

Batch analysis data of batches have been presented and the data are consistent within each process. Process IIIa batches, manufactured using the proposed commercial process, were manufactured at commercial scale and were used in the phase 3 clinical study.

Reference materials

An in-house primary reference standard has been established, which was prepared from a batch that was manufactured according to process IIIA (commercial process) and was used in clinical studies. This reference standard has been characterised extensively; reference is made to the characterisation section of this report. The secondary reference material(s) used in the testing of production lots are calibrated against this primary reference material.

A detailed protocol for new reference standards has been provided. Qualification includes all release tests and additional biochemical, biophysical, and biological characterisation methods as specified in the protocol. The homogeneity of the primary reference standards is evaluated by protein concentration and the potency of new reference standards will be adequately calibrated. In addition, a protocol for monitoring the stability of the primary and secondary reference standards has been included. The provided information is sufficiently detailed to allow assessment and is satisfactory.

Stability

The stability results indicate that the AS is sufficiently stable and justify the proposed shelf life in the proposed container.

Real time, real condition stability data on commercial scale batches and additional full scale batches (including PPQ batches) of AS from the commercial manufacturing process stored in scaled down containers that are representative of the commercial AS container and closure system according to the ICH guidelines were provided. In addition to the accelerated stability studies, the batches were also stored to support the out of storage temperature excursion claims.

No statistically significant changes were observed during long term storage. No significant trends are observed for any attributes when tested on stability.

Freeze/thaw studies sufficiently indicate that there is no impact to stability of the AS when subjected to freeze/thaw cycles.

2.5.3. Finished medicinal product

The FP is presented as a powder (and solvent) for solution for injection containing 45 or 60 mg of sotatercept as AS.

The product is intended to be reconstituted at the point of administration. As per the SmPC, the powder is either provided as a vial only presentation, or as a kit co-packaged with a syringe containing the required volume of sterile water for injection (sWFI) and with medical devices i.e. a graduated dosing syringe, a vial adapter, a needle for injection and alcohol wipes; the two options are clearly described in the SmPC.

After reconstitution, a solution with a protein concentration of 50 mg/mL in a citrate based buffer (10 mM citrate, pH 5.8, 8% w/v sucrose and 0.02% w/v polysorbate 80) for subcutaneous administration is obtained. Two different strengths are proposed.

2.5.3.1. – Finished medicinal product - Power for solution for injection

Description of the product and pharmaceutical development – power for solution for injection

Sotatercept powder for solution injection is a sterile, preservative-free, white to off-white lyophilised cake or powder in single-dose vials for subcutaneous (SC) administration after reconstitution. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the FP formulation.

The final FP vial contains an overfill, to compensate for the holdup volume of the vial, needle and syringe to ensure correct dose delivery. The use of the overfill and of nitrogen gas as backfilling excipient have now been included in the dossier.

The FP is packaged in a glass vial, stoppered with a rubber stopper, and sealed with an aluminium crimp seal with a flip-off cap, the materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Two presentations of sotatercept FP, 45 mg/vial and 60 mg/vial have been developed for Phase III clinical trials. The two FP presentations are identical in their formulation composition prior to

lyophilisation and upon reconstitution with sWFI. They differ only in their fill volumes, which are adjusted to meet the label claim of the two presentations and are being advanced to minimize drug-wastage in the weight-based dosing format.

The process development history includes adequate details on the changes in the process, with the reasons for the change.

The comparability assessment of Process IIa and Process III included evaluation of release data and stability data, as well as extended characterisation. In general, sufficient data is provided to demonstrate comparability of Process II and III.

Comparability between Process III to Process IIIa (used for Phase II and Phase III clinical studies and the commercial manufacturing process) is evaluated by comparison of release testing, stability testing and degradation profile assessment and extended characterisation. In general, sufficient data is provided to demonstrate comparability of Process III and IIIa based on release and stability data and extended characterisation. Analytical comparability of FP lots from Process IIIa, manufactured at the different manufacturing sites and scales is sufficiently demonstrated.

The applicant provides a list of critical quality attributes, see table below, and describes the general methodology and identification of critical quality attributes (CQAs) of the AS and FP. The severity ranking of product quality attributes (PQA) is defined in terms of impact of known or potential impact on efficacy, PK/PD, immunogenicity and safety and is endorsed. Based on this assessment a list of quality attributes assessed as critical are presented with their severity ranking (major or moderate), with the justification. On request, the applicant also provided a summary of the product quality attribute assessment for those attributes which were considered non-critical (severity ranking as minor or insignificant). The assessment is mainly based on the structural features of sotatercept and is substantiated by data provided in the AS characterisation section and by literature data.

A control strategy for the sotatercept AS and FP manufacturing processes has been developed based on scientific and risk-based approaches. The overall risk for all PQAs for sotatercept during the AS and FP manufacturing process is evaluated based on the severity, likelihood of occurrence, and detection/ testing strategy in place using a failure mode effect analysis (FMEA). Based on the control strategy it is concluded that the overall risk to CQAs is low. The control strategy has been updated to include potency as a CQA and its control throughout the manufacturing process is adequately described in the dossier.

The compatibility of sotatercept FP with sWFI and dosing syringe is sufficiently demonstrated through hold time of reconstituted product in the original vial and in the dosing syringe.

Manufacturing process development studies

The FP manufacturing process has been adequately characterised using combination of clinical manufacturing experience, laboratory studies and large-scale process characterisations to determine the proven acceptance ranges (PAR) for process parameters for thawing of frozen AS, FP formulation, sterile filtration, filling and partial stoppering, lyophilisation and capping and to identify critical process parameters.

The impact on product quality through the various manufacturing steps is studied to obtain information on size heterogeneity, molecular mass and particle size, and where relevant on charge variants, protein concentration and pH. The Applicant has further clarified that the impact of potency has also been studied for establishing the PARs, the results have now been included in the dossier.

The same lyophilisation cycle and parameters are used for the 45 mg and 60 mg/vial fill sizes.

Container-closure system

The proposed container-closure for sotatercept FP is compendial grade Type I glass vial and bromobutyl rubber stopper. The same vial and stopper are used for both the 45mg/ vial and 60 mg/ vial presentations.

An adequately detailed description of the vial, stopper and seal, and drawings with dimensions are presented. The container closure for proposed routine use has been used throughout process IIIa, for Phase 3 clinical and stability studies. Suitability of the container closure system is adequately addressed.

An extractable and leachable assessment has been performed on the vial and stopper using a surrogate FP solution due to expected interference with formulated FP. The use of the surrogate solution is accepted, also keeping in mind that the sotatercept FP is a lyophilised powder and therefore the risk for leachables during its shelf-life is limited. No extractables and leachables above reporting threshold were detected. Container closure integrity has been sufficiently demonstrated in stability studies using oxygen headspace analysis.

Manufacture of the product and process controls – powder for solution for injection

Sotatercept FP is manufactured in Italy. Batch release is performed at MSD in Haarlem, the Netherlands.

Batch formula for representative batches at minimum and maximum with amounts of AS and excipients is provided.

FP manufacturing consists of thawing and pooling of AS lots, followed by formulation. Thawing temperature and duration and mixing speed and times are monitored during the process. The formulated bulk undergoes bioburden reducing filtration followed by sterile filtration, and is filled into vials, partially stoppered and lyophilized. The same lyophilisation cycle is used for both the fill sizes – 45 mg and 60 mg. Additional information regarding the number of AS batches pooled, description of how the correct final target FP concentration is achieved and controlled, details on composition of formulation buffer and sterilisation conditions of vials and stoppers has been included during the procedure.

Sufficient details on bioburden reducing and sterilizing filter have been provided, in line with EMA/CHMP/CVMP/QWP/850374/2015.

Assembly and co-packaging processes and process controls for the co-packaged WFI pre-filled syringe and medical devices have been described in sufficient detail.

Process controls

(Critical) process parameters are defined and in general, parameter ranges included are in line with the process development studies. In process controls for bioburden reduction, pH control of buffers, total protein concentration at end of formulation, sterile filtration and filling are adequately defined.

The processing times for FP manufacturing are in line with process development study results and/or maximum hold time challenged during validation.

Process validation / verification

The process validation adopted a bracketing approach across the two FP strengths.

The process validation reports cover the process of AS thawing and pooling, buffer preparation, formulation, filling, lyophilisation, capping, visual inspection and release testing. Sufficient details on the process and results are provided. Adequate justification on the homogeneity of formulated FP and content homogeneity from start to end of filling has been provided.

Lyophilisation uniformity is sufficiently demonstrated by taking samples from the corners and centre of each shelf of the freeze-dryer. Lot homogeneity testing included measurement of appearance, of purity by cIEF, of charge distribution by desialylated icIEF, of purity by SEC-HPLC, and of particulate matter and of reconstitution time. All data met pre-defined acceptance criteria. In addition to these, moisture content, protein concentration and content uniformity were measured.

Hold times are considered adequately validated. Sterilisation filter validation study is included and shows that the filter is suitable for its purpose.

Product specification – power for solution for injection

Specifications

The commercial release and stability specification (attributes, test methods, and acceptance criteria) established to ensure the identity, strength, quality, potency, and purity of the FP were provided , they include tests for: description (cake appearance and colour, visual; appearance of reconstituted solution - visible particles, colour, clarity and degree of opalescence all Ph. Eur.); identity (peptide mapping); Potency (functional cell-based assay); Strength (protein concentration); assay of polysorbate 80 (UV Fluorescence); Purity/Product Related Impurities (Charge Distribution by de-sialylated iCIEF; size heterogeneity, by size exclusion chromatography (SECHPLC); Intact (Major Peak) Minor Peaks (LMW species) by CE-SDS non-reduced; minor peaks (LMW species) by CE-SDS Reduced); physico-chemical tests (uniformity of dosage units, osmolality, pH, moisture content, all Ph. Eur.; particulate matter, USP; reconstitution time, visual); Microbial Quality (Bacterial Endotoxins and Sterility, Ph. Eur.; container closure integrity, USP).

The release and stability specification are in line with ICH Q6B. The acceptance limits are based on clinical experience and statistical tolerance intervals calculated from the batch data results.

FP specifications are based on data from FP batches.

No new product-related impurities are observed in FP relative to the AS. Potential FP manufacturing process and product related impurities are adequately controlled during the manufacturing process or at release and during stability studies. No extractables or leachables above the reporting thresholds were observed for the container closure.

The potential presence of elemental impurities in the FP has been assessed in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data was provided, demonstrating that each relevant elemental impurity was well below 30% of the respective PDE. Based on these data, it is concluded that the residual risk of elemental impurities is considered negligible, and it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the FP has been performed for both the lyophilisate vials and the WFI syringes, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on

the possible presence of nitrosamine impurities in the AS or the related FP components. Therefore, no additional control measures are deemed necessary.

Analytical methods

The assessment of analytical methods shared between sotatercept AS and FP, and their validations are provided in the AS section. Non-compendial methods specific to FP (description of cake appearance and colour, polysorbate concentration, reconstitution time and container closure integrity) are described in adequate detail. Validations of non-compendial methods is considered sufficient.

Unique in-house method identification numbers in specifications table, method descriptions and method validation summaries are included in line with EMA Q&A for biologicals.

Batch analysis

Batch data of FP lots from development to commercial processes are provided. Results from FP lots (Phase 3 clinical and commercial process) are consistent.

Reference materials

The reference standard used for Sotatercept FP is the same as the one used for the AS.

Stability of the product – power for solution for injection

The proposed shelf-life for sotatercept FP is 36 months when stored in the refrigerator (2 – 8 °C), in the original package in order to protect from light. Biochemical and biophysical in-use stability has been demonstrated for 4 hours at 30 °C. The proposed shelf-life of 36 months at 2 – 8 °C is sufficiently supported by stability studies performed in accordance with ICH Q5C. Stability data on three primary stability lots under the recommended long-term storage conditions were provided. The three primary stability lots (clinical batches) are manufactured with the commercial IIIa process at the proposed commercial scale and are stored in the proposed container. The stability studies of the commercial batches are still ongoing and available long-term data show no stability trends.

Photostability study indicates that sotatercept FP is sensitive to light and the product should be stored in the secondary package to protect from light. Ancillary studies support the stability of the FP to temperature cycling

The Applicant has updated 3.2.P.8 with details on batches used, time points and temperature for the in-use stability study. In-use stability data at end of shelf-life supports the recommended in-use stability shelf life of 4 hours at 30°C.

2.5.3.2. Finished Medicinal Product – sWFI

The solvent used for reconstitution of the FP is sterile water for injection (sWFI), provided in a 1.5 ml prefilled syringe (PFS). The PFS is filled with sWFI, to accompany the 45 mg/vial and 60 mg/vial presentations, respectively.

The PFS consists of a siliconized glass barrel, a siliconized plunger, and a closure system composed of a tip cap with a Luer lock and a tamper-evident seal. The container closure material complies with Ph. Eur. An extractable and leachable assessment has been performed on the primary packaging components.

The sWFI PFS release happens at Vetter Pharma sites located in Ravensburg, Germany.

For sWFI manufacturing, the WFI produced by distillation of Purified Water is subjected to an inline filtration before filled into the syringe. The syringe is stoppered after filling and transferred to an autoclave for terminal sterilisation following visual inspection. The chemical and microbiological testing on WFI system is according to a defined schedule and according to Ph. Eur. requirements.

Process validation is described in detail. All equipment and primary packaging components used for sWFI manufacturing is adequately qualified and the terminal sterilisation cycle is adequately validated. For process validation, a bracketing approach has been used. The Applicant also states that a risk assessment supports the bracketing approach used for the present validation. All data meet the acceptance criteria.

The specifications of the sWFI, the analytical methods used and their validation are stated to be in compliance with Ph. Eur.

Container-closure is described in sufficient details. Drawings, detailed specifications, and certificates of analyses are included.

A bracketing approach has been used for the stability studies. Stability of batches stored under worst-case conditions, plus supportive batches has been studied. This approach is considered acceptable for stability testing. Data up to 60 months for long term conditions: 2-8 °C/ ambient humidity and 30 ± 2°C/ 65 ± 5% RH and data up to 6 months for accelerated conditions: 40 ± 2°C/ 75 ± 5% RH are presented and fulfil the acceptance criteria.

The proposed shelf-life of 60 months at 2 – 32 °C is acceptable.

Medical device

The selection of device components to reconstitute and subcutaneously administer the sotatercept FP was based upon both the pharmacological requirements of the FP formulation, learnings from the iterative human factors evaluations of the co-packaged drug-device combination user interface, and additional feedback from the intended user population.

Sotatercept in a kit is co-packaged with sWFI PFS (part of the FP) and medical devices (i.e., a graduated dosing syringe, a vial adapter, a needle for injection and alcohol wipes). Valid EC certificates of compliance with the general safety and performance requirements (GSPR) have been provided for the co-packed devices.

The syringe for administration provided in the kits, is a sterile 3 mL syringe, which is used to withdraw the reconstituted FP from the vial and measure the prescribed dose. The dose is patient weight dependent and can vary from 0.2 mL tot 2.4 mL. In the case of a two-vial presentation, the syringe for administration is also used to combine the contents of both vials to enable the withdrawal and administration of a single dose. The use and handling of the syringe is described in the instructions for use (IFU) and in the SmPC section 4.2, both of which have been tested in a human factor validation study included in module 5.3.5.4. The inclusion of a 3.0 ml syringe in the 1x 45 mg vial kit presentation was initially considered not acceptable and a multidisciplinary major objection (MO) was raised. In response, the Applicant has justified that the accuracy of dosing low volumes with the 3 mL syringe, as tested by trained laboratory personnel is sufficiently high and would only lead to small deviations. Combined with the exposure-response modelling and the wide clinical comparability bounds, small deviations in exposure due to dosing error are not expected to meaningfully impact safety and efficacy. Also, clinical data from the phase 3 studies together with testing per harmonized standards, demonstrate the acceptable performance of the kit with the 3.0 mL dosing syringe. Therefore, the MO is considered solved. The Applicant is recommended to include a suitably smaller syringe for the 45 mg kit in the future This would also be beneficial if in future a paediatric indication is pursued (REC).

In addition to the MO, the Applicant has justified that the risks linked to self-administration are considered relatively low, based on routine risk minimisation measures as proposed in the SmPC (i.e., training by HCPs with a subsequent check if the technique is correct, monitoring hemoglobin and platelets at defined intervals, and dose modifications). It was agreed that the risks are outweighed by the benefits for patients.

Adventitious agents

No raw materials of human or animal origin are used in the AS and FP manufacturing processes. Exposure to animal derived raw materials was limited to the initial stages of sotatercept cell line development. Adequate information has been presented on these. The sotatercept cell banks have been tested in accordance with EMEA/CHMP/BWP/398498/2005, including *in vitro* tests.. Test results confirm the absence of adventitious agents and infectious retroviruses in the cell banks.

Results of adequate virus validation studies are provided. Xenotropic murine leukaemia virus (XMuLV) represents the retrovirus-like particles found in CHO cells. The choice of the other model viruses is considered appropriate to resemble a broad range of physico-chemical structures. The small-scale models are the same as those used for process characterisation studies and have been adequately qualified for each unit operation by determining comparability of output parameters between lab scale and commercial scale.

Overall, the virus validation studies adequately demonstrate that the sotatercept AS downstream process has effective viral clearance across the panel of the four model viruses, X-MuLV, MMV, Reo-3 and PRV. An acceptable rodent retrovirus-like particle risk assessment is presented; the risk of a retrovirus-like particle contamination in the final product is considered to be negligible.

Post approval change management protocols

The applicant provided two post approval change management protocols (PACMP). The first one concerns upscaling of the AS manufacturing process. Changes to the process are limited to scale and facility fit. The justification and impact of changes are sufficiently discussed in the corresponding sections of this protocol. The approach to demonstrate comparability consists of assessing comparability of results of in-process controls and process validation tests, release tests, extended characterisation tests and stability. Overall, the approach can be supported and is in line with ICH 5E. The Applicant has addressed the concerns regarding comparability acceptance criteria of release tests. The PACMP pertaining the scaling up of the AS manufacturing process is considered acceptable.

The second PACMP concerns the introduction of additional analytical testing sites in the EU. In addition to the new sites, method changes are proposed. These three methods will be fully validated at the new site and an appropriate bridging study with the current site will also be performed. Detailed protocols with justified acceptance criteria are provided. Comparative testing is proposed for the potency assay, residual HCP test and N-glycan distribution. These protocols are satisfactory. The other non-compendial methods will be fully re-validated at the new site. Detailed protocols with justified acceptance criteria are provided. In addition, a common sample will be measured by both testing sites for these analytical test methods. In conclusion, the PACMP is considered acceptable.

2.5.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the AS and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity

of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure a multidisciplinary MO was raised with regards to the suitability of the co-packed presentation device, the applicant has provided adequate reassurance of the accuracy of the device also for low volumes.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to reviewing the specification limits of the AS, to update some of the AS analytical methods, and the development of an alternative measuring/delivery options for volumes less than 1 mL. These points are put forward and agreed as recommendations for future quality development.

2.5.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.5.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Area	Number	Description
Quality	1	The applicant is recommended to include a release specification for total sialic acid content in the AS specification.
Quality	2	The Applicant is recommended to characterize the levels of sequence variants based on the evaluation of data from commercial sotatercept AS batches using the newly introduced analytical method. In case all results comply with the proposed acceptance criteria, consistent control of this impurity will have been demonstrated and the inclusion of this test in the active substance batch release specification panel will be deemed unnecessary.
Quality	3	The Applicant is recommended to re-evaluate the different acceptance criteria for N-glycan species based on the evaluation of data from commercial active substance batches.
Quality	4	The Applicant is recommended to update the analytical method description of the iCIEF, SEC-HPLC and CE-SDS (reduced and non-reduced) with additional context regarding acceptance criteria.
Quality	5	The applicant is recommended to perform supplemental intermediate precision validations for the protein concentration, iCIEF, SEC, and CE-SDS methods.
Quality	6	The Applicant is recommended to re-assess the acceptance criteria for host cell protein (HCP) in sotatercept AS based on the evaluation of data from commercial AS batches.

Multi-disciplinary (Quality/Clinical)	7	The Applicant is recommended to explore the possibility of including a suitably smaller syringe for the 1 x 45 mg vial kit. This would also be beneficial if in future a paediatric indication is pursued. If post-marketing data would hint towards dosing errors, a change may be necessary.

2.6. Non-clinical aspects

2.6.1. Introduction

The Applicant provided a comprehensive package of non-clinical studies for sotatercept. Pharmacology was studied *in vitro* and *in vivo* in mice and rats models of PAH. Consistent with ICH S6(R1), safety pharmacology evaluations (neurological, body temperature, respiration rate, ECG, and blood pressure measurements) were performed as components of the GLP chronic toxicity study in monkeys. The pharmacokinetics of sotatercept have been evaluated in rats, rabbits and monkeys, the non-clinical species used in the non-clinical safety program, using SC administration, which is the intended clinical route. No traditional distribution, metabolism and excretion studies were conducted with sotatercept per current ICH S6 (R1). The sotatercept non-clinical toxicology program included repeat-dose GLP toxicity studies of up to 3 months duration in rats and 9 months duration in monkeys, fertility and early embryonic development studies in rats, EFD studies in rats and rabbits, a pre- and post-natal development study in rats, and juvenile toxicity studies in rats. In addition, investigative toxicology studies were completed in mice and rats to better characterize the renal toxicity of sotatercept observed in rats and monkeys. All pivotal toxicology studies were in full compliance with OECD GLP regulations.

Sotatercept is a recombinant human homodimeric fusion protein consisting of the extracellular domain (ECD) of human activin receptor type IIA (ActRIIA) linked to Fc domain of human IgG1. Each monomer consists of 344 amino acids. In PAH the TGF- β -activin-nodal branch is overexpressed compared to the BMP-GDF branch. The proposed mechanism of action of sotatercept is to restore the balance between those two branches by trapping specifically TGF-β superfamily ligands. Therefore, sotatercept functions as a soluble form of ActRIIA that binds TGF-β superfamily ligands such as activin A and B, GDF-11 and GDF-8, preventing them from activating the TGF- β -activin-nodal branch.

2.6.2. Pharmacology

2.6.2.1. Primary pharmacodynamic studies

In vitro

Sotatercept functions as a soluble form of ActRIIA that traps TGF-β superfamily ligands such as activin A and B, GDF-11 and GDF-8. In PAH the TGF- β -activin-nodal branch is overexpressed compared to the BMP-GDF branch. Binding of different ligands to ActRIIA and ActRIIB normally induces the downstream Smad2/3 or Smad 1/5/8 signaling, depending on the ligands that bind. Activin A and GDF-11 (both TGF- β -activin-nodal branch ligands) have been associated with hyperproliferation. In the lung, activin A seems to primarily localize at the bronchial epithelial cells and macrophages and has been reported to promote smooth muscle cell (SMC) proliferation and expression of ET-1, a key modulator of PAH. While activin A stimulates proliferation of SMCs, SMCs from PAH patients also

display enhanced synthesis of activin A, providing a local feed-forward loop of proliferation. GDF-11's participation to PAH appears to be restricted to the endothelial cell compartment. Other functions of GDF-11 include regulation of renal fibrosis and tubular function. It also plays a role in embryonic and postnatal angiogenesis.

The affinity and binding kinetics of different ligands for sotatercept was investigated *in vitro* with surface plasmon resonance. These studies demonstrated high affinity of sotatercept for TGF-β superfamily ligands activin A and B, GDF-11 and GDF-8. BMP-10 was also shown to have high affinity for sotatercept. BMP-10 is involved in several cardiac pathways, such as cardiac remodelling and cardiovascular homeostasis. However, this ligand belongs to the BMP-GDF branch, which is under-expressed in PAH. The inhibitory concentrations (IC_{50}) for sotatercept for these ligands were investigated with a cell based reporter gene assay (study PD002). In this cell based assay IC_{50} values were low for TGF-β superfamily ligands and high for BMP-GDF branch ligands. It was noted, that different cell lines and different concentrations of ligands were used in the cell based assay. The Applicant discussed the choice of cell lines and set-up of the receptor-gene assay. Cell lines were selected based on the expression level of ligands, combined with the Smad signalling. Concentrations of sotatercept were then chosen based on the response curves for the pathways and ligands of interest. The EC_{50} or EC_{75} were chosen to ensure a decent signal-to-noise ratio in the assay.

The clinical implications of the inhibition of ligands of the BMP-GDF branch due to the high concentrations of sotatercept seen in humans at clinical dosages and the relevance of the difference observed between K_D values and IC_{50} values with regard to the specificity of sotatercept and the natural affinity of these ligands to the ActRIIA receptor is not established. However, complete inhibition of BMP10 signaling by therapeutic concentrations of sotatercept is considered unlikely. Because BMP10 has a binding affinity that is about 200-fold weaker than Activin A and Activin B, these high affinity ligands will compete more efficiently for available sotatercept ligand binding sites and reduce the potential for BMP10 binding. Based on the described physiological effects of BMP10, there does not seem to be clear non-clinical toxicity related to BMP10 inhibition.

In vivo

For the *in vivo* studies a murine surrogate of sotatercept was constructed, named RAP-011, where the human IgG1 was replaced with a murine IgG2a. The ActRIIA ECD was not altered. The ECD amino acid sequence and structure of ActRIIA is highly conserved across species including rat, rabbit, cynomolgus monkey, and human, and is identical between sotatercept and RAP-011. Amino acid sequence alignment shows 100% homology between rodent, cynomolgus monkey, and human species for activin A and GDF 11, and 97 to 98% homology for activin B and BMP10. A detailed kinetic analysis of SPR binding data was performed for sotatercept and RAP-011 binding to its main ligands of murine origin; sotatercept and RAP-011 bind to its murine and human ligands very similarly. Therefore it was concluded that RAP-011 is a suitable surrogate of sotatercept to use in *in vivo* murine pharmacology and toxicology studies.

In rats, monocrotaline and sugen-hypoxia models were used to induce PAH-like disease in rats. The sugen-hypoxia-normoxia model in rats was used to study lasting effects of sotatercept on PAH symptoms and to mimic administration of sotatercept in different stages in disease development. In mice, the Bmpr2+/R899X model was used to mimic hereditary PAH and pulmonary artery banding was used as a model for acquired, rather than hereditary PAH. No elaborate justification for the use of these models was provided, however, they appear to capture the most pronounced symptoms of PAH and the effects of RAP-011 in both acquired and hereditary PAH could be studied using those models. Therefore, the use of these models is considered acceptable to study the *in vivo* pharmacodynamics of (a surrogate of) sotatercept.

Endpoints consistently covered across these studies are right ventricular pressure and right ventricular hypertrophy. Other endpoints, such as right ventricular medial wall thickness and CD11b+ macrophage response, was not evaluated in all studies. Sildenafil was used in the Sugen-hypoxia models as comparison to reflect currently available standard-of-care for PAH. Overall, RAP-011 appears to significantly reduce right-ventricular pressure almost to a level seen in healthy non-treated animals. RAP-011 also significantly outperforms sildenafil on this endpoint. A similar effect is seen for right ventricular hypertrophy in the different models. The effects on right ventricular wall thickness are slightly less pronounced, yet still significant compared to vehicle control. These results are seen consistently across the different *in vivo* rat and mice models of both acquired and hereditary PAH. After 4 weeks of recovery, the positive effects of 4 weeks RAP011 treatment on right-ventricular pressure and right-ventricular hypertrophy were still present in rats, although recovery was only included in one study.

Multiple dose levels (1-10 mg/kg BW) were used in the studies published by Yung et al. 2020. This paper was submitted to support the PD dossier. There seems to be no dose-response for right ventricular pressure and right ventricular hypertrophy. However, a decreasing trend is visible for medial wall thickness at 10 mg/kg compared to 1 mg/kg. The apparent lack of a dose-response relationship between the different doses on hemodynamic responses is explained by the fact that already at 1 mg/kg RAP-011 the inhibition of activin A, activin B, GDF-8, and GDF-11 may have been sufficient to reach maximum efficacy. To strengthen this conclusion, the estimated exposure (AUC) of the animals in these studies was determined by extrapolation from the PK measured in the repeat-dose toxicity studies. The exposure at 1 mg/kg would, according to the established IC50 values, indeed be sufficiently high to support a maximum effect.

2.6.2.2. Secondary pharmacodynamic studies

Secondary pharmacology studies were mostly covered by the primary *in vitro* pharmacology studies. Binding studies revealed a high selectivity for TGF-B superfamily ligands. One additional secondary pharmacology study was submitted. This study, performed in C57BL/6 mice studied the effect of RAP-011 on hematologic endpoints due to known role of activin in regulating the terminal differentiation of developing erythrocytes. In a series of experiments ranging from 3-14 days of treatment with RAP-011, it was shown that RAP-011 treatment induced significant increases in the numbers of RBC, HgB, and HCT, as well as a significant increase in erythropoietin protein. Although the effects seen in non-clinical species in this study as well as in the toxicity studies are of small magnitude and at exposure multiples of 13-to-18-fold, the relevance to the human situation is uncertain. In the SmPC it is advised that HgB is monitored in patients, as well as platelet counts, and the dose should be decreased if the platelets drop too low.

2.6.2.3. Safety pharmacology programme

Two GLP compliant safety pharmacology studies were submitted by the Applicant. The first concerns a dedicated *in vitro* hERG inhibition study. From this study it could be concluded that sotatercept is not a hERG channel inhibitor as is expected from a recombinant protein. The IC_{50} was estimated to be >1000 ug/mL. Since the clinical Cmax at 0.7 mg/kg was measured to be 9.7 ug/mL there is no concern for hERG inhibition based on these study results.

In vivo safety pharmacology was incorporated in the 9-month toxicity study in cynomolgus monkeys in line with the recommendations of ICH S6 guidelines. There were no sotatercept-related abnormalities at neurological, cardiovascular or respiratory endpoints.

2.6.2.4. Pharmacodynamic drug interactions

Non-clinical studies evaluating pharmacodynamic drug interactions with sotatercept have not been conducted, which is acceptable given the product characteristics. Drug interactions are discussed further in the Clinical section below.

2.6.3. Pharmacokinetics

The single dose pharmacokinetics (PK) of sotatercept (MK-7962, ACE-011) has been characterized in the species used in pivotal toxicology studies, Sprague-Dawley rats and cynomolgus monkeys upon intravenous (IV) and subcutaneous (SC) administration. In addition, multiple dose toxicokinetics (TK) of sotatercept was examined upon SC administration, which is the intended clinical route, in Sprague-Dawley rats (QW), pregnant NZW rabbits (QW), and in cynomolgus monkeys (Q2W, 27-wk, 9-mth). In the non-clinical PK and toxicology studies, sotatercept was administered as a solution in either PBS or citrate buffer.

Analytical methods

Assays were developed for the evaluation of exposure and immunogenicity in the non-clinical studies. Sotatercept was quantified in rat and rabbit serum and in cynomolgus plasma using competitive enzyme-linked immunosorbent assays (ELISA) and in rat and cynomolgus serum using sandwich ELISAs. The sotatercept assays used in the PK studies were not validated (and only informative) but the assays used in the pivotal studies, however, were validated. The provided validation reports, which included (amongst others) the evaluation of precision and accuracy (intra- and inter-assay), specificity, selectivity, and sample stability (long-term, freeze-thaw), demonstrate that the assays were suitable for quantification of sotatercept in rat, rabbit and monkey serum used in the pivotal toxicology studies (including incurred sample reanalysis).

For the detection of antibodies against sotatercept (ADAs) in rat and monkey serum, bridging ELISAs were developed and validated having a sensitivity of 500 ng/mL anti-sotatercept ADAs. In addition, bridging electrochemical luminescent immunoassays (ECL) were developed and validated for the detection of anti-sotatercept antibodies in rat, rabbit and cynomolgus serum. The sensitivity of the ECL assay was found to be 9.3, 24.5 and 17.1 ng/mL for the detection of anti-sotatercept ADAs in rat, rabbit and monkey serum, respectively. Drug tolerance of sotatercept was 10 µg/mL in the rat and 60 µg/mL in monkey serum, above which the presence of ADAs may be masked.

Absorption

Single dose

Upon single dose intravenous (SD, IV) administration of 1, 10 or 30 mg/kg sotatercept to male Sprague-Dawley rats (n=3), the plasma concentration profile was characterized by a biphasic distribution and elimination pattern. The exposure ($AUC_{0\text{-}inf}$) increased dose-proportional over the dose range. The total body clearance and volume of distribution were ~0.12 mL/h/kg and ~35 mL/kg, respectively. The terminal elimination half-life ($t_{1/2}$) ranged from 5.8 to 8.5 days and was studied up to 14 days after dosing.
Following SD subcutaneous (SC) administration of 3, 10 or 30 mg/kg sotatercept to male Sprague-Dawley rats (n=12), the mean maximal serum concentration (C_{max}) was found to be dose proportional (~7.8 µg/ml per mg/kg dosed) and was observed 32 - 48 hours post-dose (t_{max}). Exposure ($AUC_{0\text{-}672}$) increased less than proportional, *i.e.* 6-fold over the 3 to 30 mg/kg dose range. The mean elimination $t_{1/2}$ was about 4 – 8 days after SC dosing in rats.

Upon SD, IV administration of 1, 10 or 30 mg/kg sotatercept to female cynomolgus monkeys (n=2), the plasma concentration profile was characterized by a biphasic distribution and elimination pattern. The exposure (AUC_{0-672}) increased less than dose-proportional (11-fold over the 1 - 30 mg/kg dose range). The low total body clearance increased from 0.3 to 0.8 mL/h/kg and volume of distribution from 108 to 252 mL/kg over the 1 - 30 mg/kg dose range. The terminal elimination half-life ($t_{1/2}$) was found to be approximately 9.0 – 10.5 days.
Following SD SC administration of 1, 10 or 30 mg/kg sotatercept to male cynomolgus monkeys (n=3), the mean maximal plasma concentration (C_{max}), increasing from ~9 to 133 µg/ml, was found to be less than dose-proportional and t_{max} declined with increasing dose from 48 to 4 hours. Exposure (AUC_{0-672}) also increased less than dose-proportional, *i.e.* 13-fold over the 30-fold dose range. The mean elimination $t_{1/2}$ was approximately 7 – 9 days. The mean absolute bioavailability (F_{sc}) of sotatercept for the SC route was found to be 71% – 96%.

Multiple dose

In a 3-month repeat-dose toxicology study, 0.3, 3 and 30 mg/kg sotatercept was administered once weekly SC to male and female rats (n=10). The serum toxicokinetics (TK) parameters were measured at D1 and D92 and showed no clear or consistent sex difference. Systemic exposure (AUC_{0-166} = AUC_{tau}) to sotatercept was roughly dose proportional. Upon repeated administration, AUC_{tau} accumulation was low and the accumulation ratio's (Ra) were 2.6, 1.0 and 1.2 for the 0.3, 3 and 30 mg/kg, respectively.
There was a positive signal of ADA formation in 44% of the animals with a stronger effect in the higher doses in this study. ADA formation generally resulted in a lower exposure.

Following two SC QW administrations of 0.5, 1.5, and 5 mg/kg sotatercept to pregnant rabbits on gestation day (GD) 7 and GD14, serum exposure and C_{max} increased dose proportional. Maximal serum concentration was reached ~2.5 days after dosing. After GD14, the terminal elimination $t_{1/2}$ was found to be about 55 hours (2.3 d). A positive signal of ADA formation was seen in 41% of the animals, which was similar over the three dose groups and impacted serum exposure. Foetal exposure was measured and discussed in the Distribution section below.

In a 27-week repeat-dose toxicology study, 10, 30 and 50 mg/kg sotatercept was administered every two weeks (Q2W) SC to male and female cynomolgus monkeys (n=6). The serum toxicokinetics (TK) parameters were measured at D1 and D183 and showed no clear or consistent sex difference. Systemic exposure (AUC_{0-336} = AUC_{tau}) to sotatercept was dose proportional and maximal serum concentration was reached 1.5 – 2 days after dosing. A mean terminal elimination $t_{1/2}$ of approximately 1 week was observed after the first week of dosing (sexes-combined). Upon repeated administration, AUC_{tau} accumulation was low with Ra's below 2.0 (1.3 – 1.5).
There was a positive signal of ADA formation with 2 of the 12 animals dosed with 10 or 30 mg/kg and in 4 of the 12 animals dosed with 50 mg/kg in this study. After Day 85 of dosing, two of the six female animals in the 30 mg/kg and one male monkey in the high-dose (50 mg/kg) group had a clearly decreased sotatercept exposure profile.

Distribution

In accordance with ICH S6(R1), formal tissue distribution and protein binding studies were not conducted with sotatercept.

The low volume of distribution in cynomolgus monkeys ranging between 108 and 252 ml/kg suggests a distribution to the plasma and the extravascular fluid as it is within 2 to 5 times that of plasma volume (45 mL/kg). This is consistent with the known biodistribution of antibodies.

Repeat-dose PK of sotatercept (5, 15, and 50 mg/kg) was evaluated following SC administration to pregnant rabbits on GD7 and GD14, showing a mean t_{max} of 2.5 days and an elimination half-life of 2.3 d. Sotatercept was detected in pooled foetal serum samples on GD29 but since this was determined at more than 5 times the elimination half-life after administration foetal levels were BLQ or very low and highly variable. However, the remaining foetal exposure indicates that the fusion protein can cross the placental barrier.

Distribution of sotatercept to milk has not been examined. However, as a fusion protein containing an IgG1 Fc-part, and, the fact that sotatercept-related effects in the rat suckling offspring were observed, sotatercept is expected to be present in the (first) milk.

Metabolism

No metabolism studies with sotatercept were conducted in animals. The absence of metabolism studies is acceptable as it is in accordance with ICH S6(R1).

Excretion

As sotatercept is a protein therapeutic, no renal excretion is anticipated due to its molecular size. Therefore, no specific studies to measure excretion of sotatercept were conducted. The absence of excretion studies in accordance with ICH S6(R1).

Pharmacokinetic drug interactions

Drug-drug interaction at the PK level is highly unlikely for this type of product since biotechnology-derived substances do not metabolize via CYP450 enzymes. In addition, the mechanism of action of sotatercept is not expected to have an effect on CYP450 enzymes or on transporters.

2.6.4. Toxicology

2.6.4.1. Single dose toxicity

Single dose toxicity was assessed in rats in a non-GLP-study to specifically characterize the time course of adrenal gland necrosis, which was observed 4 weeks after intravenous (IV) administration at ≥10 mg/kg. No toxicokinetics (TK) data is provided in this study, although the same IV dose in a repeat-dose study resulted in a mean plasma concentration of at least 16-fold the maximum serum concentration (C_{max}) observed at the NOAEL of 3.0 mg/kg SC (2-fold exposure margin to clinical). Adrenal toxicity was also seen in the repeat-dose rat studies in rat, although it was reversible in SC-treated animals. The Applicant has explained that this toxicity may be caused by pharmacological features of sotatercept given that in the rat adrenal gland, activin signaling via activin receptor Type IIA (ActRII) appears to play a role in adrenal remodeling that occurs during fetal development and continues into early adulthood. In human, activin-A has effects on fetal but not adult adrenal cell growth. Therefore, the observed adrenal toxicity is not expected to translate to human.

Table 1. Single dose toxicity study

Study details Species Duration + recovery (weeks) Route GLP status (Study ID)	**No:Sex/ Group**	**Dose** (mg/kg/ day)	**Exposure**		**Major (alt. Salient) findings**
			Cmax µg/ml	AUC µg/ml /h	
Single-dose toxicity studies (MTDs highlighted)					
Rat (Sprague Dawley) 1 week or 4 week recovery IV Non-GLP (TT #06-7825/AP076)	Main: 12F control 14F per treated group TK satellites: 0	0	N.D.	N.D.	≥10: dose-dependent moderate bilateral adrenal gland necrosis with mineralization after 4 weeks

2.6.4.2. Repeat dose toxicity

GLP-compliant repeat-dose studies were conducted in rats with a duration of 3 months and in monkeys with a duration of 6 months and 9 months. The rat and monkey species were considered relevant for toxicity assessments based on the highly conserved (≥97%) sequence homology of the ActRIIA target ligands across rats, monkeys and humans, and the ability to show pharmacologic responsiveness and acceptable PK profiles in these species.

In rats, sotatercept was administered subcutaneously (SC) at doses of 0.3, 3, or 30 mg/kg per week (Q1W) for 3 months followed by a recovery period of 1 month. At 30 mg/kg, non-reversible aspermatogenesis was observed in two males. At both lower doses, microscopic testicular toxicity was also observed, which was reversible. Other reversible changes that occurred in males and females of all dose groups included hematological changes (increased red blood cell count (RBC)/ reticulocyte count (RTC)/ red cell distribution width (RDW) and decreased mean corpuscular volume (MCV)/ mean corpuscular haemoglobin (MCH)), decreased heart weight (without microscopic changes), and kidney and adrenal toxicity. A second SC study with similar design was conducted to evaluate kidney toxicity specifically with a focus on macroscopic and microscopic examinations as well as biomarkers for kidney injury, possibly following the observation of kidney toxicity in an earlier IV study in rat. Kidney changes were positively correlated with sotatercept serum concentrations and mostly occurred in serum anti-drug antibodies (ADA)-negative animals, suggesting that the observed renal pathology was not due to formation of ADA but rather a direct effect of sotatercept. However, contribution to renal pathology of potential immune complex deposition that was un-associated with circulating ADA was not investigated and can therefore not be ruled out. There was one male mortality at 30 mg/kg (18-fold exposure margin to clinical) with an uncertain relationship to treatment as no post-mortem kidney toxicity was observed and no other organs were analysed. Non-reversible kidney toxicity was present at all doses (though more severe at the high dose) and changes were correlated with increases in the urinary kidney injury biomarkers osteopontin, lipocalin-2, and albumin. Dose-dependent hematological changes (increased RBC/RTC/RDW/haemoglobin (HGB)/ hematocrit (HCT)/, decreased MCH/MCV/mean corpuscular haemoglobin concentration (MCHC)) were also observed in all

sotatercept-treated groups and mostly persisted at the end of recovery. In addition, in males of the high-dose group only, platelets (PLT) were decreased. In this study, the no observed adverse effect level (NOAEL) was 3.0 mg/kg (2-fold exposure margin to the MRHD) based on the non-adverse nature of effects at this dose level.

The safety profile of sotatercept after IV administration was also evaluated in a non-pivotal 4-week rat repeat-dose toxicity study where rats received either 1, 10 or 30 mg/kg sotatercept 1QW. While IV dosing is not the intended clinical route of administration, the observed toxicities were largely comparable to SC dosed rats but with higher incidence and severity. This is likely due to the fact that dosing from 10 mg/kg IV led to mean peak plasma concentrations that were at least 16-fold higher than the Cmax observed at the NOAEL of 3.0 mg/kg SC in rats, although toxicokinetics were not fully evaluated in this study, which complicates the interpretation. Adverse changes were observed at all dose levels and a NOAEL could not be established. Two mortalities were Sotatercept-related (mid and high dose). Target organs of toxicity were kidney, heart, liver, testes and adrenal glands.

In monkeys (aged 2.5-3.5 years and weighing 2.1-2.9 kg at the start of the study), sotatercept was well tolerated after SC administration of 10, 30, or 50 mg/kg biweekly (Q2W) for 3 months with a recovery period of 1 month. The NOAEL was 30 mg/kg, corresponding to a 32-fold clinical exposure margin. At 30 mg/kg mild, reversible microscopic changes in kidney, which progressed to non-reversible and adverse kidney findings in the high dose group. Furthermore, non-adverse hematology changes such as increased RBC/HGB/HCT/RTC/RDW and decreased MCH were observed from 10 mg/kg (13-fold clinical exposure margin), without a clear dose-response pattern.

At comparable dose levels following biweekly administration for 6 months in monkeys (aged 3-5 years and weighing 1.7-3.3 kg at the start of the study), sotatercept was not tolerated as well as in the 3-month study. Adverse changes were observed at all dose levels and a NOAEL could not be established. From the lowest dose of 10 mg/kg (11-fold clinical exposure margin), non-reversible kidney discoloration was observed, which correlated microscopically to tubulointerstitial nephritis/glomerulonephritis. At this dose level, reversible effects included non-adverse hematological changes, such as increased RBC/HGB/HCT/RTC, increased blood urea nitrogen (BUN)/ creatinine (CREA) and increased kidney weight. At 30 mg/kg (32-fold clinical exposure margin), 2 females were euthanised after 4-5 months due to kidney toxicity. Dose-related thymus toxicity was observed and was most apparent in the mid and high dose groups, with findings including reversible decreased thymus weight and lymphoid depletion, and haemorrhage, which was still present after recovery. The lymphoid depletion in the thymus was considered as a potential secondary change to renal morbidity and haemorrhage was considered of agonal origin, although a treatment-related effect could not be ruled out. Foamy macrophage infiltrates were occasionally observed in the choroid plexus of the brain in mid- and high-dose animals, which was non-reversible in males. Because of the low severity and incidence, the toxicological significance of this finding is unclear. Very few animals had serum ADAs, suggesting that the observed pathologies were not due to formation of ADA but rather a direct effect of Sotatercept. Given that exposure levels were very similar in this 6-month study as compared to the 3-month study, it seems that the longer duration of repeated sotatercept dosing led to the markedly reduced tolerability.

Finally, the Applicant conducted a 9-month repeat dose toxicity study where monkeys received lower doses, including 1, 2.6 or 10 mg/kg sotatercept every 4 weeks (Q4W), or 10 mg/kg Q2W. Animals were between 2.4 and 3.7 years old and weighed between 2.1 and 3.8 kg at the start of the study. In the high dose group, Q2W treatment resulted in similar systemic exposure as compared to the same dose in the 3- and 6-month monkey studies. Administration of sotatercept for 9 months did not result in any remarkable adverse changes in the lowest dose group of 1 mg/kg, but at this dose, no exposure margin was established (1-fold clinical exposure margin). At this dose, minimal, non-adverse and reversible changes in hematology (increased RBC/HGB/HCT/RTC), kidney (increased interstitial matrix

at corticomedullary junction), brain (mononuclear cell infiltrates in choroid plexus), liver (mononuclear cell infiltrates) and aorta/heart/pancreas (perivascular basophilic deposits) were observed. Changes in kidney became adverse at higher doses due to increased incidence and severity. Monthly dosing from the lowest observed adverse effect level (LOAEL) of 2.6 mg/kg (2-fold clinical exposure margin) onward resulted in non-reversible decreased glomerular tuft size in kidney, which correlated with adverse, but reversible increased serum BUN/CREA and increased urinary protein. From 2.6 mg/kg there was also reversible lymphoid depletion in spleen. At the highest dose of 10 mg/kg (6-fold clinical exposure margin), and especially when administered Q2W (13-fold clinical exposure margin), there were additional adverse effects, including non-reversible kidney toxicity (interstitial renal inflammation with fibrosis) as well as reversible decreased body weight gain and reversible toxicity in liver (hepatocellular rarefaction) and brain (foamy macrophage infiltrates and arterial wall thickening in choroid plexus). In males dosed at 10 mg/kg Q2W, there was a reversible, non-adverse decrease in PLT count. One 10 mg/kg Q2W animal deteriorated clinically due to kidney toxicity and was euthanised at the end of the dosing period. The (peri)vascular basophilic deposits (heart, aorta, or pancreas) that occurred in all dose groups were not considered adverse due to the mild degree, sporadic nature, and lack of a dose-response. No thymus toxicity was observed in this 9-month study, likely due to the lower dosing as compared to the 6-month monkey study. While granular deposits containing monkey IgG, IgM, and/or C3 were clearly associated with the kidney glomerular alterations and choroid plexus vascular alterations, it could not be established that the immune complexes also contained sotatercept. Furthermore, there were no confirmed ADA-positive serum samples. Kidney and choroid plexus changes were therefore likely not the result of ADA-drug complexes, but rather a direct effect of sotatercept.

One sotatercept study in monkeys (10, 30, 50 mg/kg Q2W SC, for an intended duration of 9 months) was terminated early (week 9) due to high incidence of plasmodium infection, mainly in sotatercept-treated animals but also some controls. It is unlikely that the increased incidence and severity of plasmodium infection in the early-terminated SC study was sotatercept-related. No evidence of an immunosuppressive basis for increased susceptibility to infection has been observed in any test species treated with sotatercept, and the Applicant plausibly argued that the modest effects of sotatercept on red cell maturation increased the susceptibility of plasmodium-infected monkeys to the development of overt malaria.

In a 4-week non-pivotal IV study, sotatercept treatment (1, 10, 30 mg/kg Q1W) resulted in increased red blood cell parameters at all dose levels. Other toxicity was likely not observed due to the short duration of the study. The NOAEL was 30 mg/kg (mean peak plasma concentration at least 78-fold higher than the Cmax observed at the NOAEL of 1 mg/kg SC in monkeys).

Taken together, in all repeat-dose toxicity studies, in both rats and monkeys, sotatercept caused an increase in erythroid parameters and kidney toxicity at exposure margins that are within the clinical exposure window. The increased erythroid maturation is an anticipated effect of activin A/GDF11 inhibition and were non-adverse at the highest tested doses. The Applicant explained that the kidney injury in healthy animals may have resulted from exaggerated pharmacology and that the response in patients with PAH may differ.

SC dosing of sotatercept in rat resulted in non-reversible hematological, kidney and testis/epididymis toxicity at exposures 18-times higher than the anticipated clinical exposure. The choice of dosing intervals precluded establishing a more appropriate interval since the established NOAEL equals only a 2-fold clinical exposure margin. Testis toxicity observed in rats was considered to be a pharmacologically driven but species-specific effect and unlikely to translate to humans. Blockage of the efferent ducts, an effect consistent with sotatercept-mediated inhibition of ActRIIsignaling, was the primary toxicity in rats that led to unilateral or bilateral testicular degeneration/atrophy. Because of anatomical differences between the efferent ducts of rats and humans (also section on DART), the

Applicant argues that the risk of testicular toxicity resulting from efferent duct blockage in humans is low.

After SC dosing of sotatercept in monkeys, target organs of toxicity were kidney, spleen, brain and liver, with mild hematological findings, at clinically relevant exposures. Across the repeat-dose toxicity studies in monkeys, there appears to be variation in the tolerability of sotatercept. Whereas the NOAEL after 3 months exposure is 30 mg/kg, although in a 6-month study at the same dose levels, a NOAEL could not be established and the NOAEL in a 9-month repeat dose toxicity study following monthly administrations, the NOAEL was 2.6 mg/kg, which did not represent a meaningful clinical exposure multiple. Therefore, it should be considered that findings in the monkey studies are all clinically relevant, including observations that were not seen in rat, such as hepatic inflammatory infiltrates and perivascular basophilic deposits (aorta/heart/pancreas), lymphoid depletion in spleen/thymus, and inflammatory infiltrates in the brain. There was no evidence of degeneration or necrosis in the thymus or spleen, no adverse findings in other lymphoid tissues, and no meaningful change in circulating white blood cells.

No effects on heart, adrenal gland or testes, as observed in rats, were found in monkeys. The findings in heart and adrenal gland are considered unlikely to translate to adult humans based on known species differences in target organ maturation. The Applicant explained that modulation of BMP-10 signalling, which is important in cardiac muscle development and growth, may have played a role in heart weight changes in very young and adolescent rapidly growing rodents only. In juveniles, however, the decreased heart weight is of concern (see section on DART). Similarly, sotatercept-mediated decreases in ActRIIsignalling during the critical adrenal gland remodelling period in the rat likely led to the observed histological changes (also see section on DART). Where testicular effects in rats may be explained by their different efferent duct anatomy, most monkeys in the studies were not sexually mature precluding an assessment of testis toxicity in this species.

Table 2. Repeat-dose toxicity studies

Study details Species Duration + recovery (weeks) Route GLP status (Study ID)	**No:Sex/ Group**	**Dose** (mg/ kg/ day)	**Exposure**		**Major findings & NOAEL**
			Cmax µg/ml	AUC µ/ml/h	
Repeat-dose toxicity studies		**(NOAELs highlighted)**			
Rat (Sprague Dawley) 90 + 30 d SC, Q1W GLP (TT #06-7823/1619-06231)	Main: 10M/10F Recovery: 5F/5M TK satellites: 0	0 0.3 **3.0** 30	N.D.	N.D.	Hematology ≥0.3 M/F: dose-dependent ↑ RBC, RTC and % RBC distribution width ≥0.3 F: ↓ MCV and MCH Macroscopic ≥3.0 M/F: ↓ heart weight =30 M/F: ↑ adrenal gland weight =30 M: ↓ kidney weight =30 F: ↑ liver weight Microscopic ≥0.3 M/30 F: dose-dependent membranous or membranoproliferative glomerulonephritis, tubular-cell basophilia, focal tubular degeneration/atrophy ≥0.3 M: hypospermatogenesis, aspermatogenesis, multifocal unilateral atrophy of the testis ≥0.3 M/F: congestion of the adrenal cortex or multifocal mineralization of the adrenal cortex Recovery 30 M: 2/5 aspermatogenesis **NOAEL 3.0 mg/kg**
Rat (Sprague Dawley) 90 + 30 d SC, Q1W GLP (TT #12-7833/20027785)	Main: 10M/10F Recovery and TK: 6M/6F	0 0.3 **3.0** 30	- D1: 1.65 D92: 3.94 D1:16.1 D92: 14.2 D1: 179 D92: 162	- D1: 233 D92: 610 D1: 2170 D92: 2090 D1: 2740 D92: 2650	Mortalities 30M: 1 uncertain relationship to treatment Hematology ≥0.3 M/F: dose-dependent ↑ RBC, HGB, HCT, RTC and RDW, ↓ MCH, MCHC, MCV =30 M: ↓ PLT Urinalysis ≥0.3 M/F: ↑ albumin =30 M/F: ↑ lipocalin-2 and osteopontin Macroscopic Fluid accumulation adjacent to kidney in two 30 mg/kg animals (1M, 1F) Microscopic ≥3.0M/0.3F: minimal-mild membranoproliferative glomerulonephritis ≥3.0F: minimal-mild chronic progressive nephropathy =30M/F: minimal-mild interstitial mineralization in kidney Recovery

					≥3.0M/30 F: majority of hematology findings persisted =30 M/F: strong ↑ urinary albumin =30 M: fluid accumulation adjacent to kidney in two animals ≥3.0M/0.3F: microscopic kidney findings persisted **NOAEL 3 mg/kg**
Rat (Sprague Dawley) 4 + 4 w IV, Q1W Non-Pivotal (TT #05-7846/ WHH00034)	Main: 10M/10F Recovery: 5M/5F	0 1 10 30	N.D.	N.D.	<u>Mortalities</u> 1x 10M + 1x 30M: potentially related to treatment, post-mortem changes consistent with findings in treated animals at scheduled necropsy <u>Hematology</u> ≥10M/1F: ↑ RBC, HGB, HCT + ↑ erythroid count in bone marrow ≥1M/F: ↑ RTC, ↓ MCH ≥10M/F: ↓ MCHC ≥10M: ↓ PLT, BSO, LUC <u>Clinical chemistry</u> ≥10M/F: dose-dependent ↑ ALT, AST, ALP <u>Urinalysis</u> ≥1F: proteinuria in 1 female per group =10M: proteinuria in 2 males =30M: proteinuria in 4 males <u>Macroscopic</u> ≥1M/F: ↓ heart weight ≥10M: epididymides nodules/foci =30M: ↑ testes weight =30M/10F: ↑ adrenal weight <u>Microscopic</u> ≥1F/30M: adrenal necrosis/chronic necrosis ≥10M: sperm granulomas =30M: testicular degeneration, ↓sperm motility and epididymal count for the 30 mg/kg dose group on Day 29. ≥10M/F: dose-dependent zymogen granule depletion and atrophy of pancreatic acini <u>Recovery</u> ≥10F: ↑ RBC, HGB, and HCT ≥10M/F: ↓ MCH, ↓ heart weight ≥10M/30F: ↑ ALT, ALP ≥10M: epididymides nodules/foci, sperm granulomas ≥10F: adrenal necrosis/chronic necrosis ≥10M/F: dose-dependent zymogen granule depletion and atrophy of pancreatic acini **NOAEL < 1 mg/kg**
Monkey (Cynomolgus) 3 m + 2 m SC, Q2W GLP	Main: 4M/4F Recovery: 2F/2M TK satellites: 0	0	-	-	<u>Hematology</u> ≥10M/F: ↑ RBC, HGB, HCT, RTC, RDW and ↓ MCH ≥50M/F: ↓ MCHC <u>Microscopic</u> ≥30M/F: mild (1x moderate) membranoproliferative, hypercellularity of kidney glomeruli
		10	D1: 142	D1:32139	
		30	D1: 351	D1:82389	
		50	D1: 530	D1:107155	

(TT #06-7824/1619-06233)					Recovery ≥50M/F: mild membranoproliferative, hypercellularity of kidney glomeruli **NOAEL 30 mg/kg**
Monkey (Cynomolgus) 6 m + 3 m SC, Q2W GLP (TT #07-7812/1619-06691)	Main: 3M/3F Recovery: 3F/3M TK satellites: 0	0	-	-	Mortalities =30F: after 4-5 m, 2 moribund females euthanised, showing ↑ creatinine/BUN and tubulointerstitial nephritis/ glomerulonephritis, ↑ AST/ALT, thymus lymphoid depletion Hematology ≥10M/F: ↑ RBC/HGB/HCT/RTC Clinical chemistry ≥10M/30F: ↑ BUN 30F: ↑ CREA Macroscopic ≥10M/30F: kidney discoloration, ↑ kidney weight, thymus discoloration, ↓ thymus weight Microscopic ≥10M/F: tubulointerstitial nephritis/glomerulonephritis, thymus hemorrhage, thymus lymphoid depletion ≥50M/30F: foamy macrophage infiltrates in choroid plexus Recovery ≥10M/F: tubulointerstitial nephritis ≥10M/30F: kidney discoloration, thymus hemorrhage ≥30M: foamy macrophage infiltrates in choroid plexus **NOAEL < 10mg/kg**
		10	D1: 103 W27: 187	D1:21942 W27: 29336	
		30	D1: 283 W27: 443	D1: 59828 W27: 87598	
		50	D1: 676 W27:1404	D1: 104022 W27: 165039	
Monkey (Cynomolgus) 9 m + 3 m SC, Q2W or Q4W GLP (TT #08-7938/WHH00061)	Main: 4M/4F Recovery: 2F/2M TK satellites: 0	0	-	-	Mortalities = 10M Q2W: one animal deteriorated due to kidney toxicity Clinical =10M/F Q2W: ↓ BW gain Hematology ≥1M/F: ↑ RBC/HGB/HCT/RTC =10M/F: ↓ MCV, ↑ RDW =10M Q2W: ↓ PLT =10M/F Q2W: ↓ BM M:E ratio Clinical chemistry ≥2.6M/F: ↑ BUN and CREA Urinalysis ≥2.6M/F: ↑ protein =10M/F: occult blood Macroscopic =10M/F: ↓ spleen weight, ↑ kidney weight, irregular renal cortical surfaces Microscopic *Kidney:* ≥2.6M/F: ↓ glomerular tuft size ≥1M/F: ↑ interstitial matrix at corticomedullary junction =10M/F: membranoproliferative
		1 Q4W	D1: 11.4 W17: 10.1 W37: 21.4	D1: 3945 W17: 3365 W37: 6030	
		2.6 Q4W	D1: 40.8 W17: 30.1 W37: 51.2	D1: 12188 W17: 8441 W37: 11729	
		10 Q4W	D1: 85.6 W17: 119.0 W37: 126.7	D1: 26116 W17: 28724 W37: 30776	
		10 Q2W	D1: 104.9 W17: 162.6 W39: 164.4	D1: 22617 W17: 32019 W39: 34555	

					glomerulopathy, renal fibrosis/ inflammation, basophilic tubular luminal deposits *Brain:* ≥1M/F: mononuclear cell infiltrates in choroid plexus =10M/F Q2W: foamy macrophage infiltrates and arterial wall thickening in choroid plexus *Spleen:* =10M Q2W/2.6F: lymphoid depletion *Liver:* ≥1M/F: mononuclear cell infiltrates =10M/F: hepatocellular rarefaction (consistent with glycogen storage) *Aorta, heart, pancreas:* ≥1M/F: perivascular basophilic deposits <u>Recovery</u> ≥2.6M/F: ↓ glomerular tuft size =10M/F Q2W: interstitial renal inflammation with fibrosis **<u>NOAEL 1 mg/kg</u>**
Monkey (Cynomolgus) 9 m + 2 m SC, Q2W Failed study (TT #06-7826/1619-06392)	Main: 4M/4F Recovery: 2F/2M TK satellites: 0	0 10 30 50	N.D.	N.D.	Study terminated early (week 9) due to high incidence of plasmodium infection, mainly in Sotatercept-treated animals but also some controls. <u>Mortalities</u> =50F: 1 moribund due to malaria <u>Hematology</u> ≥10M/F: ↑ RTC/RDW
Monkey (Cynomolgus) 4 w + 4 w IV, Q1W Non-pivotal (TT #05-7847/WHH00004)	Main: 3M/3F Recovery: 2F/2M TK satellites: 0	0 1 10 **30**	N.D.	N.D.	<u>Hematology</u> ≥1M/F: ↑ RBC/HGB/HCT/RTC ≥10M/F: ↓ BM M:E ratio **NOAEL 30 mg/kg**

2.6.4.3. Genotoxicity

In accordance with the ICH S6(R1) guideline, "The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology derived pharmaceuticals and therefore are not needed. Moreover, the administration of large quantities of peptides/proteins may yield uninterpretable results". Sotatercept is an IgG-based therapeutic fusion protein, consisting entirely of naturally occurring canonical amino acids, and is not expected to interact directly with DNA or have any genotoxic potential.

2.6.4.4. Carcinogenicity

As outlined in guideline ICH S6 (R1) "Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals", therefore the Applicant has not conducted any carcinogenicity studies but provided a 'weight of evidence' risk assessment regarding carcinogenicity potential. As a biologic compound, sotatercept does not pose a risk for genotoxicity, and based on literature there is no direct association of sotatercept ligand receptors with potential human carcinogenic concerns. In the non-clinical program, sotatercept treatment did not result in proliferative or pre-neoplastic changes in any species. The data from the rat/monkey repeat-dose studies and the juvenile study also indicate that sotatercept does not have toxicologically meaningful immunomodulatory effects that could impact its carcinogenic potential. Furthermore, non-clinical results as well as scientific literature suggest that sotatercept is unlikely to modulate hormonal signaling in a pro-carcinogenic manner. Taken together, sotatercept is considered to have low carcinogenic potential.

2.6.4.5. Reproductive and developmental toxicity

Activins A and B are known to play a critical role in diverse physiological processes required for normal reproduction and development. Activins A and/or B modulate FSH signalling within the hypothalamic-pituitary-gonadal axis and have direct effects on reproductive tissues. Developmental and reproductive toxicity studies in rats and rabbits showed efferent duct/testes toxicity, decreases in male and female fertility, increases in pre- and post-implantation loss, and delays in fetal/postnatal growth and maturation, consistent with decreased ActRII signaling. A weight of evidence approach in line with ICH S5(R3), could have been sufficient for this application, although it is understood that the studies were performed before the revision came into effect. Furthermore, anatomical differences between rat, rabbit and human placenta limit interpretation of the study. Nevertheless, the Applicant conducted GLP compliant fertility studies in male rats; fertility and early embryofetal development in female rats; embryofetal development studies in rats and rabbits; and pre- and postnatal development studies in rats. High incidence of immunogenicity across all study groups in both rats and rabbits further complicated the interpretation of the studies. Nevertheless, sufficient animals were exposed to provide an assessment of risk for sotatercept.

In the male fertility study, rats were administered 0.3, 3 or 30 mg/kg SC sotatercept Q1W before cohabitation through mating with untreated female rats, and included a 13-week recovery period. Other than a transient decease in body weight change at the start of the study, there were no other clinical observations in sotatercept-treated animals. The fertility index and the pregnancy index were reduced at 30 mg/kg compared to controls, which resolved after the recovery period. Animals with small size or abnormal consistency of testis and epididymis, unilateral or bilateral were observed in all dose groups, correlating with histopathological degeneration or atrophy in the testis or decreased cellularity of luminal sperm in the epididymis. Histopathologically, minimal to marked sperm granuloma, minimal to mild sperm stasis, minimal fibrosis, minimal to mild mineralization, and/or minimal to mild mixed cell infiltration were observed and increased in incidence and severity in a dose-dependent manner from 0.3 mg/kg. However, overall incidence was low. These changes were often unilateral and occasionally bilateral, ranging from small areas of focal mineralization and/or fibrosis within the efferent ducts to larger areas with sperm stasis and a surrounding mixed infiltrate. In several animals, sperm granulomas were present with evidence of occlusion of the efferent ducts. Changes in the seminiferous tubules in rats dosed from 0.3 mg/kg onwards were generally associated with efferent duct changes, and included an increased incidence and severity of unilateral or bilateral degeneration/atrophy of the seminiferous tubules with occasional animals at 30 mg/kg having additional changes including mild tubular dilation, dilation/sperm stasis in the rete testis, and/or sperm

granuloma. After the recovery period, mild sperm granuloma, minimal sperm stasis, minimal fibrosis, minimal mineralization, and/or minimal to mild mixed cell infiltration and incidentally, degeneration/atrophy of the seminiferous tubules with/without tubular dilation, sperm granuloma, sperm stasis, and/or mineralization and decreased epididymal sperm cellularity were still noted. Fertility findings in male rats were comparable with findings in others studies and driven by the pharmacology of sotatercept.

These findings are in line with blockade of efferent ducts and sequelae due to altered fluid dynamics. These effects are not anticipated to be relevant to humans because of anatomical differences between these species: in rats efferent ductules are long and merge into a single duct that enters the epididymis, whereas in humans the efferent ductules are shorter, do not merge into a single duct and enter the epididymis at several sites allowing fluid outflow even if several ducts become blocked or fluid reabsorption is inhibited. ADAs were detected in 0 of 30 control animals, 16 of 30 (53.3%) animals at 0.3 mg/kg Q1W, 17 of 30 (56.7%) animals at 3 mg/kg Q1W, and 18 of 29 (62.1%) animals at 30 mg/kg Q1W, for a total incidence rate of 57.3% (51 of 89). The NOAEL for adverse histopathology findings was 0.3 mg/kg. Due to the decreased fertility and pregnancy index at 30 mg/kg, the reproductive NOAEL was 3 mg/kg once weekly, which corresponds to an estimated Cmax and AUC0-168h of 20.3 µg/mL and 2960 µg.h/mL, respectively, which is below the clinical exposure at the MRHD (exposure multiple is ~0,7x).

Table 3. Fertility studies in male animals

Study details	**No:Sex/ Group** <text>	**Dose** (mg/ kg/ day)	**exposure**		**Major (alt salient) findings & NOAEL**
			Cmax µg/ml	AUC µg/ml/h	
Fertility and early embryonic development studies (NOAELs highlighted)					
Rat, Crl:CD(SD) 10 weeks prior to mating until day 85 SC, 1QW GLP TT #19 7840/20175739 *TK estimated based on TT #12-7833/20027785	20M	0	-	-	Clinical observations ≥0.3:↓BWg Fertility parameters =30:↓ferility index, ↓pregnancy index Pathology ≥0.3: unilateral or bilateral small size or abnormal consistency of testis and/or epididymis Histopathology ≥0.3: minimal to mild mineralization of efferent ducts, marked to severe decreased cellularity of sperm in epididymis, minimal to marked degeneration/atrophy of seminiferous tubules, minimal to mild mixed cell infiltration of efferent duct, minimal efferent duct mineralization and fibrosis, mild sperm granuloma ≥3: sperm stasis Recovery ≥0.3: mild sperm granuloma, minimal sperm stasis, minimal fibrosis, minimal mineralization, and/or minimal to mild mixed cell infiltration
		0.3	ND	ND	
		3	ND	ND	
		30	ND	ND	

To evaluate female fertility, female rats were administered 5, 15 or 50 mg/kg SC sotatercept Q1W starting 2 weeks prior to mating and continuing through GD7. Two females were terminated early due to severe swelling of hind limbs and decreased mobility on GD5 or 8. These animals had an enlarged red adrenal gland and moderate to severe edema in the hindlimb, which was considered test-article related. Hindlimb swelling and enlarged or discolored adrenal glands were also observed in animals dosed with 15 mg/kg and in surviving 50 mg/kg animals. Fertility was generally affected due to sotatercept. During the premating period, increased estrous cycle length was noted at 50 mg/kg Q1W (6.7 days vs. 4.6 days in controls) and correlated with a lower mean number of cycles (1.7 vs. 2.4 in controls). Fertility and fecundity indices were lower from 15 mg/kg onwards compared to concurrent and historical control data. High dose females also had a lower mating index compared to controls and the historical control range. From 15 mg/kg onward, lower pregnancy rates, increased pre- and post-implantation loss; fully resorbed litters; and reductions in litter size were observed on GD 13. In these dose groups, lower gravid uterine with cervix weights (absolute and relative to body weight) were also observed and were associated with a reduction in the number of viable embryos and an increase in post-implantation loss. ADAs were detected in 1 mid-dose and one high-dose TK group animal. Antibody formation may have lowered the exposure in these animals but did not have an apparent effect on the overall serum profiles for the dose groups. The overall incidence of ADAs in the 0, 5, 15, and 50 mg/kg Q1W dose groups was 0/28, 14/30, 12/30, and 6/30, respectively.

Based on the early sacrifice of 2 females at 50 mg/kg Q1W, the NOAEL for maternal toxicity was 15 mg/kg Q1W, corresponding to an AUC0-168h of 12,300 µg.h/mL, which is approximately 9-fold above the clinical exposure at the MRHD. The NOAEL for female fertility and early embryonic development was 5 mg/kg Q1W, corresponding to an AUC0-168h of 2,735 µg.h/mL, which is approximately 2 times the clinical exposure at the MRHD.

Fertility risk in male and female animals has been adequately reflected in the SmPC.

Table 4. Fertility studies in female animals

Study details Species Treatment period GLP status (Study ID)	**No:Sex/ Group** <text>	**Dose** (mg/ kg/ day)	**exposure**		**Major (alt salient) findings**
			Cmax µg/ml	AUC µg/ml/h	
Fertility and early embryonic development studies (NOAELs highlighted)					
Example: Rat, Crl:CD(SD) 2 weeks prior to mating through GD7 s.c., 1Qw GLP TT #10 7863/847-057	25F	0	-	-	Mortality =50: 2F, euthanised on GD 5 or 8 with moderate to severe swelling of hindlimb, enlarged red adrenal gland, moderate to severe hindlimb edema Fertility parameters ≥15: ↓fertility index, ↓fecundity index, ↓pregnancy rates, ↑pre- and postimplantation loss ↓litter size on GD13 =50: ↓mating index, ↑estrous cycle length and lower mean cycles,
		5	**106 ± 64.9**	**2,735**	
		15	165 ± 60.9	12,300	
		50	211 ± 104.7	28,761	

					Clinical observations ≥50: hindlimb swelling, impaired mobility Pathology ≥15: enlarged and or discolored adrenal glands, ↓gravid uterine with cervix weight (abs and rel to bw)

Embryofetal development studies were conducted in rat and rabbit. In the GLP compliant embryofetal development (EFD) study, pregnant female rats were administered sotatercept at doses of 5, 15 or 50 mg/kg SC Q1W between GD6 and GD 13. No maternal toxicity was observed, which is discrepant with the fertility and early embryofetal toxicity study where maternal toxicity was observed from 15 mg/kg onward. The Applicant explained that the main driver for differences between these studies was considered to be the increased number of doses and increased dosing period of the FEED study. At 50 mg/kg, post-implantation loss was increased, as were the mean number of resorptions per litter. As a result, the average litter size was decreased as were the number of live fetuses. Where decreased fetal body weight was still within historical control values in fetuses exposed to 5 mg/kg sotatercept, a drug-related decrease in fetal body weight was apparent from 15 mg/kg onwards. This decrease was correlated with delayed ossification of vertebrae, metatarsals or phalanges. At 50 mg/kg, the highest dose tested, increased skeletal variations were also observed. No visceral variations or malformations were noted at any dose. Based on the adverse magnitude of decreased fetal weights at 15 mg/kg, the developmental NOAEL was 5 mg/kg, corresponding to an AUC0-168h of 2642 µg.h/mL, which is below the clinical exposure at the MRHD.

A rabbit EFD dose range finding study using dose levels of 5, 15 or 50 mg/kg showed considerable maternal and fetal toxicity, after which the pivotal rabbit EFD study was conducted using lower dose levels. In this pivotal GLP compliant EFD study, rabbits received 0.5; 1.5; or 5 mg/kg sotatercept SC Q1W between GD7 and GD14. There was no maternal toxicity at any dose level. Dose dependent decreases in lower fetal body weight were noted from 1.5 mg/kg onward. In the 5 mg/kg dose group this was correlated with lower mean ossification sites. Furthermore in pregnant rabbits receiving 5 mg/kg, additional fetal toxicity was observed in the form of increased post-implantation loss and lower number of live fetuses. ADAs were detected in 64% of the treated main study rats and 83% of the treated satellite TK rats. The development of ADAs following the second injection did not significantly reduce serum levels of sotatercept prior to GD 18. The NOAEL for maternal toxicity was 5 mg/kg, which corresponded to a maternal AUC0-366h of 10,900 µg.h/mL and an exposure multiple of approximately 2 times above the MRHD. ADAs were detected in one 5 mg/kg rabbit on GD 14 only and had no apparent effect on sotatercept serum concentrations in that animal. The developmental NOAEL was considered to be 0.5 mg/kg, corresponding to a maternal AUC0-366h of 1070 µg.h/mL following dosing on GD 14, which is below the exposure at the MRHD (0.36x EM). The human relevance of these findings is unknown due to the anatomical differences of the placenta between species. Nevertheless, the risk is adequately reflected in the SmPC.

Table 5. Embryofetal toxicity studies in rat and rabbit

Study details Species treatment period Route GLP status (Study ID)	**No:Sex/ Group**	**Dose** (mg/ kg/ day)	**exposure**		**Major (alt salient) findings & NOAEL**
			Cmax µg/ml	AUC (GD13) µg/ml/h	
Embryo-fetal toxicity studies (NOAELs highlighted)					
Rat, Crl:CD(SD) GD 6 and 13 s.c. 1Qw GLP TT #09-7913 (WHH00069)	28F	0	-	-	Mortality =50: one TK satellite animal, non-drug related. Pregnancy parameters =50: ↑postimplantation loss, ↑resorptions per litter, ↓average litter size, ↓live fetuses F1 parameters ≥15: ↓fetal body weight, delayed ossification thoracic vertebrae; lumbar vertebrae; hindlimb metatarsal; hindlimb phalanges =50: ↑variations (supernumerary thoracic ribs with associated significant increases, decreases in the numbers of thoracic and lumbar vertebrae)
		5	**ND**	**2642**	
		15	ND	5088	
		50	ND	19885	
Embryo-fetal toxicity studies (NOAELs highlighted)					
Rabbit, New Zealand White GD7-14 s.c. 1Qw GLP TT #19-7841 (20183480)	23F	0	-	-	Fertility parameters ≥1.5: ↓fetal weight =5: ↑postimplantation loss, ↓live fetuses, lower mean ossification sites in metacarpals; forlimb phalanges; hindlimb phalanges
		0.5	**6.89**	**1070**	
		1.5	17.6	1780	
		5	61.5	10900	

In the rat prenatal and postnatal development study, F0 generation maternal rats were treated with sotatercept either during gestation or during the lactation period because of anticipated immunogenicity. An evaluation of Caesarean-delivered fetuses was evaluated in a supplementary study. Pregnant rats received 1.5 or 5 mg/kg sotatercept SC Q1D between GD6 and GD113. Lactating rats received 1.5, 5 or 10 mg/kg sotatercept SC Q1D on LD1, LD8 and LD15.

All F0 generation females survived to the scheduled euthanasia. No sotatercept-related effects were observed in the F0 generation females during the gestation or lactation periods for any of the following parameters: clinical signs, mean maternal body weights or body weight gains, natural delivery, maternal behaviour, and macroscopic observations. Decreased but non-adverse food-consumption was observed in F0 animals receiving 10 mg/kg sotatercept from LD10-15. No litter effects were observed in the F0 generation at any dose level administered during gestation or lactation as evaluated by the number of dams delivering litters, the duration of gestation, implantation sites per delivered litter, the gestation index (percentage of pregnancies that result in birth of live litters), the number of liveborn and stillborn pups, the viability index (percentage of pups that survived from birth to LD 4), the

lactation index (percentage of pups born that survived to weaning), surviving pups per litter, the sex ratio, and live litter size at weighing.

In pre-weaned F1 animals from the 5 mg/kg dose groups onward, there was a dose-dependent adverse decrease in body weight and body weight gain in both male and female animals which persisted into adulthood. From 5 mg/kg onward, delayed sexual maturation was observed in males (increased mean day of preputial separation) and females (increased mean day of vaginal patency). There were no changes in the F1 generation when F0 rats were dosed during gestation, nor were there effects on male or female reproductive performance in F1 animals at any dose level from either maternal segment, nor was there a sotatercept related effect on fetuses generated by F1 animals. No test article-related effects were observed during the acoustic startle, motor activity and Morris Water Maze evaluations.

The maternal NOAEL for sotatercept was 5 mg/kg or 10 mg/kg when administered during gestation or lactation, respectively, and the reproductive NOAEL is 5 mg/kg when administered during gestation and 10 mg/kg when administered during lactation. NOAEL for viability and growth in the offspring when sotatercept is administered to pregnant rats during gestation or lactation was 5 mg/kg and 1.5 mg/kg, respectively.

Table 6. Prenatal and postnatal development studies in rats

Study details Species treatment period Route GLP status (Study ID)	**No:Sex/ Group**	**Dose** (xg/kg/ day)	**exposure**		**Major (alt salient) findings & NOAEL**
			Cmax xg/ml	AUC xg/ml/h	
Prenatal and postnatal development studies (NOAELs highlighted)					
Rat, Crl:CD(SD) GD 6-PND15 s.c. GLP TT #20-7830 (20245155)	22F	0	-	-	<u>F0</u> None <u>F1</u> <u>Clinical observations</u> ≥5: dose dependent ↓body weight and ↓body weight gain, ↑ day preputial separation, ↑ day vaginal patency.
		1.5	ND	ND	
		5	ND	ND	
		10*	ND	ND	
*dose level used for lactating females only					

Two juvenile animal studies were conducted in rats, in which animals were S.C. dosed once weekly from PND7-91 following a 13-week recovery period (first study) or 18 weeks (second study). The second study was conducted as a result over concerns about the quality of the first study and high mortality observed. Neither study was able to establish a NOAEL. Furthermore at PND 7, rat kidney is not fully formed and in active development whereas in children from 1 year old onwards, kidney

development is complete and maturing (in line with table 1A of ICH S11). In the second study, animals were given 0-1-3 or 10 mg/kg sotatercept S.C. Mortality in the first study occurred at 30 mg/kg, the highest dose tested but was not observed in the second study at any dose and where the high dose group received 10 mg/kg. Because the 30 mg/kg dose group was terminated early, the current assessment has evaluated the second study in more detail. Overall, the safety profile of sotatercept in both studies was generally comparable. At all dose levels tested, sotatercept administration generally resulted in decreases in body weight and food consumption and developmental delays in sexual maturation. The data from this juvenile animal study are not relevant for the current indication but are for the further paediatric development plan.

In juvenile rats given sotatercept from 3 mg/kg onward, decreased hindlimb grip strength decreased in males and at 10 mg/kg swollen hindlimbs with decreased function was observed in both males and females.

Decreased heart weights and post mortem findings in the kidney, adrenal gland, and testes/epididymides generally occurred at all doses and were similar to those observed in adult rats. Erythroid parameters were increased at all doses, and clinical chemistry and urinalysis changes consistent with renal toxicity were present and persisted after the recovery period.

In recovery animals, there were decreases in mating and fertility parameters, minor clinical chemistry changes persisted, in line with the anticipated pharmacological effects of sotatercept, and post-mortem findings were generally similar to those observed at the earlier necropsy. The effects of sotatercept on growth, development, reproduction, erythroid cell and adrenal gland maturation, and testicular function in juvenile rats are all similar to effects observed in rats in other sotatercept toxicity studies and are consistent mechanistically with decreases in ActRIIsignaling.

T-cell dependent antibody response (TDAR) assays and immunophenotyping assessments were performed in the juvenile animal studies. Sotatercept does not alter IgG or IgM mediated responses to a KLH challenge. Immunophenotyping showed small fluctuations in B-cell and NK-cells but was not adverse due to a low magnitude of change and a trend for recovery. ADAs were not detected in animals tested on PND 128. However, ADAs were detected in 1 female at 0.3 mg/kg Q1W and 1 female at 3 mg/kg Q1W on GD 13, and in 1 male on PND 239 at 3 mg/kg Q1W. At some timepoints, elevated levels of circulating sotatercept may have interfered with the detection of ADAs, leading to false negative results. The NOAEL for the pivotal juvenile toxicity study was below 1 mg/kg per week (AUC0-168h = 3080 µg*h/mL, corresponding to less than the clinical exposure at the MRHD.

Table 7. Juvenile animal studies in rats

Study details Species treatment period Route GLP status (Study ID)	**No:Sex/ Group**	**Dose** (mg/ kg/ day)	**exposure**		**Major (alt salient) findings & NOAEL**
			Cmax µg/ml	AUC µg/ml/h	
Juvenile animal toxicity studies (NOAELs highlighted)					
Example: Rat (Crl-WI/Han) PND 6-63 PO GLP TT #14-7864 (WIL-553095)	Control: 56/s/g, Sotaterce pt: 74/s/g	0	-	-	Clinical observations ≥1: impaired or swollen hindlimbs, ↓bw,↓fc, delayed sexual maturation, ≥3M: ↓hindlimb grip strength =10M: decreased fertility and conception index Hematology ≥1: ↑Ret, , ↑HCT, ↑HGB, ↓MCH, ↓platelet, ↑RBC, ↑RBV =10: ↓Fibrinogen, ↑MPV Hormone analysis =3M: ↓FSH =10F:↓Estradiol Pathology ≥1: dilated pelvis ≥1M: small or soft epididymides and testes, decreased epididymis weight, decreased heart weight (absolute and relative), increased prostate weight (absolute and relative) 3M: ↓testes weight (absolute and relative) 10F: increased ovaries weight (absolute and relative) Histopatholgy ≥1: minimal to moderate hypertrophy in zona fasciculata, minimal to moderate medullary atrophy/hypoplasia (one severe case), minimal to mild increased medullary stoma (one moderate case), minimal to moderate dilatation of kidney tubules, minimal to mild dilatation of pelvis, minimal to moderate mebranoproliferative glomerulonephriotis,
		1	21.2	3085	
		3	34	5020	
		10	99,7	14100	

					minimal to moderate chronic progressive nephropathy, minimal to mild hepatocellular vacuolation, ≥1M: moderate to severe reduced luminal sperm and minimal to mild luminal cellular debris, minimal mineralization of glandular stomach, moderate to severe tubular degeneration of testes (bilateral) ≥3: mild to severe necrosis in adrenal cortex, minimal to moderate medullary hemorrhage (one moderate case in low dose), minimal to mild decreased cellularity of hymphoid marginal zone in spleen <u>Recovery</u> ≥1: ↓Body weight, small or soft testes and epididymis, dilated pelvis, epididymis weight, heart weight (M), histopathological adrenal cortex, histopathology, kidney, spleen, testes and stomach findings 3M: Testes weight 10F: Kidney weight

2.6.4.6. Toxicokinetic data

Kinetics data from toxicity studies, where available, are included in the relevant toxicology sections above.

2.6.4.7. Local Tolerance

Local tolerance was assessed in repeat-dose toxicity studies in rats and monkeys. No pathological findings were detected at the site of IV or SC injection.

2.6.4.8. Other toxicity studies

Antigenicity

The Applicant has assessed tendency of ADA formation in repeat-dose toxicity studies in rats, rabbits and monkeys. In the rat and rabbit, the overall ADA-positive rate in all sotatercept-dosed animals during the dosing phase was 43.6% and 41%, respectively. ADAs generally lead to decreased exposure. In the monkey, there was a positive signal of ADA formation with 2 of the 12 animals dosed with 10 or 30 mg/kg and in 4 of the 12 animals dosed with 50 mg/kg in the 6-month study. After Day 85 of dosing, two of the six female animals in the 30 mg/kg and one male monkey in the high-dose (50 mg/kg) group had a clearly decreased sotatercept exposure profile. Predictivity for the immunogenicity potential in humans is low.

There were no ADA-mediated toxicity findings. ADA positivity did not correlate with the observed kidney changes in rats or monkeys. The potential for sotatercept ADAs to form immune complex deposits within the monkey glomerulus and choroid plexus was investigated using IHC on kidney and

brain tissues from a subset of animals from the 9-month study. No ADA-drug complex deposits were observed.

Immunotoxicity

Sotatercept has the potential to modulate immune function, given that activin signalling is involved in the activation or function of macrophages, B cells and T cells, as described in literature. However, in the non-clinical studies of sotatercept, no toxicologically meaningful immunomodulatory effects were observed. Sotatercept did result in lymphoid depletion in thymus in the 6-month monkey study and lymphoid depletion in spleen in the 9-month monkey studies, but these findings were reversible and not associated with changes in circulating white blood cells. Therefore, immunotoxicity by sotatercept is not expected.

Dependence

No dependence studies are needed as sotatercept does not act on the central nervous system.

Studies on metabolites

According to ICH S6, degradation of biotechnology-derived pharmaceuticals to small peptides and individual amino acids is generally understood. Therefore, no specific studies on metabolites are required.

Studies on impurities

Impurities were detected at very low levels and no specific toxicology studies are necessary.

Phototoxicity studies

Phototoxicity of protein drugs is not relevant.

Excipient studies

All excipients are well-known and suitable for use in medicinal products and therefore no specific studies on excipients are necessary.

Other toxicity studies

Additional non-GLP studies were conducted in animal models of renal disease to assess the potential immunogenicity of sotatercept. In mice, mortality and severe toxicity were observed at 10-50 mg/kg, but these results are not toxicologically relevant given the use of a murine surrogate of sotatercept (RAP-011) and the IP route of administration. In rats, SC-treatment with sotatercept at 1-10 mg/kg Q1W exacerbated kidney lesions in the 5/6 nephrectomised model but not the renal compromise (unilateral ureter ligation) model, though ADA complex formation did not seem a primary mechanism, similar to observations in the GLP repeat-dose studies.

2.6.5. 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).

2.6.6. Discussion on non-clinical aspects

Pharmacology

The Applicant provided a comprehensive package of non-clinical pharmacology studies.

Primary pharmacodynamics were studied in several *in vitro* and *in vivo* studies. Sotatercept was developed as a soluble ActRIIA receptor, in order to scavenge the ligands of the TGF- β-activin nodal branch, which is overexpressed compared to the BMP-GDF branch in pulmonary arterial hypertension. Sotatercept needs to bind members of the TGF- β-activin nodal branch, to prevent over-activation of the pSMAD2/3 pathway in relation to the pSMAD 1/5/8 pathway. However, it also appears to bind to ligands of the BMP-GDF branch *in vitro*. The selectivity of sotatercept for only capturing ligands of the TGF- β-activin nodal branch is not clear. The Applicant discussed the physiological effects of Activin A, Activin B, GDF11 and BMP10 in more detail, both within the pathology of PAH as well as general effects in the body in order to support the mechanism of action of sotatercept in the clinical indication in PAH. The selection of cell lines and ligand concentrations for the cell based reporter gene assay (PD002) was driven by ligand/Smad expression. With regard to these data, the clinical implications of the complete inhibition of ligands of the BMP-GDF branch due to the high concentrations of sotatercept seen in humans at clinical dosages was discussed. Complete inhibition of BMP10 signaling by therapeutic concentrations of sotatercept is considered unlikely. Because BMP10 has a binding affinity that is about 200-fold weaker than Activin A and Activin B, these high affinity ligands will compete more efficiently for available sotatercept ligand binding sites and reduce the potential for BMP10 binding. Based on the described physiological effects of BMP10, there does not seem to be clear non-clinical toxicity related to BMP10 inhibition.

In vivo, effects of RAP-011 (a murine surrogate of sotatercept) on cardiovascular endpoints were presented in different PAH models of rats and mice. A clear dose-response could not be determined based on the provided data. There appears to be no dose response (but there is an effect compared to vehicle), so either there is no dose-response or the dosages applied in the studies were too high/at maximum response. The Applicant indeed argues that already at 1 mg/kg RAP-011 the inhibition of activin A, activin B, GDF-8, and GDF-11 may have been sufficient to reach maximum efficacy. To strengthen this conclusion, the estimated exposure (AUC) of the animals in these studies was determined by extrapolation from the PK measured in the repeat-dose toxicity studies. The exposure at 1 mg/kg would, according to the established IC50 values, indeed be sufficiently high to support a maximum effect.

Secondary pharmacodynamics were only studied in one *in vivo* study in mice in order to understand the effects of sotatercept on heamatologic endpoint. This study did not evaluate the effects of RAP-011 administration on platelet number. In toxicology studies in rats increases in RBC, HgB and HCT were seen (not considered adverse) and this is consistent with mechanism-based decreases in Activin A and GDF11. The decreases in platelet count in the repeat dose toxicity studies were small in magnitude and not anticipated to impact primary hemostatis. However, the Applicant agrees that although the effects seen in non-clinical species are of small magnitude and at exposure multiples of 13-to-18-fold, the relevance to the human situation is uncertain.

Safety pharmacology studies revealed no sotatercept-related abnormalities at neurological, cardiovascular or respiratory endpoints in monkey (9-month repeat-dose toxicity study), nor any concerns regarding hERG inhibition (IC50 > 1000 ug/mL *in vitro*).

Pharmacokinetics

Three animal species were used for pharmacokinetics/ toxicokinetics testing: Cynomolgus monkey (SD, Q2W) and Sprague-Dawley rat (SD, QW) using IV or SC sotatercept dosing and pregnant NZW rabbit

(only SC, QW). The sotatercept PK profile in rats, rabbits, and monkeys was characterized by a biphasic distribution and elimination pattern with a low volume of distribution (2 to 5-fold plasma volume), which is consistent with the known biodistribution of antibodies, and a low clearance resulting in a long terminal elimination half-life (SC) ranging from 2 to 3 days in rabbit, 4 to 8 days in rats, and 7 to 9 days in monkey, which is lower than in human (21 d). Exposure (Cmax, AUC) was found to be roughly proportional to the dose. Accumulation upon multiple dosing is generally absent or low. Rats and rabbits developed anti-drug antibodies (ADA) responses (approximately 44%) that resulted generally in lower exposures. A positive ADA response was also observed in monkeys although the overall incidence of ADA was less with the lower doses (16.7%) as compared to the high dose (33.3%), leading to decreased sotatercept exposure levels in a few animals. In the single-dose (pk006mk7962) and repeated-dose (TT#07-7812) study, similar doses (10 and 30 mg/kg) were administered subcutaneously to monkeys. However, significant differences in the pharmacokinetic profile were observed after the first dose in both studies: exposure values (AUC and C_{max}) were higher in the repeated-dose study, while $t_{1/2}$, Vd and CL were higher in the single-dose study. Different AUC values can explain the different CL/F and Vd/F values and the PK curves during 7 days support drug clearance was similar in both studies. Therefore, despite the reasons of the differences in sotatercept systemic levels in pharmacokinetic and toxicokinetic studies remain unknown, these do not raise concerns regarding the PK profile of sotatercept in monkeys (e.g. distribution, clearance…). At the current stage of clinical development, when the posology of the treatment and the drug PK profile in humans have been defined, the most relevant data from PK and TK analysis in animals are those used to calculate safety margins. Since consistency of exposure data was demonstrated in independent studies at the NOAELs determined for clinically relevant effects, the issue is not further pursued.

Toxicology

GLP-compliant repeat-dose studies were conducted in rats with a duration of 3 months and in monkeys with a duration of 6 months and 9 months. Though kidney toxicity was observed consistently in both rat and monkey repeat-dose studies at clinically relevant exposure levels, it has not translated to human to date. The non-clinical kidney observations may be immunologically mediated but did not seem to be associated with ADA-formation, as demonstrated by IHC, and could therefore be directly mediated by sotatercept. Given the markedly increased toxicity in the 6/9-month versus the 3-month monkey studies, it was unclear why longer duration of repeated sotatercept administration in monkeys led to the markedly reduced tolerability, in particular regarding kidney toxicity. The Applicant explained that membranoproliferative glomerulonephritis was likely the initiating change in the cascade of kidney toxicities that were observed in animal studies at higher doses or with longer treatment. Potential pharmacological mechanisms of kidney toxicity may be related to PD since decreased BMP10 signaling has been linked to glomerular injury (through decreased ALK1 signaling). In addition, literature suggests a potential role of GDF-11 in renal tubular pathophysiology. Although it is plausible that the kidney injury in animals resulted from exaggerated pharmacology by sotatercept, it cannot be ruled out that the kidney toxicities are clinically relevant. The Applicant also noted that there may be differences in response between healthy animals and patients with PAH, and that no clinical findings related to kidney toxicity have been identified so far.

Testis/epididymis toxicity, in line with efferent duct blockage that may result from sotatercept-mediated inhibition of ActRIIsignaling, was observed in rat at all doses. This finding could not be investigated in monkey because the majority of monkeys were not sexually mature. Activin-A subunits are present in the Sertoli cells, Leydig cells, and seminal fluid of adult humans. Despite limited evidence and lack of expression in testis, it could conservatively be assumed this can include ActRIIa. As such, ductule blockade is a theoretical possibility. However, the anatomical differences in the efferent duct between rats and humans greatly reduce the potential for adverse effects on male reproductive organs even if some ductules would become occluded. This correlates with the absence of

AEs consistent with sperm granuloma or testis atrophy have been reported in patients to date. Nevertheless, the potential risk of impairment of male fertility has been adequately reflected in the SmPC and RMP.

In the repeated dose toxicity studies in rats, mild focal or diffuse congestion within the adrenal cortex was observed at sotatercept SC doses ≥0.3 mg/kg Q1W, whereas the NOAEL of these studies was 3 mg/kg. The Applicant explained that mild focal or diffuse congestion within the adrenal cortex observed at 0.3 and 3 mg/kg in rats was considered non-adverse based on the lack of structural changes in the adrenal cortex and the reversibility of the changes. The potential risk is adequately reflected in the SmPC and RMP.

The cause of the inflammatory infiltrates observed in the monkey choroid plexus is unknown. IHC data indicates that these changes are unlikely the result of ADA/immune complex deposition. The Applicant suggests this is directly related to sotatercept. Given that sotatercept is considered unlikely to cross the blood-brain-barrier, additional information was requested on how it may have caused inflammatory brain lesions. The Applicant hypothesized based on literature that reduced Activin A activity in endothelial cells that form part of the blood brain barrier result in increased VEGF activity, which has been linked to tissue inflammation. Translation to human is uncertain due to the complexity of the Activin A pathways in the choroid plexus, though the Applicant noted that so far no related serious adverse events have been found. The potential risk has now been adequately reflected in the SmPC and RMP.

Inflammatory infiltrates were observed in liver at clinical exposure margins in monkeys. The Applicant provided literature information on how Sotatercept may be linked to hepatic inflammation via GDF-11 and activin signaling. Translation to human is uncertain though the Applicant noted that so far no related adverse events have been found. The potential risk has now been adequately reflected in the SmPC and RMP.

Perivascular basophilic deposits were observed in aorta/heart/pancreas. The Applicant explained that these were acellular accumulations of haematoxylin-bound components and therefore potentially not inflammatory. Although the cause and content of the basophilic deposits are unknown, their toxicological significance is agreed to be low because there was no corresponding tissue injury and the findings were reversible.

The weight of evidence (WOE) discussion on the carcinogenicity risk of sotatercept does not mention the haematological malignancies (lymphoma, myeloid- and lymphoid leukaemia) that were observed in a juvenile toxicity study in rats with the related approved product luspatercept (Reblozyl) which has a similar pharmacological target and toxicological profile as sotatercept. The Applicant discussed the impact of the malignant findings in the juvenile study with luspatercept on the WOE carcinogenicity assessment for sotatercept. Luspatercept and sotatercept are pharmalogically related since they may both affect blood cell formation via GDF-11, although there is no clear link with leukemic malignancies. Though the incidence of the haematological malignancies observed with luspatercept was low and no dose-response was apparent, the occurrence of these tumours in young animals was unusual and the relationship to luspatercept therapy could not be ruled out. In contrast, no haematological malignancies were observed in the two comparable sotatercept juvenile rat studies or in any sotatercept non-clinical study. The WOE carcinogenicity assessment for sotatercept is therefore unchanged.

Embryofetal development studies were conducted in rat and rabbit. In the GLP compliant embryofetal development (EFD) study, pregnant female rats were administered sotatercept at doses of 5, 15 or 50 mg/kg SC Q1W between GD6 and GD 13. No maternal toxicity was observed, which is discrepant with the fertility and early embryofetal toxicity, but which can be explained by the increased number of doses and increased dosing period of the FEED study. The exposure at the end of the fertility study

was roughly double that of the high dose in females in this EFD study where the NOAEL for pregnant females was the highest doses tested, corresponding to an AUC0-168h of 19,885 µg.h/mL, which was due to an error in calculating the AUC, which has been corrected. The overestimation of AUC does not affect the risk assessment in any way.

Decreased heart weight was observed in juvenile and young adult rats. Decreases in heart weight were noted in animal studies but were without histological or functional correlates or changes. Although a sotatercept-mediated pharmacological effect on cardiac muscle development and growth cannot be fully ruled out, a risk for paediatric patients is unlikely. Because the rat is rapidly growing at a rate not seen in humans, the observed changes heart in juvenile animals are unlikely to be relevant.

Luspatercept, which shares the MoA of sotatercept does contain a contraindication for pregnancy. The Applicant was requested to discuss whether there are compelling arguments against a CI for pregnancy for sotatercept. Literature shows that Activins A and B play a critical role in diverse physiological processes required for normal reproduction and development, including maintenance of pregnancy, which is confirmed by the observed reproductive toxicity in animal studies at clinically relevant doses. Animal data showed embryofetal lethality but did not suggest that sotatercept is a teratogen as no malformations were observed. The risk has been adequately described in the SmPC and a contra-indication for pregnancy is not needed, given the severity of the disease and the overall detrimental effect of the disease on pregnancy.

With respect to the ecotoxicity/environmental risk assessment (ERA), the active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, sotatercept is not expected to pose a risk to the environment.

2.6.7. Conclusion on the non-clinical aspects

In general, sotatercept is a recombinant human homodimeric fusion protein consisting of the extracellular domain (ECD) of human activin receptor type IIA (ActRIIA) linked to Fc domain of human IgG1. In PAH the TGF- β -activin-nodal branch is overexpressed compared to the BMP-GDF branch. Binding of different ligands to ActRIIinduces the downstream Smad2/3 or Smad 1/5/8 signaling, depending on the ligands that bind. Sotatercepts mode of action consists of binding of TGF- β -activin-nodal branch ligands so that the Smad 2/3 pathway is inhibited and balance between Smad 2/3 and Smad 1/5/8 is restored.

Binding of sotatercept to ligands of the TGF- β -activin-nodal branch has been shown *in vitro* and an effect of sotatercept on cardiological endpoints compared to vehicle has been shown in *in vivo* studies.

From the pharmacokinetic point of view, no objections or concerns have been identified and the cynomolgus monkey was the most relevant species for non-clinical safety studies.

Overall, the toxicology programme showed that in all repeat-dose toxicity studies, in both rats and monkeys, sotatercept caused an increase in erythroid parameters and kidney toxicity at exposure margins that are within the clinical exposure window. The increased erythroid maturation is an anticipated effect of activin A/GDF11 inhibition and was non-adverse at the highest tested doses. The adverse kidney toxicity observed in both species may be related to decreased BMP10/GDF-11 signaling, although the clinical relevance is unclear. PD-mediated testicular toxicity was observed in rats at clinical exposure margins and may be related to rat-specific anatomy, though a risk for humans cannot be excluded since this toxicity was not investigated in monkey. Inflammatory infiltrates in brain and liver, which were observed in monkey only after 9 months of treatment at clinical exposure margins, are also toxicologically relevant. The toxicities observed in the repeat-dose studies have been adequately described in the SmPC.

Sotatercept was well-tolerated locally after SC and IV administration. Genotoxicity, carcinogenicity, immunotoxicity, dependence and phototoxicity are not expected. Any metabolites, impurities and excipients are not toxicologically relevant.

Activins A and B are known to play a critical role in diverse physiological processes required for normal reproduction and development. Unsurprisingly, developmental and reproductive toxicity studies in rats and rabbits showed efferent duct/testes toxicity, decreases in male and female fertility, increases in pre- and post-implantation loss, and delays in fetal/postnatal growth and maturation, consistent with decreased ActRII signaling. While it is unlikely that fertility findings translate to humans, this cannot yet be fully ruled out. Reproductive risk as a result of sotatercept exposure has been adequately addressed in the SmPC.

2.7. Clinical aspects

2.7.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Overview of clinical studies

The clinical pharmacology program consists of two completed Phase 1 studies in healthy postmenopausal women (PMW), including 1 single IV/SC dose escalation study (P009/A011-01, hereafter referred to as P009), and 1 multiple SC dose escalation study (P010/A011-02, hereafter referred to as P010).

Three studies were conducted in the PAH population including two completed Phase 2 studies in participants with PAH of WHO Group 1 with FC II or III (P001/A011-09/PULSAR and P002/A011-10/SPECTRA); and one completed Phase 3 study in participants with PAH of WHO Group 1 with FC II or III (P003/A011-11/STELLAR). P001, P002, and P003 are hereafter referred to by their study names PULSAR, SPECTRA and STELLAR, respectively. In addition, SOTERIA (ongoing) is a Phase 3, open-label, follow-up study to evaluate the long-term efficacy and safety of sotatercept in participants with PAH.

Table 8. Overview of Clinical Pharmacology Studies in Healthy PMW

Study Number/ Phase	Study Title	Participants	Dosage and Duration
P009 Phase 1a	Single-center, randomized, double-blind, placebo-controlled, single-dose, dose-escalation study to evaluate the safety, tolerability, PK, and effects on bone biomarkers of ACE-011 (ActRIIA-IgG1) administered to healthy PMW	Healthy PMW (N = 40 sotatercept; N = 8 placebo)	Single dose IV infusion over approximately 1 hour or SC injection: 0.01 mg/kg IV 0.03 mg/kg IV 0.1 mg/kg IV 0.3 mg/kg IV 1.0 mg/kg IV 3.0 mg/kg IV Placebo IV 0.03 mg/kg SC 0.1 mg/kg SC Placebo SC
P010 Phase 1b	Randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation study to evaluate the safety, tolerability, PK, and PD of ACE-011 in healthy PMW	Healthy PMW (N = 24 sotatercept; N = 7 placebo)	1 SC injection every 28 days for a total of 4 doses: 0.1 mg/kg 0.3 mg/kg 1.0 mg/kg Placebo

ACE-011=sotatercept; ActIIA=activin receptor type IIA; IgG1=immunoglobulin G1; IV=intravenous; N=number of participants; PD=pharmacodynamics; PK=pharmacokinetics; PMW=postmenopausal women; SC=subcutaneous

Table 9. Overview of the Sotatercept Clinical Development Program

Study Number (Status) [CTD Location] Number of Study Sites (Countries)	Design	Number of Participants by Intervention Group	Study Population (N)	Efficacy Endpoint(s)/Results
Phase 2 Studies				
MK-7962-001/A011-09/PULSAR (completed) [Ref. 5.3.5.1: P001MK7962] 43 sites (Australia, Brazil, France, Germany, Israel, Spain, United Kingdom, United States)	Multicenter, randomized, double-blind, parallel group study in participants aged ≥18 years with PAH (WHO Group 1, WHO FC II or III), baseline PVR ≥400 dynes*sec/cm^5 (≥5 Wood units) by RHC, 6MWD of ≥150 and ≤550 meters, on stable background PAH therapy, including mono, double, and triple therapies. Treatment Periods Placebo-controlled Treatment Period: 24 weeks Extension Period: 30 months	Placebo-controlled Treatment Period (randomized 3:3:4): Placebo SC Q3W plus background PAH therapy: 32 randomized/32 treated/30 completed Sotatercept (0.3 mg/kg, SC) Q3W plus background PAH therapy: 32 randomized/32 treated/31 completed Sotatercept (0.7 mg/kg, SC) Q3W plus background PAH therapy: 42 randomized/42 treated/37 completed Extension Period: Participants who completed the Placebo-controlled Treatment Period were able to continue directly into the Extension Period. Placebo participants were re-randomized 1:1 to sotatercept 0.3 or 0.7 mg/kg (placebo-crossed group); sotatercept participants continued their latest dose (continued-sotatercept group). *Placebo-crossed Group* Sotatercept (0.3 mg/kg, SC) Q3W plus background PAH therapy: 15 randomized/13 completed Sotatercept (0.7 mg/kg, SC) Q3W plus background PAH therapy:	Placebo-controlled Treatment Period Sex, n (%): 14 (13.2%) males and 92 (86.8%) females Median age: 48.0 years Length of time since PAH diagnosis (mean): 7.70 years WHO Diagnostic PH Group I: PAH, n (%): Idiopathic PAH: 61 (57.5%) Heritable PAH: 17 (16.0%) Drug/toxin-induced PAH: 6 (5.7%) PAH associated with connective tissue disease: 19 (17.9%)	Primary endpoint *Change from Baseline in PVR at Week 24* Decreases from baseline in PVR were significantly greater in the sotatercept 0.7 and 0.3 mg/kg groups compared with placebo (LS mean differences [SE]: -269.4 [48.48] dynes*sec/cm^5, p<0.0001 and -151.1 [49.53] dynes*sec/cm^5, p=0.0030, respectively) Select secondary endpoints *Change from baseline in 6MWD, WHO FC, and NT-proBNP at Week 24* Improvements from baseline in 6MWD were significantly greater in the sotatercept 0.7 and 0.3 mg/kg groups compared with placebo (LS mean differences [SE]: 22.3 [13.81] meters, p=0.1072 and 24.6 (13.98) meters, p=0.0790, respectively)

Study Number (Status) [CTD Location] Number of Study Sites (Countries)	Design	Number of Participants by Intervention Group	Study Population (N)	Efficacy Endpoint(s)/Results
		15 randomized/15 completed *Continued-Sotatercept Group* Sotatercept (0.3 mg/kg, SC) Q3W plus background PAH therapy: 31 entered Extension Period/28 completed Sotatercept (0.7 mg/kg, SC) Q3W plus background PAH therapy: 36 entered Extension Period/31 completed	PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair: 3 (2.8%) WHO functional classification for symptomatic PAH, n (%): Class II: 57 (53.8%) Class III: 49 (46.2%) Type of background PAH therapy, n (%): Mono: 10 (9.4%) Double: 37 (34.9%) Triple: 59 (55.7%) Prostacyclin infusion therapy, n (%): 39 (36.8%) Demographics and baseline characteristics in the Placebo-controlled Treatment Period were consistent with Extension Period.	Observed proportion of participants with ≥1 class improvement from baseline in WHO FC was higher in the sotatercept 0.7 and 0.3 mg/kg groups than the placebo group (6 participants (20.0%) in the sotatercept 0.7 mg/kg group, 8 (29.6%) in the sotatercept 0.3 mg/kg group, and 4 (13.3%) in the placebo group). Clinically meaningful reductions from baseline in NT-proBNP were seen in the sotatercept 0.7 and 0.3 mg/kg groups compared with the placebo group (LS mean differences [SE]: -671.5 (164.71) pg/mL and -812.1 (169.45) pg/mL, respectively) <u>Extension Period:</u> Placebo-crossed efficacy analysis: At [§]Months 18 to 24 in the combined placebo-crossed group, significant improvements from baseline were seen in PVR, 6MWD, and WHO FC (PVR, mean [SE]: -223.2 [57.45] dynes*sec/cm^5, p<0.0001; 6MWD, mean [SE]: 60.5 [13.21] meters, p<0.0001; and WHO FC, mean [SD]: -0.6 [0.74], p<0.0001).

Study Number (Status) [CTD Location] Number of Study Sites (Countries)	Design	Number of Participants by Intervention Group	Study Population (N)	Efficacy Endpoint(s)/Results
				Delayed-start efficacy analysis: At Months 18-24, improvement from baseline in PVR was not significantly different between the combined continuing sotatercept group and the combined placebo-crossed group; additionally, improvements in 6MWD, WHO FC (≥1 class) and NT-proBNP were not different between the combined continuing sotatercept group and the combined placebo-crossed group.
MK-7962-002/A011-10/SPECTRA (completed) [Ref. 5.3.5.2: P002MK7962] 4 sites (United States)	Multicenter, single-arm, open-label, exploratory study in participants aged ≥18 years with PAH (WHO Group 1, WHO FC III), baseline PVR ≥4 Wood units (≥320 dynes*sec/cm^5) by RHC, 6MWD ≥100 and ≤550 meters, on stable double or triple background PAH therapy. Treatment Periods Treatment Period: 24 weeks Extension Period: 18 months	Treatment Period Sotatercept[‡] Q3W plus background PAH therapy: 21 allocated/21 treated/20 completed Extension Period Participants continued to receive sotatercept at comparable dose levels, based on exposure-matching, to maintain steady-state exposures through the Extension Period, plus background PAH therapy. 20 entered the Extension Period/19 completed [‡] Participants received sotatercept at an initial dose of 0.3 mg/kg followed by 0.7 mg/kg for the remainder of the study, unless dose modifications were required.	Sex, n (%): 4 (19.0%) males and 17 (81.0%) females Median age: 44.0 years Length of time since PAH diagnosis (mean): 6.0 years WHO Diagnostic PH Group I: PAH, n (%): Idiopathic PAH: 14 (66.7%) Heritable PAH: 1 (4.8%) PAH associated with connective tissue disease: 6 (28.6%)	Primary endpoint *Change from baseline in VO_2 max at EOP (EOP defined as Week 24, early end-of-treatment visit, or a visit within 12 weeks of Week 24 for participants' visits affected by the COVID-19 pandemic)* Sotatercept significantly improved mean VO_2 max from baseline at EOP (mean change [SD]: 1.28 [2.628] mL/min/kg, p=0.0624). Select secondary endpoints *Change from baseline in RV SV by cardiac magnetic resonance imaging at EOP* Sotatercept did not improve RV SV from baseline at EOP (mean RV SV decreased from baseline (mean [SD]: -27.306 [26.5786] mL).

Study Number (Status) [CTD Location] Number of Study Sites (Countries)	Design	Number of Participants by Intervention Group	Study Population (N)	Efficacy Endpoint(s)/Results
			Type of background PAH therapy, n (%): Double: 10 (47.6%) Triple: 11 (52.4%) Prostacyclin infusion therapy, n (%): 12 (57.1%)	*Change from baseline at EOP in PVR, 6MWD, NT-proBNP, and WHO FC* Improvements were seen from baseline at EOP in PVR (during peak exercise), 6MWD, NT-proBNP, and WHO FC: (mean [SD]: PVR, -230.281 [216.3682] dynes*sec/cm^5; 6MWD, 66.35 (85.659) meters; NT-proBNP, -623.1 [840.56] pg/mL; WHO FC, -0.76 [0.903]). Extension Period (Month 12) Improvements from baseline at EOP in mean VO_2 max were maintained at Month 12 (mean [SD]: 1.83 [2.926] mL/min/kg, p=0.0298) Improvements from baseline at EOP were maintained for PVR, 6MWD, and WHO FC at Month 12: (mean [SD]: PVR, -180.160 (194.5108) dynes*sec/cm^5; 6MWD, 98.63 [99.683] meters; WHO FC, -1.06 [0.680]).
Phase 3 Studies				
MK-7962-003/A011-11/STELLAR (completed) [Ref. 5.3.5.1: P003V01MK7962]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study in participants aged ≥18 years with PAH (WHO Group 1, WHO FC II or III),	DBPC Treatment Period (randomized 1:1) Placebo SC Q3W plus background PAH therapy: 160 randomized/160 treated/148 completed	Sex, n (%): 67 (20.7%) males and 256 (79.3%) females	Primary endpoint *Change from baseline in 6MWD (meters) at Week 24* Sotatercept significantly improved 6MWD compared with placebo at

Study Number (Status) [CTD Location] Number of Study Sites (Countries)	Design	Number of Participants by Intervention Group	Study Population (N)	Efficacy Endpoint(s)/Results
126 sites (Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, France, Germany, Israel, Italy, Mexico, Netherlands, New Zealand, Poland, Serbia, South Korea, Spain, Sweden, Switzerland, United Kingdom, and United States)	baseline PVR ≥400 dynes*sec/cm^5 (≥5 Wood units) by RHC, 6MWD of ≥150 and ≤500 meters, on stable background PAH therapy, including mono, double, and triple therapies. <u>Treatment Periods</u> DBPC Treatment Period (Visit 9): 24 weeks LTDB Treatment Period: up to 72 weeks	Sotatercept[‡] Q3W plus background PAH therapy: 163 randomized/163 treated/159 completed <u>LTDB Treatment Period</u> Participants continued on their assigned dose in the LTDB Treatment Period. Placebo SC Q3W plus background PAH therapy: 32 participants completed the study Sotatercept Q3W plus background PAH therapy: 5 participants completed the study [‡]Participants received sotatercept at an initial dose of 0.3 mg/kg followed by 0.7 mg/kg for the remainder of the study, unless dose modifications were required.	Median age: 48.0 years Length of time since PAH diagnosis (mean): 8.76 years WHO Diagnostic PH Group I: PAH, n (%): Idiopathic PAH: 189 (58.5%) Heritable PAH: 59 (18.3%) Drug/toxin-induced PAH: 11 (3.4%) PAH associated with connective tissue disease: 48 (14.9%) PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair: 16 (5.0%) WHO functional classification for symptomatic PAH, n (%): Class II: 157 (48.6%) Class III: 166 (51.4%)	Week 24 (H-L location shift from placebo estimate [ASE]: 40.8 [6.79]; p<0.001) <u>Selected secondary endpoints</u> *Multicomponent improvement, (defined as increase ≥30 m in 6MWD, decrease in NT-proBNP ≥30% or maintenance/achievement of NT-proBNP level <300 ng/L, and improvement of WHO FC or maintenance of WHO FC II), change from baseline in PVR, and NT-proBNP at Week 24* Proportion of participants achieving MCI was significantly greater in the sotatercept group (38.9%) than in the placebo group (10.1%) (p<0.001). Decreases from baseline in PVR was significantly greater in the sotatercept group compared with the placebo group (H-L location shift from placebo estimate [ASE]: -234.6 [27.45] dynes*sec/cm^5; p<0.001). Sotatercept significantly improved NT-proBNP compared with placebo (H-L location shift from placebo estimate [ASE]: -441.6 [67.33] pg/mL; p<0.001).

Study Number (Status) [CTD Location] Number of Study Sites (Countries)	Design	Number of Participants by Intervention Group	Study Population (N)	Efficacy Endpoint(s)/Results
			Type of background PAH therapy, n (%): Mono: 13 (4.0%) Double: 112 (34.7%) Triple: 198 (61.3%) Prostacyclin infusion therapy, n (%):129 (39.9%)	*Proportion of participants with improvement from baseline in WHO FC at Week 24* Proportion of participants with improvement from baseline in WHO FC was significantly greater in the sotatercept group (29.4%) than in the placebo group (13.8%) (p<0.001). *Time to death or the first occurrence of a clinical worsening events (time to clinical worsening through the data cutoff (26-AUG-2022)* The risk of death or a first clinical worsening event was 84% lower in the sotatercept group compared with the placebo group (HR: 0.163; 95% CI, 0.076, 0.347). *Proportion of participants with maintenance or achievement of a low-risk score at Week 24 versus baseline* Proportion of participants who maintained or achieved a low-risk-score (French Risk score calculator) relative to baseline was significantly greater in the sotatercept group (39.5%) than in the placebo group (18.2%) (p<0.001).

Study Number (Status) [CTD Location] Number of Study Sites (Countries)	Design	Number of Participants by Intervention Group	Study Population (N)	Efficacy Endpoint(s)/Results
				Change from baseline in the Physical Impacts domain score of Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®), Cardiopulmonary Symptoms domain score of PAH-SYMPACT® at Week 24 Sotatercept significantly improved participant scores in the Physical Impacts Domain of the PAH-SYMPACT® questionnaire compared with placebo (H-L location shift from placebo estimate [ASE]: -0.26 [0.115]; *p*=0.010). Sotatercept significantly improved participant scores in the Cardiopulmonary Symptoms Domain of the PAH-SYMPACT® questionnaire compared with placebo (H-L location shift from placebo estimate [ASE]: -0.13 [0.062]; *p*=0.028).
MK-7962-004/A011-12/SOTERIA (ongoing) 162/197 sites active (Argentina, Australia, Austria, Belgium, Brazil, Canada, Colombia, Croatia, Czech Republic, Denmark, France, Germany, Greece,	A Phase 3, open-label, long-term follow-up study to evaluate the long-term safety and tolerability of sotatercept when added to background PAH therapy in adult participants with PAH. Treatment Period Open-label Treatment Period: One dose every 21 days plus	Participants from a blinded study: Starting dose: 0.3 mg/kg SC for cycle 1 escalated to 0.7 mg/kg Q3W for subsequent cycles. Participants from an unblinded study: Continue sotatercept SC Q3W at their current dose (with option to titrate to 0.7 mg/kg if on <0.7 mg/kg).	Participants rolling over from parent PAH sotatercept clinical studies.	No efficacy results are available.

Study Number (Status) [CTD Location] Number of Study Sites (Countries)	Design	Number of Participants by Intervention Group	Study Population (N)	Efficacy Endpoint(s)/Results
Israel, Italy, Mexico, Netherlands, New Zealand, Poland, Portugal, Serbia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, United States)	background PAH therapy for up to 7 years			

6MWD=6-minute walk distance; ASE=asymptotic standard error; CI=confidence interval; DBPC=Double-Blind Placebo-controlled; EOP= End of period (EOP visit was Week 24 [Cycle 9], early End of Treatment visit, or a visit within 12 weeks of Cycle 9 for participants' visits affected by the pandemic); EOT=End of Treatment; FC=functional class; HR=Hazard Ratio; H-L=Hodges-Lehmann; LS=Least squares; LTDB=Long-Term Double-Blind; MCI=multi-component improvement; NT-proBNP=N-terminal prohormone of brain natriuretic peptide; PAH=pulmonary arterial hypertension; PH=pulmonary hypertension; PVR=pulmonary vascular resistance, Q3W=every 3 weeks; RHC=right heart catheterization; RV SV=right ventricular stroke volume; SC=subcutaneous; SD=standard deviation; SE=standard error; VO_2 max=peak O_2 uptake; WHO=World Health Organization

[§]The main analysis including delayed-start efficacy analysis and placebo-crossed efficacy analysis of the extension period was performed on the primary and secondary endpoints after the last participant completed the third right heart catheterization at Month 18-24 or passed the Month 18-24 window for the third right heart catheterization or had an early EOT visit.

2.7.2. Clinical pharmacology

2.7.2.1. Pharmacokinetics

Methods

Bioanalytical methods

Serum concentrations of both free and Activin A bound forms of sotatercept in human serum were determined with a validated competitive ELISA method. The calibration ranges were 8 to 400 ng/mL for the phase 1 studies P009 and P010 in healthy subjects and 40 to 2000 ng/mL in the patient studies. The analyses of the phase 1 were conducted between June 2006 and October 2008, and validation of the assay does not fully comply with the ICH-M10 guideline. Nevertheless, the accuracy and precision, dilution integrity and stability testing is acceptable. An issue for the first generation method was positive pre-dose levels in serum of the subjects in studies P009 and P010. Repeat analysis of the predose levels and incurred sample reanalysis showed that the responses were reproducible. The predose/placebo treated levels were in general between 10-40 ng/mL. In the protocol of the study bioanalysis of studies P009 and P010 a decision tree for positive pre-dose concentration <5% of Cmax and >5 % of Cmax was incorporated. If the samples complied to the decision tree, the predose concentration was subtracted from all other serum concentrations from that subject for the non-compartmental PK analysis. In the phase 2 and 3 studies, the 2nd generation assay with a higher LLOQ of 40 ng/mL was used and therefore, there were no subjects with positive pre-dose concentrations. The performance of the assay in presence of ADAs was not reported, however, impact is unlikely since the assay uses as capture a polyclonal antibody.

A multi-tiered testing strategy was applied to assess sotatercept immunogenicity. Serum samples were evaluated initially by an assay that included both screening and confirmation. ADA positive samples subsequently underwent additional characterization for titer and NAb activity. Throughout the course of clinical development of sotatercept, numerous assays were utilized for immunogenicity assessment, including two generations of ADA assay, and three generations of NAb assay.

PopPK analysis

A population pharmacokinetic model was developed using non-linear mixed effects modelling software (NONMEM, version 7, Level 3.0). The first-order conditional estimation method with interaction was used to obtain model parameters. Model evaluation was conducted using standard goodness-of-fit plots, prediction-corrected visual predictive checks (pcVPCs), and several numeric diagnostics (standard errors [obtained by bootstrapping], plausibility of parameter estimates, condition number and eta and epsilon shrinkage).

The population PK model was based on PK rich data observations of healthy volunteers (studies P009 and P010) and sparse PK data sampling PAH patients (PULSAR, SPECTRA and STELLAR). The analysis population consisted of 298 females (85%) and 52 males (15%) with a median (range) age of 50 years (18 to 81 years; 81% of the subjects was < 65 years, 15% was between 65 and 75 years, and 4% was > 75 years), a median (range) baseline body weight of 67.2 kg (39.6 to 136 kg), and a median (range) baseline albumin concentration of 4.5 g/dL (2.9, 5.8 g/dL) at the baseline visit. The majority (83%) of participants identified as white, while 25 (7%) participants identified as Asian, 11 (3%) as black or African American, 4 (1%) as Native Hawaiian or other Pacific Islander, and 19 (5%) as other race. The majority (52%) of participants were classified as having mild renal impairment,

while 33% were classified as having normal renal function and 15% as having moderate renal impairment.

A 2-compartment model with linear elimination, first-order absorption for the SC route of administration, and data-defined rates for IV infusions was selected to describe the PK of sotatercept in the healthy participants and participants with PAH.

The parameter estimates for the final integrated Phase 1/2/3 PK model, along with corresponding precision estimates (%RSE), are provided below.

Table 10. Parameter estimates and standard errors for the final integrated Phase 1/2/3 PK model

Parameter		Final Parameter Estimate			Magnitude of Variability		
		Population Mean	%RSE	Bootstrap Mean (95% CI)	Final Estimate	%RSE	Bootstrap Mean (95% CI)
CL	Central Clearance in Typical Participant (L/day)[a]	0.177[b]	6.22	0.176 (0.150, 0.200)	28.3 %CV	16.9	28.2 %CV (23.1%, 32.8%)
	Exponent of Body Weight Power Effect (-)[a]	0.814	11.9	0.809 (0.604, 1.00)			
	Exponent of Baseline Albumin Effect (-)[a]	-0.849	24.2	-0.851 (-1.27, -0.454)			
VC	Central Volume (L)[c]	3.60	5.50	3.61 (3.25, 4.11)	24.7 %CV	31.0	24.0 %CV (15.3%, 31.7%)
	Exponent of Body Weight Power Effect (-)[c]	1.02	11.8	0.999 (0.732, 1.25)			
Q	Distribution Clearance (L/day)	0.487	20.5	0.476 (0.239, 0.677)	NE	NA	NA
VP	Peripheral Volume (L)	1.71	15.8	1.66 (0.740, 2.24)	73.3 %CV	28.2	81.9 %CV (52.9%, 188.2%)
KA	First-Order Absorption Rate Constant (1/day)	0.273	16.0	0.275 (0.199, 0.371)	60.4 %CV	24.2	60.4 %CV (41.6%, 77.3%)
F1	SC Bioavailability (-)	0.659[b]	6.29	0.657 (0.557, 0.745)	11.9 %CV[d]	26.3	11.9 %CV (5.8%, 19.8%)
Residual Variability in HV (log units)		0.0570	20.2	0.0574 (0.0376, 0.0838)	0.239 SD	NA	0.240 SD (0.194, 0.289)
Residual Variability in PAH (log units)		0.0357	12.6	0.0357 (0.0279, 0.0456)	0.189 SD	NA	0.189 SD (0.167, 0.214)
Minimum Value of the Objective Function = -6707.007							

Abbreviations: ALB, baseline albumin; CI, confidence interval; %CV, coefficient of variation expressed as a percent; HV, healthy participant; IIV, interindividual variability; MM, multiple myeloma; NA, not applicable; NE, not estimated; PAH, pulmonary arterial hypertension; PK, pharmacokinetic; %RSE, relative standard error expressed as a percent; SC, subcutaneous; SD, standard deviation; WTKGT, time-varying body weight.

[a] The typical value of clearance, $\widehat{CL}$, for an individual with WTKGT and ALB can be calculated as follows.

$$\widehat{CL} = 0.177 \times \left(\frac{WTKGT}{70}\right)^{0.814} \times \left(\frac{ALB}{4.5}\right)^{-0.849}$$

[b] The following parameter estimates were found to be highly correlated ($r^2 \geq 0.81$): F1: SC bioavailability (-), CL: central clearance in typical participant (L/day).

[c] The typical value of central volume, $\widehat{VC}$, for an individual with WTKGT can be calculated as follows.

$$\widehat{VC} = 3.60 \times \left(\frac{WTKGT}{70}\right)^{1.02}$$

[d] The magnitude of interindividual variability (%CV) of SC bioavailability (-) was calculated using the following equation: $100 \times (1\text{-}0.659) \times 0.348$.

Shrinkage estimates: 17.3% for IIV in CL, 51.9% for IIV in VC, 34.6% for IIV in VP, 48.3% for IIV in KA, and 36.8% for IIV in F1.

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Exposure-response analysis

The exposure-response analyses aimed to:

- A population pharmacokinetic/pharmacodynamic (PK/PD) model describing the relationship between sotatercept plasma concentrations and haemoglobin (Hgb) concentration;

- An exposure-response model describing the relationship between sotatercept exposure and 6-minute walking distance (6MWD);
- An exposure-response model describing the relationship between sotatercept exposure and pulmonary vascular resistance (PVR); and
- An exposure-response model describing the relationship between sotatercept exposure and the time to N-terminal prohormone of brain natriuretic peptide (NT-proBNP) concentration < 300 pg/mL

The final population PK model developed from final pooled Phase 1/2/3 data was used to predict and update exposures for final exposure-response model development.

Population PK/PD and exposure-response models were described by the estimation of typical structural model parameters (such as, baseline response, maximum pharmacologic effect and concentration at which pharmacologic effect is half maximum), magnitude of IIV in relevant parameters, and magnitude of RV. The first-order conditional estimation with interaction method was used during all stages of the model development process. Possible covariates were analysed and selected via stepwise forward inclusion ($P < 0.01$) and backward elimination method ($P < 0.001$). Covariates contributing a change in the minimum VOF of at least 6.64 ($P < 0.01$, 1 df) and resulting in a decrease in IIV of at least 5% in the parameter of interest were considered significant in this forward selection process. The error models for IIV and RV in the full multivariable models were evaluated following completion of forward selection.

The PK/PD model describing the relationship between sotatercept serum concentrations and haemoglobin concentration was adapted from the PKPD model describing the effects of recombinant human erythropoietin in healthy volunteers (Woo et al. 2008). This concerns a catenary, life span–based, indirect response model where increase blood haemoglobin reflects the stimulation in bone marrow of the production and conversion of early progenitor cells to erythroblasts and subsequently to blood reticulocytes and red blood cells. A negative feedback regulation, inhibition by the Hb change relative to its baseline (ΔHb) on the production rate of progenitor cells was described using an inhibitory Hill function with Imax = 1, and IC50 is the Hb change that induces half-maximum inhibition.

The model that best described 6MWD response in patients with PAH included baseline World Health Organization (WHO) function class, age, and time-varying haemoglobin, a maximum pharmacologic effect (Emax) function of time, and a power function of Cavg. The typical 6MWD was described by the following equation:

$$6MWD = 398 + (-3.17) \times (\text{Age} - 48) \times \text{AgeI} + (-3.17) \times (48.7 - 48) \times (1 - \text{AgeI}) \times (1 + 0.139 \times \text{WHO}) + 5.50 \times (\text{Hgb} - 13.9) + \left[\frac{(20.1) \times t}{6.93 + t}\right] + C_{avg}(t)^{0.292}$$

The model that best described PVR response in patients with PAH was a decreasing power function of Cavg, dependent on the baseline infusion therapy (PROSINF), the duration of PAH pathology (PAHDUR, in years), and the observed baseline PVR (PVRBL, in dynes.s/cm^5). The typical PVR was described by the following equations:

$$PVR = 719.9 \times C_{avg}(t)^{-0.05164 \times (1 - 0.3623 \times PROSINF) + 0.001570 \times (PAHDUR - 7.1) - 0.00002567 \times (PVRBL - 664)}$$

The final exposure-response time to NT proBNP < 300 pg/mL model was a Cox proportional hazard model including the effect of sotatercept Cavg at 24 weeks and WHO functional class. None of the covariates tested (including body weight, age, sex, duration of PAH disease, PAH etiology, background PAH therapy, infusion therapy) were found to be statistically significant predictors of time to NT proBNP < 300 pg/mL.

Table 11. Parameter estimates and standard errors from the exposure-response base model for time to NT-proBNP < 300 pg/mL using final data from studies MK-7962-001, MK-7962-002, and MK-7962-003

Variable	Coefficient	SE	%RSE	*P* value	Hazard Ratio (95% CI)
BSLFLAG	2.597676	0.164593	6.336168	<1E-6	13.43248 (9.72869, 18.54634)
CAVG	0.000297	3.05E-05	10.28303	<1E-6	1.000297 (1.000237, 1.000357)
WHO Class III	-0.30988	0.116874	37.71578	0.008016	0.7335335 (0.5833594, 0.9223667)

Abbreviations: BSLFLAG, flag for patients whose event occurred at baseline; Cavg, average sotatercept concentration; CI, confidence interval; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; *P*, probability; %RSE, relative standard error expressed as a percent; SE, standard error; WHO, World Health Organization.

Source: d2pd-ntpbnp-blinded\R\export\tte-ntpbnp3-coxph-final-model-param.csv.

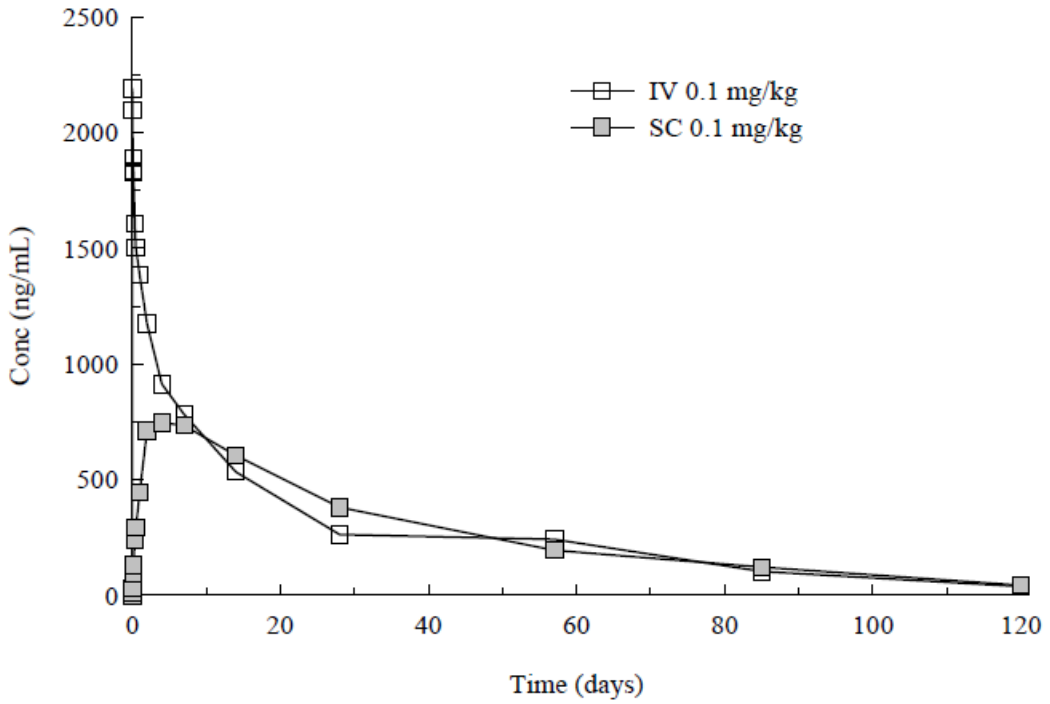
Pharmacokinetics

The clinical pharmacology program consists of two completed Phase 1 studies in healthy postmenopausal women and three studies in the PAH population i.e. PULSAR (0.3 and 0.7 mg/kg Q3W), SPECTRA (0.7 mg/kg Q3W after single dose 0.3 mg/kg) and the pivotal phase 3 study STELLAR (0.7 mg/kg Q3W after single dose 0.3 mg/kg). PopPK analysis and exposure-response analyses for efficacy and safety were also conducted.

Absorption

Following SC administration, sotatercept is slowly absorbed. The maximum sotatercept concentration is achieved at a median Tmax of approximately 7 days after SC injection. Cmax values of sotatercept were 2- to 3-fold lower following SC compared to IV administration but the AUCinf values were comparable for both administration routes. Based on the integrated popPK modelling, the estimated bioavailability was approximately 66% (11.9%CV) (086H0S).

Figure 2. Mean plasma concentrations of ACE-011 after intravenous and subcutaneous administration of single 0.1 mg/kg doses to healthy postmenopausal females (study P009)



PK parameter estimates for sotatercept in patients with PAH are summarised below for 0.3 or 0.7 mg/kg of sotatercept every 3 weeks (21 days) for each patient in the Phase 2/3 studies.

Table 12. Summary statistics of model-predicted Sotatercept exposures at steady state for the phase 2/3 studies, stratified by phase. (086H0S)

Exposure	Statistics	0.3 mg/kg Q3W Dose			0.7 mg/kg Q3W Dose		
		MK-7962-001 and MK-7962-002	MK-7962-003	Overall	MK-7962-001 and MK-7962-002	MK-7962-003	Overall
AUCss (µg × d/mL)	Mean, (SD)	74.31, (25.18)	79.69, (23.91)	77.36, (24.57)	173.39, (58.75)	185.94, (55.79)	180.50, (57.33)
	Geometric Mean (%CV)	70.01 (36.61)	76.11 (31.78)	73.40 (34.16)	163.35 (36.61)	177.58 (31.78)	171.26 (34.16)
	Median (Range)	72.94 (26.08, 146.68)	78.74 (30.03, 175.38)	76.08 (26.08, 175.38)	170.19 (60.86, 342.26)	183.73 (70.07, 409.22)	177.53 (60.86, 409.22)
	n	124	162	286	124	162	286
Cavg,ss (µg/mL)	Mean, (SD)	3.54, (1.20)	3.79, (1.14)	3.68, (1.17)	8.26, (2.80)	8.85, (2.66)	8.60, (2.73)
	Geometric Mean (%CV)	3.33 (36.61)	3.62 (31.78)	3.50 (34.16)	7.78 (36.61)	8.46 (31.78)	8.16 (34.16)
	Median (Range)	3.47 (1.24, 6.98)	3.75 (1.43, 8.35)	3.62 (1.24, 8.35)	8.10 (2.90, 16.30)	8.75 (3.34, 19.49)	8.45 (2.90, 19.49)
	n	124	162	286	124	162	286
Cmax,ss (µg/mL)	Mean, (SD)	4.17, (1.28)	4.43, (1.15)	4.32, (1.21)	9.73, (2.98)	10.34, (2.68)	10.08, (2.82)
	Geometric Mean (%CV)	3.97 (33.24)	4.28 (26.92)	4.15 (30.00)	9.26 (33.24)	10.00 (26.92)	9.67 (30.00)
	Median (Range)	4.15 (1.45, 7.73)	4.39 (1.82, 9.36)	4.27 (1.45, 9.36)	9.68 (3.39, 18.03)	10.24 (4.24, 21.85)	9.95 (3.39, 21.85)
	n	124	162	286	124	162	286
Cmin,ss (µg/mL)	Mean, (SD)	2.66, (1.05)	2.89, (1.03)	2.79, (1.04)	6.21, (2.45)	6.74, (2.41)	6.51, (2.44)
	Geometric Mean (%CV)	2.46 (43.27)	2.70 (39.48)	2.59 (41.39)	5.73 (43.27)	6.30 (39.48)	6.04 (41.39)
	Median (Range)	2.59 (0.89, 5.71)	2.85 (0.83, 6.64)	2.77 (0.83, 6.64)	6.05 (2.07, 13.31)	6.65 (1.93, 15.50)	6.47 (1.93, 15.50)
	n	124	162	286	124	162	286
$t_{½}$ (days)	Mean, (SD)	22.05, (11.32)	22.79, (7.91)	22.47, (9.53)	22.05, (11.32)	22.79, (7.91)	22.47, (9.53)
	Geometric Mean (%CV)	20.56 (35.67)	21.65 (32.19)	21.17 (33.78)	20.56 (35.67)	21.65 (32.19)	21.17 (33.78)
	Median (Range)	21.05 (9.40, 124.07)	21.36 (7.12, 56.64)	21.23 (7.12, 124.07)	21.05 (9.40, 124.07)	21.36 (7.12, 56.64)	21.23 (7.12, 124.07)
	n	124	162	286	124	162	286

Abbreviations: AUCss, area under the concentration-time curve at steady state; Cavg,ss, average concentration at steady state; Cmax,ss, maximum concentration at steady state; Cmin, maximum concentration at steady state; %CV, coefficient of variation expressed as a percent; n, number of participants; Q3W, every 3 weeks; SD, standard deviation; $t_{½}$, terminal elimination half-life.

The sotatercept product used in early clinical phases (Studies 009 and 010) was formulated in phosphate buffered saline as a frozen solution. The product for commercialisation and used in the phase 2 and 3 studies in subjects with PAH (PULSAR, SPECTRA and STELLAR) was a lyophilized citrate buffer formulation of the drug product containing sucrose and polysorbate 80. No bioequivalence studies were conducted between the two formulations but across study comparison showed no

differences in the actual dose-normalized sotatercept serum concentrations between Phase 1 and PULSAR, SPECTRA and STELLAR. Formulation was not a covariate in the popPK model.

Distribution

After single IV doses of sotatercept ranging from 0.1 through 3.0 mg/kg the mean Vz ranged from 73.7 to 110 mL/kg (study P009).
Based on the integrated popPK analysis, the central volume of distribution of sotatercept is approximately 3.6 L and the peripheral volume of distribution is approximately 1.7 L.

Elimination

Sotatercept is catabolized by general protein degradation processes.
Following SC administration CL/F ranged from 0.11 to 0.16 mL/h/kg and mean t½ ranged from 21-31 days in studies P009 and P010.

Sotatercept clearance following SC administration was estimated based on integrated popPK analysis at approximately 0.18 L/day and its average elimination half-life is approximately 21 days (086H0S).

Dose proportionality and time dependencies

The single dose ascending studies showed that the pharmacokinetics of sotatercept was dose proportional over the dose ranges studied i.e. 0.01 to 3 mg/kg IV administration and for 0.03 to 1.0 mg/kg SC administration (studies P009 & P010) and are shown in for SC administration following single and multiple dosing. Mean AUC0-28d and Cmax values increased linearly and in a manner proportional to the dose of sotatercept. The mean accumulation index of at 4th SC dose of 0.1 mg/kg Q4W, on the basis of Cmax and AUC0-28d, was 2.27 and 2.25 respectively, which can be expected for a drug with an elimination half-life of 21days and a Q3W dosing interval.

Table 13. Summary of pharmacokinetic parameters for sotatercept after 1st SC dose or last dose of sotatercept in healthy postmenopausal female volunteers (study P010).

	First SC dose (N=8)			Mulitple SC Q4W dose (N=8)
	0.1 mg/kg	0.3 mg/kg	1.0 mg/kg	0.1 mg/kg
$AUC_{0\text{-}28d}$ AUCtau (d*ng/mL)	15493 (25%)	54548 (24%)	147952 (23%)	33018 (23%)
Cmax (ng/mL)	746 (30%)	2460 (24%)	7394 (16%)	1544 (22%)
Tmax (d)	7.0 (3.0-14)	7.0 (7.0-14.0)	7.0 (7.0-26.9)	7.0 (2.0-8.0)
T1/2 (d)	ND	ND	ND	23.4 (15%)
Accumulation[a] index for AUC	ND	ND	ND	2.25 (38%)

AUC=area under the curve; Cmax=maximum concentration; CV=coefficient of variation; N=number of participants; ND=not determined; Q4W=once every 4 weeks; SC=subcutaneous; t1/2=terminal half-life; Tmax= time to maximum concentration, median (range[a]calculated as AUC0-28days following 4th dose divided by AUC0-28days following 1st dose.

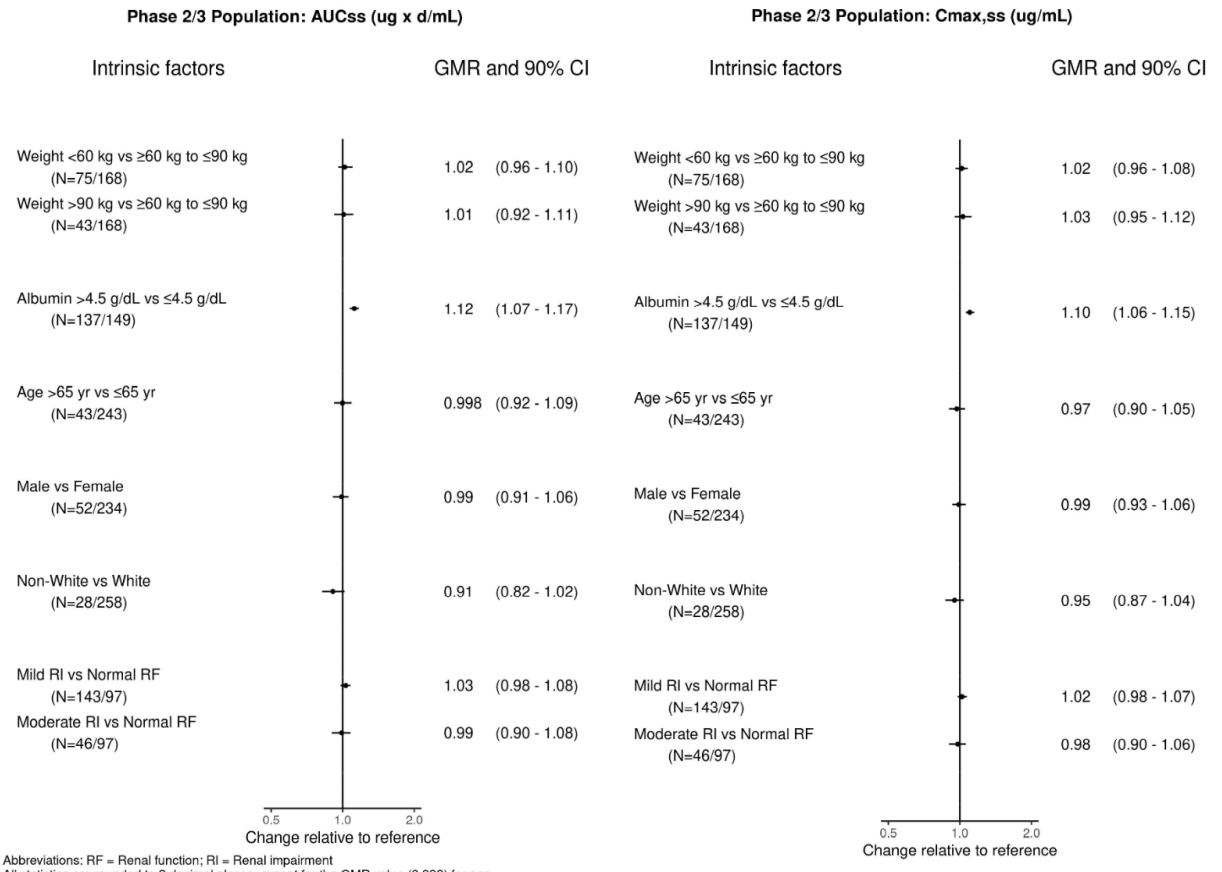
The final popPK model does not include time dependency of PK parameters; the pharmacokinetics of sotatercept is linear over time with an accumulation ratio of approximately 2.2 upon multiple dosing at Q3W regimen (086H0S). The steady state is achieved at approximately 15 weeks.

Special populations

The impact of intrinsic factors on sotatercept PK was assessed using the integrated population PK model. The model-predicted exposures, in terms of AUCss and Cmax,ss, were used to assess the

clinical relevance of the statistically significant covariate-parameter relationships included in the model (body weight and albumin) as well as other intrinsic factors of interest (age, sex, racial classification, and renal function). The resultant GMRs (90% CIs) are displayed in the figure below.

Figure 3. Forest plot of geometric mean ratios (90% confidence intervals) of estimated covariate effects on sotatercept exposure following hypothetical subcutaneous doses of 0.7 mg/kg every 21 days for 24 weeks in the pooled Phase 2/3 analysis population



Abbreviations: RF = Renal function; RI = Renal impairment
All statistics are rounded to 2 decimal places, except for the GMR value (0.998) for age.
Abbreviations: RF = Renal function; RI = Renal impairment
Abbreviations: AUCss, area under the concentration-time curve at steady state; CI, confidence interval; Cmax,ss, maximum concentration at steady state; GMR, geometric mean ratio.

Pharmacokinetic interaction studies

No studies were conducted as sotatercept is a fusion protein. Hence, the drug interaction potential is low. This approach is acceptable.

Pharmacokinetics using human biomaterials

No studies conducted because sotatercept is a fusion protein, which is acceptable.

2.7.2.2. Pharmacodynamics

Mechanism of action

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 and Secondary pharmacology

Primary pharmacology

The clinical pharmacology program consists of two completed Phase 1 studies in healthy postmenopausal women including 1 single IV/SC dose escalation study (P009) and 1 multiple SC dose escalation study (P010). However, the evaluated PD parameters (bone biomarkers) are not in relation to the proposed indication, and, therefore, not discussed here. The Phase 2 study P001 (PULSAR) can be considered the proof-of-concept and main dose-finding study in relation to the proposed indication and is discussed in the section "Dose response study" below.

Secondary pharmacology

Effect on QTc interval

Therapeutic proteins are typically not associated with clinically meaningful effects on QTc interval owing to their large size, which prevents interaction with the pore of hERG channels. Also, in cells overexpressing hERG potassium channels, the IC50 was estimated to be greater than 1000 µg/mL (corresponding to ≥ 100-fold the clinical Cmax at 0.7 mg/kg SC Q3W). Thus, a thorough QTc study was not performed for sotatercept.

Participants enrolled in the Phase 1 studies (P009 and P010) did however have safety ECG monitoring after IV single dose administration of 0.01 mg/kg to 3.0 mg/kg and SC single dose administration of 0.03 mg/kg and 0.1 mg/kg of sotatercept. Overall, these data indicate no clinically significant effect of sotatercept on QTc interval.

Participants in PULSAR, SPECTRA, and STELLAR were also monitored for ECG changes before and after SC administration of sotatercept at 0.3 mg/kg and 0.7 mg/kg. Despite the potential effect of co-morbidities or concomitant medications in participants that may also affect QTc interval, no clinically significant effect on QTc interval was observed after administration of sotatercept.

All QTc measurements were <500 msec at all doses and timepoints for Phase 1 studies, PULSAR, SPECTRA, and STELLAR. All changes from baseline were <60 msec. Hence, across healthy participants and participants with PAH, sotatercept does not affect QTc interval as reflected in these QTc summary data.

Immunological events

A multi-tiered testing strategy was applied to assess sotatercept immunogenicity for PULSAR, SPECTRA, and STELLAR. PULSAR and SPECTRA applied ADA cut points established from healthy serum matrix, while STELLAR applied in-study cut points established from STELLAR pre-treatment samples. For PULSAR and SPECTRA combined, 13 (10.4%) of 125 sotatercept treated participants developed

ADA against sotatercept, and 1 ADA positive participant (0.8% of all sotatercept treated participants) showed neutralizing activity. In STELLAR, 42 (25.9%) of 162 sotatercept treated participants developed anti sotatercept antibodies. Among these 42 participants, 11 tested positive for neutralizing antibodies against sotatercept (6.8% of all sotatercept treated participants). The majority of ADA were detected shortly after the initial sotatercept dose, with a median ADA onset of ~3 weeks after the 1st dose of sotatercept. The ADA response was transient in ~55% of ADA positive participants in all 3 PAH studies. Anti-sotatercept antibodies had a median maximum titer of 40 (PULSAR and SPECTRA combined) or 30 (STELLAR) (overall range <20 to 640).

Immunogenicity impact analyses for PK, PD (haemoglobin concentration) and efficacy (6MWD, PVR, and NT-proBNP) were conducted for pooled PULSAR and SPECTRA and individually for STELLAR. The formation of anti-sotatercept antibodies and neutralizing antibodies did not meaningfully affect sotatercept PK, PD, or efficacy.

Pharmacodynamic interactions with other medicinal products

No pharmacodynamic interactions has been found.

Genetic differences in PD response

Mutations in bone morphogenetic protein receptor type II (BMPR2) gene is a common causal factor for hereditary pulmonary arterial hypertension (HPAH) contributing for up to 70% of familial PAH (FPAH) and 26% of idiopathic PAH (IPAH). Specifically, impairment of the BMPR2-associated signal pathway appears to lead to uncontrolled proliferation of pulmonary VSMCs, the principal cause of PAH. These genetic findings and functional animal studies using PAH-relevant BMPR2 mutations demonstrate BMPR2 haploinsufficiency as a molecular mechanism in HPA. In addition to these BMPR2 mutations, Activin A, GDF-8, and GDF-11 were upregulated in the intima and media of small arterioles in human PAH (IPAH and HPAH). These data strongly suggest a key role of TGF-β family members in the pathogenesis of PAH. Treatment of cultured rat PASMCs with monocrotaline (MCT) pyrrole enhances expression of ACTRIIA, the principal type 2 receptor for activin and GDF ligands, while diminishing expression of BMPR2, suggesting a reciprocal relationship between BMP and activin signaling in PH. Despite the numerous BMPR2 mutations identified in FPAH, disease penetrance is only 20% with a higher risk in female population than male with a 1.7:1 ratio. Thus, in individuals with BMPR2 disease mutations, a subsequent event such as microenvironmental exposure to other cytokines, inflammatory molecules, etc., might be required for disease progression.

Pulmonary vascular quiescence is largely determined by an equilibrium between constitutive Smad1/5/8 signaling (BMP-family ligands) and pathogenic Smad2/3 signaling (mediated by Activin A, B, GDF-8, and GDF-11). In PAH due to BMPR2 haploinsufficiency, a common outcome is reduced Smad1/5/8 signaling compared to pathogenic Smad2/3 signaling. In addition, even in PAH due to BMPR2 mutation such as HPAH and IPAH, Activin A, GDF-8, and GDF-11 were upregulated. Therefore, sotatercept will inhibit activin and GDF-induced pathogenic Smad2/3 signaling pathway regardless of the genetic mutation. Indeed, RAP-011 (the murine equivalent of sotatercept) corrected cardiopulmonary remodeling and improved function in both the BMPR2 haploinsufficient mouse model and the Sugen-Hypoxia rat model, whose disease effects are not contingent upon BMPR2 mutation.

To further confirm the Applicant’s data in the preclinical study, baseline pharmacogenetic samples were analyzed in PULSAR for several genes, including single variation in BMPR2, variation in BMPR2 and SMAD9, or genetic variation in other genes (ACVLR1, CAV1, ENG, KCNA3, KCNK3, and EIF2AK4). Results are available from 94 participants;

- 64 participants (68.1%) had no detectable variation in any of the genes tested,
- 23 participants (24.4%) had at least one detectable variation in *BMPR2*,
- 2 participants (2.1%) had single heterozygous variations in both BMPR2 and SMAD9,
- 5 participants (5.3%) had at least one detectable variation in one of the other genes.

BMPR2 mutation had no effect on 6MWD and PVR in PULSAR in PULSAR. No pharmacogenetic analysis was conducted in STELLAR.

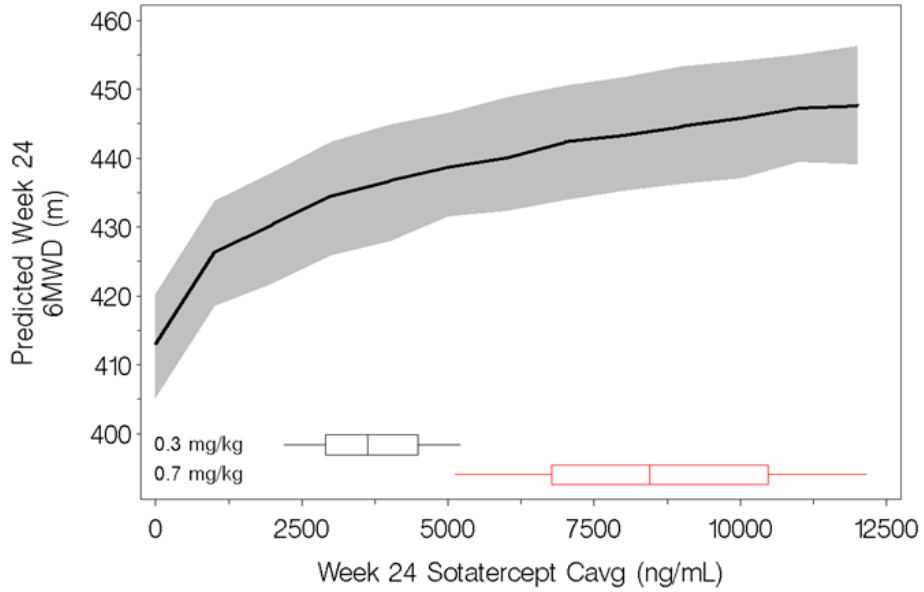
Pharmacokinetics-Pharmacodynamics (PK/PD)

Exposure-response analyses (report 086H0L) were conducted using a nonlinear mixed effect modeling approach to examine the relationships between sotatercept exposure and the efficacy endpoints 6MWD, PVR, NT-proBNP from the SPECTRA, PULSAR, and STELLAR studies. In addition, population PK/PD modeling of the safety endpoint Hgb was conducted. For both exposure-respone and PK/PD analyses, individual predicted sotatercept exposures, based on the integrated popPK model, were used as PK predictors.

The pharmacodynamic parameters including PVR, 6MWD, and NT-proBNP were considered for exposure response analysis as they are all relevant to understanding the effect of sotatercept in PAH patients. Hemoglobin was evaluated in this program as a safety measure to provide dosing guidance for PAH patients.

Exposure-response 6MWD model
Modelling results show that 6MWD is projected to increase with increasing sotatercept exposure. Part of this drug effect may be mediated by Hgb, which also increases with increased sotatercept concentration. WHO FC and age were identified as statistically significant covariates on the baseline 6MWD: patients classified into WHO Class III were predicted to have an approximately 14% lower baseline 6MWD when compared to patients in WHO Class II. The baseline 6MWD is also dependent on the age. For each additional year of age beyond 48 years, there would be a decrease in the 6MWD of 3.17 m at baseline. The mean increase in 6MWD from baseline at Week 24, corresponding to median Cavg of 0.7 mg/kg, was approximately 41 meters, which is equivalent to approximately 31 meters after adjusting for placebo effect.

Figure 4. Model predicted 6MWD versus week 24 sotatercept Cavg.

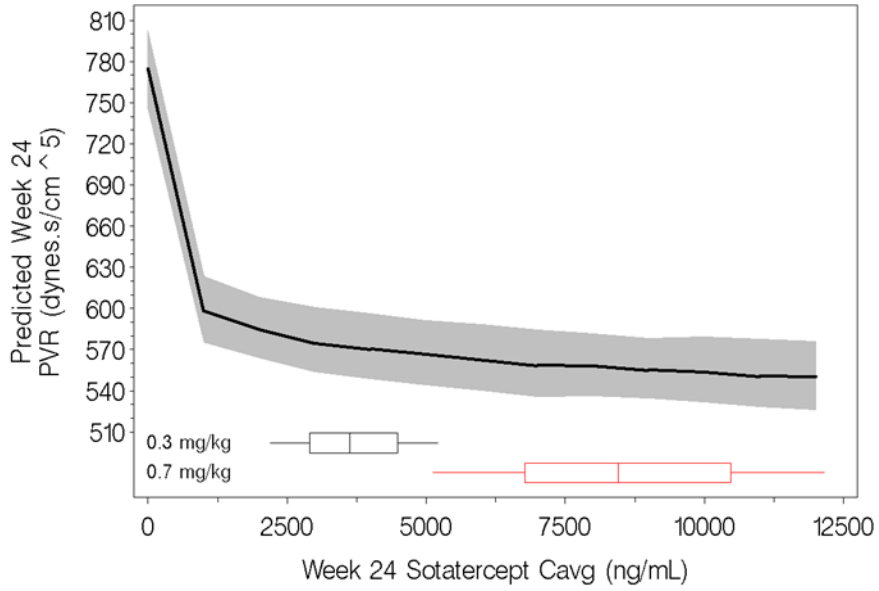


The line and shaded region represent the mean and 90% confidence interval, respectively. Week 24 sotatercept Cavg (ng/mL) refers to AUC from Week 21 to Week 24 divided by 21 days. Boxes in the horizontal boxplots represent the 25th, 50th, and 75th percentiles; whiskers extend to the 10th and 90th percentiles of sotatercept Cavg.

Exposure-response PVR model

The relationship between sotatercept exposure and PVR was best described by a saturable inhibitory function of model-predicted sotatercept Cavg at the time of PVR measurement. Baseline PVR also varied substantially across participants and ranged from 335 to 2760 dynes.s/cm^5. The analysis suggests that no significant change in PVR was observed in participants who received placebo + background PAH therapy, while for participants receiving sotatercept, PVR decreased with increasing sotatercept exposure approaching a plateau at the Cavg range corresponding to 0.7 mg/kg dose. The mean decrease from baseline at week 24, corresponding to median Cavg of 0.7 mg/kg, was -217 dynes*sec/cm^5. PAH duration, baseline PVR and prostacyclin infusion were identified as significant covariates impacting the exposure-PVR relationship. None of the other variables tested during the covariate analysis (that is, body weight, age, sex, PAH etiology, SOC therapy, and WHO functional class) were found to be statistically significant predictors of the PVR response. Prostacyclin infusion was associated with lower PVR measurements. With prostacyclin infusion, PVR was projected to be approximately 16% lower than with non-prostacyclin infusion. Longer PAH disease duration was associated with higher PVR measurements across exposure. With increased duration of disease of every 5 years, PVR is projected to be approximately 7% higher. Higher baseline PVR was associated with a lower postdose PVR across exposure. With every 100 dynes.sec/cm^5 increase in baseline PVR, postdose PVR was projected to be approximately 2% lower.

Figure 5. Model predicted PVR versus week 24 sotatercept Cavg.

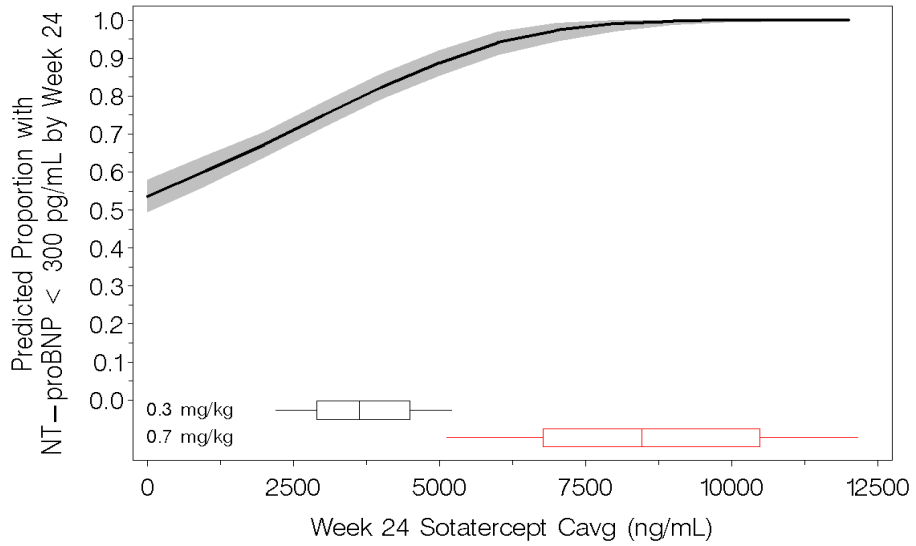


The line and shaded region represent the mean and 90% confidence interval, respectively. Week 24 sotatercept Cavg (ng/mL) refers to AUC from Week 21 to Week 24 divided by 21 days. Boxes in the horizontal boxplots represent the 25th, 50th, and 75th percentiles; whiskers extend to the 10th and 90th percentiles of sotatercept Cavg.

Exposure-response NT-proBNP model

The final exposure-response time to NT proBNP < 300 pg/mL model was a Cox proportional hazard model with Cavg at week 24 as the predictor of sotatercept effect. Since 41.5% of the participants achieved NT-proBNP < 300 pg/mL at baseline, the baseline probability of achieving NT-proBNP < 300 pg/mL needed to be incorporated during the base model development. After incorporation of the baseline probability, sotatercept Cavg was found to be a significant predictor of time to NT-proBNP < 300 pg/mL. The final exposure-response time to NT-proBNP < 300 pg/mL model was a Cox proportional hazards model including the effect of sotatercept Cavg and WHO functional class. The probability of NT proBNP < 300 pg/mL increased with increasing sotatercept exposures approaching a plateau at sotatercept exposures corresponding to 0.7 mg/kg dose: for each increase of 1 ng/mL of sotatercept Cavg, the predicted hazard for NT-proBNP < 300 pg/mL increased by 0.0297%. The hazard ratio for the effect of baseline WHO functional Class III on time to NT-proBNP < 300 pg/mL was 0.734 (95% CI = 0.583, 0.922), indicating that for a patient with WHO functional Class III at baseline compared to a patient with WHO functional Class II at baseline, the predicted hazard for NT-proBNP < 300 pg/mL was 73.4%. None of the covariates tested (including body weight, age, sex, duration of PAH disease, PAH etiology, background PAH therapy, infusion therapy) were found to be statistically significant predictors of time to NT proBNP < 300 pg/mL.

Figure 6. Model predicted proportion of participants with NT-proBNP < 300 pg/mL versus week 24 sotatercept Cavg

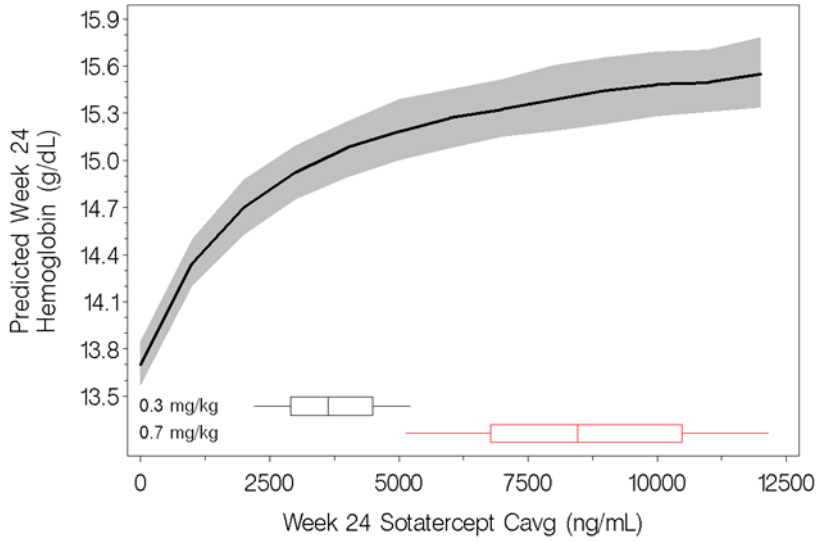


The line and shaded region represent the mean and 90% confidence interval, respectively. Week 24 sotatercept Cavg (ng/mL) refers to AUC from Week 21 to Week 24 divided by 21 days. Boxes in the horizontal boxplots represent the 25th, 50th, and 75th percentiles; whiskers extend to the 10th and 90th percentiles of sotatercept Cavg.

Exposure-response haemoglobin model

The semi mechanistic PK/PD model Hgb increases with increasing sotatercept concentration approaching a plateau at concentrations corresponding to the 0.7 mg/kg dose. Iron supplementation was associated with lower baseline RBC counts and higher stimulation of the production and maturation rates of progenitor cells. As a result, the median Week 24 Hgb change from baseline was slightly higher for participants who received iron supplementation versus participants without iron supplementation (1.88 g/dL versus 1.74 g/dL). Age, body weight, sex, racial classification, and calculated glomerular filtration rate were not found to be statistically significant covariates on Hgb dynamic.

Figure 7. Model predicted haemoglobin response versus Week 24 sotatercept Cavg.



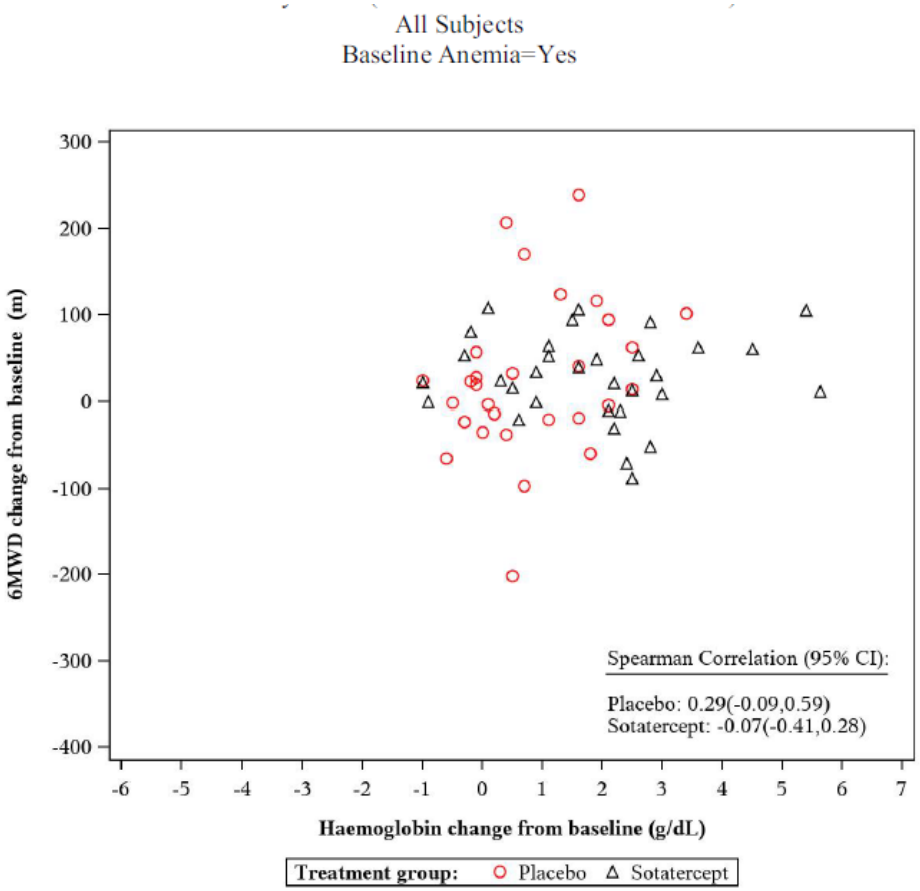
The line and shaded region represent the mean and 90% confidence interval, respectively. Week 24 sotatercept Cavg (ng/mL) refers to AUC from Week 21 to Week 24 divided by 21 days. Boxes in the horizontal boxplots represent the 25th, 50th, and 75th percentiles; whiskers extend to the 10th and 90th percentiles of sotatercept Cavg.

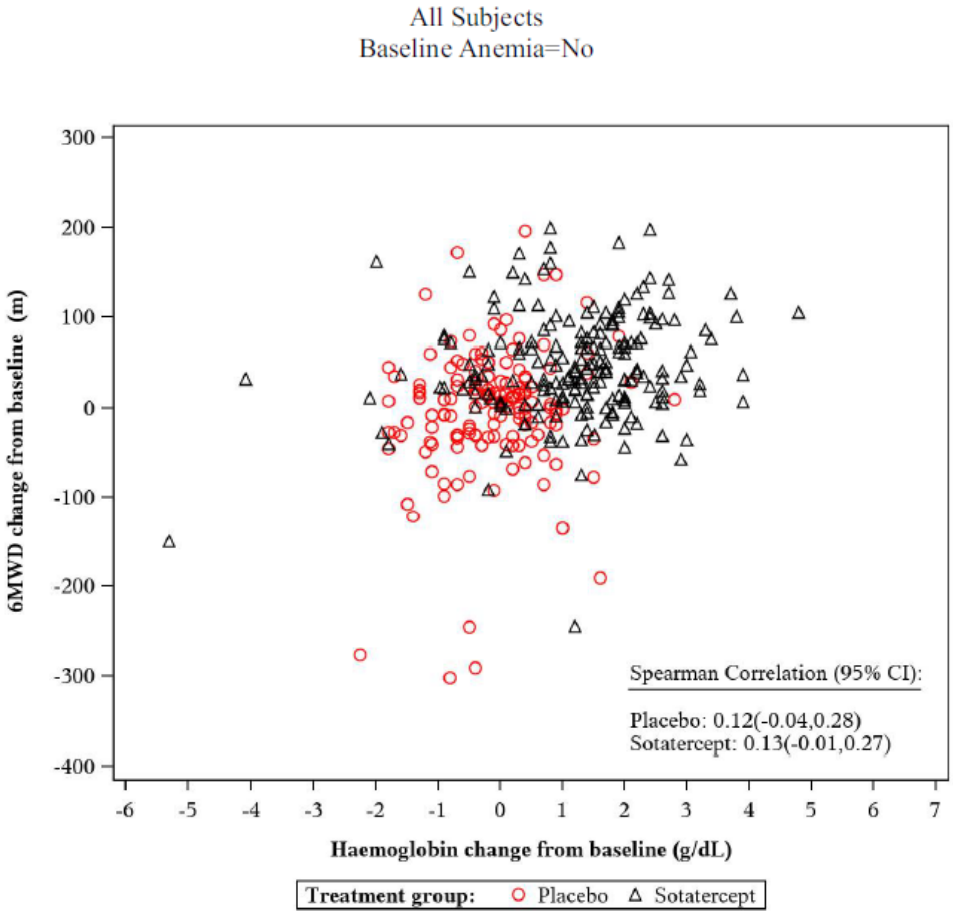
Stochastic simulations, including the contribution of IIV and demographic characteristics of the Phase 2/3 analysis population (n = 449 patients), were performed to predict Hgb response following a single dose of either 0.3 or 0.7 mg/kg sotatercept to examine the probability of a change in Hgb from baseline 2 g/dL and a maximum Hgb concentration reaching 18 g/dL within 21 days after dosing. A total of 7 (1.6%) patients and 21 (4.7%) patients were predicted to meet these criteria following a single 0.3 mg/kg dose versus a single 0.7 mg/kg dose, respectively.

Correlation analyses change in haemoglobin- change in 6MWD

Correlation analysis between Week 24 change in hemoglobin from baseline and Week 24 change in 6MWD from baseline was conducted by classification of anemia at baseline for pool of STELLAR and PULSAR participants.

Figure 8. Scatterplot of Week 24 6MWD change from baseline vs Week 24 Haemoglobin change from baseline by classification of anemia at baseline (FAS; Pool STELLAR and PULSAR)



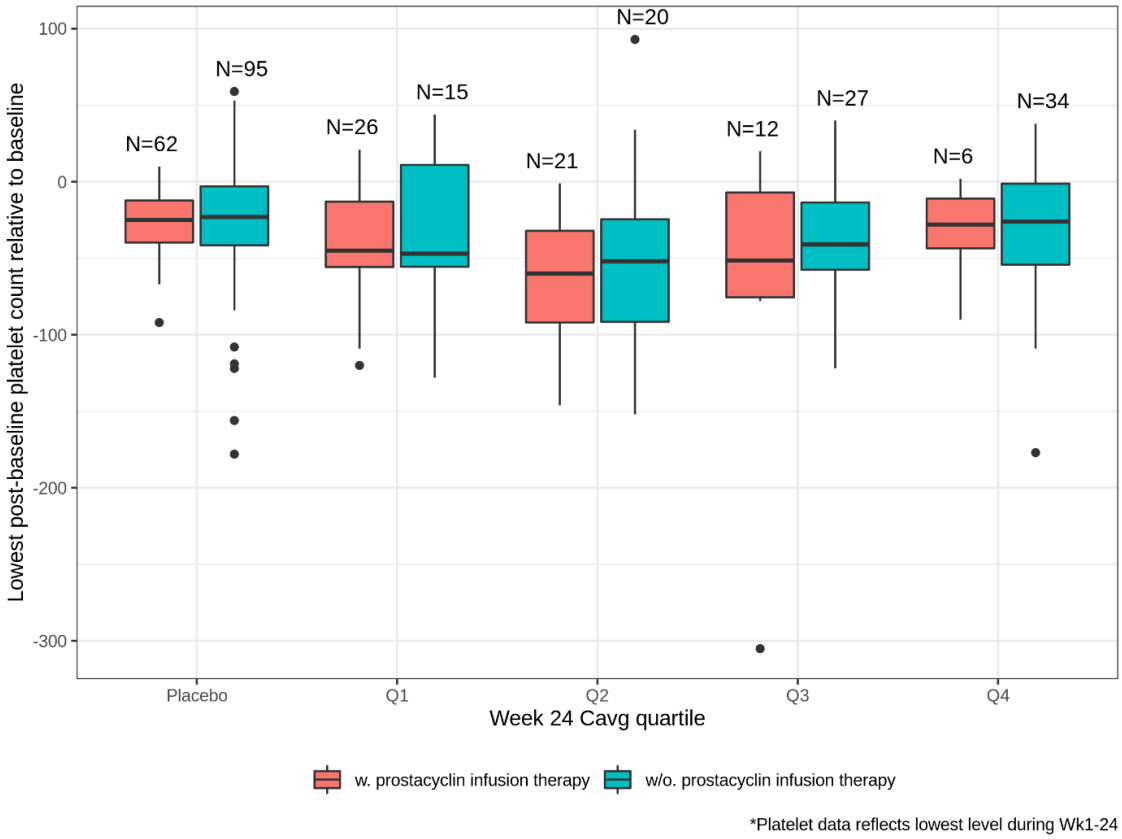


Exposure-platelet response relationship

To evaluate exposure-platelet response relationship, change from baseline for participant-specific lowest post-baseline platelet counts were summarized for quartiles of steady-state Cavg (week 22-24). Participants in the sotatercept treated group had numerically greater median decrease in platelet count relative to placebo for both groups (with or without baseline prostacyclin therapy). However, there was considerable variability in platelet response. Furthermore, within the sotatercept treated group there was no trend across exposure quartiles. In conclusion, there was no meaningful trend observed in exposure-platelet relationship stratified by use of prostacyclin infusion therapy. Consistent with this, no exposure-response trend was observed for thrombocytopenia and epistaxis overall or stratified by use of prostacyclin therapy.

Participants in the sotatercept treated group had numerically greater median decrease in platelet count relative to placebo for both groups (with or without baseline prostacyclin therapy). However, there was considerable variability in platelet response. Furthermore, within the sotatercept treated group there was no trend across exposure quartiles. In conclusion, there was no meaningful trend observed in exposure-platelet relationship stratified by use of prostacyclin infusion therapy.

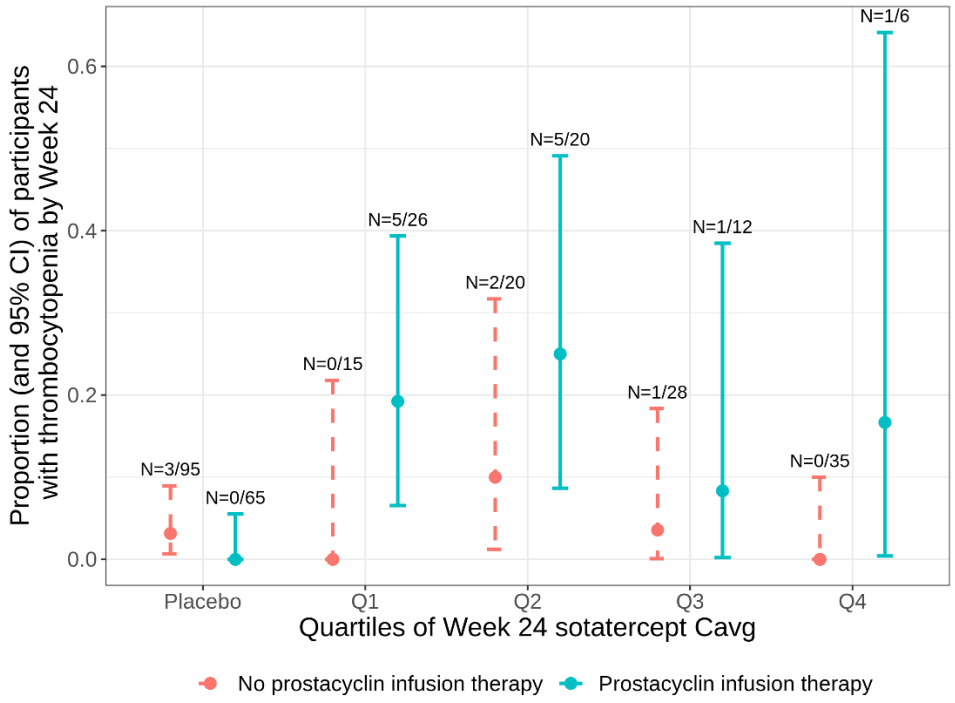
Figure 9. Platelet Response by Exposure Quartiles



Exposure-platelet response relationship

The figure below shows the proportion of participants in STELLAR who had thrombocytopenia by Week 24 for each quartile of predicted Week 21-Week 24 Cavg. The number and proportion of events are low with wide confidence intervals. There was no clear exposure response trend in either group (participants who received prostacyclin therapy as well as participants who did not receive prostacyclin therapy).

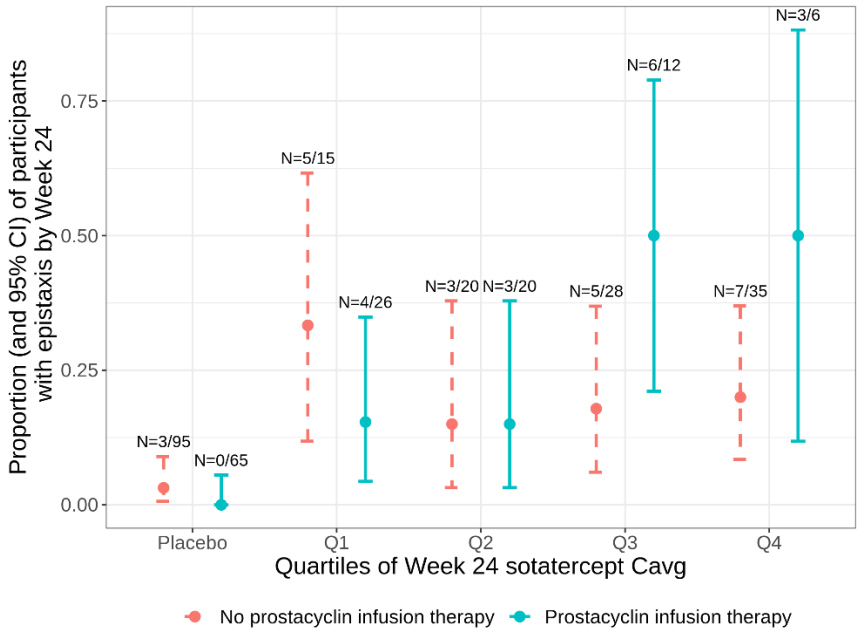
Figure 10. Thrombocytopenia results for STELLAR by Exposure Quartiles



Week 24 Cavg refers to average concentration over Week 21 to Week 24;
Q1: Cavg <= 6.14 ug/mL; Q2: 6.14 ug/mL < Cavg <= 8.10 ug/mL;Q3: 8.10 ug/mL < Cavg <= 9.84 ug/mL; Q4: 9.84 ug/mL < Cavg <= 18.6 ug/mL; CI= Confidence Interval

The figure below shows the proportion of participants in STELLAR who had epistaxis by Week 24 for each quartile of predicted Week 21-Week 24 Cavg. The number and proportion of events are low with wide confidence intervals. There was no clear exposure response trend in either group (participants who received prostacyclin therapy as well as participants who did not receive prostacyclin therapy).

Figure 11. Epistaxis results for STELLAR by Exposure Quartiles



Week 24 Cavg refers to average concentration over Week 21 to Week 24; Q1: Cavg <= 6.14 ug/mL; Q2: 6.14 ug/mL < Cavg <= 8.10 ug/mL; Q3: 8.10 ug/mL < Cavg <= 9.84 ug/mL; Q4: 9.84 ug/mL < Cavg <= 18.6 ug/mL
CI = Confidence Interval

2.7.3. Discussion on clinical pharmacology

Sotatercept is a first-in-class human fusion protein consisting of the extracellular domain of the ActRIIA linked to IgG1 FC, which act as a ligand trap that scavenges excess activin A and other ligands for ActRII to inhibit activin signaling. Activin A levels are increased in PAH patients. Activin A binding to ActRII promotes proliferative signaling while there is a decrease in anti-proliferative BMPR-II signaling. Sotatercept rebalances the pro-proliferative (ActRII/Smad2/3-mediated) and anti-proliferative (BMPRII/Smad1/5/8 mediated) signaling to modulate pulmonary vascular proliferation, although no clinical data has been provided to support this claim. In this respect, pulmonary vascular resistance measurements are considered important to elucidate the mechanism of action or to define the dose-response relationship. In PAH clinical studies, treatment with sotatercept resulted in a significant reduction in pulmonary vascular resistance (see clinical efficacy below). However, although the Applicant has sufficiently described the mechanism of action of sotatercept as activin signaling inhibition in relation to vascular remodeling, activin-A, which belongs to the TGF-beta superfamily, is also involved in the regulation of many other biological functions including hemopoiesis, bone remodeling, hormonal homeostasis, inflammation, cell proliferation and tissue fibrosis (Morianos I et al. 2019). Due to its effects on hematopoiesis, efficacy of sotatercept was initially investigated in patients with anaemia for different reasons. The clinical data submitted demonstrated that sotatercept also increases erythrocytes and Hgb levels in patients with PAH. Although increases in erythrocytes and Hgb may not improve hemodynamic parameters, exercise capacity in terms of 6MWD may increase. Correlation analyses between change in hemoglobin and change in 6WMD from baseline thereby

discriminating in baseline anaemia (yes/no), showed that there is no correlation, also not in relation to baseline anaemia (yes/no). Subgroup analyses by gender also did not show a correlation. Additionally, exposure-response model for 6MWD suggests that both 6MWD and hemoglobin increase with increasing sotatercept concentration. As such, the effect of sotatercept and hemoglobin on 6MWD are confounded and it is not possible to separate the independent effect of hemoglobin on 6MWD. Other mechanisms that may contribute to the beneficial effect of sotatercept in patients with PAH are effects on cardiac structure and function, skeletal muscle wasting, and vascular wall calcification. Nevertheless, it is acknowledged that vascular remodeling is still most likely contributing to the majority of the observed effect, although a strong relationship between PVR and exercise capacity has not been shown.

Additionally, due to the broad effects of activin-A, the possibility for producing untoward adverse effects is high. Therefore, the Applicant was requested to discuss the potential mechanism of action of sotatercept for inducing some adverse events that could alter benefit-risk in the long-term, like thrombocytopenia, bleeding events, and telangiectasias (signal of vessel frailty). The Applicant is of the view that the significant reductions in mean platelet count (thrombocytopenia) observed in PAH clinical studies with sotatercept are mild and remain within the normal range. In clinical trial subjects who experienced severe thrombocytopenia ($<50\times10^9$/L), any potential contribution of sotatercept was obscured by confounding effects of other therapies and comorbidities. The increase in nonserious bleeding observed in the clinical studies indicates an effect on hemostasis beyond thrombocytopenia, but no mechanistic explanation is currently available. Non-clinical data indicated that sotatercept did not cause bleeding or adverse effects on platelet counts. Further, it seems that the potential risk of thrombosis could be associated with the ability of sotatercept to increase hemoglobin levels via the reduction of circulating levels of activins and GDF-11 and not by inducing a prothrombotic risk via other mechanisms. Regarding telangiectasia, the potential for decreased BMP10 signaling to influence vessel integrity at some level cannot be ruled out. Current data do not suggest that cutaneous telangiectasia indicates vascular pathology elsewhere in the body. Based on the discussion provided, this issue is not further pursued.

The clinical pharmacology program consists of two completed Phase 1 studies in healthy postmenopausal women and three studies in the PAH population PULSAR (0.3 and 0.7 mg/kg Q3W), SPECTRA (0.7 mg/kg Q3W after single dose 0.3 mg/kg) and the pivotal phase 3 study STELLAR (0.7 mg/kg Q3W after single dose 0.3 mg/kg). PopPK analysis and exposure-response analyses for efficacy and safety were also conducted.

No dedicated studies in subjects with renal or hepatic impairment were conducted, which is acceptable because sotatercept is a protein and catabolized by general protein degradation processes. Similarly no drug-drug interaction studies were conducted because large proteins do not directly interact with (CYP) enzymes. Finally, a thorough QTc study has not been performed for sotatercept, which is considered appropriate. Nevertheless, safety ECG monitoring in Phase 1 studies, PULSAR, SPECTRA and STELLAR indicated that sotatercept is not associated with clinically relevant QTc prolongation.

Methods

In the pivotal study STELLAR, a lower in-study cut point for the ADA assay was used to achieve a false positive rate between the 2-11%. The higher incidence in ADA positive and NAb positive subjects in STELLAR compared with the Phase 2 studies could be explained by the lower in-study cut points for the ADA assay used in STELLAR. In addition, the higher incidence of NAb in STELLAR could also be due to a better drug-tolerant NAb assay applied in STELLAR.

PopPK analysis

In general, model development steps, covariate analysis, model validation, and model application appear adequate and are satisfactorily summarised. The final 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 pcVPCs seem to indicate adequate performance for Phase 2/3 PK data in patients, however, misspecification was observed for Phase 1 data in healthy subjects. The data in Phase 2 and 3 studies seem to be too sparse to adequately characterise the absorption of sotatercept. A model misspecification seems to occur during the absorption phase in data from healthy volunteers. This is also reflected in relatively high shrinkage for IIV on Vc (51.9%), Ka (48.3%), Vp (34.6%), and F1 (36.8%). In addition, it is highly unexpected to observe larger residual error in healthy volunteers (0.057) vs PAH patients (0.0357). Additional analyses indicate a difference in bioavailability between phase 1 studies (healthy volunteers) and phase 2 or 3 studies (PAH patients), which could have been taken into account in model development and optimization. Nevertheless, the relevant PK parameters seem to be relatively stable during model development and the sparse data from Phase 2/3 studies are described sufficiently.

Pharmacokinetics

Bioavailability

Following SC administration, absolute bioavailability estimated in healthy subjects was 100%, but with popPK analysis the estimated bioavailability was approximately 66%. The injection sites used in the studies has not been recorded, but according to the pharmacy manual use of different injections sites from visit to visit were recommended. The sparse data collection in patients and the fact that the injection site, which can influence the absorption rate of antibodies, is not known and is likely to cause more variability in patients in absorption rate than in healthy volunteers. Still, the variability of sotatercept PK in patients is moderate. Overall, it can be concluded that the absolute bioavailability following SC administration is at least 66% based on the population PK model.

Bioequivalence

Drug substance and product have undergone several manufacturing changes during clinical development. No comparative PK studies have been conducted to demonstrate bioequivalence between the sotatercept (process I and II) frozen solution used in the phase 1 studies 009 and 010 and sotatercept process IIIa lyophilised powder for solution used in the phase 2 and phase 3 studies in patients with PAH. The products used in the phase 2 and phase 3 study are representative for the commercial formulation. Across study comparison of measured serum sotatercept concentrations did not indicate differences in PK of sotatercept of early formulation and the commercial formulation.

The slow clearance, low volume of distribution and elimination half-life are typical for the aspecific clearance of IgG molecules; there is no indication target mediated clearance in the dose range 0.03 - 3 mg/kg doses. Pharmacokinetics of sotatercept were dose proportional and not time-dependent.

Special populations

Time varying body weight and baseline albumin were considered significant predictors of sotatercept exposures. The impact of body weight on sotatercept exposure is corrected by using weight-based dosing regimen, supporting the weight-based dosing. Baseline albumin was identified to be statistically significant for clearance but the 12% increase in AUC in subjects with low albumin is not clinically

relevant. Therefore, no dose adjustment is necessary for any population using a body weight-based dosing.

Pharmacodynamics

The clinical pharmacology program consists of two completed Phase 1 studies in healthy postmenopausal women including 1 single IV/SC dose escalation study (P009) and 1 multiple SC dose escalation study (P010). However, the evaluated PD parameters (bone biomarkers) are not in relation to the proposed indication, and, therefore, not discussed in the section primary pharmacology. The Phase 2 study P001 (PULSAR) can be considered the proof-of-concept and main dose-finding study in relation to the proposed indication and is discussed in the section "Dose response study" below.

Regarding PD interactions, exposure-platelet response relationship analyses, in which the change from baseline for participant-specific lowest post-baseline platelet counts were summarized for quartiles of steady-state Cavg (week 22-24) showed that sotatercept resulted in numerically greater median decrease in platelet count compared with placebo but there was no trend across exposure quartiles. Moreover, there was also no trend observed in exposure-platelet relationship stratified by use of prostacyclin infusion therapy. However, due to the imbalance of thrombocytopenia in users versus non-users of prostacyclin infusion therapy, information on the use of prostacyclin and the risk of thrombocytopenia has been included in section 4.4 of the SmPC. Additionally, although there is no exposure-platelet response relationship, there still appears an interaction between sotatercept and prostacyclin infusion therapy based on the large imbalance (20% vs 3.1%) of thrombocytopenia in users versus non-users of prostacyclin infusion therapy. Since there is no plausible mechanism underlying a PD interaction this is reflected in sections 4.4 and 4.8 of the SmPC. Further, the Applicant has provided data showing that no exposure-response trend was observed for thrombocytopenia and epistaxis overall or stratified by use of prostacyclin therapy. Regarding genetic differences in PD response, the Applicant has adequately shown, based on pre-clinical and clinical data, that sotatercept inhibits activin and GDF-induced pathogenic Smad2/3 signaling pathway regardless of the genetic mutation in BMPR2.

PK/PD – exposure-response analyses

Observed 6MWD generally increased over time in patients treated with sotatercept. The difference in sotatercept exposure between 0.3 and 0.7 mg/kg was estimated to result in an increase of the 6MWD with <5 m. Hence, the sotatercept exposure 6MWD is estimated to be flat in the dose range 0.3-0.7 mg/kg, which is in in line with the observations in the dose response study PULSAR. An increase in Hgb of more than 2 g/dL was estimated to increase the 6MWD with more than 10 m. As both 6MWD and hemoglobin show a shallow sotatercept exposure-response increase with increasing sotatercept concentration, the effect of sotatercept and hemoglobin on 6MWD are confounded and it is not possible to separate the independent effect of hemoglobin on 6MWD. Iron supplementation affected haemoglobin levels. Iron supplementation, however, was no covariate for 6MWD.

Similarly, the exposure-response modelling for PVR was also rather flat in the 0.3-0.7 mg/kg dose range: the difference in sotatercept exposure between 0.3 and 0.7 mg/kg was estimated to decrease the PVR with ~15 dynes*sec/cm^5 which is small to the estimated overall decrease of 217 dynes*sec/cm^5.

At this clinical dose range of 0.3-0.7 mg/kg the sotatercept exposure-response analyses is very shallow for 6MWD, NT-proBNP < 300 pg/mL and PVR, and other factors such as hemoglobulin and age (6MWD), baseline NT-proBNP (NT-proBNP) and prostacyclin, PAH duration and baseline PVR levels (PVR) have larger effects than sotatercept exposure range. Hence, the exposure response might be more sensitive for inter-study and inter-participant variability and might explain some of the apparent numerical different effects in PVR and NT-proBNP between PULSAR and STELLAR studies. Since the

exposure-response analysis are descriptive and not pivotal for this application the uncertainties in the exposure-response analyses can be accepted.

Dose modifications are proposed for too high Hb levels and for too low platelet counts. Exposure-platelet response relationship analyses showed that sotatercept resulted in numerically greater median decrease in platelet count compared with placebo. However, there was no trend across exposure quartiles. Moreover, there was also no trend observed in exposure-platelet relationship stratified by use of prostacyclin infusion therapy. Although there is no exposure-platelet response relationship, there still appears an interaction between sotatercept and prostacyclin infusion therapy based on the larger imbalance (20% vs 3.1%) of thrombocytopenia in users versus non-users of prostacyclin infusion therapy, this is reflected in both sections 4.4 and 4.8 of the SmPC.

Dose justification

Exposure-response analyses showed an increased effect on 6MWD, PVR, NT-proBNP and increase in haemoglobin with increasing sotatercept concentrations. However, the exposure-response relationships were rather flat in the dose range 0.3 mg/kg and 0.7 mg/kg. Hence, estimated differences between 0.3 and 0.7 mg/kg which, although predicted to be numerically better for the 0.7 mg/kg, seem not clinically relevant.

For further discussion on the dose justification see section 'Dose response study' below.

Immunogenicity

Sotatercept induced anti-drug antibody (ADA) responses in 10.4% and 25.9% and Nab in 0.8% and 6.8% of treated subjects with PAH in Phase 2 and 3. The majority of ADA were detected shortly after the initial sotatercept dose, with a median ADA onset of ~3 weeks after the 1st dose of sotatercept and the ADA response was transient in ~55% of ADA positive participants in all 3 PAH studies. Although the incidence in ADA positive and Nab positive subjects was relatively high and a large proportion of ADA response was not transient (~45%), these ADAs did not clinical relevantly affect the PK, PD (haemoglobin) and efficacy (6MWD, PVR, and NT-proBNP) profiles of sotatercept.

2.7.4. Conclusions on clinical pharmacology

Generally, the pharmacology of sotatercept has been sufficiently evaluated. The Applicant has sufficiently described the mechanism of action of sotatercept as activin signalling inhibition in relation to vascular remodeling. Although, activin-A, which belongs to the TGF-beta family, is involved in the regulation of many other biological functions including hemopoiesis, bone remodeling, hormonal homeostasis, inflammation, cell proliferation and tissue fibrosis (Morianos I et al. 2019) it is acknowledged that vascular remodeling is still most likely contributing to the majority of the observed effect, although a strong the relationship between PVR and exercise capacity has not been shown.

Sotatercept is immunogenic, as shown by the high rate of ADA responses detected in 10.4% and 25.9% of PAH participants in Phase 2 and 3, respectively. However, the ADAs did not affect sotatercept exposure or the efficacy and safety outcomes of sotatercept treatment in PAH participants. Finally, sotatercept does not cause clinically relevant QTc prolongation. Due to their large size, therapeutic proteins do not interact with the pore of hERG channels and thus do not have clinically meaningful effects on QTc interval. Safety ECG monitoring performed in healthy participants and participants with PAH supports this conclusion.

2.7.5. Clinical efficacy

This application is based on efficacy data obtained from the flowing studies:

- Two Phase 2 studies (PULSAR and SPECTRA)
    - PULSAR (N=106) was a placebo-controlled study that evaluated the effects of sotatercept on standardized endpoints (eg, 6MWD, PVR, NT-proBNP, and WHO FC) in participants with PAH.
        - Final data from the 24-week Placebo-controlled and the 30-month Extension Periods.
    - SPECTRA was a small (N=21), exploratory, open-label study designed to evaluate the effects of sotatercept on iCPET measures of cardiopulmonary health and hemodynamics in participants with PAH.
        - Final data from the 24-week Treatment Period and the 18-month Extension Period.
- Phase 3 study (STELLAR)
    - STELLAR (n=323) was a placebo-controlled study that evaluated the effects of sotatercept on standardized endpoints (eg, 6MWD, PVR, NT-proBNP, and WHO FC) in participants with PAH
        - Complete efficacy and safety data from the 24-week DBPC Period.
        - All available efficacy and safety data from the up to 72-week LTDB Extension Period through the data cut-off (26-AUG-2022).
        - Available PK and immunogenicity data from the DBPC and LTDB Extension Periods through a data cut-off (05-AUG-2022)

SOTERIA is an ongoing open-label extension study to provide longer-term efficacy and safety data on participants treated with sotatercept. Currently no efficacy results from this study are available.

2.7.5.1. Dose response study(ies)

PULSAR study

In the randomized, double-blind, parallel group study PULSAR the efficacy and safety of sotatercept in adults ≥18 years old with PAH (WHO Group 1, FC II or III) on stable treatment (≥90 days) with background PAH therapy (monotherapy or combination therapy with ERA, PDE5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists) was evaluated.

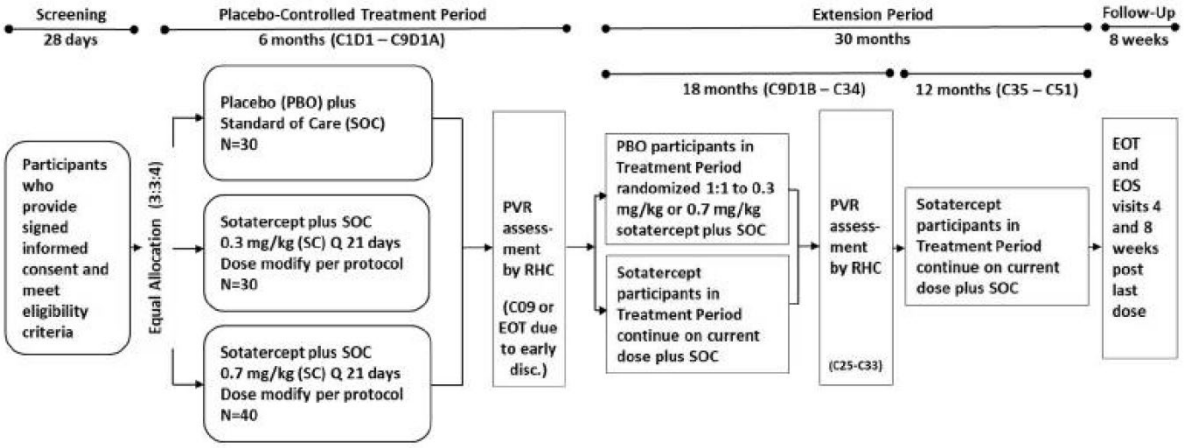
Methods

The study had a 24-week placebo-controlled primary treatment period (referred to as the Placebo-controlled Period) and an extension period (referred to as the Extension Period). The open-label Extension Period was up to 30 months in duration.

Participants were randomized to placebo, sotatercept 0.3 mg/kg, or sotatercept 0.7 mg/kg in the 24-week Placebo-controlled Period (3:3:4). Randomization was stratified by baseline WHO Functional Class (FC) (Class II or III). Participants in the placebo group were re-randomized (1:1) to treatment with either sotatercept 0.3 or 0.7 mg/kg (collectively referred to as the placebo crossed group) in the 30-month open-label Extension Period. Dose delay and/or reduction or discontinuation were required due to adverse events, increased blood pressure, or increased haemoglobin in either treatment arm

(sotatercept or placebo). The primary endpoint of the study was change from baseline in PVR at 24 weeks. Secondary endpoint included change from baseline in 6MWD, WHO FC, NT-proBNP, TAPSE and QoL at 24 weeks and clinical worsening.

Table 14. PULSAR study design



Abbreviations: Cx=Cycle x; CxDy=Cycle x Day y; EOS=End of Study; EOT=End of Treatment; N=number; PBO=placebo; PVR=pulmonary vascular resistance; Q=every; RHC=right heart catheterization; SC=subcutaneous; SOC=standard of care.

Table 15. Dose Modification: Dose Delay, Dose Reduction, and Discontinuation Guideline for Sotatercept

Event at the Day of Dosing[a] (Assessed prior to each IP administration)	Action
Adverse Events (AE)	
Any related AE Grade 2[b]	Dose delay until resolved to ≤ Grade 1 or baseline, and then reduce dose level by one dose level
Any related AE ≥ Grade 3[b]	Dose delay for 3 weeks/visit; if not resolved to ≤ Grade 1, discontinue treatment; if resolved, restart dosing and reduce by one dose level
2 prior dose reductions (due to BP, Hgb, or AE) and now require a dose reduction related to AE[b]	Discontinue treatment
Blood Pressure (BP)	
Systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg	(1) Treat with BP medications and dose delay for up to 1 cycle until SBP below 140 mmHg and DBP below 90 mmHg. Restart study drug at same dose level. (2) If SBP still ≥140 mmHg (but < 160 mmHg) or DBP still ≥ 90 mmHg (but < 100 mmHg) after being treated with BP medications and dose delay for 1 cycle, restart study drug and reduce by one dose level. (3) If SBP still ≥ 160 mmHg or DBP still ≥ 100 mmHg after the above steps, discontinue study drug treatment
Hemoglobin (Hgb)	
Predose Hgb ≥ 18.0 g/dL	Phlebotomy[c] until Hgb < 16.0 g/dL for males and < 15.0 g/dL for females; restart dosing and reduce by one dose level
ΔHgb ≥+ 2.0 g/dL (not influenced by RBC transfusions) compared to predose Hgb of the previous sotatercept administration	Dose delay for one cycle; reduce dose by one dose level if below threshold of ≥ + 2.0 g/dL per cycle (each cycle is approximately 3 weeks) rate of increase over two dosing periods; if rate exceeds ≥ + 2.0 g/dL per cycle (each cycle is approximately 3 weeks) rate over two dosing periods, discontinue treatment.
ΔHgb < + 2.0 g/dL (not influenced by RBC transfusions) compared to predose Hgb of the previous sotatercept administration	Continue dosing if no AE or BP criteria met

All AEs coded with National Cancer Institute-Common Toxicity Criteria for Adverse Events, version 4.0 (NCI-CTCAE), current active minor version
[a] No more than 2 dose reductions are allowed
[b] At least possibly related to study drug
[c] Therapeutic phlebotomy procedures should be performed in a location designated to provide monitoring of vital signs (i.e., pulse and blood pressure) where IV resuscitation fluids are available

Table 16. Dose reductions for Sotatercept

Starting Dose Level	1st Dose Level Reduction	2nd Dose Level Reduction	No additional dose reductions permitted; discontinue treatment
0.3 mg/kg	0.1 mg/kg	0.05 mg/kg	
0.7 mg/kg	0.3 mg/kg	0.1 mg/kg	

Results

A total of 106 participants were randomized. In the Placebo-controlled Period, the proportion of participants who discontinued study intervention was 14.3% (6 participants) in the sotatercept 0.7 mg/kg group, 3.1% (1 participant) in the sotatercept 0.3 mg/kg group, and 6.3% (2 participants) in the placebo group. The most common reason for discontinuation from study intervention and from the

study was a TEAE (n=7, 6.6%). One death, in the sotatercept 0.7 mg/kg group, was reported during the Placebo-controlled Period. TEAEs leading to discontinuation included neutropenia, thrombocytopenia polycythaemia, haemoglobin increased, red blood cell count increased, cardiac arrest, dyspnoea (all events occurred in no more than 1 subject).

The majority of randomized participants (n= 97, 91.5%) completed the Placebo-controlled Period and entered the Extension Period. In the Extension Period, no trends in the disposition of participants were identified between the treatment groups. Of those who entered the Extension Period, 89.7% completed the study, 89.7% completed the study intervention regimen, and 89.7% transitioned into SOTERIA. Four deaths were reported in this study period (3 deaths in the combined continuing sotatercept group, and 1 death in the combined placebo-crossed group).

Placebo-controlled period

PVR (primary endpoint)

The decrease from baseline in PVR was significantly greater in the sotatercept 0.7 and 0.3 mg/kg groups compared with the placebo group. The placebo-adjusted LS mean difference from baseline was -269.4 dynes*sec/cm^5 (p<0.0001) for the sotatercept 0.7 mg/kg group and -151.1 dynes*sec/cm^5 (p=0.0030) for the sotatercept 0.3 mg/kg group.

When haemoglobin and hematocrit increase, blood viscosity increases, which can increase PVR. In the Evaluable Population at Week 24 relative to baseline, when adjusted for hematocrit, the reductions in PVR in the sotatercept groups compared with placebo were greater than that observed in the primary analysis.

6MDW

The increase from baseline in 6MWD was significantly greater at the prespecified 0.2 alpha level in the sotatercept 0.7 and 0.3 mg/kg groups compared with the placebo group. The placebo-adjusted LS mean difference from baseline was 22.3 meters (p=0.1072) for the sotatercept 0.7 mg/kg group and 24.6 meters (p=0.0790) for the sotatercept 0.3 mg/kg group.

WHO FC

The observed proportion of participants with ≥1 class improvement from baseline in WHO FC was higher in the sotatercept 0.7 mg/kg (20.0%; p=0.4911) and 0.3 mg/kg (29.6%; p=0.1503) groups compared with the placebo group (13.3%).

NT-proBNP

Clinically meaningful reductions from baseline in NT-proBNP were observed in the sotatercept 0.7 and 0.3 mg/kg groups compared with the placebo group. The placebo adjusted LS mean difference from baseline was -671.5 pg/mL (p=0.0015) for the sotatercept 0.7 mg/kg group and -812.1 pg/mL (p<0.0001) for the sotatercept 0.3 mg/kg group.

TTCW

The proportion of participants with clinical worsening events at Week 24 relative to baseline was low in both the sotatercept and placebo groups and not sufficient to meaningfully interpret the results (1 vs. 2 in the sotatercept and placebo group, respectively).

Extension period

Delayed-start efficacy analysis

The delayed-start analyses were performed to assess the disease modifying potential of sotatercept. They included comparisons between the combined continuing sotatercept group and the combined

placebo-crossed group at Months 18-24 relative to baseline and Month 12 relative to baseline. Greater efficacy in the continuing sotatercept group would provide evidence that sotatercept has potentially modified the trajectory of the disease.

- The LS mean improvement from baseline in PVR was not significantly different between the combined continuing sotatercept group (-233.1 dynes*sec/cm5) and the combined placebo crossed group (-219.2 dynes*sec/cm5) at Months 18 to 24. Based on this result, sequential testing of subsequent endpoints was not performed.
- The LS mean improvements from baseline were not different between the combined continuing sotatercept group and the combined placebo-crossed group, respectively, in 6MWD (55.7 and 60.1 meters) and NT-proBNP (-497.8 and -462.0 pg/mL) at Months 18 to 24. The observed proportion of participants with improvements from baseline in WHO FC (≥1 class improvement) was not different between the combined continuing sotatercept group (40.9%) and the combined placebo-crossed group (55.2%) at Months 18 to 24.
- The effects of sotatercept on PVR, 6MWD, WHO FC, and NT-proBNP were generally consistent across the prespecified subgroups with a sample size ≥10 participants at Months 18 to 24.

Continued-improvement efficacy analyses

The combined continuing sotatercept group is the sum of continuing sotatercept 0.7 kg/mg and continuing sotatercept 0.3 mg/kg groups

- In the combined continuing sotatercept group, the improvements from baseline in PVR, 6MWD, WHO FC, and NT-proBNP at Week 24 were maintained or further enhanced at Months 18 to 24.

2.7.5.2. Main study(ies)

Study P003MK7962 – STELLAR - A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Compare the Efficacy and Safety of Sotatercept Versus Placebo When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy for the Treatment of PAH

- ***Methods***

Study design

STELLAR was a Phase 3 randomized, multicenter, double-blind, placebo-controlled, parallel group intervention study designed to evaluate the efficacy and safety of sotatercept versus placebo in adult participants with PAH (WHO group 1) on stable treatment with background PAH therapy.

The study consisted of four periods, including two treatment periods:

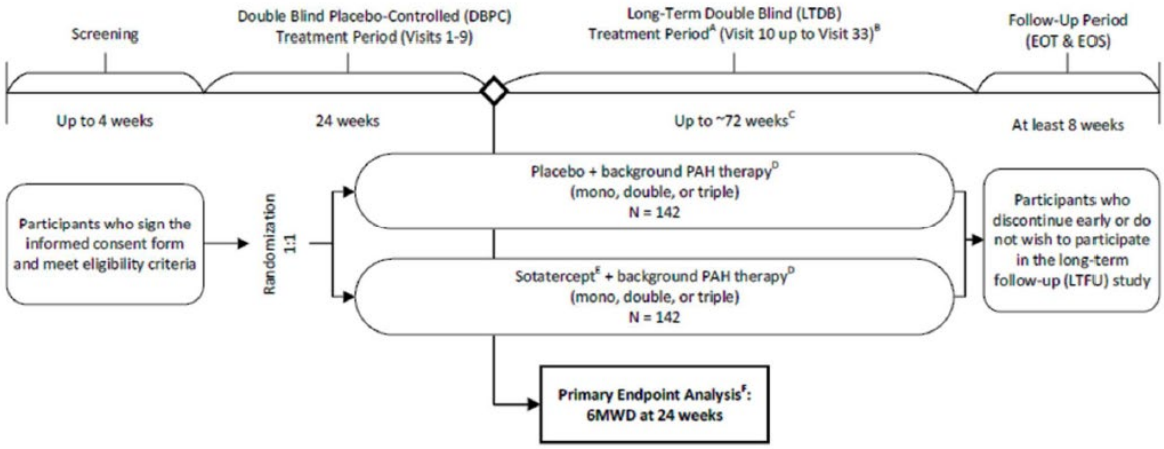
- Screening period: Prospective participants were screened up to 28 days prior randomization. Informed consent was obtained prior to initiation of any screening procedures
- Double-blind placebo-controlled treatment (DBPC) period:

  Participants who met entry criteria were randomized in a 1:1 ratio to receive either sotatercept or placebo (subcutaneous [SC]) every 21 days in addition to background PAH therapy in the DBPC period. The starting dose of sotatercept was 0.3 mg/kg at Visit 1, followed by 0.7 mg/kg for the remainder of the study, unless dose modifications were required. Randomization was

stratified by baseline WHO Functional Class (FC) (Class II or III) and background PAH therapy (mono/double or triple therapy). The duration of the DBPC treatment period was 24 weeks (Visit 1 to Visit 9).

- Long-term double-blind treatment (LTDB) period: Participants who completed the DBPC treatment period entered the LTDB treatment period, which was up to 72 weeks or until the last randomized participant completed the DBPC treatment period and the study was unblinded (Visit 10 up to Visit 33). After the study is unblinded, participants who complete the DBPC Treatment Period and are currently on treatment (sotatercept or placebo) in the LTDB Treatment Period may be eligible to participate in the separate open-label LTFU study (SOTERIA).
- Follow-up period: This study had a Follow-up Period (non-treatment period) of at least 8 weeks, which included at least 2 visits. Participants who prematurely discontinued study intervention during the DBPC or LTDB treatment period or who did not transition to the LTFU study entered the follow-up period.

Figure 12. Study schema



A During the LTDB treatment period, select study visits may be performed as home health care visit.

B LTDB treatment period will last until the last participant randomized completes the DBPC treatment period, at which point the study will be unblinded and participants may rollover into the LTFU study.

C LTDB treatment period duration is estimated based on projected enrollment duration and time required for the last participant to complete the DBPC treatment period.

D Background PAH refers to approved PAH-specific medications and may consist of monotherapy or combination therapy with ERA, PDES inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists.

E Sotatercept at a starting dose of 0.3 mg/kg SC with a target dose of 0.7 mg/kg SC.

F Primary endpoint analysis will be completed after the last participant randomized completes the DBPC treatment period.

6MWD = 6-minute walk distance; EOS = end of study; EOT = end of treatment; PAH = pulmonary arterial hypertension

Study population

Clinical investigator study sites were across 126 study sites in the following 21 countries:

Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, France, Germany, Israel, Italy, Mexico, Netherlands, New Zealand, Poland, Serbia, South Korea, Spain, Sweden, Switzerland, United Kingdom, and United States of America.

Key inclusion/exclusion criteria are presented below.

Table 17. Key inclusion/exclusion criteria of STELLAR

STELLAR study
Inclusion Criteria
- Male or female ≥ 18 years
- Documented diagnostic right heart catheterization (RHC) at any time prior to screening confirming diagnosis of WHO PAH Group 1 in any of the following subtypes: idiopathic PAH, heritable PAH, drug/toxin-induced PAH, PAH associated with connective tissue disorders (CTD), or PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair
- Symptomatic PAH classified as WHO FC II or III
- Baseline RHC of PVR of ≥5 WU and a pulmonary capillary wedge pressure (PAWP) or left ventricular end-diastolic pressure of ≤15 mmHg at screening
- At stable doses of background PAH therapy and diuretics (i.e., patient-specific dose goal for each therapy already achieved) for at least 90 days prior to screening; for infusion prostacyclins, dose adjustment within 10% of optimal dose is allowed per medical practice. Background PAH therapy refers to approved PAH-specific medications and may consist of monotherapy or combination therapy with ERA, PDE5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists.
- 6MWD ≥ 150 and ≤ 500 m repeated twice at screening (measured at least 4 hours apart, but no longer than 1 week), and both values are within 15% of each other (calculated from the highest value)
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. Exclusions in PAH Group 1 should also include schistosomiasis-associated PAH and pulmonary veno-occlusive disease
- Haemoglobin at screening above gender-specific ULN, per local laboratory test
- Baseline platelet count <50,000/mm3 (<50.0 × 109/L) at screening
- Uncontrolled systemic hypertension as evidenced by sitting systolic BP >160 mmHg or sitting diastolic BP >100 mmHg during screening visit after a period of rest
- Baseline systolic BP <90 mmHg at screening
- Pregnant or breastfeeding women
- Any of the following clinical laboratory values at the screening visit: • eGFR < 30 mL/min/m2 (as defined by MDRD equation) • Serum alanine aminotransferase or aspartate aminotransferase levels > 3 × upper limit of normal (ULN) or total bilirubin > 1.5 × ULN

Randomisation and blinding

Participants who signed the informed consent and met all eligibility criteria were stratified by baseline WHO FC and background PAH therapy and then randomized to receive placebo plus background PAH therapy or sotatercept plus background PAH therapy. Randomization assignments were generated through a computerized system, provided by an Interactive Response Technology (IRT). Recruitment was controlled to ensure that at least 50% of enrolled participants are PAH in WHO FC III.

In the event of a medical emergency for an individual participant in which knowledge of the study drug is critical to the participant's medical management, the investigator could break the blind for that participant via the IRT. The investigator was free to break the blind if it was required to manage the participant's medical emergency, based on their judgment.

In non-urgent situations, the investigator should consult with the study medical monitor prior to breaking the blind. Where the investigator has broken the blind without prior discussion, they were requested to inform the sponsor/medical monitor at the earliest opportunity. 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 investigator would determine, in consultation with the medical monitor as needed, if the participant should continue on treatment or be discontinued from the study. The investigator should not inform the participant of their treatment assignment under any circumstances.

Description of trial intervention

Trial intervention

Each eligible participant will be randomly assigned in a 1:1 ratio to one of the two treatment arms:

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

Table 18. Study interventions

Treatment Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Placebo	Matching Placebo	0 mg/kg	Every 21 days	SC injection	Treatment Period: DBPC – 24 weeks LTDB – up to 72 weeks	Placebo
Sotatercept	Sotatercept	Starting dose 0.3 mg/kg with a target dose of 0.7 mg/kg	Every 21 days	SC injection	Treatment Period: DBPC – 24 weeks LTDB – up to 72 weeks	Test Product

DBPC=Double-Blind Placebo-Controlled; LTDB=Long-Term Double-Blind; SC=subcutaneous

The tables below lists the injection volume for study drug dose level 0.3 mg/kg and 0.7 mg/kg, respectively. To allow the use of a standard 3.0 mL syringe provided in the study drug kit with a calibration of 0.1 ml, the injection volume is rounded to the 1st decimal place (Rounding follows the standard rounding rules: if 1.01 mL–1.04 mL, round down to 1.0 mL and if 1.05 mL–1.09 mL, round up to 1.1 mL).

Table 19. Injection volume and number of injections for dose of 0.3 mg/kg

Participant weight ranges (kg)	Study Drug Dose 0.3 mg/kg			
	Rounded Injection Volume (mL)	Actual Dose administered (mg)	Number of Kits	Number of Injections
30.0 - 40.8	0.2	10.0	1	1
40.9 - 57.4	0.3	15.0	1	1
57.5 - 74.1	0.4	20.0	1	1
74.2 - 90.8	0.5	25.0	1	1
90.9 - 107.4	0.6	30.0	1	1
107.5 - 124.1	0.7	35.0	1	1
124.2 - 140.8	0.8	40.0	1	1
140.9 - 157.4	0.9	45.0	1	1
157.5 - 174.1	1.0	50.0	1	1
174.2 - 180.0	1.1	55.0	1	1

Table 20. Injection volume and number of injections for dose of 0.7 mg/kg

Participant weight ranges (kg)	Study Drug Dose 0.7 mg/kg			
	Rounded Injection Volume (mL)	Actual Dose administered (mg)	Number of Kits	Number of Injections
30.0 - 31.7	0.4	20.0	1	1
31.8 - 38.9	0.5	25.0	1	1
39.0 - 46.0	0.6	30.0	1	1
46.1 - 53.2	0.7	35.0	1	1
53.3 - 60.3	0.8	40.0	1	1
60.4 - 67.4	0.9	45.0	1	1
67.5 - 74.6	1.0	50.0	1	1
74.7 - 81.7	1.1	55.0	1	1
81.8 – 88.9	1.2	60.0	1	1
89.0 - 96.0	1.3	65.0	2	1
96.1 - 103.2	1.4	70.0	2	1
103.3 - 110.3	1.5	75.0	2	1
110.4 - 117.4	1.6	80.0	2	1
117.5 - 124.6	1.7	85.0	2	1
124.7 - 131.7	1.8	90.0	2	1
131.8 - 138.9	1.9	95.0	2	1
139.0 - 146.0	2.0	100.0	2	1
146.1 - 153.2	2.1	105.0	2	2
153.3 - 160.3	2.2	110.0	2	2
160.4 - 167.4	2.3	115.0	2	2
167.5 - 174.6	2.4	120.0	2	2
174.7 - 180.0	2.5	125.0	3	2

Dose modification

The dose modification rules for sotatercept in PULSAR were established based on previous experience with luspatercept (human activin receptor type IIB ligand trap for a treatment for anemia). The Applicant engaged in discussions with health authorities (FDA and CHMP) regarding the dose modification rule for luspatercept. Subsequently, the dose modification rules for sotatercept were refined over time as experience with the clinical response to sotatercept evolved through Phase 2 and 3 clinical studies. The design of the dose modification rules in STELLAR was informed by PULSAR, the first Phase 2 clinical study involving sotatercept in PAH patients.

Blood samples were taken and assessed for Hgb and platelet count levels on the same day of study drug administration or up to 3 days prior to that day if available.

Dose delay, reduction, or discontinuation could be performed in any treatment arm (sotatercept or placebo). Dose delays always preceded dose reductions. Dose delays or reductions could be implemented for safety reasons at any time per the investigator's assessment and were not limited to the dose modification guidance provided.

Escalation to target dose (0.7 mg/kg)

All participants began treatment at a starting dose of 0.3 mg/kg at Visit 1. At Visit 2, the dose was 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 as described below were met. However, if at Visit 2 Hgb increases by more than 2.0 g/dL from baseline and this value is above the gender-specific upper limit of normal (ULN) per local laboratory test, dosing should be delayed. All other study procedures, with the exception of study drug administration, were performed. At Visit 3, if Hgb has increased by less than 2.0 g/dL from baseline or Hgb value is below the gender-specific upper limit of normal (ULN) per local laboratory test, dosing should be restarted at 0.3 mg/kg. At Visit 4, if Hgb has increased by less than 2.0 g/dL from baseline or Hgb value is below the gender-specific upper limit of normal (ULN) per local laboratory test, the dose will be escalated to the target dose of 0.7 mg/kg.

Dose modifications due to haemoglobin increase

From Visit 3 onward, if Hgb level increased by more than 2 g/dL from the previous dosing visit, and this value was above the gender-specific upper limit of normal per local laboratory test, then a maximum of 3 consecutive dose delays were allowed during the study treatment period. After the third dose delay, if Hgb level persisted at more than 2 g/dL above the previous dosing visit, and this value was above the gender-specific upper limit of normal per local laboratory test then the dose was reduced to 0.3 mg/kg. If the participant was already at a dose of 0.3 mg/kg, the study medical monitor was consulted, and study drug discontinuation was 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

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 drug 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 drug 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.

Dose modifications due to adverse events of telangiectasia

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 one visit if the participant was receiving 0.7 mg/kg study drug, or for three 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.

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 reescalated to 0.7 mg/kg after 2 consecutive visits at which Hgb values are stable and equal or lower than the upper limit of normal. 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 adverse events of bleeding. In cases of dose reduction due to events of telangiectasia, the dose may be re-escalated to 0.7 mg/kg only if the event has completely resolved.

Figure 13. Guidelines for target dose escalation (0.7 mg/kg)

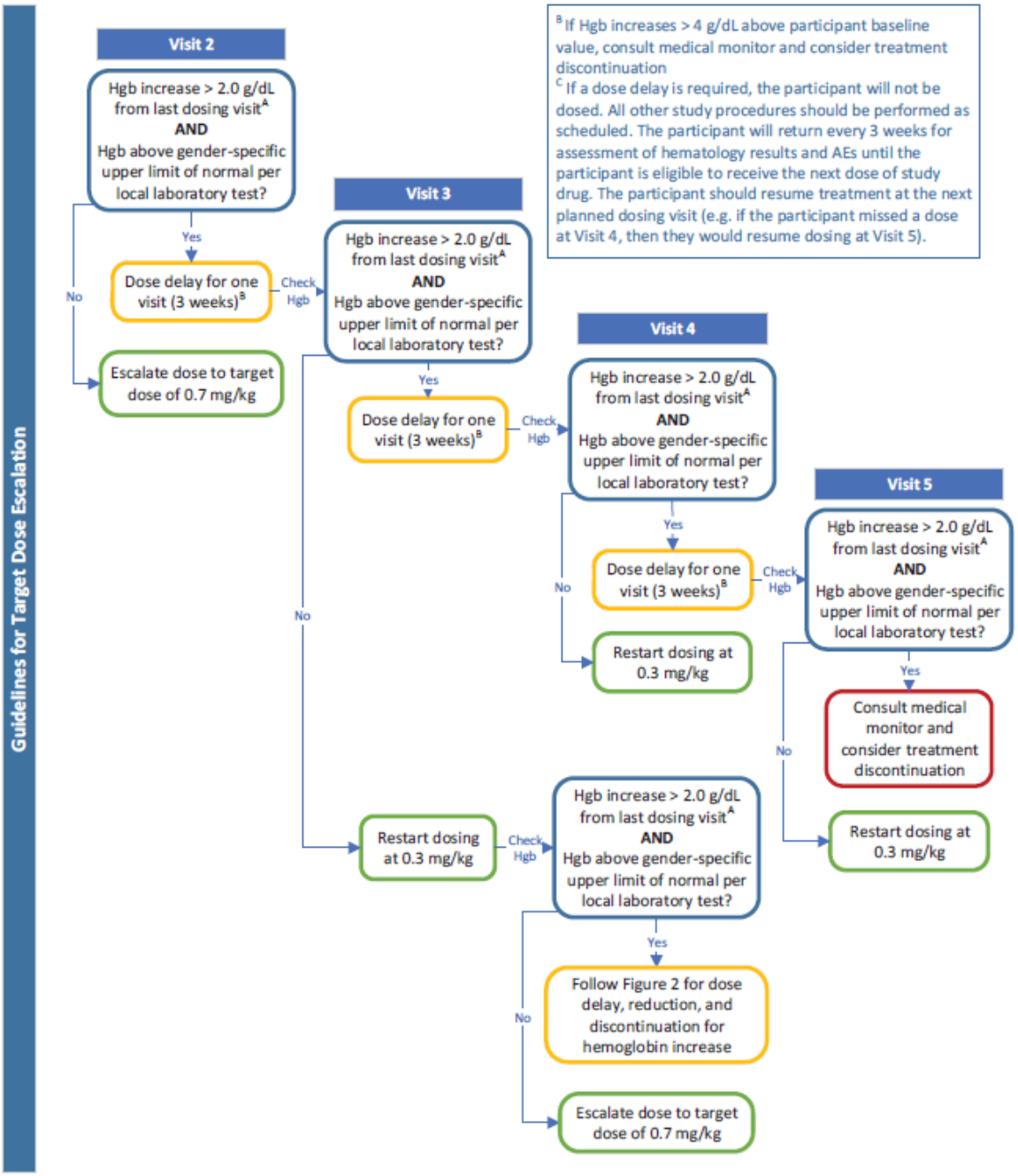


Figure 14. Guidelines for dose modifications due to haemoglobin increase from visit 2 onward

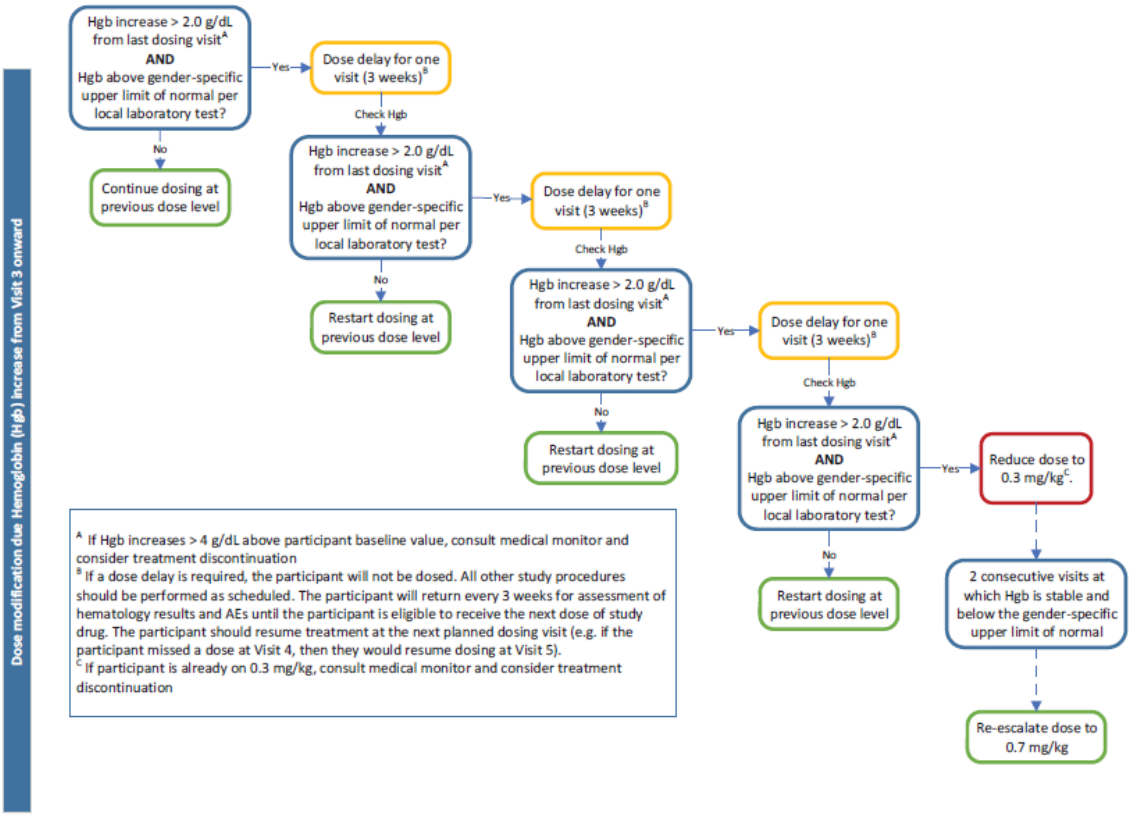
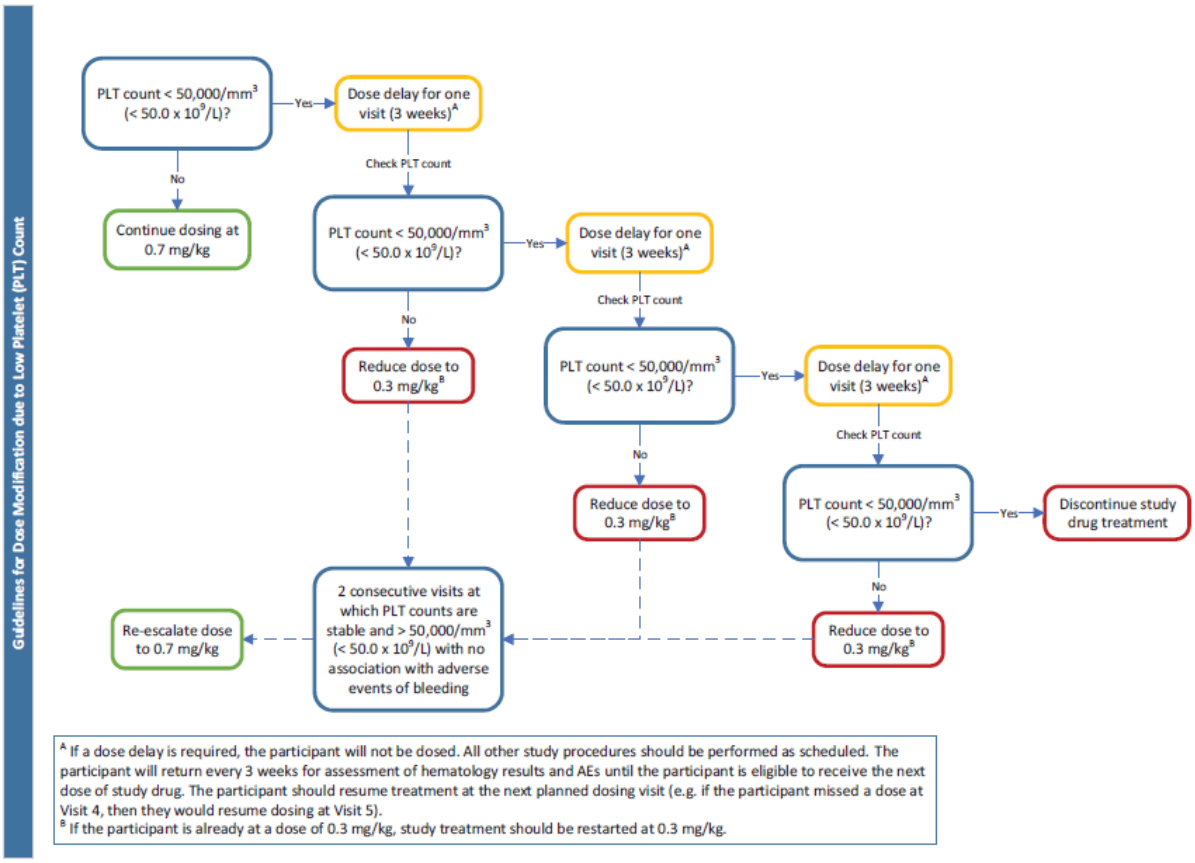


Figure 15. Guidelines for dose modifications due to low platelet count



Objectives, endpoints and estimands

Primary objective, endpoint and estimand

The *primary efficacy objective* is to evaluate the efficacy of sotatercept treatment (plus background PAH therapy) versus placebo (plus background PAH therapy) at 24 weeks in adults with PAH.

The *primary efficacy endpoint* was the change from baseline in 6MWD at Week 24. The estimands for the primary objective can be found below.

Table 21. Estimands for primary objective

Population	**Male and female patients with Group 1 PAH ≥18 years of age who would encounter the Intercurrent Events of death and change in the use of sotatercept, placebo or background PAH therapy (dose reduction, dose delay, or discontinuation) under any treatment assignment.**
Treatment condition<s>	Assignment to Sotatercept, regardless of discontinuation and change in the use and added to background PAH therapy compared to assignment to Placebo, regardless of discontinuation and change in the use, added to background PAH therapy.
Endpoint (variable)	Change from baseline in 6MWD at week 24, with death prior to Week 24 represented quantitatively by any fixed worst-rank change from baseline (e.g. -2000m) to reflect the worst clinical outcome
Population-level summary	Hodges Lehman location-shift estimate of the treatment difference between Sotatercept and placebo arms
Intercurrent events and strategy to handle them	
Death	Composite
Changes in the use of sotatercept, placebo, or background PAH therapy	Treatment policy

Secondary objectives, endpoints and estimands

The secondary objectives, endpoints and estimands are presented in the tables below.

Table 22. Secondary objectives and endpoints of STELLAR

Secondary	
To evaluate the efficacy of sotatercept treatment (plus background PAH therapy) versus placebo (plus background PAH therapy) at 24 weeks in adults with PAH	(1) Multicomponent improvement endpoint measured by the proportion of participants achieving all of the following at Week 24 relative to baseline: - Improvement in 6MWD (increase ≥30 m) - Improvement in NT-proBNP (decrease in NT-proBNP ≥30%) or maintenance/achievement of NT-proBNP level <300 ng/L - Improvement in WHO FC or maintenance of WHO FC II (2) Change from baseline in PVR at Week 24 (3) Change from baseline in NT-proBNP levels at Week 24 (4) Proportion of participants who improve in WHO FC at Week 24 from baseline (5) Time to death or the first occurrence of any of the following clinical worsening events: - Worsening-related listing for lung and/or heart transplant - Need to initiate rescue therapy with an approved background PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more - Need for atrial septostomy - Hospitalization for worsening of PAH (≥24 hours) - Deterioration of PAH defined by both of the following events occurring at any time, even if they began at different times, as compared to their baseline values: -- Worsened WHO FC -- Decrease in 6MWD by ≥15% confirmed by 2 tests at least 4 hours apart, but no more than 1 week (6) Proportion of participants who maintain or achieve a low risk score at Week 24 versus baseline using the simplified French Risk score calculator (7) Change from baseline in the Physical Impacts domain score of Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) at Week 24 (8) Change from baseline in the Cardiopulmonary Symptoms domain score of PAH-SYMPACT® at Week 24 (9) Change from baseline in the Cognitive/Emotional Impacts domain score of PAH-SYMPACT® at Week 24

Tertiary/Exploratory	
To evaluate the efficacy of sotatercept treatment (plus background PAH therapy) versus placebo (plus background PAH therapy) at 24 weeks	The following indices will be evaluated: - Change in ECHO parameters at Week 24 versus baseline - Change in dyspnea score (assessed by Borg CR10 scale®) at Week 24 versus baseline - Proportion of participants who achieve PVR <3 WU at Weeks 24 - Proportion of participants who achieve mPAP <25 mmHg at Week 24 - Change from baseline in mPAP at Week 24 - Change from baseline in hematocrit-adjusted PVR at Week 24 - Change from baseline in the Cardiovascular Symptoms domain score of PAH-SYMPACT® at Week 24 - Change from baseline in the EQ-5D-5L index score at Week 24 - Change from baseline in the EQ-5D-5L VAS at Week 24 - Change from baseline in Cardiac Index at Week 24

Table 23. Estimands for multicomponent improvement objective

Population	Male and female patients with Group 1 PAH ≥18 years of age who would encounter the Intercurrent Events of death and change in the use of sotatercept, placebo or background PAH therapy (dose reduction, dose delay, or discontinuation) under any treatment assignment.
Treatment condition<s>	Assignment to Sotatercept, regardless of discontinuation and change in the use and added to background PAH therapy compared to assignment to Placebo, regardless of discontinuation and change in the use, added to background PAH therapy.
Endpoint (variable)	Indicator variable (Yes/No) for meeting the response criteria for multicomponent, where death prior to Week 24 is defined not having met the criteria
Population-level summary	Odds ratio (sotatercept/ placebo) comparing the proportion of responders according to the criteria for multicomponent improvement
Intercurrent events and strategy to handle them	
Death	Composite
Changes in the use of sotatercept, placebo, or background PAH therapy	Treatment policy

Table 24. Estimands for PVR

Population	Male and female patients with Group 1 PAH ≥18 years of age who would encounter the Intercurrent Events of death and change in the use of sotatercept, placebo or background PAH therapy (dose reduction, dose delay, or discontinuation) under any treatment assignment.
Treatment condition<s>	Assignment to Sotatercept, regardless of discontinuation and change in the use and added to background PAH therapy compared to assignment to Placebo, regardless of discontinuation and change in the use, added to background PAH therapy.

Endpoint (variable)	Change from baseline in PVR at week 24, with death prior to Week 24 represented quantitatively by any fixed worst-rank change from baseline (e.g. 20000) to reflect the worst clinical outcome
Population-level summary	Hodges Lehman location-shift estimate of the treatment difference between Sotatercept and placebo arms
Intercurrent events and strategy to handle them	
Death	Composite
Changes in the use of sotatercept, placebo, or background PAH therapy	Treatment policy

The change from baseline in PVR at week 24 is analysed incorporating death using a worst clinical outcome score and regardless of any changes in the use of study and/or background medication. The results is planned to be presented using Hodges Lehman location shift estimate of the difference between groups.

Table 25. Estimands for time to first clinical worsening or death

Population	Male and female patients with Group 1 PAH ≥18 years of age who would encounter the Intercurrent Events of death and change in the use of sotatercept, placebo or background PAH therapy (dose reduction, dose delay, or discontinuation) under any treatment assignment.
Treatment condition<s>	Assignment to Sotatercept, regardless of discontinuation and change in the use and added to background PAH therapy compared to assignment to Placebo, regardless of discontinuation and change in the use, added to background PAH therapy.
Endpoint (variable)	Time to first clinical worsening or death
Population-level summary	hazard ratio (sotatercept vs placebo)
Intercurrent events and strategy to handle them	
Death	Composite
Changes in the use of sotatercept, placebo, or background PAH therapy	Treatment policy

The time to first clinical worsening event or death is analysed incorporating intercurrent event of death in the endpoint and regardless of any changes in the use of study and/or background medication. The results is planned to be presented using log rank test and hazard ratio and its 95% confidence interval.

Statistical methods for estimation and sensitivity analysis

Planned analyses

Analysis of primary endpoint of change from baseline to week 24 in 6MWD was planned to be analysed using the aligned rank stratified Wilcoxon test with randomisation factors as strata. The output from this test is a Hodges-Lehman location-shift estimate of the overall treatment difference with 95% confidence interval and 2-sided p-value.

The binary secondary endpoints (e.g. multicomponent improvement endpoint) are planned to be analysed the Cochran-Mantel-Haenszel test, stratified by the randomization factors.

Time to first clinical worsening event or death is planned to be analyzed using the log-rank test with randomization factors as strata to test the treatment difference of sotatercept versus placebo. A Cox proportional hazards model stratified by randomization factors was planned to be used to estimate the hazard ratio and the corresponding 95% confidence interval.

Additionally, Kaplan-Meier curves were planned to be generated for each arm with randomization factors as strata.

A gatekeeping method is planned to be used to control the Type I error rate in the primary and secondary efficacy endpoints. After testing the primary efficacy endpoint and then one can proceed in the prespecified order of the secondary efficacy endpoints listed in Table 22 Secondary objectives and endpoints of STELLAR. Missing data is planned to be imputed using multiple imputation. For continuous secondary endpoints, the same multiple imputation approach will be used. For binary secondary endpoints, when a subject has missing the data not due to Covid-19 it will be set to non-responder.

Different approaches are described as sensitivity analyses based on changing the imputed values assumed values for death and non-fatal clinical worsening.

Planned subgroup analyses

Subgroup analyses are defined for the following factors:

- Sex (male and female)
- PAH etiological subgroups (idiopathic PAH, heritable PAH, Drug/Toxin-induced PAH,connective Tissue disease, congenital heart disease with s/p Shunt Repair)
- Monotherapy vs. Double vs. Triple combination therapy at baseline
- Prostacyclin infusion therapy vs. Non-Prostacyclin Infusion at baseline
- Baseline WHO functional class (II or III)
- Baseline PVR (≤800 or >800 dynes*sec/cm^2)

Subgroup analyses are planned for primary efficacy endpoint and the following secondary endpoints: PVR, NT-proBNP is the sample size at each level of the subcategory ≥10.

Sample size determination

Sample size calculation is based on the 6MWD, and the secondary endpoint of improvement in WHO FC. The assumptions for the variability and the desired treatment effect are based on the phase 2 PULSAR study and a published clinical trial on subjects with PAH disease. Assuming a type I error rate of 0.05 and a 25-m improvement in sotatercept arm compared to placebo with a common standard deviation of 50m, 121 patients per arm would result in 96% power under the Wilcoxon rank-sum test for 6MWD endpoint.

For the secondary endpoint of improvement in WHO FC, proportion of participant treated with sotatercept and placebo arms are assumed to be 0.25 and 0.11 respectively. Assuming a type I error rate of 0.05 and 121 patients per arm would provide 80% power based on a chi-square test.

The sample size is adjusted to account for 15% dropout rate where in 142 participants per arm would be required. For randomisation 1:1 scheme will be used.

Error probabilities, adjustment for multiplicity and interim analyses

A gatekeeping method was planned to be used to control the Type I error rate in the primary and secondary efficacy endpoints by testing first the primary endpoint and then moving to the secondary

endpoints in the order of the secondary endpoints listed in Table 22: Secondary objectives and endpoints of STELLAR using a two-sided type I error rate of 0.05.

No interim analysis was planned.

Changes from protocol-specified analyses

The changes in the planned statistical analysis in SAP version 1.0 from protocol specified analysis are listed in a table. Main changes from protocol are introduction of estimands, and removal of PPS dataset, and aligning the PVR endpoint analysis with primary endpoint of 6MWD using aligned rank sum test.

Location	Description of Change	Brief Rationale
Section 3.2.3 Exploratory Endpoints	Added the parameter "Change in hematocrit-adjusted PVR at Week 24 from baseline"	Hemoglobin change could potentially affect the change in PVR. This endpoint that adjusts PVR for the measured hematocrit is useful.
Section 3.2.3 Exploratory Endpoints	Added the parameter "Change in Cardiac Index at Week 24 from Baseline"	Potentially useful parameter. Was assessed and reported in the Phase 2 PULSAR study.
Section 8.6 Analysis of the Primary Efficacy Endpoint	Clarified the aligned rank stratified Wilcoxon test will be used as the primary analysis method	
Section 8.7 Analysis of the Secondary Efficacy Endpoints	Changed the primary analysis method from ANCOVA to the aligned rank stratified Wilcoxon test for change from baseline in PVR at Week 24, change from baseline in NT-proBNP at Week 24, and change from baseline in selected domain scores from PAH-SYMPACT® at Week 24	To align better with the estimands for these secondary endpoints and for consistency with the primary endpoint.
Section 8.8 Analysis of the Exploratory Efficacy Endpoints	Added analysis methods for two exploratory endpoints (change in hematocrit-adjusted PVR at Week 24 from baseline and change in Cardiac Index at Week 24 from Baseline)	
Section 11.3 Populations for Analysis	Per Protocol Set (PPS) analysis population removed	Given that this is a registrational study, any differences between the Full Analysis Set (prespecified as the primary analysis population for efficacy analyses) and this population would likely not be considered by regulatory authorities when evaluating the efficacy of sotatercept versus placebo.
Section 11.5.1.1 Handling of Missing Data	Sensitivity analysis D removed	Given that this is a registrational study, this analysis will not be considered by regulatory authorities when evaluating the efficacy of sotatercept.
	Sensitivity analysis E removed	If the assumptions for ANCOVA are violated, the validity of an ANCOVA analysis might be questionable.
	Revised the conditions for performing the tipping point analysis from a "highly significant" result to a "significant" result.	So that the tipping point sensitivity analysis will be performed in the event of any statistically significant treatment effect.

The changes in the SAP version 2.0 from SAP V1.0 are listed below:

Location	Description of Change	Brief Rationale
Section 3.2.2 Secondary Endpoints Section 3.2.3 Exploratory Endpoints	Added text for handling missing data for the domain scores of PAH-SYMPACT®	To provide how to handle missing data for the domain scores of PAH-SYMPACT®
Section 5.2 Final Analyses Section 6.2 General Post Text Summary Table, Figure, and Individual Subject Data Listing Format Considerations	Added text that available data at the end of the DBPC treatment period will be summarized in a CSR and a separate CSR will be provided at the end of the LTDB treatment and follow-up period. Added text that selected summary tables and figures will be reported based on the DBPC treatment period	To align with the study objective of evaluating the efficacy and safety of sotatercept at 24 weeks and to provide data summaries that do not have a scheduled or analysis visit timepoint associated with the summary table such as compliance calculations.
Section 6.6.1 Primary Efficacy Endpoint	Added baseline definition for one additional scenario for the primary efficacy endpoint	To provide a more comprehensive method for deriving the baseline for the primary efficacy endpoint
Section 6.7.4 Analysis Visit Windows	Updated the analysis visit windows	To cover all the scheduled visits for efficacy endpoints
Section 6.8.1.1 Primary Efficacy Endpoint	Updated text for FCS regression	To clarify the standard MI using the FCS regression
Section 6.8.1.2 Secondary Endpoints	Added text for data transformation in selected endpoints before applying the standard MI	To provide a description of the data transformation of selected endpoints deemed to be necessary for standard MI to perform properly
Section 8.1 General Considerations	Added text for handling mis-stratification at the time of randomization Added text for dealing 6WMD if a participant discontinues the 6MWT prematurely	To provide details for handling mis-stratification at the randomization in the analysis To clarify that the total distance walked at the time of discontinuation will be the 6MWD used in the analysis
Section 8.6 Analysis of the Primary Efficacy Endpoint Section 8.7 Analysis of the Secondary Efficacy Endpoint	Revised the missing data imputation methods in Table 5 and Table 6	To clarify the imputation methods for missing data
Section 10.1 Compliance (Medication Adherence)	Updated the definition for compliance	To clarify the calculation of the compliance, taking the dose delays/hold per protocol in consideration
NA	Minor corrections in terminology and/or grammar made throughout the SAP	Minor updates made for consistency and/or accuracy of the text

Data quality assurance

Several quality oversight activities are implemented at the study investigative site or centrally by the sponsor to all clinical study related activities in accordance with ICH GCP 5.1.

Results

Changes in the planned conduct of the study

Changes in the conduct of the study implemented by protocol amendment are summarized in the table below. There were no changes in the planned conduct of the study implemented by protocol amendment due to the COVID-19 pandemic.

Table 26. Summary of protocol amendments

Amendment Number	Date of Issue	Key Changes
P003-00	12-SEP-2020	Original study protocol
P003-01	06-OCT-2021	• Updated text regarding the detection of antidrug antibodies, and added text regarding the risk of telangiectasia • Added telangiectasia as the only AESI and provided monitoring parameters • Added dose modifications required for AEs of telangiectasia • Added new exclusion criterion on platelet counts • Provided additional guidance on 6MWT • Updated secondary and exploratory endpoints • Modified the criteria for discontinuation due to a clinical worsening event and altered the instructions for further study visits • Removed "hematology (complete blood count)" assessment from Visits 10-12, 14-16, 18-20, 22-24, 26-28, and 30-32

6MWT=6-minute walk test; AESI=adverse event of special interest; AE=adverse event

Participant flow and numbers analysed

Disposition of Participants

The first participant first visit was on the 25th January 2021 and the last participant last visit on the 6th December 2022.

A total of 434 participants were screened and 323 participants were randomized (excluding 1 screen-failed participant randomized in error) across 126 study sites. The proportion of participants who completed Visit 9 (Week 24 of the DBPC Treatment Period) was greater in the sotatercept group (97.5%) than in the placebo group (92.5%). The proportion of participants who completed the overall study was also greater in the sotatercept group (95.1%) than in the placebo group (88.8%).

In the DBPC and LTDB Treatment Periods combined, fewer participants in the sotatercept group (6.1%) than in the placebo group (25.0%) discontinued study intervention. Two (1.2%) participants in the sotatercept group discontinued study intervention due to death and 4 (2.5%) discontinued due to an AE. No other discontinuation category had >1 participant in the sotatercept group. The most common reasons for discontinuation of study intervention in the placebo group were clinical worsening event (10 [6.3%]), death (6 [3.8%]) and other (11 [6.9%]). All 11 participants in the placebo group who discontinued due to reason "other" discontinued due to a clinical worsening event that occurred after Visit 9 and after approval of protocol amendment P003-01.

Table 27. Disposition of subjects (FAS)

	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)
Total Number of Subjects			
Randomized [1]	160 (100.0)	163 (100.0)	323 (100.0)
Completed Visit 9	148 (92.5)	159 (97.5)	307 (95.0)
Completed Study	142 (88.8)	155 (95.1)	297 (92.0)
Discontinued Study Treatment	40 (25.0)	10 (6.1)	50 (15.5)
Withdrew from Study	18 (11.3)	8 (4.9)	26 (8.0)
Primary Reason for Discontinuation of Study Treatment [2]			
Adverse Event	2 (1.3)	4 (2.5)	6 (1.9)
Participant request (withdrawal of consent)	4 (2.5)	1 (0.6)	5 (1.5)
Participant's unwillingness or inability to comply with the protocol	2 (1.3)	1 (0.6)	3 (0.9)
Clinical worsening event	10 (6.3)	1 (0.6)	11 (3.4)
Pregnancy	1 (0.6)	0 (0.0)	1 (0.3)
Study terminated by sponsor [3]	4 (2.5)	0 (0.0)	4 (1.2)
Death	6 (3.8)	2 (1.2)	8 (2.5)
Other	11 (6.9)	1 (0.6)	12 (3.7)
Primary Reason for Withdrawal from Study [2]			
Adverse Event	1 (0.6)	3 (1.8)	4 (1.2)
Participant request (withdrawal of consent)	6 (3.8)	2 (1.2)	8 (2.5)
Participant's unwillingness or inability to comply with the protocol	2 (1.3)	1 (0.6)	3 (0.9)
Clinical worsening event	2 (1.3)	0 (0.0)	2 (0.6)
Death	6 (3.8)	2 (1.2)	8 (2.5)
Other	1 (0.6)	0 (0.0)	1 (0.3)

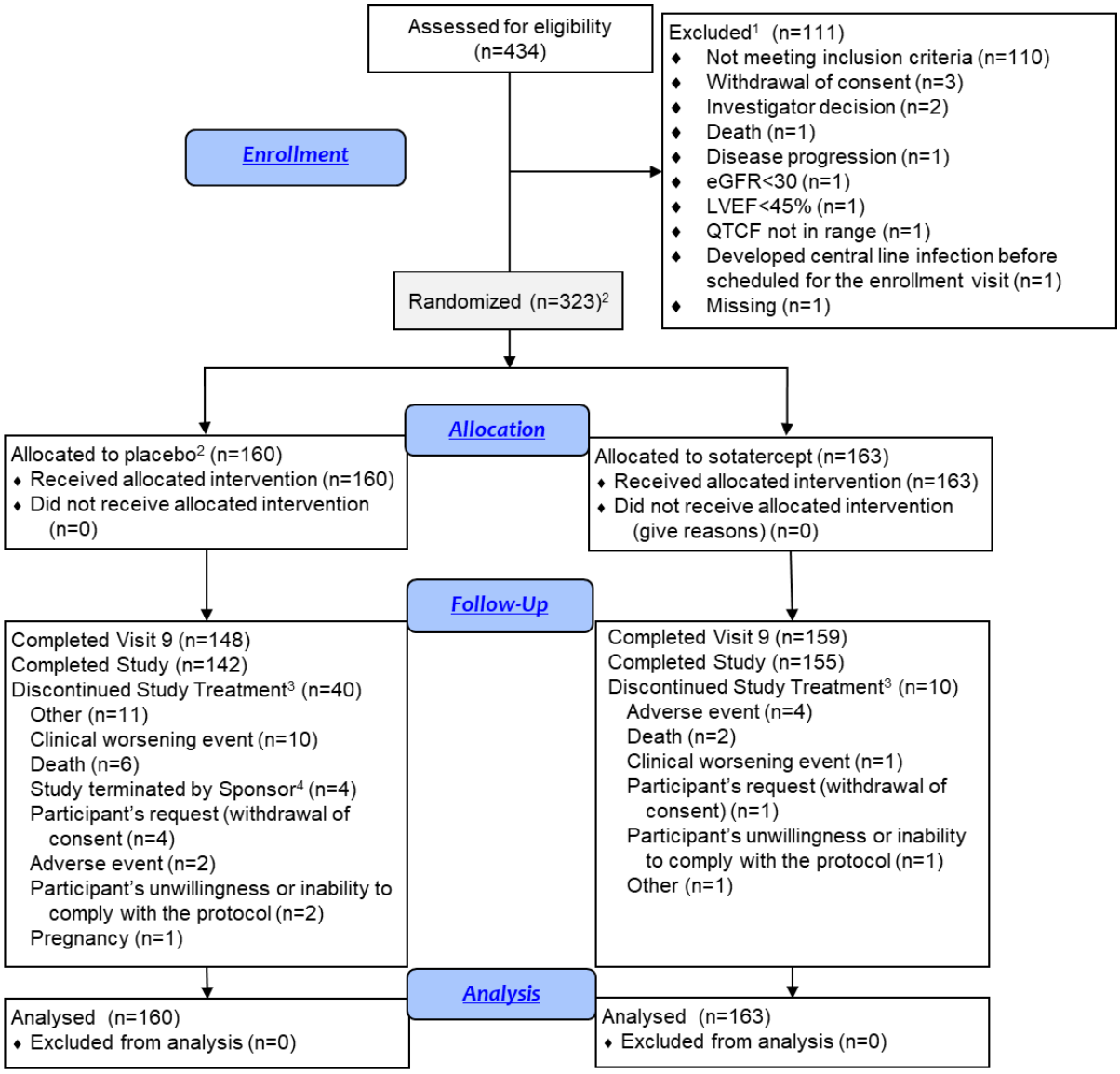
N = number of subjects in the treatment group or overall. n = number of subjects in the category. Percentages are calculated as (n/N)*100.

[1] Excludes one subject (Placebo group) who was inadvertently randomized and did not receive any study medication. Tis subject is also excluded from all analyses.

[2] Subjects may have only one primary reason for discontinuation and withdrawal.

[3] Subjects were incorrectly identified as having discontinued the study treatment due to "study terminated by sponsor"; in fact, all 4 subjects have successfully completed the study and rolled over to the Long-Term Follow-Up study (SOTERIA).

Figure 16. Participant flow



[1] Participants may have more than 1 reason for screen failure and may be counted more than once in the categories
[2] Excludes one participant (Placebo group) who was inadvertently randomized and did not receive any study medication. This participant is also excluded from all analyses.
[3] Participants may have only one primary reason for discontinuation and withdrawal.
[4] Participants were incorrectly identified as having discontinued the study treatment due to "study terminated by sponsor"; in fact, all 4 participants have successfully completed the study and rolled over to the Long-Term Follow-Up study (SOTERIA).

Dose modifications

A total of 35 participants in the STELLAR sotatercept group received dose modifications (dose reduction or delay). Of the 35 participants, 10 participants experienced a subsequent AESI/AEOI after a dose modification. While one participant with multiple comorbidities died from an acute myocardial infarction approximately 4 months after the dose hold/reduction, 9 of the 10 participants successfully completed STELLAR and continued sotatercept treatment in SOTERIA.

DBPC period

The median duration of exposure to study intervention was 168.0 days in the sotatercept and placebo groups.

Dose delays occurred in 12 participants in the sotatercept group and 5 in the placebo group. Among these participants, the median time to first dose delay was 44.0 days for sotatercept and 71.0 days for placebo.

Dose reductions occurred in 10 participants in the sotatercept group and 3 in the placebo group. Among these participants, the median time to first dose reduction was 64.0 days for both groups.

Dose re-escalation occurred in 5 participants in the sotatercept group and 2 in the placebo group. Among these participants, the median time to first re-escalation was 84.0 days for sotatercept and 75.5 days for placebo.

In the sotatercept group, the majority of dose delays were due to either increased hemoglobin or, to a lesser degree, thrombocytopenia/low platelet count. Few dose delays were due to AEs (3 instances with verbatim terms: “As per protocol due to AE teleangiectasia [sic]”, “development of telangiectasia”, and “per PI dose will be held due to AE”).

In the placebo group, dose delays were largely due to clinical worsening or study discontinuation. Dose delays due to AEs were also infrequent in this group (2 instances with verbatim terms “dose delay per PI discretion due to elevated hematocrit” and “by decision of the investigator due to neutropenia”). There were additional dose delays in the placebo group due to other reasons (“pregnancy” and “due to plates [sic] count value”).

Almost all participants (99.4%) in the sotatercept group reached the 0.7 mg/kg dose. One participant did not up-titrate to the 0.7 mg/kg dose due to consistently high haemoglobin levels. All the other participants reached the 0.7 mg/kg dose.

Table 28. Dose modification - Safety Set - Week 24 Results (DBPC)

	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)
Number of subjects with no dose reductions or dose delays	152 (95.0)	145 (89.0)	297 (92.0)
Number of dose reductions per subject			
0	157 (98.1)	153 (93.9)	310 (96.0)
1	2 (1.3)	7 (4.3)	9 (2.8)
2	1 (0.6)	3 (1.8)	4 (1.2)
Number of dose delays per subject			
0	155 (96.9)	151 (92.6)	306 (94.7)
1	5 (3.1)	5 (3.1)	10 (3.1)
2	0 (0.0)	5 (3.1)	5 (1.5)
3	0 (0.0)	2 (1.2)	2 (0.6)
Number of dose re-escalations per subject			
0	158 (98.8)	158 (96.9)	316 (97.8)
1	1 (0.6)	3 (1.8)	4 (1.2)
2	1 (0.6)	2 (1.2)	3 (0.9)
Reasons for dose reduction [1]			
Per protocol dose modification guidelines due to hemoglobin increase	1 (0.6)	5 (3.1)	6 (1.9)
Per protocol dose modification guidelines due to low platelet count	0 (0.0)	1 (0.6)	1 (0.3)
Adverse Event or Adverse Event of Special Interest	2 (1.3)	3 (1.8)	5 (1.5)
Other	0 (0.0)	1 (0.6)	1 (0.3)
Time to first reduction (day [2])			
n	3	10	13
Mean (SD)	86.7 (58.40)	78.2 (33.09)	80.2 (37.46)
Median	64.0	64.0	64.0
Q1, Q3	43.0, 153.0	63.0, 105.0	63.0, 105.0
Min, Max	43, 153	41, 148	41, 153

	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)
Visit of first reduction			
Visit 3	1 (0.6)	2 (1.2)	3 (0.9)
Visit 4	1 (0.6)	4 (2.5)	5 (1.5)
Visit 5	0 (0.0)	1 (0.6)	1 (0.3)
Visit 6	0 (0.0)	2 (1.2)	2 (0.6)
Visit 8	1 (0.6)	1 (0.6)	2 (0.6)
Time to second reduction (day [2]) [1]			
n	1	3	4
Mean (SD)	84.0 (NE)	99.0 (28.58)	95.3 (24.51)
Median	84.0	83.0	83.5
Q1, Q3	84.0, 84.0	82.0, 132.0	82.5, 108.0
Min, Max	84, 84	82, 132	82, 132
Visit of second reduction			
Visit 5	1 (0.6)	2 (1.2)	3 (0.9)
Visit 7	0 (0.0)	1 (0.6)	1 (0.3)
Time to first delay (day [2])			
n	5	12	17
Mean (SD)	86.6 (62.40)	64.9 (42.70)	71.3 (48.28)
Median	71.0	44.0	61.0
Q1, Q3	65.0, 148.0	43.0, 85.0	43.0, 106.0
Min, Max	1, 148	22, 154	1, 154

	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)
Visit of first delay			
Visit 2	1 (0.6)	2 (1.2)	3 (0.9)
Visit 3	0 (0.0)	6 (3.7)	6 (1.9)
Visit 4	2 (1.3)	1 (0.6)	3 (0.9)
Visit 6	0 (0.0)	1 (0.6)	1 (0.3)
Visit 7	0 (0.0)	1 (0.6)	1 (0.3)
Visit 8	2 (1.3)	1 (0.6)	3 (0.9)
Time to first re-escalations (day [2])			
n	2	5	7
Mean (SD)	75.5 (17.68)	80.0 (19.43)	78.7 (17.57)
Median	75.5	84.0	84.0
Q1, Q3	63.0, 88.0	62.0, 85.0	62.0, 88.0
Min, Max	63, 88	61, 108	61, 108

DBPC = double-blind placebo-controlled period.
N = number of subjects in the treatment group or overall. n = number of subjects in the category. Percentages are calculated as (n/N)*100. SD = Standard deviation, Q1 = First quartile, Q3 = Third quartile, NE = Not evaluable.
[1] Subjects with multiple reductions or delays may have more than one reason presented.
[2] Day reflects total time on treatment, calculated as [event date - treatment start date] + 1.

Source: [P003V01MK7962: adam-adsl; adex; adexsum]

Cumulative results (DBPC + LTDB period)

The median duration of exposure to study intervention was longer in the sotatercept group (313.0 days) than in the placebo group (273.0 days) through the data cutoff of Dec 2022.

Dose delays increased to 22 participants in the sotatercept group and 11 in the placebo group. The median time to first dose delay increased to 143.0 days for sotatercept and 161.0 days for placebo.

The number of participants who had dose reductions increased to 18 participants in the sotatercept group with a median time to first dose reduction of 127.0 days. The placebo group increased to 4 participants and the median time increased to 108.5 days.

Dose re-escalation increased to 9 participants in the sotatercept with the median time to first re-escalation of 108.0 days. No dose re-escalation changes were observed in the placebo group.

Regarding the reason "adverse events or adverse event of special interest", six subjects experienced dose reduction due to adverse events (AE/AESI/AEOI) which included telangiectasia (n=2), injection site swelling (n=1), epistaxis (n=1), and two subjects had dose reductions dues to multiple AE/AESI (1. chapped lips, eye discomfort, erythema, urticaria, swelling 2. telangiectasia, epistaxis, and limb pain). There were 4 subjects whose dose reduction was attributed to "other" reasons which included COVID-19, platelet levels below normal as well as epistaxis and gum bleeding, nosebleed and "skin patches" and telangiectasia. Although the "other" reasons also appeared related to low platelet counts or AESI, with the exception of COVID-19.

Table 29. Dose Modifications - Safety Set - Cumulative Results (DBPC + LTDB)

	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)
Number of subjects with no dose reductions or dose delays	146 (91.3)	132 (81.0)	278 (86.1)
Number of dose reductions per subject			
0	156 (97.5)	145 (89.0)	301 (93.2)
1	3 (1.9)	14 (8.6)	17 (5.3)
2	1 (0.6)	4 (2.5)	5 (1.5)
Number of dose delays per subject			
0	149 (93.1)	141 (86.5)	290 (89.8)
1	10 (6.3)	13 (8.0)	23 (7.1)
2	1 (0.6)	5 (3.1)	6 (1.9)
3	0 (0.0)	2 (1.2)	2 (0.6)
4	0 (0.0)	2 (1.2)	2 (0.6)
Number of dose re-escalations per subject			
0	158 (98.8)	154 (94.5)	312 (96.6)
1	1 (0.6)	6 (3.7)	7 (2.2)
2	1 (0.6)	3 (1.8)	4 (1.2)
Reasons for dose reduction [1]			
Per protocol dose modification guidelines due to hemoglobin increase	1 (0.6)	8 (4.9)	9 (2.8)
Per protocol dose modification guidelines due to low platelet count	0 (0.0)	2 (1.2)	2 (0.6)
Adverse Event or Adverse Event of Special Interest	2 (1.3)	5 (3.1)	7 (2.2)
Other	1 (0.6)	3 (1.8)	4 (1.2)
Time to first reduction (day [2])			
n	4	18	22
Mean (SD)	107.3 (62.99)	138.2 (76.91)	132.5 (74.19)
Median	108.5	127.0	127.0
Q1, Q3	53.5, 161.0	64.0, 211.0	64.0, 190.0
Min, Max	43, 169	41, 274	41, 274

	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)
Visit of first reduction			
Visit 3	1 (0.6)	2 (1.2)	3 (0.9)
Visit 4	1 (0.6)	4 (2.5)	5 (1.5)
Visit 5	0 (0.0)	1 (0.6)	1 (0.3)
Visit 6	0 (0.0)	2 (1.2)	2 (0.6)
Visit 8	1 (0.6)	1 (0.6)	2 (0.6)
Visit 9	1 (0.6)	2 (1.2)	3 (0.9)
Visit 10	0 (0.0)	1 (0.6)	1 (0.3)
Visit 11	0 (0.0)	2 (1.2)	2 (0.6)
Visit 12	0 (0.0)	1 (0.6)	1 (0.3)
Visit 13	0 (0.0)	1 (0.6)	1 (0.3)
Visit 14	0 (0.0)	1 (0.6)	1 (0.3)
Time to second reduction (day [2]) [1]			
n	1	4	5
Mean (SD)	84.0 (NE)	126.5 (59.75)	118.0 (55.12)
Median	84.0	107.5	84.0
Q1, Q3	84.0, 84.0	82.5, 170.5	83.0, 132.0
Min, Max	84, 84	82, 209	82, 209
Visit of second reduction			
Visit 5	1 (0.6)	2 (1.2)	3 (0.9)
Visit 7	0 (0.0)	1 (0.6)	1 (0.3)
Visit 11	0 (0.0)	1 (0.6)	1 (0.3)
Time to first delay (day [2])			
n	11	22	33
Mean (SD)	138.7 (65.61)	163.2 (134.73)	155.1 (115.74)
Median	161.0	143.0	154.0
Q1, Q3	71.0, 172.0	43.0, 211.0	61.0, 211.0
Min, Max	1, 211	22, 498	1, 498
Visit of first delay			
Visit 2	1 (0.6)	2 (1.2)	3 (0.9)
Visit 3	0 (0.0)	6 (3.7)	6 (1.9)
Visit 4	2 (1.3)	1 (0.6)	3 (0.9)
Visit 6	0 (0.0)	1 (0.6)	1 (0.3)
Visit 7	0 (0.0)	1 (0.6)	1 (0.3)
Visit 8	2 (1.3)	1 (0.6)	3 (0.9)
Visit 9	4 (2.5)	1 (0.6)	5 (1.5)
Visit 11	1 (0.6)	2 (1.2)	3 (0.9)
Visit 12	1 (0.6)	1 (0.6)	2 (0.6)
Visit 13	0 (0.0)	2 (1.2)	2 (0.6)
Visit 14	0 (0.0)	1 (0.6)	1 (0.3)
Visit 20	0 (0.0)	1 (0.6)	1 (0.3)
Visit 21	0 (0.0)	1 (0.6)	1 (0.3)
Visit 25	0 (0.0)	1 (0.6)	1 (0.3)
Time to first re-escalations (day [2])			
n	2	9	11
Mean (SD)	75.5 (17.68)	135.0 (68.86)	124.2 (66.36)
Median	75.5	108.0	88.0
Q1, Q3	63.0, 88.0	84.0, 197.0	63.0, 197.0
Min, Max	63, 88	61, 234	61, 234

DBPC = double-blind placebo-controlled period; LTDB = long-term double blind period.
N = number of subjects in the treatment group or overall. n = number of subjects in the category. Percentages are calculated as (n/N)*100. SD = Standard deviation, Q1 = First quartile, Q3 = Third quartile.
[1] Subjects with multiple reductions or delays may have more than one reason presented.
[2] Day reflects total time on treatment, calculated as [event date - treatment start date] + 1.

Source: [P003V01MK7962: adam-adsl; adex; adexsum]

Protocol deviations

Major protocol deviations were reported for 139 participants across the DBPC and LTDB Treatment Periods. The proportions of participants with major protocol deviations were comparable in the sotatercept and placebo groups.

The most common major protocol deviation categories (incidence ≥10% in at least 1 group) were study treatment administration/dispensation, study procedures/assessments, visit scheduling, and missing endpoint assessments.

Major protocol deviations associated with the pandemic were reported for 20 participants. These deviations were in the category of visit scheduling and were balanced between the intervention groups.

None of the protocol deviations were classified as a serious GCP compliance issue.

Table 30. Major protocol deviations (FAS)

Category Coded Term	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)
Protocol Deviation	66 (41.3)	73 (44.8)	139 (43.0)
Concomitant Medication	1 (0.6)	1 (0.6)	2 (0.6)
Exclusion Criteria	2 (1.3)	2 (1.2)	4 (1.2)
Inclusion Criteria	4 (2.5)	4 (2.5)	8 (2.5)
Missing Endpoint Assessments	23 (14.4)	23 (14.1)	46 (14.2)
Study Procedures/Assessments	21 (13.1)	22 (13.5)	43 (13.3)
Study Treatment Admin/Dispense	13 (8.1)	22 (13.5)	35 (10.8)
Study Treatment Randomization	1 (0.6)	5 (3.1)	6 (1.9)
Visit Scheduling	17 (10.6)	20 (12.3)	37 (11.5)
ICH/GCP Deviation	70 (43.8)	75 (46.0)	145 (44.9)
Data Privacy	9 (5.6)	24 (14.7)	33 (10.2)
ICF Process/Timing	22 (13.8)	25 (15.3)	47 (14.6)
Inv Qualifications/Agreements	3 (1.9)	4 (2.5)	7 (2.2)
Inv Record Keeping CRF	17 (10.6)	17 (10.4)	34 (10.5)
Inv Record Keeping Source Docs	9 (5.6)	8 (4.9)	17 (5.3)
Inv Safety Reporting (CRF)	9 (5.6)	8 (4.9)	17 (5.3)
Other GCP Deviation	17 (10.6)	12 (7.4)	29 (9.0)
Study Trtmt Supplies/Control	2 (1.3)	4 (2.5)	6 (1.9)

N = number of subjects in the treatment group or overall. n = number of subjects in the category. Percentages are calculated as (n/N)*100.

The major protocol deviations of "missing endpoint assessments" (14.1% vs. 14.4% for the sotatercept and placebo group, respectively), "study procedures/ assessments" (13.5% vs. 13.1%), and "study treatment admin/dispense" (13.5% vs. 8.1%) did not have a clinically relevant impact on the primary outcome of the study.

The majority of "missing endpoints assessments" major protocol deviations were related to the PRO assessment (secondary endpoint), while only a relatively low number was related to the primary endpoint of 6MWD (7 vs 5 in the sotatercept and placebo group, respectively). Further, the majority of "study procedures/assessments" major protocol deviations was related to "any assessment done after IP administration", which does not have an impact on the primary outcome. Further, the major protocol deviations "study procedures/assessments" were related to study drug preparation and/or administration timelines not done as per pharmacy manual or failure to retain all used vials on site, which did not indicate to have had a clinically relevant impact the clinical outcome.

Compliance with intervention

Compliance with study intervention was high (mean >98% in each group) in both groups during the DPBC treatment period and the cumulative DBPC and LTDB Treatment Periods combined.

Table 31. Dose Summary of Treatment Compliance Safety Set - Cumulative Results (DBPC + LTDB)

	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)
Number of subjects	160	163	323
Treatment compliance			
100%	140 (87.5)	138 (84.7)	278 (86.1)
>80% to <=99%	18 (11.3)	22 (13.5)	40 (12.4)
>60% to <=80%	2 (1.3)	3 (1.8)	5 (1.5)
>40% to <=60%	0 (0.0)	0 (0.0)	0 (0.0)
>20% to <=40%	0 (0.0)	0 (0.0)	0 (0.0)
<=20%	0 (0.0)	0 (0.0)	0 (0.0)
Summary statistics for treatment compliance (%)			
Mean (SD)	98.85 (3.683)	98.31 (4.798)	98.57 (4.284)
Median	100.00	100.00	100.00
Min, Max	72.7, 100.0	66.7, 100.0	66.7, 100.0

DBPC = double-blind placebo-controlled period; LTDB = long-term double blind period. SD = standard deviation.
Treatment compliance for each subject (%) = (Number of visits where study medication was administered / Number of visits in the treatment period where study medication should have been administered)*100%.

Numbers analysed

All randomized participants were included in the FAS, except the participant randomized in error who did not receive study intervention. Safety analyses were based on the Safety Set and included all participants who received at least 1 dose of study intervention. The number of participants included in the FAS and Safety Set was similar in both intervention groups.

The PK population consisted of all randomized participants who received at least 1 dose of sotatercept and had sufficient PK samples collected and assayed for PK analysis.

Table 32. Analysis Sets (All Randomized Subject)

	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)
Full Analysis Set (FAS) [1]	160 (100.0)	163 (100.0)	323 (100.0)
Safety Set [2]	160 (100.0)	163 (100.0)	323 (100.0)
PK Population [3]	0 (0.0)	163 (100.0)	163 (50.5)

N = number of subjects in the treatment group or overall. n = number of subjects in the category. Percentages are calculated as (n/N)*100.
[1] Full Analysis Set (FAS): All randomized subjects, regardless of whether or not study treatment was administered. Excludes one subject (Placebo group) who was inadvertently randomized and did not receive any study medication. This subject is also excluded from all analyses.
[2] Safety Set: Subjects who received at least 1 dose of study treatment.
[3] PK population: Subjects who received least 1 dose of Sotatercept and had sufficient data for PK analysis.

Baseline data

Demographics and baseline disease characteristics were generally comparable in the sotatercept and placebo groups, including disease history associated with PAH and baseline laboratory and clinical assessments. Participants in this study were adults with a median age of 48.0 years; 89.2% of participants were white, 79.3% were female, and 79.3% were not Hispanic or Latino. The mean time from PAH diagnosis to screening was 8.8 years. The 3 most common WHO PAH (Group 1) subtypes

were idiopathic PAH (58.5%), heritable PAH (18.3%), and PAH associated with CTD (14.9%). The proportions of participants in WHO FC II (48.6%) and WHO FC III (51.4%) were similar in both groups. Most participants were receiving either triple (61.3%) or double (34.7%) background PAH therapy, and more than a third (39.9%) were receiving prostacyclin infusion therapy. A total of 66 (20.4%) participants in STELLAR received selexipag as a background PAH therapy, including 32 participants in the sotatercept group and 34 participants in the placebo group.

Table 33. Demographics and Baseline Characteristics (FAS)

	Placebo (N=160)	Sotatercept (N=163)	Total (N=323)
Age (Years)			
n	160	163	323
Mean (SD)	48.3 (15.50)	47.6 (14.09)	47.9 (14.79)
Median	49.0	47.0	48.0
Min, Max	18, 82	18, 81	18, 82
Age Group, n (%)			
18 to <45	65 (40.6)	69 (42.3)	134 (41.5)
45 to <65	66 (41.3)	69 (42.3)	135 (41.8)
65 to <75	24 (15.0)	20 (12.3)	44 (13.6)
>=75	5 (3.1)	5 (3.1)	10 (3.1)
Sex, n (%)			
Male	33 (20.6)	34 (20.9)	67 (20.7)
Female	127 (79.4)	129 (79.1)	256 (79.3)
Race, n (%)			
White	141 (88.1)	147 (90.2)	288 (89.2)
Black or African American	5 (3.1)	2 (1.2)	7 (2.2)
Asian	6 (3.8)	1 (0.6)	7 (2.2)
American Indian or Alaska Native	1 (0.6)	0 (0.0)	1 (0.3)
Native Hawaiian or Other Pacific Islander	1 (0.6)	0 (0.0)	1 (0.3)
Multiple	0 (0.0)	2 (1.2)	2 (0.6)
Other	4 (2.5)	5 (3.1)	9 (2.8)
Missing	2 (1.3)	6 (3.7)	8 (2.5)
Ethnicity, n (%)			
Hispanic or Latino	31 (19.4)	27 (16.6)	58 (18.0)
Not Hispanic or Latino	124 (77.5)	132 (81.0)	256 (79.3)
Not Reported	5 (3.1)	4 (2.5)	9 (2.8)
Height (cm)			
n	160	163	323
Mean (SD)	165.3 (9.14)	165.1 (8.86)	165.2 (8.99)
Median	165.0	165.0	165.0
Min, Max	147.3, 195.0	144.0, 193.0	144.0, 195.0
Weight (kg)			
n	160	163	323
Mean (SD)	72.8 (17.64)	71.8 (19.00)	72.3 (18.32)
Median	70.2	67.0	68.2
Min, Max	38.0, 141.3	39.6, 135.0	38.0, 141.3
BMI (kg/m^2)			
n	160	163	323
Mean (SD)	26.6 (6.06)	26.1 (5.70)	26.4 (5.87)
Median	25.7	25.3	25.5
Min, Max	15.0, 54.2	15.1, 50.3	15.0, 54.2

N = number of subjects in the treatment group or overall. n = number of subjects in the category. Percentages are calculated as (n/N)*100.
cm = centimeters, kg = kilograms, m = meters, BMI = body mass index, SD = standard deviation.

Source: [P003V01MK7962: adam-adsl]

Table 34. Disease History Associated with PAH (FAS)

	Placebo (N=160)	Sotatercept (N=163)	Total (N=323)
Length of time since PAH diagnosis (years) [1]			
n	160	163	323
Mean (SD)	8.28 (6.698)	9.22 (7.324)	8.76 (7.026)
Median	6.78	7.51	7.26
Min, Max	0.08, 40.21	0.67, 38.31	0.08, 40.21
Missing	0	0	0
WHO Diagnostic pulmonary hypertension Group I: PAH, n (%)			
Idiopathic PAH	106 (66.3)	83 (50.9)	189 (58.5)
Heritable PAH	24 (15.0)	35 (21.5)	59 (18.3)
Drug or toxin-induced PAH	4 (2.5)	7 (4.3)	11 (3.4)
PAH associated with connective tissue disease	19 (11.9)	29 (17.8)	48 (14.9)
PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair	7 (4.4)	9 (5.5)	16 (5.0)
WHO functional classification for symptomatic pulmonary hypertension, n (%)			
Class II	78 (48.8)	79 (48.5)	157 (48.6)
Class III	82 (51.3)	84 (51.5)	166 (51.4)
Type of background PAH therapy, n (%)			
Mono	4 (2.5)	9 (5.5)	13 (4.0)
Double	56 (35.0)	56 (34.4)	112 (34.7)
Triple	100 (62.5)	98 (60.1)	198 (61.3)
Exercise program for cardiopulmonary rehabilitation, n (%)			
Yes	22 (13.8)	17 (10.4)	39 (12.1)
No	138 (86.3)	146 (89.6)	284 (87.9)
Reason for not being on exercise program for cardiopulmonary rehabilitation, n (%)			
Not reimbursable	19 (11.9)	11 (6.7)	30 (9.3)
Not recommended for this patient	76 (47.5)	73 (44.8)	149 (46.1)
Not available locally	32 (20.0)	32 (19.6)	64 (19.8)
Refused by the patient	10 (6.3)	26 (16.0)	36 (11.1)
Missing	1 (0.6)	4 (2.5)	5 (1.5)

N = number of subjects in the treatment group or overall. n = number of subjects in the category. Percentages are calculated as (n/N)*100.
[1] Length of time in years = (date of randomization - date of diagnosis of PAH)/365.25. Partial diagnosis dates were imputed as follows: if month is unknown set to January, if day is unknown then set to the 15 of the month; if both month and day are unknown then set to January 1st; if year is unknown then do not impute.

Source: [P003V01MK7962: adam-adsl]

Table 35. Baseline Laboratory and Clinical Assessments (FAS)

	Placebo (N=160)	Sotatercept (N=163)	Total (N=323)
Pulse Rate (beats/min)			
n	160	163	323
Mean (SD)	77.8 (12.32)	79.6 (12.78)	78.7 (12.56)
Median	77.0	78.0	78.0
Min, Max	50.0, 120.0	47.0, 117.0	47.0, 120.0
Missing	0	0	0
Cumulative distance at 6 Minutes (meters)			
n	158	163	321
Mean (SD)	407.0 (78.19)	398.5 (83.45)	402.7 (80.89)
Median	427.9	417.0	424.5
Min, Max	151.5, 514.5	160.5, 497.5	151.5, 514.5
Missing	2	0	2
Pulmonary Vascular Resistance (dynes*sec/cm^5)			
n	160	163	323
Mean (SD)	745.8 (313.53)	781.3 (398.47)	763.7 (358.80)
Median	684.0	624.0	664.0
Min, Max	400.0, 2624.0	400.0, 2688.0	400.0, 2688.0
Missing	0	0	0
Cardiac Index (L/min/m^2)			
n	160	163	323
Mean (SD)	2.7 (0.61)	2.7 (0.62)	2.7 (0.62)
Median	2.6	2.6	2.6
Min, Max	1.4, 4.9	1.0, 4.2	1.0, 4.9
Missing	0	0	0
Hemoglobin (g/dL) (Males)			
n	33	34	67
Mean (SD)	14.5 (1.94)	15.1 (1.53)	14.8 (1.75)
Median	15.4	15.4	15.4
Min, Max	9.5, 17.4	9.4, 16.9	9.4, 17.4
Missing	0	0	0
Hemoglobin (g/dL) (Females)			
n	127	128	255
Mean (SD)	13.5 (1.45)	13.5 (1.53)	13.5 (1.49)
Median	13.6	13.7	13.7
Min, Max	9.8, 16.0	9.2, 16.0	9.2, 16.0
Missing	0	1	1
Hemoglobin (g/dL) (Overall)			
n	160	162	322
Mean (SD)	13.7 (1.61)	13.9 (1.65)	13.8 (1.63)
Median	13.8	14.1	13.9
Min, Max	9.5, 17.4	9.2, 16.9	9.2, 17.4
Missing	0	1	1
Systolic Blood Pressure (mmHg)			
n	160	163	323
Mean (SD)	111.5 (14.68)	112.4 (14.17)	112.0 (14.41)
Median	109.5	110.0	110.0
Min, Max	86.0, 154.0	79.0, 152.0	79.0, 154.0
Missing	0	0	0
Diastolic Blood Pressure (mmHg)			
n	160	163	323
Mean (SD)	69.3 (9.63)	67.5 (11.29)	68.4 (10.52)
Median	70.0	66.0	68.0
Min, Max	40.0, 93.0	44.0, 111.0	40.0, 111.0
Missing	0	0	0

N = number of subjects in the treatment group or overall. n = number of subjects in the category, SD = standard deviation.

Source: [P003V01MK7962: adam-adsl]

Table 36. Concomitant Standard of Care (SOC) Medications (FAS)

SOC Medications	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)
Prostacyclin Infusion Therapy			
Yes	64 (40.0)	65 (39.9)	129 (39.9)
No	96 (60.0)	98 (60.1)	194 (60.1)
Monotherapy	4 (2.5)	9 (5.5)	13 (4.0)
PDE5 inhibitor	1 (0.6)	5 (3.1)	6 (1.9)
sGC	1 (0.6)	0 (0.0)	1 (0.3)
ERA	1 (0.6)	2 (1.2)	3 (0.9)
Prostacyclin	1 (0.6)	2 (1.2)	3 (0.9)
Double Therapy	55 (34.4)	56 (34.4)	111 (34.4)
ERA+PDE5 inhibitor	38 (23.8)	36 (22.1)	74 (22.9)
ERA+sGC	2 (1.3)	6 (3.7)	8 (2.5)
ERA+Prostacyclin	5 (3.1)	4 (2.5)	9 (2.8)
PDE5 inhibitor+Prostacyclin	7 (4.4)	9 (5.5)	16 (5.0)
sGC+Prostacyclin	3 (1.9)	1 (0.6)	4 (1.2)
Triple Therapy	101 (63.1)	98 (60.1)	199 (61.6)
ERA+Prostacyclin+PDE5 inhibitor	85 (53.1)	79 (48.5)	164 (50.8)
ERA+Prostacyclin+sGC	16 (10.0)	19 (11.7)	35 (10.8)

N = number of subjects in the treatment group or overall. n = number of subjects in the category. Percentages are calculated as (n/N)*100.
PDE5 Inhibitor= phosphodiesterase type 5 inhibitor, sGC= soluble guanylate cyclase, ERA= endothelin receptor antagonist. Prostacyclin includes prostacyclin analogs and prostacyclin receptor analogs.

Source: [P003V01MK7962: adam-adsl]

Medical History and concurrent illnesses

Medical history conditions in the sotatercept and placebo groups were generally comparable.

The most commonly reported medical history conditions by system organ classes were Surgical and medical procedures (54.5%), Cardiac disorders (44.3%), Gastrointestinal disorders (43.3%), Metabolism and nutrition disorders (44.3%), and Respiratory, thoracic and mediastinal disorders (44.3%). Other than PAH, the most commonly reported medical history conditions (by preferred term) were gastroesophageal reflux disease (19.2%), hypothyroidism (18.9%), hypertension (18.6%), and menopause (18.6%). The medical history condition of thrombocytopenia was more commonly reported in the sotatercept group (16 participants [9.8%]) than in the placebo group (4 participants [2.5%]).

Outcomes and estimation

Primary efficacy endpoint

In adults with PAH (WHO Group 1, FC II or III) on background PAH therapy, the addition of sotatercept, compared with the addition of placebo, led to a significant improvement from baseline in 6MWD at Week 24. The mean 6MWD values at baseline were 397.6 meters in the sotatercept group and 404.7 meters in the placebo group. The observed mean change from baseline in 6MWD was higher in the sotatercept group (40.1 meters) compared with the placebo group (-1.4 meters). The median treatment difference (Hodges-Lehmann location shift) between the sotatercept and placebo groups was 40.8 meters ($p<0.001$).

Results from the sensitivity analyses using alternative methods of imputation for the 6MWD were consistent with those from the primary analysis.

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

change from baseline data at Week 24 in 6MWD that was not due to death or non-fatal clinical worsening event compared with the missing responses imputed by the original pattern mixture model.

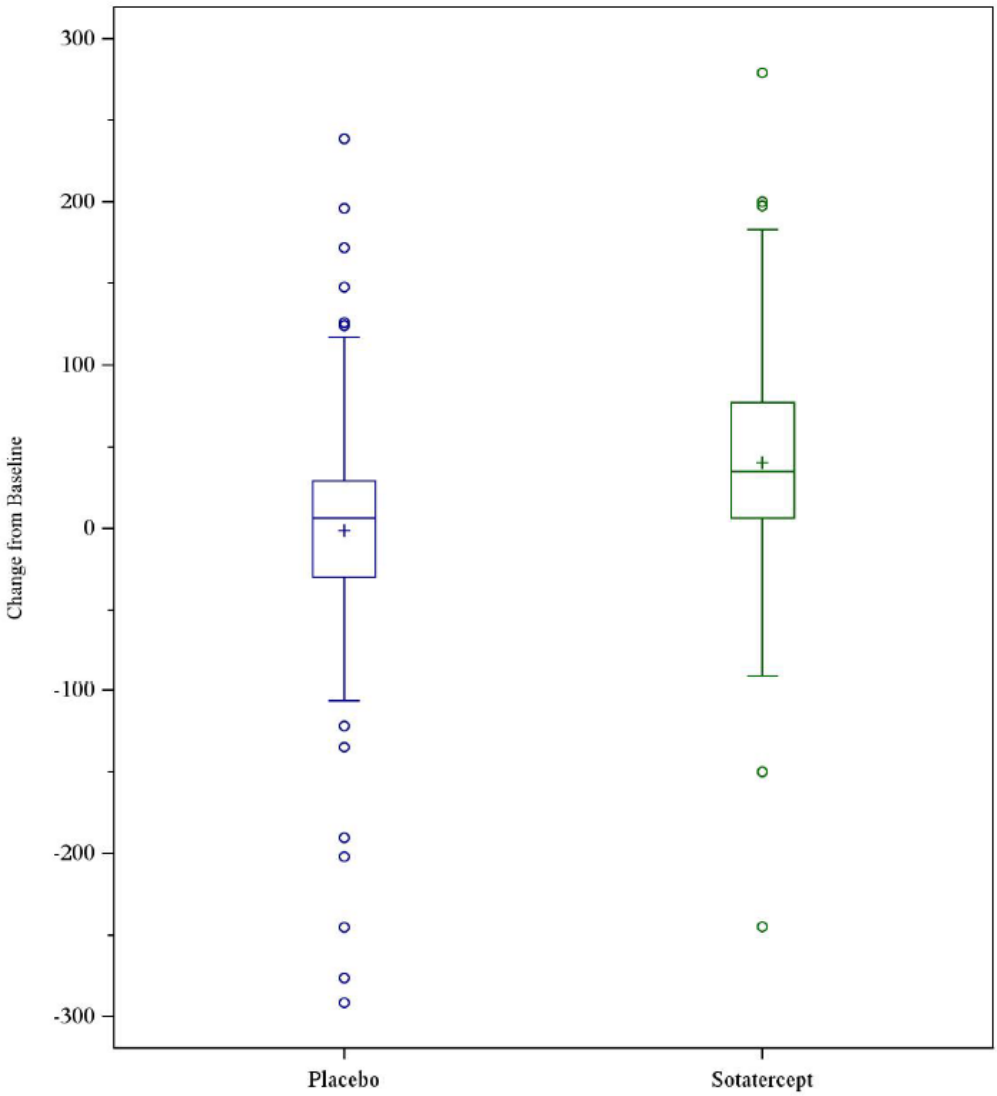
Table 37. Analysis of Change from Baseline in 6-Minute Walk Distance (meters) at Week 24 (FAS)(Standard Multiple Imputation)

	Placebo (N=160)	Sotatercept (N=163)
Median Estimate (Min, Max) [1]	1.0 (-1.0, 5.0)	34.4 (32.5, 35.5)
Hodges-Lehmann Location Shift (ASE) [2]	N/A	40.8 (6.79)
95% CI of Hodges-Lehmann Location Shift	N/A	(27.53, 54.14)
Wilcoxon p-value [3]	N/A	<.001

N = number of subjects in the treatment group. Min = minimum. Max = maximum. N/A = not applicable. ASE = asymptotic standard error. CI = confidence interval.
[1] Average, minimum, and maximum of the medians across the imputed datasets if missing data imputed.
[2] Hodges-Lehmann location shift from placebo estimate (median of all paired differences).
[3] Wilcoxon p-value refers to p-value from the aligned rank stratified Wilcoxon test with randomization factors as strata. Change from baseline in 6MWD at Week 24 for subjects who died was assigned a value of -2000 meters to receive the worst rank. Change from baseline in 6MWD at Week 24 for subjects who have missing data due to a non-fatal clinical worsening event was imputed to -1000 meters to receive the next worst-rank.

Source: [P003V01MK7962: adam-adsl; adft]

Figure 17. Boxplot of Change from Baseline in 6-Minute Walk Distance (meters) at Week 24 (FAS)



	Placebo	Sotatercept
n	147	157
Mean	-1.45	40.08
Median	6.00	34.50
Q1	-30.00	6.00
Q3	29.00	77.00
Min	-291.5	-245.0
Max	238.5	279.0

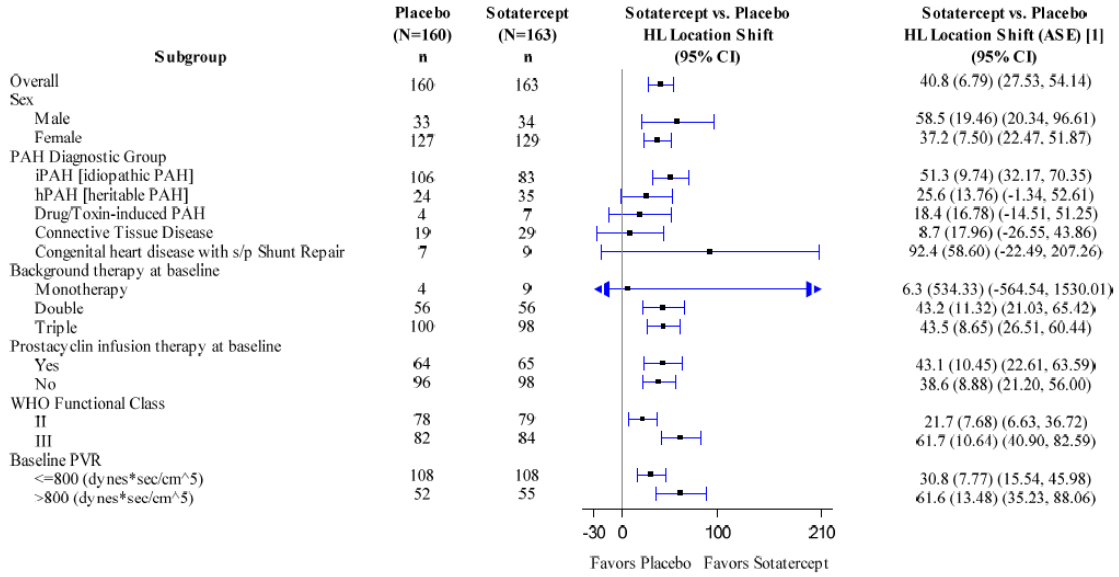
n= number of subjects evaluated at week 24, Q1 = First quartile, Q3 = Third quartile.

Source: [P003V01MK7962: adam-adft]

Subgroup analysis of the primary endpoint

The treatment effect of sotatercept on 6MWD at Week 24 was consistent across the prespecified subgroups.

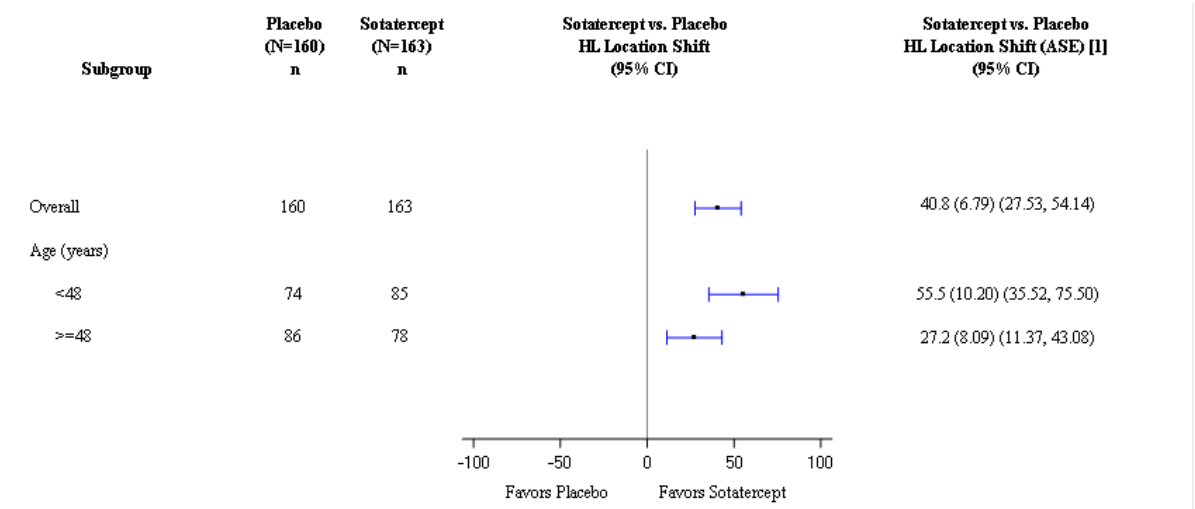
Figure 18. Forest Plot: Change from Baseline in 6-Minute Walk Distance (meters) at Week 24 in Subgroups (FAS)(Standard Multiple Imputation)



[1] Hodges-Lehmann location shift from placebo estimate (median of all paired differences).

Change from baseline in 6MWD at Week 24 for subjects who died was assigned a value of to -2000 meters to receive the worst rank. Change from baseline in 6MWD at Week 24 for subjects who have missing data due to a non-fatal clinical worsening event was imputed to -1000 meters to receive the next worst-rank.

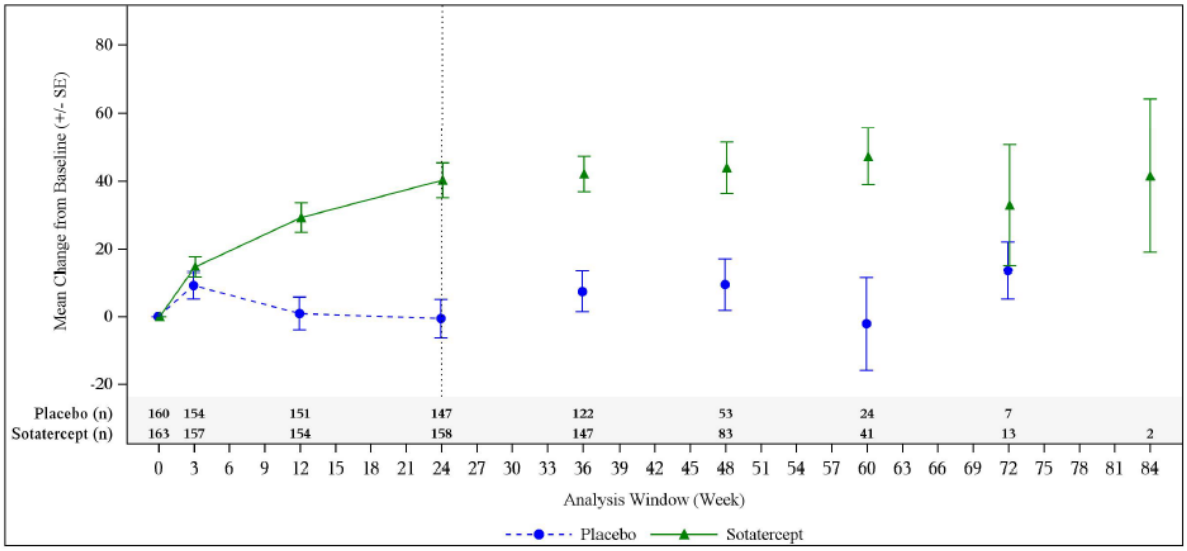
Source: [P003V01MK7962: adam-adft]



Long-term effect

Consistent with the primary analysis results, the observed mean change from baseline in 6MWD remained higher in the sotatercept group than in the placebo group after Week 24.

Figure 19. Change from Baseline in 6-Minute Walk Distance (meters) by Visit (FAS)



Only visits with at least 2 subjects are shown.
n= Number of subjects in the analysis window.
BL= Baseline, SE = Standard error.

Source: [P003MK7962: adam-adft]

Secondary efficacy endpoint

Multicomponent improvement (MCI)

The proportion of participants achieving MCI at week 24 (defined as increase ≥30 meters in 6MWD, decrease in NT-proBNP ≥30% or maintenance/achievement of NT-proBNP level <300 ng/L, and improvement of WHO FC or maintenance of WHO FC II) was significantly greater in the sotatercept group (63 [38.9%]) than in the placebo group (16 [10.1%]) (p<0.001).

Table 38. Multicomponent Improvement Endpoint at Week 24 (FAS)

	Placebo (N=160)	Sotatercept (N=163)
Individual component:		
Improvement of WHO FC or maintenance of WHO FC II, m	159	163
Yes, n (%)	82 (51.6)	115 (70.6)
No, n (%)	77 (48.4)	48 (29.4)
p-value [1]	N/A	<.001
Missing due to COVID-19	1	0
Improvement in NT-proBNP by at least 30% or maintenance/achievement of NT-proBNP level < 300 ng/L, m	159	162
Yes, n (%)	64 (40.3)	138 (85.2)
No, n (%)	95 (59.7)	24 (14.8)
p-value [1]	N/A	<.001
Missing due to COVID-19	1	1
Improvement in 6MWD by at least 30 meters, m	159	163
Yes, n (%)	35 (22.0)	87 (53.4)
No, n (%)	124 (78.0)	76 (46.6)
p-value [1]	N/A	<.001
Missing due to COVID-19	1	0
Multicomponent improvement of all three criteria above, m	159	162
Yes, n (%)	16 (10.1)	63 (38.9)
No, n (%)	143 (89.9)	99 (61.1)
p-value [1]	N/A	<.001
Missing due to COVID-19	1	1

[1] Comparison with placebo uses Cochran-Mantel-Haenszel (CMH) method stratified by randomization factors.
6MWD = six-minute walk distance. COVID-19 = coronavirus disease of 2019. WHO FC = world health organization functional class. N = number of subjects in the treatment group. m = number of subjects in treatment group excluding missingness due to COVID-19. NT-proBNP = N-terminal prohormone of brain natriuretic peptide. n = number of subjects in the category. N/A = not applicable. Percentages are calculated as (n/m)*100.
A missing result at week 24 not due to COVID-19 was considered a non-responder. Subjects who missed assessments due to COVID-19 were taken out of the denominator.

Source: [P003V01MK7962: adam-adsl; adef]

Pulmonary vascular resistance (PVR)

The decrease from baseline in PVR was significantly greater in the sotatercept group than in the placebo group at Week 24 (Visit 9). The mean PVR values at baseline were 781.3 dynes*sec/cm5 in the sotatercept group and 745.8 dynes*sec/cm5 in the placebo group. The observed mean change from baseline in PVR was lower in the sotatercept group (-234.5 dynes*sec/cm5) compared with the placebo group (42.4 dynes*sec/cm5). The median treatment difference (Hodges-Lehmann location shift) between the sotatercept and placebo groups was -234.6 dynes*sec/cm5 ($p<0.001$). Results from the supportive analysis using the ANCOVA model were consistent with those from the primary analysis. The treatment effect of sotatercept on PVR at Week 24 was consistent across the prespecified subgroups. The decrease from baseline in hematocrit-adjusted PVR was greater in the sotatercept group than in the placebo group at Week 24.

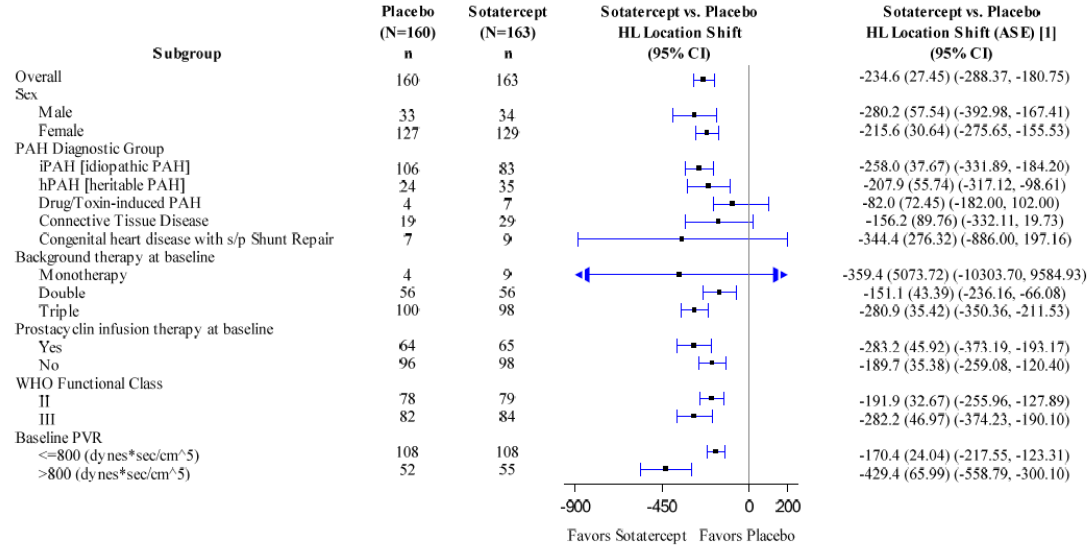
Table 39. Analysis of Change from Baseline in PVR (dynes*sec/cm^5) at Week 24 (FAS)(Standard Multiple Imputation)

	Placebo (N=160)	Sotatercept (N=163)
Median Estimate (Min, Max) [1]	32.8 (24.0, 40.0)	-165.1 (-184.0, -152.0)
Hodges-Lehmann Location Shift (ASE) [2]	N/A	-234.6 (27.45)
95% CI of Hodges-Lehmann Location Shift	N/A	(-288.37, -180.75)
Wilcoxon p-value [3]	N/A	<.001

N = number of subjects in the treatment group. Min = minimum. Max = maximum. N/A = not applicable. ASE = asymptotic standard error. CI = confidence interval.
[1] Average, minimum, and maximum of the medians across the imputed datasets if missing data imputed.
[2] Hodges-Lehmann location shift from placebo estimate (median of all paired differences).
[3] Wilcoxon p-value refers to p-value from the aligned rank stratified Wilcoxon test with randomization factors as strata. Change from baseline in PVR at Week 24 for subjects who died was assigned as 20000 to receive the worst rank. Change from baseline in PVR at Week 24 for subjects who had missing data due to a non-fatal clinical worsening event was imputed as 15000 to receive the next worst-rank.

Source: [P003V01MK7962: adam-adsl; adpr]

Figure 20. Forest Plot: Change from Baseline in PVR (dynes*sec/cm^5) at Week 24 in Subgroups (FAS)(Standard Multiple Imputation)



[1] Hodges-Lehmann location shift from placebo estimate (median of all paired differences).
Change from baseline in PVR at Week 24 for subjects who died was assigned as 20000 to receive the worst rank. Change from baseline in PVR at Week 24 for subjects who had missing data due to a non-fatal clinical worsening event was imputed as 15000 to receive the next worst-rank.
Source: [P003V01MK7962: adam-adpr]

NT-proBNP

The decrease from baseline in NT-proBNP was significantly greater in the sotatercept group than in the placebo group at Week 24 (Visit 9). The mean NT-proBNP values at baseline were 1037.5 pg/mL in the sotatercept group and 1207.8 pg/mL in the placebo group. The observed mean change from baseline in NT-proBNP was lower in the sotatercept group (-722.3 pg/mL) compared with the placebo group (-355.6 pg/mL). The median treatment difference between the sotatercept and placebo groups was -441.6 pg/mL (p<0.001). Results from the supportive analysis using the ANCOVA model were consistent with those from the primary analysis. The treatment effect of sotatercept on NT-proBNP at Week 24 was consistent across the prespecified subgroups.

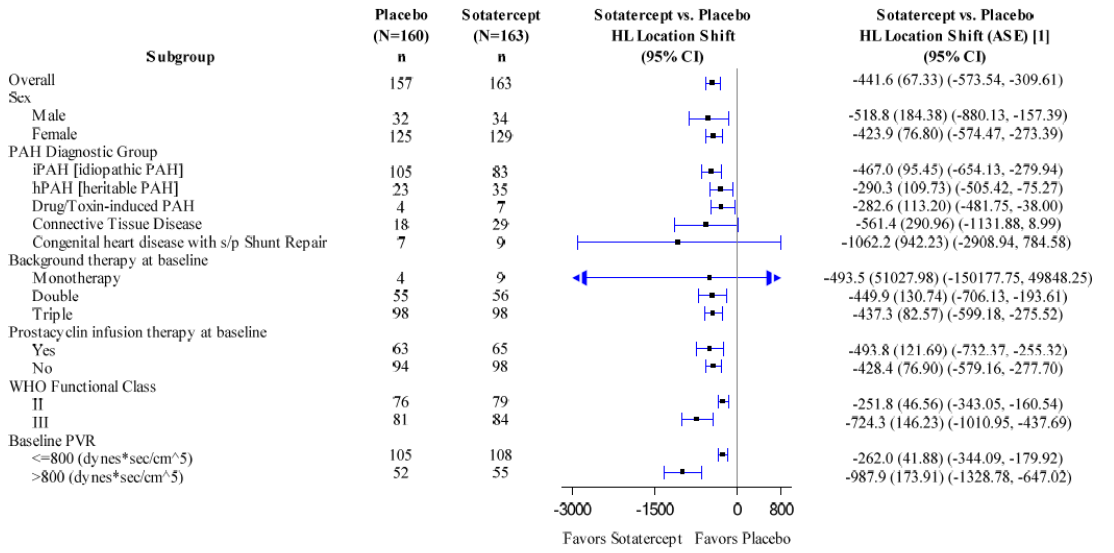
Table 40. Analysis of Change from Baseline in NT-proBNP (pg/mL) at Week 24 (FAS)(Standard Multiple Imputation)

	Placebo (N=160)	Sotatercept (N=163)
Median Estimate (Min, Max) [1]	58.6 (44.0, 73.0)	-230.3 (-236.0, -223.0)
Hodges-Lehmann Location Shift (ASE) [2]	N/A	-441.6 (67.33)
95% CI of Hodges-Lehmann Location Shift	N/A	(-573.54, -309.61)
Wilcoxon p-value [3]	N/A	<.001

N = number of subjects in the treatment group. Min = minimum. Max = maximum. N/A = not applicable. ASE = asymptotic standard error. CI = confidence interval.
[1] Average, minimum, and maximum of the medians across the imputed datasets if missing data imputed.
[2] Hodges-Lehmann location shift from placebo estimate (median of all paired differences).
[3] Wilcoxon p-value refers to p-value from the aligned rank stratified Wilcoxon test with randomization factors as strata. Change from baseline in NT-proBNP at Week 24 for subjects who died was assigned as 200000 to receive the worst rank. Change from baseline in NT-proBNP at Week 24 for subjects who had missing data due to a non-fatal clinical worsening event was imputed as 150000 to receive the next worst-rank.

Source: [P003V01MK7962: adam-adsl; adbiomk]

Figure 21. Forest Plot: Change from Baseline in NT-proBNP (pg/mL) at Week 24 in Subgroups (FAS)(Standard Multiple Imputation)



[1] Hodges-Lehmann location shift from placebo estimate (median of all paired differences).
Change from baseline in NT-proBNP at Week 24 for subjects who died was assigned as 200000 to receive the worst rank. Change from baseline in NT-proBNP at Week 24 for subjects who had missing data due to a non-fatal clinical worsening event was imputed as 150000 to receive the next worst-rank.
Source: [P003V01MK7962: adam-adbiomk]

WHO FC improvement

The proportion of participants with improvement from baseline in WHO FC at Week 24 was significantly greater in the sotatercept group (29.4%) than in the placebo group (13.8%) (p<0.001).

The proportions of participants in WHO FC II (49.1%) and WHO FC III (50.9%) were similar in the sotatercept group at baseline. Among these participants 5.0% shifted from WHO FC II to WHO FC I, 0.6% shifted from WHO FC III to FC I, and 24.5% shifted from WHO FC III to WHO FC II at Week 24.The proportions of participants in WHO FC II (48.8%) and WHO FC III (51.3%) were similar in the placebo group at baseline. Among these participants 2.0% shifted from WHO FC II to WHO FC I, 0.7% shifted from WHO FC III to FC I, and 12.2% shifted from WHO FC III to WHO FC II at Week 24.

Time to clinical worsening (TTCW)

DBPC period:

Analyses of time to death or first occurrence of a clinical worsening event were performed using data up to the data cut-off (26-AUG-2022). Fewer participants in the sotatercept group (9 [5.5%]) than in the placebo group (42 [26.3%]) died or had at least 1 clinical worsening event as of the data cutoff (Table 47). The risk of death or a first clinical worsening event was 84% lower in the sotatercept group compared with the placebo group (HR: 0.163; 95% CI, 0.076, 0.347). Kaplan-Meier curves for time to death or first occurrence of a clinical worsening showed an early separation (approximately Week 10) of the sotatercept and placebo curves that continued for the remainder of the study. This was confirmed by the stratified logrank test (p<0.001).

The proportion of participants with a clinical worsening event was lower in the sotatercept group than in the placebo group in each clinical worsening category, except for worsening related listing for lung and/or heart transplant (1 participant in both groups) and need for atrial septostomy (0 participants in each group).

The 2 deaths in the sotatercept group occurred after Week 24 in the LTDB Period.

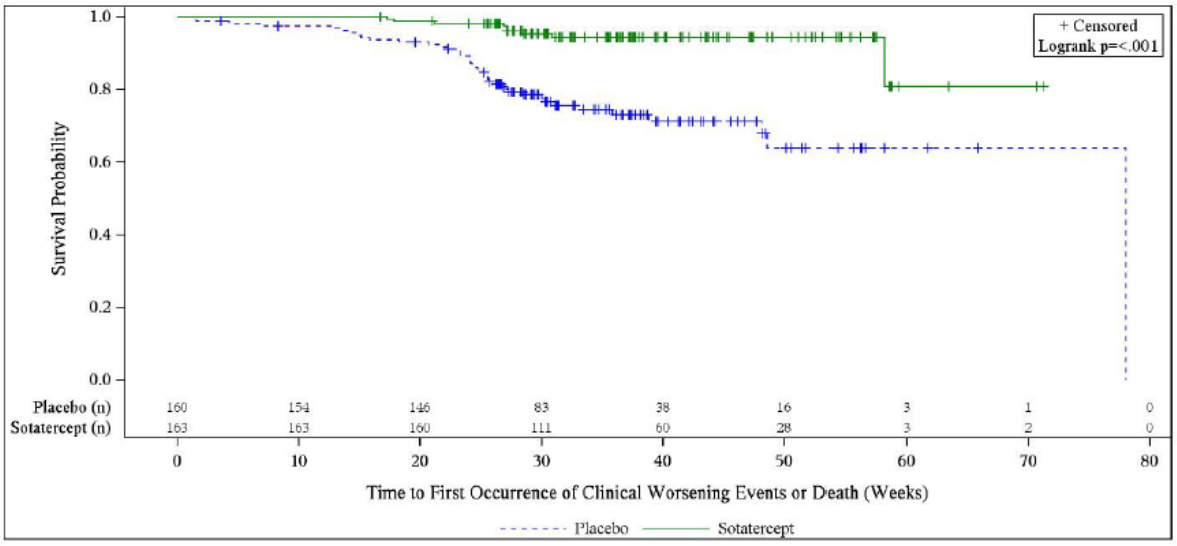
Table 41. Time to First Clinical Worsening or Death (FAS)

	Placebo (N=160)	Sotatercept (N=163)
Total number of subjects who experienced at least one clinical worsening event or death, n (%)	42 (26.3)	9 (5.5)
Total number of clinical worsening events or death	45	9
Time to first occurrence of clinical worsening events or death (weeks)		
Logrank test p-value [1]	N/A	<.001
Hazard Ratio (95% CI) [2]	N/A	0.163 (0.076, 0.347)
Assessment of first occurrence of clinical worsening events or death, n (%) [3]		
Death	6 (3.8)	2 (1.2)
Worsening-related listing for lung and/or heart transplant	1 (0.6)	1 (0.6)
Need to initiate rescue therapy with an approved PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more	17 (10.6)	2 (1.2)
Need for atrial septostomy	0 (0.0)	0 (0.0)
PAH-specific hospitalization (>= 24 hours)	7 (4.4)	0 (0.0)
Deterioration of PAH [4]	15 (9.4)	4 (2.5)

[1] Logrank test comparison with Placebo stratified by the randomization factors.
[2] The hazard ratio (Sotatercept / Placebo) is derived from a Cox proportional hazard model with treatment group as the covariate stratified by the randomization factors.
[3] A subject can have more than one assessment recorded for their first event of clinical worsening or death.
[4] Deterioration of PAH therapy is defined by both of the following events occurring at any time, even if they began at different times, as compared to their baseline values: (a) Worsened WHO functional class (II to III, III to IV, II to IV, etc), (b) Decrease in 6MWD by >= 15% (confirmed by two 6MWTs at least 4 hours apart but no more than one week).
N = number of subjects in FAS population. n = number of subjects in the category. Percentages are calculated as (n/N)*100.
N/A = not applicable.

Source: [P003V01MK7962: adam-adsl; adclin; adtte]

Figure 22. Clinical Worsening Kaplan-Meier Plot (FAS)



n= Number of subjects at Risk

Source: [P003V01MK7962: adam-adsl; adclin; adtte]

Cumulative Results:

Only 2 additional participants, in the sotatercept group, had an adjudication-confirmed clinical worsening event after the initial data cut-off. In total, the cumulative number of participants with an endpoint event was lower in the sotatercept group than in the placebo group.

Figure 23. Time to First Clinical Worsening or Death (FAS) – Cumulative Results (DBPC + LTDB)

	Placebo (N=160)	Sotatercept (N=163)
Total number of subjects who experienced at least one clinical worsening event or death, n (%)	42 (26.3)	11 (6.7)
Total number of clinical worsening events or death	45	11
Assessment of first occurrence of clinical worsening events or death, n (%) [1]		
Death	6 (3.8)	2 (1.2)
Worsening-related listing for lung and/or heart transplant	1 (0.6)	1 (0.6)
Need to initiate rescue therapy with an approved PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more	17 (10.6)	2 (1.2)
Need for atrial septostomy	0 (0.0)	0 (0.0)
PAH-specific hospitalization (>= 24 hours)	7 (4.4)	1 (0.6)
Deterioration of PAH [2]	15 (9.4)	5 (3.1)

[1] A subject can have more than one assessment recorded for their first event of clinical worsening or death.
[2] Deterioration of PAH therapy is defined by both of the following events occurring at any time, even if they began at different times, as compared to their baseline values: (a) Worsened WHO functional class (II to III, III to IV, II to IV, etc), (b) Decrease in 6MWD by >= 15% (confirmed by two 6MWTs at least 4 hours apart but no more than one week).
N = number of subjects in FAS population. n = number of subjects in the category. Percentages are calculated as (n/N)*100.
N/A = not applicable. DBPC = Double-blind Placebo-controlled. LTDB = Long Term Double-blind.

Source: [P003MK7962: adam-adsl; adclin; adtte]

Post-hoc analysis TTCW using CHMP definition (data cutoff 26-AUG-2022)

TTCW analysis presented from a modified "time to death or first occurrence of a clinical worsening event" that excludes the component "need to initiate rescue therapy with an approved PAH therapy or need to increase the dose of infusion prostacyclin by 10% or more."

In the post-hoc analysis, the risk of death or first occurrence of a clinical worsening event was 82% lower in the sotatercept group compared with the placebo group (HR: 0.182; 95% CI, 0.075, 0.441). These results are consistent with those in the primary analysis This analysis counts 8 participants in the placebo group with a first clinical worsening event of "PAH-specific hospitalization (≥24 hours)", whereas the primary analysis counts 7. The explanation for this difference is that a placebo participant had a first clinical worsening event of "need to initiate rescue therapy with an approved PAH therapy or need to increase the dose of infusion prostacyclin by 10% or more" and a subsequent event of "PAH-specific hospitalization (≥24 hours)." The primary analysis counted this participant according to the first event. Because the endpoint for the analysis in does not include "need to initiate rescue therapy with an approved PAH therapy or need to increase the dose of infusion prostacyclin by 10% or more", the first nonfatal clinical worsening event "PAH-specific hospitalization (≥24 hours)" was counted for this placebo participant.

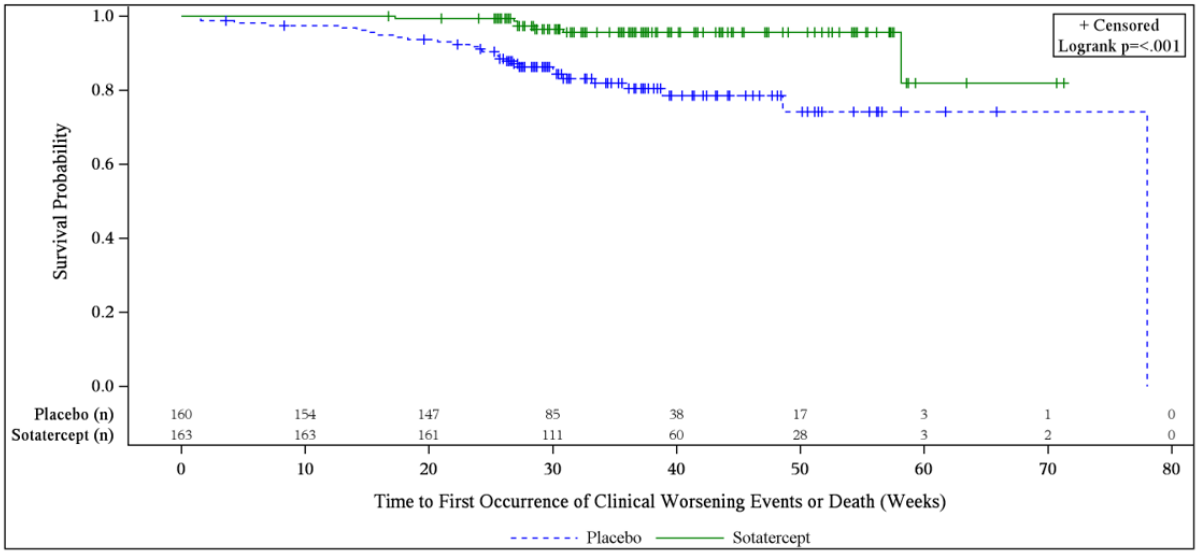
Consistent with the primary analysis, the Kaplan-Meier curves for time to death or first occurrence of a clinical worsening event in the post hoc supplemental analysis showed an early separation (approximately Week 10) of the sotatercept and placebo curves that continued for the remainder of the study. This was confirmed by stratified log-rank test (p<0.001).

Table 42. Time to First Clinical Worsening or Death (EU Guideline) (FAS) – STELLAR (DBPC)(26-Aug-2022)

	Placebo (N=160)	Sotatercept (N=163)
Total number of subjects who experienced at least one clinical worsening event or death, n (%)	29 (18.1)	7 (4.3)
Total number of clinical worsening events or death	31	7
Time to first occurrence of clinical worsening events or death (weeks)		
Logrank test p-value [1]	N/A	<.001
Hazard Ratio (95% CI) [2]	N/A	0.182 (0.075, 0.441)
Assessment of first occurrence of clinical worsening events or death, n (%) [3]		
Death	6 (3.8)	2 (1.2)
Worsening-related listing for lung and/or heart transplant	1 (0.6)	1 (0.6)
Need for atrial septostomy	0 (0.0)	0 (0.0)
PAH-specific hospitalization (>= 24 hours)	8 (5.0)	0 (0.0)
Deterioration of PAH [4]	15 (9.4)	4 (2.5)

[1] Logrank test comparison with Placebo stratified by the randomization factors.
[2] The hazard ratio (Sotatercept / Placebo) is derived from a Cox proportional hazard model with treatment group as the covariate stratified by the randomization factors.
[3] A subject can have more than one assessment recorded for their first event of clinical worsening or death.
[4] Deterioration of PAH therapy is defined by both of the following events occurring at any time, even if they began at different times, as compared to their baseline values: (a) Worsened WHO functional class (II to III, III to IV, II to IV, etc), (b) Decrease in 6MWD by >= 15% (confirmed by two 6MWTs at least 4 hours apart but no more than one week).
N = number of subjects in FAS population. n = number of subjects in the category. Percentages are calculated as (n/N)*100.
N/A = not applicable.

Figure 24. Clinical Worsening Kaplan-Meier Plot (EU Guideline) (FAS) - STELLAR



n= Number of subjects at Risk

Cumulative Results:

The Applicant has performed analyses of TTCW for STELLAR (through 06-DEC-2022), using the EU-guidelines for PAH, which demonstrated an HR of 0.274 (95% CI: 0.129, 0.582) with sotatercept treatment compared to placebo.

Table 43. Time to First Clinical Worsening or Death (EU Guideline) (FAS) - STELLAR Cumulative Results (DBPC + LTDB) (06-Dec-2022)

	Placebo (N=160)	Sotatercept (N=163)
Total number of subjects who experienced at least one clinical worsening event or death, n (%)	29 (18.1)	9 (5.5)
Total number of clinical worsening events or death	31	9
Time to first occurrence of clinical worsening events or death (weeks)		
Logrank test p-value [1]	N/A	<.001
Hazard Ratio (95% CI) [2]	N/A	0.274 (0.129, 0.582)
Assessment of first occurrence of clinical worsening events or death, n (%) [3]		
Death	6 (3.8)	2 (1.2)
Worsening-related listing for lung and/or heart transplant	1 (0.6)	1 (0.6)
Need for atrial septostomy	0 (0.0)	0 (0.0)
PAH-specific hospitalization (>= 24 hours)	8 (5.0)	1 (0.6)
Deterioration of PAH [4]	15 (9.4)	5 (3.1)

[1] Logrank test comparison with Placebo stratified by the randomization factors.
[2] The hazard ratio (Sotatercept / Placebo) is derived from a Cox proportional hazard model with treatment group as the covariate stratified by the randomization factors.
[3] A subject can have more than one assessment recorded for their first event of clinical worsening or death.
[4] Deterioration of PAH therapy is defined by both of the following events occurring at any time, even if they began at different times, as compared to their baseline values: (a) Worsened WHO functional class (II to III, III to IV, II to IV, etc), (b) Decrease in 6MWD by >= 15% (confirmed by two 6MWTs at least 4 hours apart but no more than one week).
N = number of subjects in FAS population. N = number of subjects in the category. Percentages are calculated as (n/N)*100. N/A = not applicable.

Simplified French risk score

The proportion of participants who maintained or achieved a low-risk score (French Risk score calculator) relative to baseline at Week 24 was significantly greater in the sotatercept group (39.5%) than in the placebo group (18.2%) (p<0.001).

Physical impacts (PAH-SYMPACT score)

The mean change from baseline in Physical Impacts domain score of PAH-SYMPACT® showed improvement that was significantly greater in the sotatercept group than in the placebo group at Week 24 (Visit 9) (-0.3 vs. 0, respectively). The mean Physical Impacts Doman score at baseline was 1.2 in both groups. The median of the treatment difference (Hodges-Lehman Location Shift) between the sotatercept and placebo groups was -0.26. (p=0.010). Results from the supportive analysis using the ANCOVA model were consistent with those from the primary analysis.

Cardiopulmonary symptoms (PAH-SYMPACT score)

The mean change from baseline in Cardiopulmonary Symptoms domain score of PAH-SYMPACT® showed improvement that was significantly greater in the sotatercept group than in the placebo group at Week 24 (Visit 9) (-0.1 vs. 0, respectively). The mean Cardiopulmonary Symptoms Doman score at

baseline was 0.9 and 0.8 in the sotatercept and placebo groups, respectively. The median of the treatment difference between the sotatercept and placebo groups was -0.13 (p=0.028). Results from the supportive analysis using the ANCOVA model were consistent with those from the primary analysis.

Cognitive/emotional impacts (PAH-SYMPACT score)

The mean difference in the change from baseline in Cognitive/Emotional Impacts domain score of PAH-SYMPACT® between the sotatercept and placebo groups at Week 24 (Visit 9) was not statistically significant (-0.1 vs. 0.1, respectively). The median of the treatment difference between the sotatercept and placebo groups was -0.16 (p=0.156) Results from the supportive analysis using the ANCOVA model were consistent with those from the primary analysis.

Exploratory Endpoints

Echocardiogram parameters

The changes from baseline in ECHO parameters (pulmonary artery systolic pressure, RV fractional area change, RV end diastolic area, right atrial pressure, and RV pulmonary artery contractile-pressure coupling) showed numerical greater improvements in the sotatercept group than in the placebo group at Week 24 (Visit 9). There was no notable difference in the change from baseline in tricuspid annular plane systole excursion between the groups at Week 24 (Visit 9).

Dyspnea Score

There was no notable difference in the change from baseline in dyspnea score between the sotatercept and placebo groups at Week 24 (Visit 9). No differences were observed from vital signs collected before and after the 6MWT (pre and post).

Pulmonary Vascular Resistance <3 WU

Eight (5.2%) participants in the sotatercept group achieved PVR <3 WU at Week 24 compared with none in the placebo group.

Mean Pulmonary Arterial Pressure <25 mmHg

Twelve (7.8%) participants in the sotatercept group achieved mPAP <25 mmHg at Week 24 compared with none in the placebo group.

Mean Pulmonary Arterial Pressure at Week 24

The decrease from baseline in mPAP was greater in the sotatercept group than in the placebo group at Week 24 (Visit 9).

Hematocrit-adjusted Pulmonary Vascular Resistance

The decrease from baseline in hematocrit-adjusted PVR was greater in the sotatercept group than in the placebo group at Week 24.

Cardiovascular symptoms (PAH-SYMPACT)

The decrease from baseline in Cardiovascular Symptoms domain score of PAH-SYMPACT® was greater in the sotatercept group than in the placebo group at Week 24 (Visit 9). Results from the supportive analysis using the ANCOVA model were consistent with those from the primary analysis

EQ-5D-5L

There was no notable difference in the change from baseline in EQ-5D-5L index score between the sotatercept and placebo groups at Week 24 (Visit 9).

EQ-5D-5L VAS

The increase from baseline in EQ-5D-5L VAS was greater in the sotatercept group than in the placebo group at Week 24 (Visit 9).

Cardiac index

There was no notable difference in the change from baseline in cardiac index between the sotatercept and placebo groups at Week 24 (Visit 9).

2.7.5.3. Clinical studies in special populations

No separate studies were performed in special patient populations.

2.7.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Comparison and analyses of results across studies

The results of the 3 PAH studies PULSAR, SPECTRA, and STELLAR are compared and pooled, since the populations evaluated in these studies are representative of the adult population with PAH (WHO group 1), and, therefore, results are generalizable to adults with this condition.

6MWD

In the pivotal Phase 3 study (STELLAR), and the placebo-controlled Phase 2 study (PULSAR), treatment with sotatercept compared with placebo led to significant improvements in 6MWD from baseline at Week 24 (Table 50). Results from the single-group Phase 2 study (SPECTRA) similarly showed improvements in 6MWD with sotatercept treatment at Week 24 (66.4m).

In the Efficacy Pool, results for 6MWD were consistent with those in the individual studies, showing significant improvement from baseline in the pooled sotatercept group compared with the pooled placebo group at Week 24 (Table 50). Mean 6MWD values at baseline were 396.0 and 405.4 meters in the pooled sotatercept and pooled placebo groups, respectively. The median treatment difference between the pooled sotatercept and pooled placebo groups was 41.8 meters ($p<0.001$).

Results from the sensitivity analyses were consistent with those from the primary analysis.

Table 44. Analysis of Change from Baseline in 6 Minute Walk Distance (meters) at Week 24 (FAS)(Standard Multiple Imputation)

	STELLAR (A011-11)		PULSAR (A011-09)		Pooled [2]	
	Placebo (N=160)	Sotatercept (N=163)	Placebo (N=32)	Sotatercept[1] (N=74)	Placebo (N=192)	Sotatercept (N=237)
Median Estimate (Min, Max) [3]	1.0 (-1.0, 5.0)	34.4 (32.5, 35.5)	14.8 (14.3, 15.6)	51.8 (46.7, 53.2)	3.6 (1.5, 7.3)	37.5 (36.0, 40.0)
Hodges-Lehmann Location Shift (ASE) [4]	N/A	40.8 (6.79)	N/A	32.8 (11.63)	N/A	41.8 (5.67)
95% CI of Hodges-Lehmann Location Shift	N/A	(27.53, 54.14)	N/A	(10.03, 55.61)	N/A	(30.69, 52.93)
Wilcoxon p-value [5]	N/A	<.001	N/A	0.005	N/A	<.001

N = number of subjects in the treatment group. Min = minimum. Max = maximum. N/A = not applicable. ASE = asymptotic standard error. CI = confidence interval.
[1] Sotatercept group consists of subjects who were originally randomized to Sotatercept 0.3 or 0.7 mg/kg excluding Placebo-Crossed subjects.
[2] Pooled Placebo and Pooled Sotatercept consists of subjects from STELLAR and PULSAR who were originally randomized to Placebo and Sotatercept respectively.
[3] Average, minimum, and maximum of the medians across the imputed datasets if missing data imputed.
[4] Hodges-Lehmann location shift from Placebo estimate (median of all paired differences).
[5] Wilcoxon p-value refers to p-value from the aligned rank stratified Wilcoxon test stratified by: baseline WHO FC (Class II or III) and background PAH therapy (mono/double or triple therapy).
Change from baseline in 6MWD at Week 24 for subjects who died was assigned a value of to -2000 meters to receive the worst rank. Change from baseline in 6MWD at Week 24 for subjects who have missing data due to a non-fatal clinical worsening event was imputed a value of -1000 meters to receive the next worst-rank.

MCI

In STELLAR, the proportion of participants achieving MCI was significantly greater in the sotatercept group than in the placebo group at Week 24 in the primary analysis, and in the post-hoc analysis without NT-proBNP. Consistent results were seen with sotatercept treatment at Week 24 in PULSAR and SPECTRA (Table 51).

In the Efficacy Pool, results for the proportions of participants achieving MCI (primary analysis) were consistent with those in the individual studies, with 100 participants (42.4%) in the pooled sotatercept group and 21 (11.0%) in the pooled placebo group achieving MCI (p<0.001)(Table 51). Post-hoc analyses without NT-proBNP were consistent with those in the primary analysis.

Table 45. Multi-component Improvement Endpoint at Week 24 (FAS)

	STELLAR (A011-11)		PULSAR (A011-09)		Pooled [2]		SPECTRA (A011-10)
	Placebo (N=160)	Sotatercept (N=163)	Placebo (N=32)	Sotatercept [1] (N=74)	Placebo (N=192)	Sotatercept (N=237)	Sotatercept (N=21)
Individual component:							
Improvement in WHO FC or maintenance of WHO FC II, m	159	163	32	74	191	237	21
Yes, n (%)	82 (51.6)	115 (70.6)	20 (62.5)	55 (74.3)	102 (53.4)	170 (71.7)	13 (61.9)
No, n (%)	77 (48.4)	48 (29.4)	12 (37.5)	19 (25.7)	89 (46.6)	67 (28.3)	8 (38.1)
p-value [3]	N/A	<.001	N/A	0.147	N/A	<.001	N/A
Missing due to COVID-19	1	0	0	0	1	0	0
Improvement in NT-ProBNP (decrease in NT-proBNP by at least 30%) or maintenance/achievement of NT-proBNP level < 300 ng/L, m	159	162	32	74	191	236	21
Yes, n (%)	64 (40.3)	138 (85.2)	16 (50.0)	63 (85.1)	80 (41.9)	201 (85.2)	20 (95.2)
No, n (%)	95 (59.7)	24 (14.8)	16 (50.0)	11 (14.9)	111 (58.1)	35 (14.8)	1 (4.8)
p-value [3]	N/A	<.001	N/A	<.001	N/A	<.001	N/A
Missing due to COVID-19	1	1	0	0	1	1	0
Improvement in 6MWD by at least 30 meters, m	159	163	32	74	191	237	21
Yes, n (%)	35 (22.0)	87 (53.4)	11 (34.4)	47 (63.5)	46 (24.1)	134 (56.5)	11 (52.4)
No, n (%)	124 (78.0)	76 (46.6)	21 (65.6)	27 (36.5)	145 (75.9)	103 (43.5)	10 (47.6)
p-value [3]	N/A	<.001	N/A	0.005	N/A	<.001	N/A
Missing due to COVID-19	1	0	0	0	1	0	0
Multi-component Improvement of all three criteria above, m	159	162	32	74	191	236	21
Yes, n (%)	16 (10.1)	63 (38.9)	5 (15.6)	37 (50.0)	21 (11.0)	100 (42.4)	8 (38.1)
No, n (%)	143 (89.9)	99 (61.1)	27 (84.4)	37 (50.0)	170 (89.0)	136 (57.6)	13 (61.9)
p-value [3]	N/A	<.001	N/A	<.001	N/A	<.001	N/A
Missing due to COVID-19	1	1	0	0	1	1	0

[1] Sotatercept group consists of subjects who were originally randomized to Sotatercept 0.3 or 0.7 mg/kg excluding Placebo-crossed subjects.
[2] Pooled Placebo and Pooled Sotatercept consists of subjects from STELLAR and PULSAR who were originally randomized to Placebo and Sotatercept respectively.
[3] Comparison with Placebo using Cochran-Mantel-Haenszel (CMH) method stratified by: baseline WHO FC (Class II or III) and background PAH therapy (mono/double or triple therapy).
6MWD = six-minute walk distance. COVID-19 = coronavirus disease of 2019. N = number of subjects in the treatment group. M = number of subjects in treatment group excluding missingness due to COVID-19. NT-proBNP = N-terminal prohormone of brain natriuretic peptide. N = number of subjects in the category. N/A = not applicable. WHO FC = World Health Organization functional class. Percentages are calculated as (n/m)*100. A missing result at week 24 not due to COVID-19 was considered a non-responder. Subjects who missed assessments due to COVID-19 were taken out of the denominator.

PVR

In STELLAR and PULSAR, treatment with sotatercept compared with placebo led to significant improvements in PVR from baseline at Week 24 (Table 52). Results for SPECTRA similarly showed improvements in PVR with sotatercept treatment at Week 24.

In the Efficacy Pool, results for PVR were consistent with those in the individual studies, showing significant improvement from baseline in the pooled sotatercept group compared with the pooled

placebo group at Week 24. Mean PVR values at baseline were 777.9 and 754.4 dynes*sec/cm5 in the pooled sotatercept and pooled placebo groups, respectively. The median treatment difference between the pooled sotatercept and pooled placebo groups was -234.8 dynes*sec/cm5 (p<0.001) (Table 52).

Results from the supportive analysis using the ANCOVA model were consistent with those from the primary analysis.

Table 46. Analysis of Change from Baseline in PVR (dynes*sec/cm^5) at Week 24 (FAS)(Standard Multiple Imputation)

	STELLAR (A011-11)		PULSAR (A011-09)		Pooled [2]	
	Placebo (N=160)	Sotatercept (N=163)	Placebo (N=32)	Sotatercept[1] (N=74)	Placebo (N=192)	Sotatercept (N=237)
Median Estimate (Min, Max) [3]	32.8 (24.0, 40.0)	-165.1 (-184.0, -152.0)	34.2 (0.0, 62.7)	-165.5 (-189.2, -140.4)	33.6 (24.0, 40.0)	-167.1 (-176.0, -152.0)
Hodges-Lehmann Location Shift (ASE) [4]	N/A	-234.6 (27.45)	N/A	-213.8 (56.36)	N/A	-234.8 (24.18)
95% CI of Hodges-Lehmann Location Shift	N/A	(-288.37, -180.75)	N/A	(-324.30, -103.32)	N/A	(-282.16, -187.36)
Wilcoxon p-value [5]	N/A	<.001	N/A	<.001	N/A	<.001

N = number of subjects in the treatment group. Min = minimum. Max = maximum. N/A = not applicable. ASE = asymptotic standard error. CI = confidence interval.
[1] Sotatercept group consists of subjects who were originally randomized to Sotatercept 0.3 or 0.7 mg/kg excluding Placebo-Crossed subjects.
[2] Pooled Placebo and Pooled Sotatercept consists of subjects from STELLAR and PULSAR who were originally randomized to Placebo and Sotatercept respectively.
[3] Average, minimum, and maximum of the medians across the imputed datasets if missing data imputed.
[4] Hodges-Lehmann location shift from Placebo estimate (median of all paired differences).
[5] Wilcoxon p-value refers to p-value from the aligned rank stratified Wilcoxon test stratified by: baseline WHO FC (Class II or III) and background PAH therapy (mono/double or triple therapy).
Change from baseline in PVR at Week 24 for subjects who died was assigned a value of 20000 to receive the worst rank. Change from baseline in PVR at Week 24 for subjects who had missing data due to a non-fatal clinical worsening event was as imputed a value of 15000 to receive the next worst-rank.

Source: [ISE: adam-adsl; imppvr1]
Source: [Table 5.3.5.3.2-pah: 2.2.1]

NT-proBNP

In STELLAR, treatment with sotatercept compared with placebo led to significant improvements in NT proBNP from baseline at Week 24. Results from PULSAR and SPECTRA similarly showed improvements from baseline in NT-proBNP with sotatercept treatment at Week 24 (Table 53).

In the Efficacy Pool, results for NT-proBNP were consistent with those in the individual studies, showing significant improvement from baseline in the pooled sotatercept group compared with the pooled placebo group at Week 24. Mean NT proBNP values at baseline were 1002.5 and 1150.3 pg/mL in the pooled sotatercept and pooled placebo groups, respectively. The median treatment difference between the pooled sotatercept and pooled placebo groups was 420.7 pg/mL (p<0.001) (Table 53).

Results from the supportive analysis using the ANCOVA model were consistent with those from the primary analysis.

Table 47. Analysis of Change from Baseline in NT-proBNP (pg/ml) at Week 24 (FAS) (Standard Multiple Imputation)

	STELLAR (A011-11)		PULSAR (A011-09)		Pooled [2]	
	Placebo (N=160)	Sotatercept (N=163)	Placebo (N=32)	Sotatercept[1] (N=74)	Placebo (N=192)	Sotatercept (N=237)
Median Estimate (Min, Max) [3]	58.6 (44.0, 73.0)	-230.3 (-236.0, -223.0)	6.8 (4.0, 8.5)	-102.4 (-103.5, -98.0)	52.3 (42.0, 57.0)	-170.5 (-172.0, -167.0)
Hodges-Lehmann Location Shift (ASE) [4]	N/A	-441.6 (67.33)	N/A	-404.3 (150.60)	N/A	-420.7 (59.28)
95% CI of Hodges-Lehmann Location Shift	N/A	(-573.54, -309.61)	N/A	(-699.50, -109.15)	N/A	(-536.94, -304.55)
Wilcoxon p-value [5]	N/A	<.001	N/A	<.001	N/A	<.001

N = number of subjects in the treatment group. Min = minimum. Max = maximum. N/A = not applicable. ASE = asymptotic standard error. CI = confidence interval.
[1] Sotatercept group consists of subjects who were originally randomized to Sotatercept 0.3 or 0.7 mg/kg excluding Placebo-Crossed subjects.
[2] Pooled Placebo and Pooled Sotatercept consists of subjects from STELLAR and PULSAR who were originally randomized to Placebo and Sotatercept respectively.
[3] Average, minimum, and maximum of the medians across the imputed datasets if missing data imputed.
[4] Hodges-Lehmann location shift from Placebo estimate (median of all paired differences).
[5] Wilcoxon p-value refers to p-value from the aligned rank stratified Wilcoxon test stratified by: baseline WHO FC (Class II or III) and background PAH therapy (mono/double or triple therapy).
Change from baseline in NT-proBNP at Week 24 for subjects who died was assigned a value of 200000 to receive the worst rank. Change from baseline in NT-proBNP at Week 24 for subjects who had missing data due to a non-fatal clinical worsening event was imputed a value of 150000 to receive the next worst-rank.

Source: [ISE: adam-adsl; impnbnp1]
Source: [Table 5.3.5.3.2-pah: 2.3.1]

WHO FC

In STELLAR, the proportion of participants with improvement from baseline in WHO FC was significantly greater in the sotatercept group than in the placebo group at Week 24 (Table 54). Results from PULSAR and SPECTRA similarly showed improvements from baseline in WHO FC with sotatercept treatment at Week 24.

In the Efficacy Pool, results for WHO FC were consistent with those in the individual studies, with 64 (27%) participants in the pooled sotatercept group compared with 26 (13.6%) participants in the pooled placebo group improving in WHO FC at Week 24 (p<0.001) (Table 54).

Table 48. Analysis of Change from Baseline in WHO Functional Class at Week 24 (FAS)

	STELLAR (A011-11)		PULSAR (A011-09)		Pooled [2]		SPECTRA (A011-10)
	Placebo (N=160)	Sotatercept (N=163)	Placebo (N=32)	Sotatercept [1] (N=74)	Placebo (N=192)	Sotatercept (N=237)	Sotatercept (N=21)
Improvement of WHO FC, m	159	163	32	74	191	237	21
Yes, n (%)	22 (13.8)	48 (29.4)	4 (12.5)	16 (21.6)	26 (13.6)	64 (27.0)	13 (61.9)
No, n (%)	137 (86.2)	115 (70.6)	28 (87.5)	58 (78.4)	165 (86.4)	173 (73.0)	8 (38.1)
p-value [3]	N/A	<.001	N/A	0.232	N/A	<.001	N/A
Missing due to COVID-19	1	0	0	0	1	0	0

[1] Sotatercept group consists of subjects who were originally randomized to Sotatercept 0.3 or 0.7 mg/kg excluding Placebo-crossed subjects.
[2] Pooled Placebo and Pooled Sotatercept consists of subjects from STELLAR and PULSAR who were originally randomized to Placebo and Sotatercept respectively.
[3] Comparison with Placebo using Cochran-Mantel-Haenszel (CMH) method stratified by: baseline WHO FC (Class II or III) and background PAH therapy (mono/double or triple therapy).
COVID-19 = coronavirus disease of 2019. N = number of subjects in the treatment group. M = number of subjects in treatment group, excluding missingness due to COVID-19. N = number of subjects in the category. N/A = not applicable. WHO FC = World Health Organization functional class.
Percentages are calculated as (n/m)*100. A missing result at week 24 not due to COVID-19 was considered a non-responder. Subjects who missed assessments due to COVID-19 were taken out of the denominator.

Source: [ISE: adam-adsl; adwho]
Source: [Table 5.3.5.3.2-pah: 2.4.1]

Simplified French risk score

In STELLAR, the proportion of participants who maintained or achieved a low-risk score (French Risk score calculator) relative to baseline was significantly greater in the sotatercept group than in the placebo group at Week 24 (Table 55). Consistent results from PULSAR and SPECTRA were seen with sotatercept treatment at Week 24.

In the Efficacy Pool, results for low-risk score (French Risk score calculator) were consistent with those in the individual studies, with 95 (40.3%) participants in the pooled sotatercept group compared with 37 (19.4%) in the pooled placebo group improving or maintaining a low risk score at Week 24 (p<0.001)(Table 55).

Table 49. Analysis of Change from Baseline in Low-Risk Score (French Risk Score Calculator) at Week 24 (FAS)

	STELLAR (A011-11)		PULSAR (A011-09)		Pooled [2]		SPECTRA (A011-10)
	Placebo (N=160)	Sotatercept (N=163)	Placebo (N=32)	Sotatercept [1] (N=74)	Placebo (N=192)	Sotatercept (N=237)	Sotatercept (N=21)
Maintain or Achieve a Low Risk Score Using the Simplified French Risk score Calculator at Week 24 versus Baseline, m	159	162	32	74	191	236	21
Yes, n (%)	29 (18.2)	64 (39.5)	8 (25.0)	31 (41.9)	37 (19.4)	95 (40.3)	7 (33.3)
No, n (%)	130 (81.8)	98 (60.5)	24 (75.0)	43 (58.1)	154 (80.6)	141 (59.7)	14 (66.7)
p-value [3]	N/A	<.001	N/A	0.067	N/A	<.001	N/A
Missing due to COVID-19	1	1	0	0	1	1	0

[1] Sotatercept group consists of subjects who were originally randomized to Sotatercept 0.3 or 0.7 mg/kg excluding Placebo-crossed subjects.
[2] Pooled Placebo and Pooled Sotatercept consists of subjects from STELLAR and PULSAR who were originally randomized to Placebo and Sotatercept respectively.
[3] Comparison with Placebo using Cochran-Mantel-Haenszel (CMH) method stratified by: baseline WHO FC (Class II or III) and background PAH therapy (mono/double or triple therapy).
A subject is considered to achieve a low risk score using the simplified French Risk score calculator if the following criteria are satisfied: WHO FC I or II, 6MWD > 440 m, and NT-proBNP < 300 ng/L.
COVID-19 = coronavirus disease of 2019. N = number of subjects in the treatment group. M = number of subjects in treatment group, excluding missingness due to COVID-19. N = number of subjects in the category. N/A = not applicable.
Percentages are calculated as (n/m)*100. A missing result at week 24 due to COVID-19 was considered a non-responder. Subjects who missed assessments due to COVID-19 were taken out of the denominator.

Source: [ISE: adam-adsl; adef]
Source: [Table 5.3.5.3.2-pah: 2.7.1]

Supportive study

2.7.5.6. Supportive study(ies)

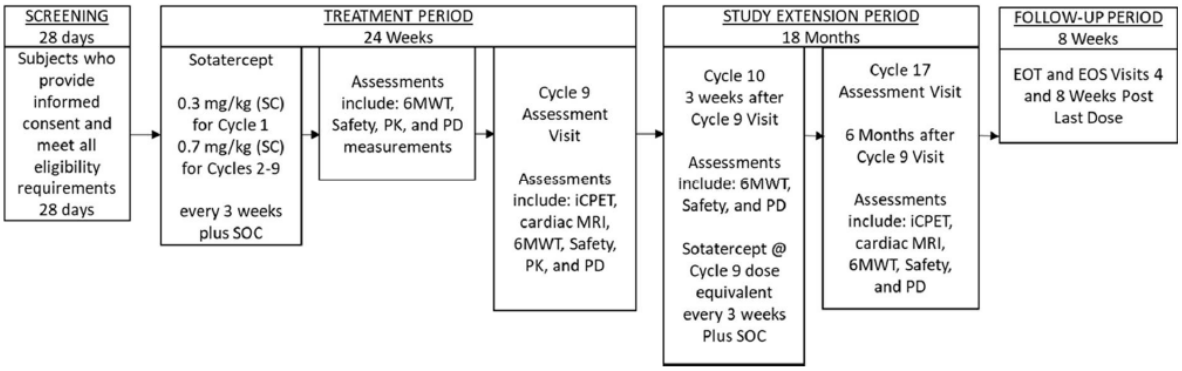
SPECTRA study

SPECTRA was a small (N=21), single-group, open-label multicenter, exploratory study designed to evaluate the effects of sotatercept on invasive cardiopulmonary exercise test (iCPET) measures of cardiopulmonary health and hemodynamics in participants with PAH.

Methods

The population in SPECTRA was similar to the populations in STELLAR and PULSAR, with some exceptions. In SPECTRA, eligible participants had PAH (WHO Group 1, but FC III only) and were on stable (≥90 days) combination background PAH therapy (monotherapy was not permitted). In SPECTRA, the baseline PVR criterion was lower (≥4 Wood units [≥320 dynes*sec/cm5]) and the baseline 6MWD range (≥100 and ≤550 meters) was larger relative to PULSAR and STELLAR. Participants in SPECTRA received an initial dose of 0.3 mg/kg at Cycle 1, followed by 0.7 mg/kg for the remainder of the study, unless dose modifications were required. Participants who completed the 24-week Treatment Period continued in the 18-month Extension Period. Participants continued to receive sotatercept (Q3W) at comparable dose levels, based on exposure-matching, to maintain steady-state exposures through the Extension Period, plus SOC. Participants entered an 8-week Follow-up Period after the last dose of study intervention in the Extension Period. The primary endpoint of the study was change from baseline in VO2max at 24 weeks. Secondary endpoints included changes in exercise measures, i.e. VE/VCO2 slope (ventilatory efficiency), cardiac index, mean pulmonary arterial pressure (mPAP), CavO2 (arteriovenous O2 content difference), cardiac MR imaging (right ventricular (RV), stroke volume (SV), right ventricular end-systolic volume (RV ESV), right ventricular end-diastolic volume (RV EDV), right ventricular ejection fraction (RV EF), right ventricular stroke volume index (RV SVI) and RV mass), PVR, 6MWD, NBT-proBNP, WHO FC at 24 weeks and clinical worsening.

Figure 25. Study design SPECTRA



6MWT = 6-minute walk test; EOS = end of study; EOT = end of treatment; iCPET = invasive cardiopulmonary exercise test; MR = magnetic resonance; PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneously; SOC = standard of care.

Results

Of the 21 allocated participants, 20 (95.2%) completed the 24-week Treatment Period and continued in the 18-month extension period. The 1 participant who discontinued study intervention and withdrew from the study did so due to personal concerns. Most participants (90.5%) completed the study and transitioned into SOTERIA. During the Extension Period, 1 participant discontinued study intervention and withdrew from the study due to an AE.

Participants in this study were adults with a median age of 44.0 years (range: 21 to 70 years); 81.0% of participants were female, 81.0% were white, and 71.4% were not Hispanic or Latino. The most common PAH etiologies were idiopathic PAH (66.7%) and PAH associated with connective tissue disease (CTD) (28.6%). The mean time since PAH diagnosis to screening was 6.0 years. Participants were receiving either triple (52.4%) or double (47.6%) background PAH therapy, and more than half (57.1%) were receiving prostacyclin infusion therapy. All participants enrolled in this study belonged to WHO FC III only.

The mean peak VO_2 at baseline was 11.74 mL/kg/min (range 6.7 to 18.1 mL/kg/min) and mean 6MWD was 390.31 meters. Peak exercise assessments at baseline showed the following mean values: VE/VCO_2 slope (49.86), cardiac index (4.69 L/min/m^2), mPAP (70.9 mm Hg), Ca-vO_2 (10.04 mL/100 mL) and RV SV (74.32 mL).

Efficacy results

- The increase from baseline in mean VO_2 max was significantly greater than baseline at EOP at the prespecified 0.10 alpha level (one-sided) (1.28 mL/min/kg; p=0.0624). The effects on mean VO_2 max were maintained at Month 12 (1.83 mL/min/kg).
- No mean improvement from baseline was seen in RV SV by cardiac MR at EOP or Month 12. Calculated RV SV (mL/beat) by hemodynamic parameters showed a slight mean increase from baseline at EOP during peak exercise that shifted to a slight mean decrease from baseline at Month 12.
- Mean improvements from baseline at EOP and Month 12, respectively, were seen in other RV measurements, including RV ESV (-39.151 and -43.871 mL), RV EDV (66.459 and -61.556 mL), RV SVI (-15.073 and -10.095 mL/m2), and RV mass (-6.240 and -6.748 g). Measurements of RV EF showed a slight mean decrease of -1.3% from baseline at EOP but increased (3.0%) from baseline at Month 12.

- Mean improvements from baseline at EOP and Month 12, respectively, were seen in peak exercise iCPET and hemodynamic measurements, including VE/VCO2 slope (-8.87 and 12.26), mPAP (-14.9 and -12.3 mmHg), PVR (-230.281 and -180.160 dynes*sec/cm5), RAP (-8.8 and -8.5 mm Hg), Ca-vO2 (0.63 and 1.78 mL/100 mL), and work (20.2 and 22.1 watts). Cardiac index (0.411 L/min/m2) only showed improvement at EOP, and no notable improvement was seen at Month 12.
- Mean improvements from baseline at EOP and Month 12, respectively, were seen in PVR (-230.281 and -180.160 dynes*sec/cm5), 6MWD (66.35 and 98.63 meters), and WHO FC (-0.76 and -1.06). An improvement from baseline in mean NT-proBNP was seen at EOP (-623.1 pg/mL). Data for NT-proBNP in the Extension Period were too limited to interpret.
- Similar results were observed for these endpoints in the FAS population.

2.7.6. Discussion on clinical efficacy

This application is based on efficacy data from a Phase 2 dose-finding study PULSAR (P001MK7962) and the pivotal study STELLAR (P003MK7962). Supportive efficacy data are obtained from the exploratory Phase 2 study SPECTRA (P002MK7962).

Dose finding

PULSAR was a randomized, double-blind, dose-finding study to evaluate the efficacy and safety of two different doses of sotatercept in patients with PAH WHO FC II or III. The study consisted of two treatment parts. In the placebo-controlled treatment period, eligible subjects were randomized to placebo, sotatercept 0.3 mg/kg, or sotatercept 0.7 mg/kg for a treatment duration of 24-weeks. In the open-label extension period, subjects in the placebo group were re-randomized (1:1) to treatment with either sotatercept 0.3 or 0.7 mg/kg (referred to as the placebo crossed group) and subjects initially randomized to sotatercept continued the same dose. In total 97 out of 106 enrolled subjects (91.5%) completed the placebo-controlled period. It is noted that the rate of patients discontinuing treatment was considerably higher in the 0.7 mg/kg arm compared to the lower dose arm and the placebo arm (14.3% vs. 3.1% vs. 6.3%), for which a TEAE was the most common reason for discontinuation of study drug (n=7, 6.6% of which 5 subjects in the 0.7 mg/kg arm). TEAEs leading to discontinuation included neutropenia, thrombocytopenia polycythaemia, haemoglobin increased, red blood cell count increased, cardiac arrest, dyspnoea (all events occurred in no more than 1 subject).

The primary endpoint of change from baseline in PVR at weeks 24 showed larger placebo-corrected reductions in the 0.7 mg/kg group compared with the 0.3 mg/kg group (LS mean difference from baseline of -269.4 dynes*sec/cm5 ($p<0.0001$) and -151.1 dynes*sec/cm5 ($p=0.0030$), respectively). The primary efficacy endpoint was further supported by improvements in the secondary endpoints 6MWD (placebo-adjusted LS mean difference of 22.3 m ($p=0.1072$) and 24.6 m ($p=0.0790$) for the sotatercept 0.7 mg/kg and 0.3 mg/kg groups, respectively), WHO FC improvement ≥ 1 class (20.0% ($p=0.4911$) and 29.6% ($p=0.1503$) for 0.7 mg/kg and 0.3 mg/kg, respectively, vs. 13.3% for placebo), and NT-proBNP (placebo-adjusted LS mean difference of -671.5 pg/mL ($p=0.0015$) and -812.1 pg/mL ($p<0.0001$) for the sotatercept 0.7 mg/kg and 0.3 mg/kg groups, respectively). It should be noted that the magnitude of effect compared with placebo for these secondary endpoints was comparably greater in the 0.3 mg/kg group than the 0.7 mg/kg group. Maintenance of effect was evaluated using the results of the combined continuing sotatercept group, which is the sum of continuing sotatercept 0.7 kg/mg and continuing sotatercept 0.3 mg/kg groups from the extension period. These long-term analyses showed that the improvements from baseline in PVR, 6MWD, WHO FC, and NT-proBNP at Week 24 were maintained or further enhanced at Months 18 to 24.

Given the numerically better PVR response in the 0.7 mg/kg group, and manageable Hgb profile in both 0.7 mg/kg Q3W and 0.3 mg/kg Q3W doses, 0.7 mg/kg Q3W was selected as the target dose for STELLAR. However, the selection of this target dose of 0.7 mg/kg Q3W *for all patients* was questioned. First, although a numerically better PVR response with the 0.7 mg/kg dose compared with the 0.3 mg/kg dose was observed in the dose-finding study PULSAR, exposure - response models for PVR as well as 6MWD and NT-proBNP show a rather flat relationship between the 0.3 mg/kg and 0.7 mg/kg Q3W dose, indicating that the lower 0.3 mg/kg dose may be sufficient. Additionally, comparable increases in 6MWD with 24.6 m and 22.3 m for 0.3 mg/kg and 0.7 mg/kg were observed in the study PULSAR. Based on this discussion, the Applicant highlighted that, in addition to the numerically better PVR response, based on echocardiographic data in PULSAR, subjects treated with 0.7 mg/kg sotatercept for 24 weeks trended towards more favorable right ventricular function outcomes compared with those treated with 0.3 mg/kg. Specifically, the 0.7 mg/kg group showed a trend towards greater improvement in RV function as indicated by the TAPSE/pulmonary arterial systolic pressure ratio, RV end-diastolic area, RV end-systolic area, and RVFAC. Additionally, the Applicant argued that integrated E-R analyses demonstrated that PVR, 6MWD and NT-proBNP responses improve as exposure increases approaching plateaus at exposures corresponding to 0.7 mg/kg Q3W. However, at this clinical dose range of 0.3-0.7 mg/kg the sotatercept exposure-response analyses is very shallow for 6MWD, NT-proBNP <300 pg/mL and PVR, and other factors such as hemoglobulin and age (6MWD), baseline NT-proBNP (NT-proBNP) and prostacyclin, PAH duration and baseline PVR levels (PVR) have larger effects than sotatercept exposure range. Hence, the exposure response might be more sensitive for inter-study and inter-participant variability and might explain some of the apparent numerical different effects in PVR and NT-proBNP between PULSAR and STELLAR studies. Since the exposure-response analyses are only descriptive and not pivotal for this application the uncertainties in the exposure-response analyses can be accepted (see also pharmacology discussion above). Although the dose selection is debatable, selection of the 0.3 mg/kg as the target dose instead of the 0.7 mg/kg Q3W dose would be inappropriate since there is no adequate efficacy data for the 0.3 mg/kg Q3W dose from a pivotal study. With respect to the option to propose 0.3 mg/kg QW3 as the target dose for those patients with multiple dose modifications due to adverse events, it is agreed that it is up to the treating physician's discretion to prescribe the 0.3 mg/kg dose in case the risk to the individual patient outweighs the potential benefits of the 0.7 mg/kg dose.

Overall, the target dose of 0.7 mg/kg is acceptable.

Design and conduct of clinical studies

The design of STELLAR generally appeared appropriate. The study consisted of four periods, including a screening period, double-blind placebo-controlled (DBPC) treatment period, a long-term double-blind treatment period and a follow-up period. In the double-blind placebo-controlled (DBPC) period of 24 weeks, 323 eligible subjects were randomized (1:1) to receive either sotatercept or placebo subcutaneous Q3W in addition to background PAH therapy. Randomization was stratified by baseline WHO FC (II or III) and background PAH therapy (mono/double or triple therapy) and is considered acceptable. The starting dose of sotatercept was 0.3 mg/kg at Visit 1, followed by 0.7 mg/kg Q3W for the remainder of the study, unless dose modifications were required. For the starting dose of 0.3 mg/kg and the target dose of 0.7 mg/kg, weight-based ranges were used to calculate the injection volume. The use of weight-based ranges resulted in actual dose administrations that deviates ~95% - 120% from the 0.3 mg/kg dose and 93% - 110% from the 0.7 mg/kg target dose, which is considered an acceptable range. The weight-based ranges included in the SmPC are similar to those used in the STELLAR study and therefore acceptable. Further, the dose modification rules for the pivotal study STELLAR were refined based on the previous experience with luspatercept (human activin receptor type IIB ligand trap for a treatment for anemia), the PULSAR study, and pharmacokinetic data. Overall,

the modification rules used in STELLAR for a decrease in platelet counts (<50.0 x 109/L) were stricter than those used for increased hemoglobin (2 d> 2.0 g/dL AND Hgb above gender specific ULN), which is acceptable, considering that the risks associated with thrombocytopenia may have a more severe outcome than those associated with increased hemoglobin. In this regard, the SmPC includes the wording "*Hgb and platelet count should be obtained again before reinitiating treatment"* and *"Hgb and platelet count should be monitored for the first 5 doses, or longer if values are unstable. Thereafter, Hgb and platelet count should be verified every 3 to 6 months and the dose be adjusted if necessary"*. In this respect, although the dose recommendations differ from those used in STELLAR, they are considered adequate to manage the risks of thrombocytopenia. In addition, the SmPC includes a statement regarding the fact that if treatment delays due to platelet counts repeatedly $<50x10^9$/L persist longer than 9 weeks (more than 3 dose delays), the physician should carry out a benefit/risk re-evaluation for the patient before reinitiating treatment. Thus, the SmPC wording highlights that it is up to the discretion of the HCP to discontinue treatment or not, which is considered acceptable.

The duration of the DBPC treatment period of 24 weeks is considered appropriated to assess the primary study objective of improvement in 6MWD. Subjects who completed the DBPC period entered the long-term double-blind treatment (LTDB) period, which was still placebo-controlled. This LTDB treatment period was up to 72 weeks or until the last randomized subjects completed the DBPC treatment period and the study was unblinded. This approach limited the study in terms of generation of long-term placebo-controlled efficacy and safety data.

Key inclusion criteria included adult males and females aged ≥18 years with a confirmed diagnosis of symptomatic PAH (WHO Group 1) in WHO FC II and III, with a confirmed hemodynamic evaluation at screening (baseline PVR of ≥5 Wood units (WU), and a pulmonary artery wedge pressure (PAWP) or left ventricular end diastolic pressure (LVEDP) ≤15mmHg). The hemodynamic definition of PAH was updated in 2019 at the 6th World Symposium on Pulmonary Hypertension (WSPH) (Simonneau, Montani et al. 2019) and is defined by the presence of a mean pulmonary artery pressure (mPAP) ≥ 20 mmHg at rest, PAWP ≤15 mmHg and a PVR ≥3 WU. As such, the RHC inclusion criteria to confirm PAH used in the STELLAR study is not in line with the definition of the WSPH. The higher PVR of ≥5 WU instead of ≥3 WU according to the WSPH definition was used to include a study population with symptomatic PAH. In view of the mechanism of action, i.e. improvement of pulmonary vascular remodeling which is anticipated to also be beneficial in lowering PVR, and given that participants with PAH have a 5- to 7-year survival probability of 50% following diagnosis, it is considered that sotatercept therapy should not exclude participants with PVR of 3 to <5 WU, and the decision to use sotatercept in this population should be up to the treating physician.

The rest of the inclusion/exclusion criteria also appear to be appropriate. Patients had to use stable doses of background PAH therapy, which included ERA, PDE5 inhibitors, soluble guanylate cyclase stimulators or prostacyclin analogues or receptor agonists, for at least 90 days prior to screening. Subjects should have a 6MWD of ≥150 - ≤500 m, which is in line with the range included in most PAH trials and therefore acceptable. Further, considering that "*Baseline platelet count <50.0 x 10^9/L at screening*" was an exclusion criterion due to the potential risk of thrombocytopenia observed with sotatercept therapy, this condition has been included as a contraindication in the product information.

Similarly, "*Haemoglobin at screening above gender-specific ULN, per local laboratory test*" was an exclusion criterion due to increased haemoglobin levels observed with sotatercept therapy. Upon request, the Applicant analysed the rate of thromboembolic events (TEE) as crude rates and time at risk exposure-adjusted incidence rates (TAR-EAIR) in SOTERIA, where no such exclusion criteria were present. When TEE rates are compared for the SUR2 population dichotomized by hemoglobin levels being ever above ULN, participants with hemoglobin always lower than ULN (N=130) had a similar TEE incidence proportion and TAR-EAIR compared to those with any Hb>ULN (n=301), with incidences of 8/130 (6.2%) vs 24/301 (8.02) and TAR-EAIR (95% CI) 3.4 (1.5, 6.6) /100 PYAR and 3.8 (2.4, 5.6)

/100 PYAR, respectively. Similarly, using a cut-off of 2 g/dL above the ULN, the participants with hemoglobin always lower than 2g/dL above ULN (N=323) had a similar TEE incidence proportion and TAR-EAIR compared to those with any Hb> 2g/dL above ULN (n=108), with incidences of 23/323 (7.1%) vs 9/108 (8.3%) and TAR-EAIR (95% CI) 3.7 (2.4, 5.6) /100 PYAR and 3.5 (1.6, 6.6) /100 PYAR, respectively. Although the limited size of the analysis population in SOTERIA should be kept in mind, these analyses are reassuring in terms of the risk of thrombotic events. The lack of observed safety issues, the current dose modification guidelines and manageability of increases in hemoglobin and the established efficacy of sotatercept support the notion that individuals with hemoglobin levels above the upper limit of normal should not be excluded from receiving potentially significant beneficial effects of sotatercept. The omission of a contraindication for hemoglobin above the ULN is therefore acceptable, also given the included warning in section 4.4 of the SmPC stating "use caution in patients with erythrocytosis who are at increased risk of thromboembolic events."

The PAH Group 1 subtypes of "HIV-associated PAH and PAH associated with portal hypertension", "schistosomiasis-associated PAH and pulmonary veno-occlusive disease" were inclusion criteria due to the understanding that PAH associated with these comorbidities is primarily a terminal condition. In the opinion of the Applicant, despite other etiologies, rebalancing growth promoting/inhibiting signals through the BMPR2/activin pathway could still be effective in patients with HIV-, portal hypertension-, schistosomiasis-, and PVOD-associated PAH. Furthermore, according to the Applicant it is not expected that the safety profile would be different in these PAH subtypes, with the potential exception of portal hypertension which may have an increased bleeding risk due to underlying liver disease. However, any evidence is currently lacking. Considering that these PAH subtypes are not excluded due to an expected poor safety profile, it is acceptable not to include these PAH subtypes as contraindications in the SmPC. Nevertheless, given the uncertainties, a warning in section 4.4 of the SmPC has been added to highlight that sotatercept use has not been evaluated in these PAH subtypes.

The methods used for the assessment of efficacy are considered appropriate and consistent in both treatment arms.

The primary endpoint of change from baseline in 6MWT after 24 weeks is considered appropriate for the indication 'to improve exercise capacity', since this is in line with CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (EMEA/CHMP/EWP/356954/2008). The secondary endpoints are relevant and provide further insight on the effects of the drug under investigation. The multicomponent improvement (MCI) was defined by the proportion of subject achieving all of the following at week 24 relative to baseline: 1) improvement in 6MDW (increase ≥ 30 m); 2) improvement in NT-proBNP (decrease in NT-proBNP ≥ 30%) or maintenance/achievement of NT-proBNP level < 300 ng/L; 3) improvement in WHO FC or maintenance of WHO FC II. Although this MCI composite endpoint has not yet been validated, it can be considered clinically relevant and informative to both the potential prescriber and the patient.

Furthermore, in STELLAR, time to clinical worsening (TTCW) was defined as any of the following: death, worsening-related listing for lung and/or heart transplant, need to initiate rescue therapy with an approved background PAH therapy or the need to increase the dose of prostacyclin iinfusion by 10% or more, need for atrial septostomy, hospitalization for worsening of PAH (≥ 24 hours), or deterioration of PAH (defined by both of the following: worsened WHO FC and decrease in 6MWD by ≥ 15%). However, this definition of TTCW is not in line with the CHMP guideline (EMEA/CHMP/EWP/356954/2008) in which TTCW is defined as all-cause death, time to non-planned PAH-related hospitalization, time to PAH-related deterioration (defined by at least one of the following: increase in WHO FC, deterioration in exercise testing, or signs or symptoms of right-sided heart failure). The components of the used definition of TTCW are not all equally robust. For example, the decision that a patient is eligible for lung and/or heart transplant, the need to initiate rescue therapy with an approved background PAH therapy or the need to increase the dose of prostacyclin infusion by

10% or more, or the need for atrial septostomy is highly dependent on local practices and is accordingly not considered appropriate, as already indicated in the CHMP scientific advice (EMA/CHMP/SAWP/370878/2020). Therefore, the Applicant has provided a post-hoc TTCW statistical analysis for STELLAR using (in part) the CHMP definition. However, the components of the TTCW have not been analyzed separately as secondary endpoints as requested in the CHMP scientific advice (EMEA/H/SA/4497/1/2020/SME/PR/II). Further, mortality should be a key secondary endpoint not only for efficacy but also for safety in order to exclude a relevant negative impact of the treatment. As already indicated in the same CHMP scientific advice, long-term safety data for sotatercept which is intended for long-term treatment is limited, particularly since it concerns a new mechanism of action. In this respect, according to the guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension, any new drug should at least be shown to have no detrimental effect on survival (see Reflection paper on assessment of cardiovascular safety profile of medicinal products; EMA/CHMP/50549/2015), which the Applicant will perform via meta-analyses post-marketing once data from the other clinical trials is available. The secondary endpoints improvements in haemodynamic parameters, WHO FC and QoL measures are in line with the CHMP guideline and acceptable. With respect to the QoL PAH-SYMPACT score, according to the letter of support for the development of the PAH-SYMACT Instrument for use in PAH trials (30 March 2023; EMADOC-1700519818-1054252), the validation is at an advanced stage, however additional supportive analyses to the analyses provided would be required for information on PAH-SYMPACT to be included in the product information of medicinal products used in the treatment of PAH. Similarly, the mortality risk assessed by simplified French Risk score is based on only one study and has not been validated. Therefore, information on this endpoint cannot be included in the product information.

Regarding statistical methods, the analysis of the primary endpoint of change from baseline to week 24 in 6MWD was done using the aligned rank stratified Wilcoxon test with randomisation factors as strata. Hodges-Lehman location-shift estimate of the overall treatment difference with 95% confidence interval and 2-sided p-value are provided based on the test.

In addition, using the observed data, boxplots for each treatment group at 24 weeks are provided together with a line plot of mean and SEM of the change from baseline in 6MWD.

For continuous secondary endpoints, i.e. PVR, NT proBNP and PAH SYMPACT®, the same approach was used. For the binary secondary endpoints (e.g. MCI, WHO FC Improvement) Cochran-Mantel-Haenszel test is used incorporating randomisation factors as strata. Time to death or first occurrence of a worsening event are analysed using a log rank test. The accompanying hazard ratio and corresponding 95% confidence interval were calculated based on Cox proportional hazards model including randomisation factors as strata and the treatment as a covariate.

Efficacy data and additional analyses

In the pivotal study (data cut-off: 6-Dec-2022), 434 subjects were screened and 323 subjects (160 subjects to sotatercept and 160 subjects to placebo) were randomized and all subjects received at least one dose of study drug. The percentage of subjects who completed study treatment was higher in the sotatercept group (93.9%) compared with the placebo group (75.0%). Similarly, the percentage of subjects who completed the study was higher in the sotatercept group (95.1%) compared with the placebo group (88.8%). The imbalance in the percentage of subjects who completed study treatment can be explained by the higher number of clinical worsening events (n=10 (6.3%) vs. n=1 (0.6%)), deaths (n=6 (3.8%) vs. n=2 (1.2%)) and "others" n=11 (6.9%) vs. n=1 (0.6%)) in the placebo group compared with the sotatercept group. The most common reason for discontinuation of study treatment in the sotatercept group was an AE (n=4 (2.5%)) and death (n=2 (1.2%)), while no other discontinuation category had >1 subject in the sotatercept group, which is reassuring.

In the DBPC period, almost all subjects (99.4%) in the sotatercept group initially reached the 0.7 mg/kg dose according to the Applicant. One participant did not up-titrate to the 0.7 mg/kg dose due to consistently high haemoglobin levels. Moreover, 150 (92.0%) and 140 (85.9%) of the subjects in the sotatercept group received the target dose of 0.7 mg/kg at the end of the Week 24 DBPC and at the end of study, respectively, which is still considered relatively high. Further, it has to be noted that these data are based on the FAS and do not include those who dropped out of the study for any reason. As such, these percentages can be an underestimation of the proportion of subjects who tolerate the 0.7 mg/kg dose, i.e. a total of 5 subjects discontinued study due to participants request (n=2), participant's unwillingness or inability to comply with the protocol (n=1) or death (n=2), which is reassuring. Dose delays occurred in 12 subjects (7.4%) in the sotatercept group and in 5 subjects (3.1%) in the placebo group with a median time to first dose delay of 44.0 days for sotatercept and 71.0 days for placebo. Dose reductions occurred in 10 subjects (6.1%) in the sotatercept group and in 3 subjects (1.9%) in the placebo group with a median time to first dose reduction of 64.0 days for both groups. Dose re-escalation occurred in 5 subjects (3.1%) in the sotatercept group and in 2 subjects (1.3%) in the placebo group.

Overall, there were 35 participants in the STELLAR sotatercept group with dose modifications (dose reduction or delay). The main reason for dose reductions was increased hemoglogin (44%: 8 out of 18), followed by adverse event or adverse events of special interest (28%: 5 out of 18). The majority of dose delays (62%: 23 out of 37 dose delays) were due to increased hemoglobin levels, whereas in the placebo group half of the discontunatiuons were due to clinical worsening or study discontinuation (50%: 6 out of 12). Only 10 subjects of the 35 subjects with dose modifications (dose reduction or delay) in the sotatercept group of STELLAR experienced a subsequent AESI/AEOI after a dose modification. The most common reported AESI/AEOI were increased hemoglobin (n=6), telangiectasia (n=4) and bleeding events (n=3). Nevertheless, 9 of the 10 subjects completed the STELLAR study and continued sotatercept treatment in SOTERIA, whereas one subject with multiple comorbidities died from an acute myocardial infarction ~4 months after the dose hold/reduction. These results have adequately shown that the dose modification rules/ dose modifications can adequately manage the adverse events regarding increased hemoglobin levels and decreased platelet levels.

Moreover, cumulative results (DBPC + LTDB) showed that first dose reductions and dose delays also occurred after long-term treatment, i.e. after 24 weeks of treatment (visit 9). These results indicate the need for close periodical monitoring, and consequently the following recommendation has been included in the SmPC:

"*Hgb and platelet count should be monitored for the first 5 doses, or longer if values are unstable. Thereafter, Hgb and platelet count should be verified every 3 to 6 months and the dose adjusted if necessary (see sections 4.4 and 4.8)"*

Regarding protocol deviations, the major deviations were categorized either as protocol deviations or ICH/GCP deviations. Overall, the proportions of subjects of each category were approximately similar in both the sotatercept and the placebo groups, which is reassuring. Furthermore, it has been adequately justified that the major protocol deviations in terms of "missing endpoint assessments" (14.1% vs. 14.4% for the sotatercept and placebo group, respectively), "study procedures/assessments" (13.5% vs. 13.1%), and "study treatment admin/dispense" (13.5% vs. 8.1%), did not have any clinically relevant impact on the outcome of the study. Major protocol deviations associated with the pandemic were reported for 20 subjects, which were categorized in "visit scheduling" and were balanced between the intervention groups.

Treatment compliance was high and approximately comparable between the sotatercept and placebo groups (cumulative results: 98.3% vs 98.9%, respectively), which is reassuring.

The recruited subjects reflect the population of PAH patients regarding demographics, medical history and guideline-directed medical therapies for PAH, which are generally well distributed across the two treatments, although some exceptions are observed. The median age was 48.0 years, and most subjects were female (79.3%), white (89.2%), and not Hispanic or Latino (79.3%). The leading etiology was idiopathic PAH (58.5%), followed by heritable PAH (18.3%) and PAH associated with CTD (14.9%), PAH associated with congenital heart disease with repaired shunts (5%), or drug or toxin-induced PAH (3.4%). A lower percentage of patients with idiopathic PAH (50.9% vs. 66.3%) and a higher percentage of patients with heritable PAH (21.5% vs. 15.0%) was enrolled in the sotatercept group compared with the placebo group. Considering that subgroup analysis with respect to WHO PAH (group 1) subtypes showed a heterogeneity in effect on 6MWD, i.e. larger placebo corrected increase in 6MWD for the subtype of idiopathic PAH compared with heritable PAH, it can be expected that this imbalance will more likely underestimate the effect size than overestimate it. The imbalance in PAH subtype is therefore not considered a concern.

Despite subjects with a slightly higher time since PAH diagnosis were enrolled in the sotatercept group compared with the placebo group (9.22 vs. 8.28 years, respectively), this did not result in a disbalance in subjects with WHO FC II (48.5% vs. 48.8% for sotatercept and placebo, respectively) or WHO III (51.5% vs. 51.3%, respectively). At baseline, most of the subjects were taking triple background PAH therapy (61.6% comprised of 50.8% on ERA + prostacyclin+ PDE5 inhibitor and 10.8% on ERA + prostacyclin + cGC) or double background PAH therapy (34.4% consisting of 22.9% ERA + PDE5 i), whereas only 4.0% received PAH monotherapy. Overall, 90.7% of subjects received an ERA, 80.5% an PDE5 inhibitor, 71.5% prostacyclin (39.9% prostacyclin infusion therapy) and 14.9% an sGC as background PAH therapy. Further, a total of 66 (20.4%) participants in STELLAR received selexipag as a background PAH therapy, including 32 participants in the sotatercept group and 34 participants in the placebo group. This is sufficiently reflected in the wording of the indication.

In the primary efficacy analysis, treatment with sotatercept resulted in a significant improvement in 6MWD from baseline to week 24 as compared to placebo in patients with PAH (WHO Group 1) on background PAH therapy (median: 34.4 m vs. 1.0 m, respectively; median treatment difference (Hodges-Lehmann location shift) of 40.8 m (95% CI : 27.5, 54.1); $p< 0.001$) from baseline levels of 397.6 m and 404.7 m for the sotatercept and placebo group, respectively. This increase is considered clinically relevant as it compares to the results of the pivotal study of already authorised products for PAH. The effect was consistent in the prespecified sensitivity analyses using alternative methods of imputation for the 6MWD. Further, the treatment effect was consistent across all prespecified subgroups, including background therapy at baseline (monotherapy, double or triple therapy), baseline PVR (≤ 800, > 800 dynes*sec/cm5, prostacyclin infusion therapy (y/n), and < or ≥ median age. As expected, patients with a better WHO FC II benefit less from sotatercept than patients with WHO FC III. Nevertheless, both subgroups showed an increase in 6MWD of >20 m, which is considered clinically relevant. Further, there appears to be a heterogeneity of effect across the PAH subtypes, however, all subtypes showed a clinically relevant increase in 6MWD of > ~20 m compared with placebo, except for PAH associated with CTD. A lower magnitude of effect in patients with PAH associated with CTD compared with other subtypes has previously been observed with other PAH medicinal products and was considered possibly related to the underlying co-morbidity in PAH associated with CTD. Further, exploratory subgroups available do not show a clearly different efficacy or safety profile of the product in the underrepresented subset of patients with simple, congenital heart disease with systemic-to-pulmonary shunts and patients with drug- or toxin-induced PAH. As such this issue is not further pursued. The increases in 6MWD were maintained through at least Week 60 (median: 47.4 m vs. 4.3 m for the sotatercept and placebo group, respectively), after which the results were more variable, which may have been due to the small patient numbers. In this respect, no efficacy results from the extension study SOTERIA have been provided. Since results on maintenance of effect from SOTERIA

will be submitted once the study has been completed, this issue is not further pursued. Moreover, additional efficacy data will be generated by the ongoing HYPERION and ZENITH studies.

In cases where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling, and findings should be robust across subgroups and studies; Reference can be made to the relevant CHMP guideline (CPMP/EWP/2330/99). The primary result was robust to sensitivity analyses, consistent in subgroup analyses and consistent with results observed in the Phase 2 PULSAR study and therefore supports the restricted indication "to improve exercise capacity" in line with the relevant CHMP guideline (EMEA/CHMP/EWP/356954/2008).

The secondary efficacy results further support the primary efficacy endpoint. The percentage of subjects achieving MCI at week 24 was higher in the sotatercept group compared with the placebo group (38.9% vs. 10.1%, respectively; p< 0.001). Significant improvements were also seen in PVR (median treatment difference of -234.6 dynes*sec/cm5 (95% CI: -288.4, -180.8; p< 0.001), NT-proBNP (median treatment difference of -441.6 pg/ml (95% CI: -573.5, -309.6; p< 0.001), WHO FC (improvement in 29.4% vs. 13.8% subjects in the sotatercept and placebo group, respectively; p< 0.001). The magnitude of effect in terms of PVR and NT-proBNP and WHO FC improvement is consistent with that observed in the pivotal study of other approved PAH medicinal products. Moreover, a consistent treatment effect in terms of PVR and NT-proBNP was observed across all prespecified subgroups. Since sotatercept appears to increase haemoglobin and hematocrit, which increase blood viscosity, and subsequently can increase PVR, hematocrit-adjusted PVR analyses have been conducted. These analyses showed that it is unlikely that increased haemoglobin affected the decrease in PVR.

The 6MWD is acceptable as primary endpoint provided that the indication is restricted to an improvement in exercise capacity. For the broader treatment of PAH indication, "hard" clinical outcomes are required such as time to clinical worsening (TTCW). In the STELLAR study using data to the data cut-off of 26-AUG-2022, treatment with sotatercept resulted in a significant improvement in the 5th secondary endpoint 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 a 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). Two patients in the sotatercept group vs. 6 subjects in the placebo group died in the initial data cut-off period. However, since the components of the TTCW are not evaluated as secondary endpoints, firm conclusions regarding exclusion of a detrimental effect on cardiovascular safety cannot be made. The Applicant has made a commitment that a meta-analysis will be performed post-marketing once the data from other clinical trials are complete.

As described above, the components of the used definition of TTCW are not all equally robust. Therefore, the Applicant has provided a post-hoc analysis of TTCW using the definition proposed in the relevant CHMP guideline, thereby excluding the component "need to initiate rescue therapy with an approved PAH therapy or need to increase the dose of infusion prostacyclin by 10% or more" (data cut-off 26-AUG-2022). However, the components "worsening-related listing for lung and/or heart transplant" and "need for atrial septostomy" were not excluded in spite of the fact these components are not part of the TTCW definition as stated in the relevant CHMP guideline. Considering that no patients had a "need for atrial septostomy" event and only 2 patients (one in each treatment group) had a "worsening-related listing for lung and/or heart transplant", this issue is not considered relevant. Additionally, the definition of deterioration of PAH used in STELLAR (defined by *both* of the following: worsened WHO FC and decrease in 6MWD by ≥ 15%) was stricter than the CHMP definition (*at least one* of the following: increase in WHO FC, deterioration in exercise testing, or signs or symptoms of right-sided heart failure) and therefore, this discrepancy is not considered problematic. The results of this post-hoc analysis of TTCW corroborate the results of the primary TTCW analysis (06-DEC-2022); 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; Logrank test p-value < 0.001). All components contributed to this effect.

In comparison, the pivotal study GRIPHON of Uptravi (selexipag) conducted in 1156 subjects with WHO FC I-IV PAH, showed a risk reduction of 40% (hazard ratio [HR] 0.60; 99% CI: 0.46, 0.78; one-sided log-rank p value < 0.0001) in TTCW using approximately the same TTCW definition as used in STELLAR. As mentioned above, in cases where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling, and findings should be robust across subgroups and studies. In this respect, the findings are not consistent to those observed in the phase 2 PULSAR study. Despite the fact that the mean duration of exposure (~160 days) and the population studied in PULSAR is comparable to STELLAR, the percentages of subjects experiencing a TTCW event is much lower in PULSAR (1.4% vs. 6.3% for sotatercept and placebo, respectively) as compared with STELLAR (5.5% vs. 26.3%, respectively) with the side note that the number of patients in the PULSAR study were limited (n= 100). Consequently, the broader long-term treatment of PAH indication that was initially proposed by the Applicant was not acceptable to the CHMP and was consequently modified by the Applicant during the procedure. The ongoing studies HYPERION (MK-7962-005) and ZENITH (MK-7962-006) will provide further insights on the effect of sotatercept on clinical worsening and might potentially result in a modification of the indication in the future.

Further, the percentage of subjects who maintained or achieved a low-risk score (French Risk score calculator) relative to baseline was significantly greater in the sotatercept group (39.5% vs. 18.2%; p<0.001). Regarding the QoL PAH-SYMPACT score, significant improvements of treatment with sotatercept compared with placebo was observed for the physical impacts (median treatment difference of -0.26; p=0.010) and the cardiopulmonary symptoms (treatment difference of -0.13; p=0.028) domain score of PAH-SYMPACT, but not for the cognitive/emotional impacts domain score of PAH-SYMPACT (treatment difference of -0.16; p=0.156).

The results of the 3 PAH studies PULSAR, SPECTRA, and STELLAR are compared and pooled (PULSAR and STELLER), since the populations evaluated in these studies are representative of the adult population. Overall, it can be concluded that the results in terms of 6MWD, MCI, PVR, NT-proBNP, WHO FC improvement, and simplified French risk score observed in the phase 2 studies PULSAR and SPECTRA were consistent with those observed in STELLAR.

Supportive data was obtained from SPECTRA, which was a Phase 2a, single group, open-label, multicentre, exploratory study undertaken to evaluate the effects of sotatercept on invasive cardiopulmonary exercise test (iCPET). The population in SPECTRA was like the populations studied in STELLAR and PULSAR, with some exceptions (WHO FC III only, stable background PAH therapy ≥90 days not permitted, lower PVR criterion of ≥ 4 WU, and larger 6MWD range of (≥100 and ≤550 meters). Similarly, as in PULSAR and STELLAR, subjects in SPECTRA received an initial dose of 0.3 mg/kg at Cycle 1, followed by 0.7 mg/kg for the remainder of the study, unless dose modifications were required. Treatment with sotatercept significantly improved cardiopulmonary health, as measured by VO2 max (primary endpoint) at Week 24 at the prespecified 0.10 alpha level (one-sided) (1.28 mL/min/kg; p=0.0624). The effects on mean VO2 max were maintained at Month 12. Mean improvements from baseline at Week 24 and Month 12, respectively, were seen in PVR (-230.281 and -180.160 dynes*sec/cm5), 6MWD (66.35 and 98.63 meters), and WHO FC (-0.76 and -1.06). An improvement from baseline in mean NT-proBNP was seen at Week 24 (-623.1 pg/mL).

2.7.7. Conclusions on the clinical efficacy

The pivotal study STELLAR demonstrated that treatment with sotatercept resulted in a significant

improvement in 6MWD from baseline to week 24 of 40.8 m (p< 0.001), which is considered clinically relevant since it is in the range observed with other approved PAH therapies. The improvement in exercise capacity was further supported by significant improvements in MCI, PVR, NT-proBNP, WHO, TTCW, low-risk score (using simplified French Risk Score) and physical impacts and cardiopulmonary symptoms domain score of PAH-SYMPACT.

2.7.8. Clinical safety

This safety analysis focuses on data from three studies of sotatercept in PAH, including two Phase 2 studies (P001/A011-09/PULSAR and P002/A011-10/SPECTRA) and one pivotal Phase 3 study (P003/A011-11/STELLAR), which are hereafter referred to as PULSAR, SPECTRA, and STELLAR.

Results from a Phase 3 open-label extension study (P004/A011-12/SOTERIA, hereafter referred to as SOTERIA), which offers enrollment to participants who complete the Phase 2/3 PAH studies of sotatercept, are provided to further support the evaluation of safety. Data from SOTERIA are included in a pooled safety analysis and not reported separately, but instead included in the treatment groups from the original parent studies.

Sotatercept was administered subcutaneously Q3W in PULSAR, SPECTRA, and STELLAR, and is also administered subcutaneously Q3W in SOTERIA.

Safety analyses sets

The STELLAR study consisted of two treatment periods. The duration of the double-blind placebo-controlled (DBPC) Treatment Period was 24 weeks. Participants who completed the DBPC Treatment Period entered the long-term double-blind (LTDB) Treatment Period, which was up to 72 weeks. The last-participant-last-visit date for the DBPC Treatment Period was 26-AUG-2022. A safety update report was submitted by the Applicant, which included updated information for longer-term follow-up with a cut-off date of 6-DEC-2022, which was the end of study (EOS) date.

For the current report, the STELLAR data is presented primarily for the 6-DEC-2022 cut-off as this provides the most complete and long-term safety data. For several tables presented by the Applicant, both the 25-AUG-2022 (in tables called "Application") and the 6-DEC-2022 (in tables called "cumulative") cut-offs are presented.

Two safety pools (Pools A and B) with data from the Phase 2 and 3 PAH studies described above were developed to supplement the safety assessment of sotatercept in the individual PAH studies. For pool A, the 26-AUG-2022 cut-off was used. For pool B, where possible data is focussed on the 8-NOV-2023 cut-off (safety update report 2 (SUR2)), but for certain tables the Applicant provided both data from the 6-DEC-2022 cut-off (SUR1) and data from the 8-NOV-2023 cut-offs.

Pool A: This pool consists of safety data from the 24-week placebo-controlled periods of STELLAR and PULSAR. In Pool A, participants randomized to sotatercept in STELLAR or PULSAR constitute the "overall sotatercept group," and participants randomized to placebo in STELLAR or PULSAR constitute the "overall placebo group." Pool A tables also present data from STELLAR and PULSAR individually. For PULSAR, the 2 sotatercept treatment groups (0.3 and 0.7 mg/kg) were combined in the presentation of Pool A results.

Pool B: This pool consists of cumulative data from STELLAR, PULSAR, SPECTRA, and SOTERIA as follows:

- PULSAR: Final safety data from the 24-week Placebo-controlled and 30-month Extension Periods.

- SPECTRA: Final safety data from the 24-week Treatment Period and the 18-month Extension Period.
- STELLAR: Complete safety data from the 24-week DBPC Period and all available safety data from the up to 72-week LTDB Extension Period.
- SOTERIA: All available safety data in SOTERIA from participants who previously participated in either PULSAR, SPECTRA, or STELLAR. Data from SOTERIA are mapped into the treatment groups from the original parent studies.

In Pool B, participants who received sotatercept in STELLAR, PULSAR, SPECTRA, or SOTERIA constitute the "overall sotatercept group." There is no pooled placebo group in Pool B because (1) participants randomized to placebo in the 24-week Placebo-controlled Period of PULSAR crossed over to sotatercept treatment in the Extension Period, and (2) SPECTRA was a single-arm uncontrolled study.

Data collected after initiation of sotatercept from participants in PULSAR who crossed over from placebo in the Placebo-controlled Period to sotatercept in the Extension Period, contributed to the "overall sotatercept group" in Pool B. Data collected while these participants were receiving placebo in the Placebo-controlled Period in PULSAR are not included in Pool B.

Pool B tables also present data from STELLAR, PULSAR, and SPECTRA individually. For PULSAR, data from participants who crossed over from placebo in the Placebo-controlled Period to sotatercept (either 0.3 or 0.7 mg/kg) in the Extension Period are combined ("Combined Sotatercept" group) in the presentation of Pool B tables. Data from SOTERIA are presented according to the parent studies.

Most safety tables in Pool B SUR2 are provided into 3 columns as follows:

- *SUR1 Cumulative dataset*: Integrates final results from PULSAR, SPECTRA, and STELLAR and cumulative results from SOTERIA through the data cut-off for SUR1 (06-DEC-2022);
- *SUR2 dataset*: Reflects new results collected from SOTERIA after the data cut-off for Pool B in SUR1 (06-DEC-2022) through the data cut-off for SUR2 (08-NOV-2023);
- *SUR2 Cumulative dataset*: Integrates final results from PULSAR, SPECTRA, and STELLAR and cumulative results from SOTERIA through the data cut-off for SUR2 (08-NOV-2023).

AE definitions

AEs were coded using MedDRA version 25.0 or higher for the Phase 2 and 3 PAH studies and Pools A and B. TEAEs were defined as any AE with onset after the first dose of study intervention, or any AE with onset before the first dose of study intervention that worsened in severity after the first dose of study intervention. TEAEs included events occurring up to 8 weeks (56 days) after the last dose of study intervention. Incidences of AEs are shown as summary statistics. AEs were categorized by system organ class and PT.

In PULSAR and SPECTRA, the severity of AEs was coded using NCI-CTCAE v4.03. In STELLAR and Pools A and B, the severity of AEs was graded as mild, moderate, or severe. For integration of PULSAR and SPECTRA into Pools A and B, the grade reported in the individual study was mapped to the appropriate intensity: Grade 1 = Mild, Grade 2 = Moderate, Grade 3 or higher = Severe.

Subgroup analyses by demographic factors (age, sex, race, BMI) of TEAEs, serious TEAEs, and discontinuations due to TEAEs were conducted in the Safety Population if the sample size in each level of the subgroup category was ≥10 participants.

Several adverse events of (special) interest for sotatercept were determined based on non-clinical observations, clinical observations in participants with PAH, sotatercept's mechanism of action, and class-related effects.

In PULSAR, events considered to be AESIs were thrombocytopenia, leukopenia, and neutropenia (including febrile neutropenia). In addition to the AESIs included in PULSAR, SPECTRA included AESIs of fertility disorders with a focus on suppression of FSH, hepatic toxicity, cardiac events, and thrombotic and thromboembolic events.

Based on a review of safety data from PULSAR and the adequacy of routine safety monitoring, in STELLAR the formerly designated AESIs in PULSAR and SPECTRA were considered AEOIs. Additional AEOIs included in STELLAR were increased haemoglobin, immunogenicity, increased blood pressure, bleeding events, renal toxicity, and embryofetal toxicity. Telangiectasia was included in STELLAR as an AESI after events were reported in the PULSAR Extension Period. Events considered to be AEOIs/AESI in Pools A and B are the same as those listed for STELLAR.

2.7.8.1. Patient exposure

STELLAR

In the cumulative data from STELLAR a total of 142 (89%) and 155 (95%) of patients completed the study in the placebo and sotatercept arms, respectively.

In the DBPC and LTDB Treatment Periods combined, fewer participants in the sotatercept group than in the placebo group discontinued study intervention. Two (1.2%) participants in the sotatercept group discontinued study intervention due to death and 4 (2.5%) discontinued due to an AE. No other discontinuation category had >1 participant in the sotatercept group. The most common reasons for discontinuation of study intervention in the placebo group were clinical worsening event, death and other.

In STELLAR, the median duration of exposure to study intervention in the cumulative dataset was longer in the sotatercept group (313.0 days) than in the placebo group (273.0 days), consistent with the application dataset. The difference in exposure between the 2 groups in both datasets reflects the lower proportion of participants who discontinued study intervention in the sotatercept group than the placebo group.

Almost all participants (99.4%) in the sotatercept group reached the 0.7 mg/kg dose. One participant did not up titrate to the 0.7mg/kg dose due to consistently high haemoglobin levels. All the other participants reached the 0.7mg/kg dose.

Table 50. Disposition STELLAR

	Placebo		Sotatercept		Total	
	Application (N=160) n (%)	Cumulative (N=160) n (%)	Application (N=163) n (%)	Cumulative (N=163) n (%)	Application (N=323) n (%)	Cumulative (N=323) n (%)
Total Number of Subjects						
Randomized [1]	160 (100.0)	160 (100.0)	163 (100.0)	163 (100.0)	323 (100.0)	323 (100.0)
Completed Visit 9	148 (92.5)	148 (92.5)	159 (97.5)	159 (97.5)	307 (95.0)	307 (95.0)
Completed Study	32 (20.0)	142 (88.8)	5 (3.1)	155 (95.1)	37 (11.5)	297 (92.0)
Discontinued Study Treatment	35 (21.9)	40 (25.0)	9 (5.5)	10 (6.1)	44 (13.6)	50 (15.5)
Withdrew from Study	16 (10.0)	18 (11.3)	8 (4.9)	8 (4.9)	24 (7.4)	26 (8.0)
Primary Reason for Discontinuation of Study Treatment [2]						
Adverse Event	2 (1.3)	2 (1.3)	4 (2.5)	4 (2.5)	6 (1.9)	6 (1.9)
Participant request (withdrawal of consent)	3 (1.9)	4 (2.5)	1 (0.6)	1 (0.6)	4 (1.2)	5 (1.5)
Participant's unwillingness or inability to comply with the protocol	2 (1.3)	2 (1.3)	1 (0.6)	1 (0.6)	3 (0.9)	3 (0.9)
Clinical worsening event	10 (6.3)	10 (6.3)	1 (0.6)	1 (0.6)	11 (3.4)	11 (3.4)
Pregnancy	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Study terminated by sponsor [3]	0 (0.0)	4 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.2)
Death	6 (3.8)	6 (3.8)	2 (1.2)	2 (1.2)	8 (2.5)	8 (2.5)
Other	11 (6.9)	11 (6.9)	0 (0.0)	1 (0.6)	11 (3.4)	12 (3.7)
Primary Reason for Withdrawal from Study [2]						
Adverse Event	1 (0.6)	1 (0.6)	3 (1.8)	3 (1.8)	4 (1.2)	4 (1.2)
Participant request (withdrawal of consent)	5 (3.1)	6 (3.8)	2 (1.2)	2 (1.2)	7 (2.2)	8 (2.5)
Participant's unwillingness or inability to comply with the protocol	1 (0.6)	2 (1.3)	1 (0.6)	1 (0.6)	2 (0.6)	3 (0.9)
Clinical worsening event	2 (1.3)	2 (1.3)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.6)
Death	6 (3.8)	6 (3.8)	2 (1.2)	2 (1.2)	8 (2.5)	8 (2.5)
Other	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)

N = number of subjects in the treatment group or overall. n = number of subjects in the category.
Percentages are calculated as (n/N)*100.
DBPC = double-blind placebo-controlled period; LTDB = long-term double-blind period.
[1] Excludes one subject (Placebo group) who was inadvertently randomized and did not receive any study medication. This subject is excluded from all analyses.
[2] Subjects may have only one primary reason for discontinuation and withdrawal.
[3] Subjects were incorrectly identified as having discontinued the study treatment due to "study terminated by sponsor"; in fact, all 4 subjects successfully completed the study and rolled over to the Long-Term Follow-Up study (SOTERIA).

Table 51. Exposure STELLAR (application refers to cut-off 26-aug-2022, cumulative to 06-12-2022)

	Placebo Application (N=160) n (%)	Cumulative (N=160) n (%)	Sotatercept Application (N=163) n (%)	Cumulative (N=163) n (%)	Total Application (N=323) n (%)	Cumulative (N=323) n (%)
Duration of exposure (days) [1]						
n	160	160	163	163	323	323
Mean (SD)	241.6 (83.19)	276.4 (95.78)	270.3 (77.86)	319.5 (84.60)	256.1 (81.70)	298.1 (92.71)
Median	229.5	273.0	252.0	313.0	235.0	290.0
Q1, Q3	190, 294	218, 335	210, 315	256, 377	208, 301	252, 357
Min, Max	21, 566	21, 566	61, 518	61, 561	21, 566	21, 566
Number of treatment visits						
n	160	160	163	163	323	323
Mean (SD)	11.3 (3.85)	12.9 (4.45)	12.4 (3.70)	14.6 (3.99)	11.8 (3.81)	13.7 (4.31)
Median	10.5	13.0	12.0	14.0	11.0	13.0
Q1, Q3	9, 13	10, 16	10, 15	12, 17	9, 14	11, 17
Min, Max	1, 27	1, 27	3, 24	3, 27	1, 27	1, 27
Total (cumulative) dose administered (mg)						
n	160	160	163	163	323	323
Mean (SD)	0.0 (0.00)	0.0 (0.00)	585.9 (252.87)	694.7 (286.57)	295.7 (343.86)	350.6 (402.90)
Median	0.0	0.0	533.8	644.5	100.1	100.1
Q1, Q3	0.0, 0.0	0.0, 0.0	419.2, 712.6	514.2, 848.4	0.0, 535.2	0.0, 646.2
Min, Max	0.0, 0.0	0.0, 0.0	90.9, 1366	90.9, 1587	0.0, 1366	0.0, 1587
Number of subjects who reached 0.7 (mg/kg) dose, n (%)	0 (0.0)	0 (0.0)	162 (99.4)	162 (99.4)	162 (50.2)	162 (50.2)

DBPC = double-blind placebo-controlled period; LTDB = long-term double-blind period.
N = number of subjects in the treatment group or overall. n = number of subjects in the category. SD = Standard deviation, Q1 = First quartile, Q3 = Third quartile.
The mg of dose administered is calculated as a function of the individual's weight.
[1] Duration of exposure = last dose date - first dose date + 21.

Pool A

In Pool A, the proportion of participants who completed Visit 9 (Week 24) was higher in the overall sotatercept group (227 [95.8%]) than in the overall placebo group (178 [92.7%]). In Pool A, the proportion of participants who discontinued study intervention was lower in the overall sotatercept group (10 [4.2%]) than in the placebo group (14 [7.3%]). While discontinuation of study intervention due to a non-fatal TEAE occurred more commonly in the overall sotatercept group (7 [3.0%]) than in the overall placebo group (3 [1.6%]), discontinuation of study intervention due to death (0 [0.0%] vs 5 [2.6%]) and due to worsening PAH (0 [0.0%] vs 2 [1.0%]) occurred less commonly in the overall sotatercept group than in the overall placebo group. In Pool A, the median duration of exposure to study intervention was 168.0 days in both the overall sotatercept and overall placebo groups. The majority of participants in both groups (>70%) received 8 doses of study intervention. Dose reductions occurred in 27 (11.4%) participants in the overall sotatercept group and 5 (2.6%) in the overall placebo group with a median time to first dose reduction of 64.0 days for the overall sotatercept group and 82.0 days for the overall placebo group. Dose delays occurred in 41 (17.3%) participants in the overall sotatercept group and 10 (5.2%) in the overall placebo group with a median time to first dose delay of 44.0 days for the overall sotatercept group and 76.5 days for the overall placebo group.

Table 52. Disposition of Pool A

	STELLAR (MK-7962-003)		PULSAR (MK-7962-001)		Overall	
	Placebo (N=160) n (%)	Sotatercept 0.3mg/kg then 0.7mg/kg (N=163) n (%)	Placebo (N=32) n (%)	Combined Sotatercept (N=74) n (%)	Placebo (N=192) n (%)	Sotatercept (N=237) n (%)
Total Number of Participants						
Completed Study at First 6 months	148 (92.5)	159 (97.5)	30 (93.8)	68 (91.9)	178 (92.7)	227 (95.8)
Discontinued Study Treatment	12 (7.5)	4 (2.5)	2 (6.3)	6 (8.1)	14 (7.3)	10 (4.2)
Withdrew from Study	12 (7.5)	4 (2.5)	2 (6.3)	6 (8.1)	14 (7.3)	10 (4.2)
Primary Reason for Discontinuation of Study Treatment [1]						
Adverse Event	2 (1.3)	2 (1.2)	1 (3.1)	5 (6.8)	3 (1.6)	7 (3.0)
Death	5 (3.1)	0	0	0	5 (2.6)	0
Pregnancy	1 (0.6)	0	0	0	1 (0.5)	0
Progressive Disease	2 (1.3)	0	0	0	2 (1.0)	0
Unwillingness Or Inability To Comply With Protocol	1 (0.6)	1 (0.6)	0	0	1 (0.5)	1 (0.4)
Withdrawal By Subject	1 (0.6)	1 (0.6)	1 (3.1)	1 (1.4)	2 (1.0)	2 (0.8)
Primary Reason for Withdrawal from Study [1]						
Adverse Event	1 (0.6)	1 (0.6)	1 (3.1)	5 (6.8)	2 (1.0)	6 (2.5)
Death	5 (3.1)	0	0	0	5 (2.6)	0
Progressive Disease	2 (1.3)	0	0	0	2 (1.0)	0
Unwillingness Or Inability To Comply With Protocol	1 (0.6)	1 (0.6)	0	0	1 (0.5)	1 (0.4)
Withdrawal By Subject	3 (1.9)	2 (1.2)	1 (3.1)	1 (1.4)	4 (2.1)	3 (1.3)

Participants from PULSAR and STELLAR are included.
All Participants received standard of care in addition to receiving study drug.
The Combined Sotatercept group from PULSAR includes participants treated with Sotatercept during the first 6 months (Placebo-controlled Period).
[1] Participants may have only one primary reason for discontinuation and withdrawal.
N = total number of participants randomized. n = number of participants in the category. Percentages are calculated as (n/N)*100, except where noted.

Table 53. Exposure pool A

	STELLAR (MK-7962-003)		PULSAR (MK-7962-001)		Overall	
	Placebo (N=160)	Sotatercept 0.3mg/kg then 0.7mg/kg (N=163)	Placebo (N=32)	Combined Sotatercept (N=74)	Placebo (N=192)	Sotatercept (N=237)
Treatment Duration (days) [1]						
n	160	163	32	74	192	237
Mean (SD)	162.2 (25.76)	166.3 (12.53)	165.2 (15.74)	161.6 (25.49)	162.7 (24.37)	164.8 (17.71)
Median	168.0	168.0	168.0	168.0	168.0	168.0
Min, Max	21, 196	61, 193	84, 183	41, 188	21, 196	41, 193
Total Person-Years [2]	76.00	79.40	15.40	34.60	91.40	114.00
Number of Doses Received, n (%)						
1	3 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.6)	0 (0.0)
2	1 (0.6)	0 (0.0)	0 (0.0)	3 (4.1)	1 (0.5)	3 (1.3)
3	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)
4	0 (0.0)	0 (0.0)	1 (3.1)	1 (1.4)	1 (0.5)	1 (0.4)
5	5 (3.1)	4 (2.5)	0 (0.0)	1 (1.4)	5 (2.6)	5 (2.1)
6	2 (1.3)	9 (5.5)	0 (0.0)	4 (5.4)	2 (1.0)	13 (5.5)
7	12 (7.5)	19 (11.7)	5 (15.6)	22 (29.7)	17 (8.9)	41 (17.3)
8	136 (85.0)	130 (79.8)	26 (81.3)	43 (58.1)	162 (84.4)	173 (73.0)
9-16	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
17-24	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
25-32	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>32	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
n	160	163	32	74	192	237
Mean (SD)	7.6 (1.25)	7.7 (0.78)	7.7 (0.77)	7.3 (1.34)	7.6 (1.18)	7.5 (1.00)
Median	8.0	8.0	8.0	8.0	8.0	8.0
Min, Max	1, 8	3, 8	4, 8	2, 8	1, 8	2, 8

Pool B

In the SUR2 cumulative dataset, the majority of participants (>90%) in the overall sotatercept group completed a parent study (STELLAR, PULSAR, or SPECTRA) and rolled over to SOTERIA. The proportion of participants who discontinued study intervention in the overall sotatercept group was low and generally consistent in the SUR2 and SUR1 Cumulative datasets. Eighteen additional participants in the overall sotatercept group discontinued study intervention in the ~11-month duration between the SUR2 and SUR1 data cut-offs. The median duration of the SUR2 cumulative dataset was 657.0 days. A total of 343 participants were exposed to sotatercept for at least 1 year.

Table 54. Disposition of Pool B

	Overall Sotatercept [1]	
	SUR1 Cumulative (N=431) n (%)	SUR2 Cumulative (N=431) n (%)
Total Number of Participants		
Completed Parent Study [2]	403 (93.5)	403 (93.5)
Rollover to SOTERIA	399 (92.6)	401 (93.0)
Did not rollover to SOTERIA	4 (0.9)	2 (0.5)
Completed Study Overall [3]	4 (0.9)	2 (0.5)
Ongoing [3]	394 (91.4)	378 (87.7)
Discontinued Study Treatment [3]	35 (8.1)	53 (12.3)
Withdrew from Study [3]	33 (7.7)	51 (11.8)
Primary Reason for Discontinuation of Study Treatment [4]		
Adverse Event	12 (2.8)	20 (4.6)
Death	10 (2.3)	14 (3.2)
Progressive Disease	1 (0.2)	3 (0.7)
Unwillingness Or Inability To Comply With Protocol	1 (0.2)	2 (0.5)
Withdrawal By Subject	7 (1.6)	8 (1.9)
Other	4 (0.9)	6 (1.4)
Primary Reason for Withdrawal from Study [4]		
Adverse Event	11 (2.6)	16 (3.7)
Death	10 (2.3)	15 (3.5)
Progressive Disease	0	3 (0.7)
Unwillingness Or Inability To Comply With Protocol	1 (0.2)	3 (0.7)
Withdrawal By Subject	8 (1.9)	9 (2.1)
Other	3 (0.7)	5 (1.2)

N = total number of participants randomized. n = number of participants in the category. Percentages are calculated as (n/N)*100, except where noted.
Note: Column SUR1 Cumulative includes completed studies PULSAR, SPECTRA, STELLAR and the ongoing SOTERIA study with data cut of 6-Dec-2022. Column SUR2 Cumulative includes the same set of completed studies as SUR1 Cumulative but with new data cut from SOTERIA of 8-Nov-2023. Participants from PULSAR, SPECTRA, STELLAR and SOTERIA are included. SOTERIA with data cut as of 8-Nov-2023. Other studies are completed studies.
[1] Overall Sotatercept includes all participants who were treated with at least one dose of Sotatercept.
[2] A participant that completes the study (STELLAR, PULSAR, or SPECTRA) is said to have completed the requirements of the study per protocol and is eligible to rollover to SOTERIA provided the participant consents to such a rollover.
[3] Status indicates overall treatment or study status, that is, if a participant has rolled over to SOTERIA then the status is from SOTERIA, if the participant has not rolled over to SOTERIA then the status is from the parent study.
[4] Participants may have only one primary reason for discontinuation and withdrawal.

Table 55. Exposure of Pool B

	Overall Sotatercept [1]	
	SUR1 Cumulative (N=431) n (%)	SUR2 Cumulative (N=431) n (%)
Treatment Duration (days) [2]		
N	431	431
Mean (SD)	483.9 (459.84)	784.0 (477.25)
Median	336.0	657.0
Min, Max	21, 1637	21, 1973
Total Person-Years [3]	571.40	923.70
Number of Doses Received, n (%)		
1	11 (2.6)	1 (0.2)
2	68 (15.8)	4 (0.9)
3	33 (7.7)	2 (0.5)
4	12 (2.8)	1 (0.2)
5	5 (1.2)	1 (0.2)
6	6 (1.4)	4 (0.9)
7	4 (0.9)	2 (0.5)
8	6 (1.4)	1 (0.2)
9-16	88 (20.4)	23 (5.3)
17-24	84 (19.5)	119 (27.6)
25-32	15 (3.5)	94 (21.8)
>32	99 (23.0)	179 (41.5)
n	431	431
Mean (SD)	20.7 (19.37)	35.3 (21.30)
Median	15.0	30.0
Min, Max	1, 77	1, 93
Average Length of Time Between Doses (days) [4]		
n	431	431
Mean (SD)	23.3 (6.16)	22.2 (1.95)
Median	21.4	21.6
Min, Max	20, 89	20, 43

	Overall Sotatercept [1]	
	SUR1 Cumulative (N=431) n (%)	SUR2 Cumulative (N=431) n (%)
Number of Participants with Dose Reduction	108 (25.1)	148 (34.3)
Time to First Reduction (days) [5]		
n	108	148
Mean (SD)	266.5 (285.57)	322.8 (297.61)
Median	169.5	232.5
Min, Max	1, 1177	1, 1380
Number of Participants with Dose Delay	135 (31.3)	187 (43.4)
Time to First Delay (days) [5]		
N	135	187
Mean (SD)	445.8 (456.71)	505.0 (519.98)
Median	253.0	322.0
Min, Max	17, 1492	17, 1828

	Overall Sotatercept [1]	
	SUR1 Cumulative (N=431) n (%)	SUR2 Cumulative (N=431) n (%)

N = total number of participants randomized. n = number of participants in the category. Percentages are calculated as (n/N)*100, except where noted. SD = standard deviation
Note: Column SUR1 Cumulative includes completed studies PULSAR, SPECTRA, STELLAR and the ongoing SOTERIA study with data cut of 6-Dec-2022. Column SUR2 Cumulative includes the same set of completed studies as SUR1 Cumulative but with new data cut from SOTERIA of 8-Nov-2023.
[1] Overall Sotatercept includes all participants who were treated with at least one dose of sotatercept.
[2] Treatment duration (days) = Treatment end date - First dose date + 1.
[3] The total person-years is defined as the sum of the treatment duration exposure in years for all participants for each pooled treatment group.
[4] The average length of time between doses (days) is defined as [(the treatment end date) – (the date of the first dose) + 1] / (the total number of doses received).
[5] Days reflects total time on treatment, calculated as [event date – corresponding treatment start date] + 1.

Table 56. Patient exposure (06 DEC 2022)

	Participants Enrolled	Participants Exposed [1]	Participants exposed to the proposed dose range [2]	Participants with long term safety data [3]
Blinded PAH studies (Placebo-controlled)	429	267	246	128
Open-label Phase 2 PAH studies	21	21	21	20
Pool A [4]	429	237	204	0
Pool B [5]	448	431	414	343

[1] Exposed is defined as exposure to sotatercept at any dose level.
[2] The proposed dose range includes at least one dose at 0.7 mg/kg.
[3] Long term safety means at least 1 year [52 weeks] of exposure to sotatercept.
[4] Pool A consists of data from PAH participants for the first 24-weeks of exposure to sotatercept. Studies in Pool A consist of the blinded, placebo-controlled studies PULSAR and STELLAR.
[5] Pool B consists of data from PAH participants for any period of exposure to sotatercept. Studies in Pool B consist of PULSAR, SPECTRA, STELLAR, and participants from those studies who rollover into SOTERIA with exposure data up to the data cut of 8-Nov-2023.

2.7.8.2. Adverse events

STELLAR

During the full study duration of STELLAR, the number of treatment-emergent adverse events was 149 (93.1%) and 151 (92.6%) in the placebo and sotatercept arm, respectively. The number of TEAE leading to study discontinuation was 9 (5.6%) and 6 (3.7%) in the placebo and sotatercept arm, respectively. Incidences of TEAEs were higher in the sotatercept group than in the placebo group in the summary categories of TEAEs considered related to treatment by the investigator and TEAE of special interest (AESI telangiectasia). Serious TEAEs and severe TEAEs occurred less commonly in the sotatercept group than in the placebo group. Additionally, incidences of TEAEs were lower in the sotatercept group than in the placebo group in the summary categories of TEAEs leading to treatment discontinuation, TEAEs leading to death, serious TEAEs leading to treatment discontinuation, and

serious TEAEs leading to death. Results in the cumulative and application datasets were generally consistent across AE summary categories.

Table 57. Overall Summary of Treatment-emergent Adverse Events in STELLAR

	Placebo			Sotatercept		
Number of subjects with any	Application (N=160) n (%)	SUR (N=117) n (%)	Cumulative (N=160) n (%)	Application (N=163) n (%)	SUR (N=152) n (%)	Cumulative (N=163) n (%)
Treatment-Emergent adverse events (TEAEs)	147 (91.9)	69 (59.0)	149 (93.1)	148 (90.8)	83 (54.6)	151 (92.6)
TEAEs related to treatment	43 (26.9)	4 (3.4)	45 (28.1)	77 (47.2)	17 (11.2)	83 (50.9)
TEAE of interest	67 (41.9)	10 (8.5)	71 (44.4)	86 (52.8)	34 (22.4)	97 (59.5)
TEAE special interest	6 (3.8)	1 (0.9)	7 (4.4)	23 (14.1)	6 (3.9)	27 (16.6)
TEAEs leading to treatment discontinuation	11 (6.9)	1 (0.9)	11 (6.9)	6 (3.7)	0 (0.0)	6 (3.7)
TEAEs leading to study discontinuation	9 (5.6)	1 (0.9)	9 (5.6)	8 (4.9)	1 (0.7)	6 (3.7)
TEAEs leading to death	7 (4.4)	0 (0.0)	7 (4.4)	2 (1.2)	0 (0.0)	2 (1.2)
Severe TEAEs	29 (18.1)	7 (6.0)	33 (20.6)	21 (12.9)	3 (2.0)	24 (14.7)
Serious TEAEs	44 (27.5)	8 (6.8)	47 (29.4)	36 (22.1)	10 (6.6)	40 (24.5)
Serious TEAEs related to treatment	2 (1.3)	0 (0.0)	2 (1.3)	3 (1.8)	0 (0.0)	3 (1.8)
Serious TEAEs leading to treatment discontinuation	9 (5.6)	1 (0.9)	9 (5.6)	4 (2.5)	0 (0.0)	4 (2.5)
Serious TEAEs leading to study discontinuation	8 (5.0)	1 (0.9)	8 (5.0)	4 (2.5)	0 (0.0)	4 (2.5)
Serious TEAEs leading to death	7 (4.4)	0 (0.0)	7 (4.4)	2 (1.2)	0 (0.0)	2 (1.2)

DBPC = double-blind placebo-controlled period; LTDB = long-term double-blind period.
N = number of subjects in the treatment group or overall. n = number of subjects in the category.
Percentages are calculated as (n/N)*100.
A treatment-emergent adverse event has a start date on or after the first dose of treatment and up to 8 weeks after the last dose of treatment in the DBPC.
Adverse events of special interest (AESI) include telangiectasia.
Adverse events of interest (AEOI) include the following: Increased haemoglobin, immunogenicity, thrombocytopenia, neutropenia (including febrile neutropenia), embryo-fetal toxicity, hepatic toxicity, cardiac events, thrombotic events,
renal toxicity, bleeding events, increased blood pressure, and suppression of FSH.
Adverse events were assessed by the investigator to be 'suspected related' or not 'suspected related'. A 'suspected related' AE is considered to be related to treatment.

Pool A

Overall, incidences of TEAEs in Pool A were generally consistent with those of STELLAR.

Table 58. Incidences of TEAEs in Pool A

	STELLAR (MK-7962-003)		PULSAR (MK-7962-001)		Overall	
Number of participant with any	Placebo (N=160) n (%)	Sotatercept 0.3mg/kg then 0.7mg/kg (N=163) n (%)	Placebo (N=32) n (%)	Combined Sotatercept (N=74) n (%)	Placebo (N=192) n (%)	Sotatercept (N=237) n (%)
Treatment-Emergent Adverse Event (TEAE)	140 (87.5)	138 (84.7)	29 (90.6)	64 (86.5)	169 (88.0)	202 (85.2)
TEAE related to treatment	41 (25.6)	67 (41.1)	9 (28.1)	37 (50.0)	50 (26.0)	104 (43.9)
Severe TEAE	21 (13.1)	13 (8.0)	5 (15.6)	14 (18.9)	26 (13.5)	27 (11.4)
Serious TEAE	36 (22.5)	23 (14.1)	3 (9.4)	12 (16.2)	39 (20.3)	35 (14.8)
Serious related TEAE	2 (1.3)	2 (1.2)	1 (3.1)	2 (2.7)	3 (1.6)	4 (1.7)
TEAE leading to treatment discontinuation	10 (6.3)	3 (1.8)	1 (3.1)	6 (8.1)	11 (5.7)	9 (3.8)
TEAE leading to dose reduction	1 (0.6)	4 (2.5)	1 (3.1)	4 (5.4)	2 (1.0)	8 (3.4)
TEAE leading to dose delay	3 (1.9)	11 (6.7)	2 (6.3)	14 (18.9)	5 (2.6)	25 (10.5)
TEAEs leading to death	6 (3.8)	0	0	1 (1.4)	6 (3.1)	1 (0.4)
Adverse Events of Interest (AEOI)	54 (33.8)	69 (42.3)	15 (46.9)	34 (45.9)	69 (35.9)	103 (43.5)
Adverse Events of Special Interest (AESI)	5 (3.1)	17 (10.4)	0	0	5 (2.6)	17 (7.2)

Participants from PULSAR and STELLAR are included.
All participants received standard of care in addition to receiving study drug.
The Combined Sotatercept group from PULSAR includes participants treated with sotatercept during the first 6 months (Placebo-controlled Period).

Pool B

Incidences of TEAEs for each summary category increased in the SUR2 Cumulative dataset relative to the SUR1 Cumulative dataset. For each AE category, the increased incidence was generally proportional to the increased duration of exposure to sotatercept. No new safety concerns for sotatercept emerged.

In the overall sotatercept group, there were 6 (1.5%) additional deaths and 10 (2.5%) additional participants who discontinued study intervention for a TEAE between the SUR2 and SUR1 Cumulative datasets.

Table 59. Overall TEAEs in Pool B

Number of participants with any	Overall Sotatercept [1] SUR1 Cumulative (N=431) n (%)	SUR2 (N=400) n (%)	SUR2 Cumulative (N=431) n (%)
Treatment-Emergent Adverse Event (TEAE)	352 (81.7)	357 (89.3)	415 (96.3)
TEAE related to treatment	219 (50.8)	161 (40.3)	288 (66.8)
Severe TEAE	94 (21.8)	81 (20.3)	153 (35.5)
Serious TEAE	107 (24.8)	97 (24.3)	173 (40.1)
Serious related TEAE	10 (2.3)	10 (2.5)	20 (4.6)
TEAE leading to treatment discontinuation	21 (4.9)	10 (2.5)	31 (7.2)
TEAE leading to dose reduction	33 (7.7)	26 (6.5)	54 (12.5)
TEAE leading to dose interruption	90 (20.9)	61 (15.3)	133 (30.9)
TEAEs leading to death	10 (2.3)	6 (1.5)	16 (3.7)
Adverse Events of Interest (AEOI)	236 (54.8)	199 (49.8)	313 (72.6)
Adverse Events of Special Interest (AESI)	73 (16.9)	56 (14.0)	120 (27.8)

N = total number of participants randomized. n = number of participants in the category. Percentages are calculated as (n/N)*100, except where noted.
Note: Column SUR1 Cumulative includes completed studies PULSAR, SPECTRA, STELLAR and the ongoing SOTERIA study with data cut of 6-Dec-2022. Column SUR2 Cumulative includes the same set of completed studies as SUR1 Cumulative but with new data cut from SOTERIA of 8-Nov-2023.
[1] Overall Sotatercept includes all participants who were treated with at least one dose of Sotatercept.

Common adverse events

The incidences of TEAEs by preferred term were generally similar in both groups. Frequently reported TEAEs (incidence ≥5%) with a higher incidence in the sotatercept group than in the placebo group were epistaxis (22%), telangiectasia (17%), dizziness (15%), nasal congestion (6%), thrombocytopenia (10%), and haemoglobin increased (6%).

Table 60. Common TEAEs (the most frequently reported TEAEs (incidence ≥5%)) from STELLAR

				Sotatercept vs. Placebo Comparison	
Preferred Term	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)	Point Estimate (%)	95% CI [1]
Subjects with events	149 (93.1)	151 (92.6)	300 (92.9)	-0.5	(-6.4, 5.4)
COVID-19	42 (26.3)	48 (29.4)	90 (27.9)	3.2	(-6.6, 12.9)
Headache	28 (17.5)	40 (24.5)	68 (21.1)	7.0	(-1.9, 15.9)
Nausea	19 (11.9)	23 (14.1)	42 (13.0)	2.2	(-5.2, 9.7)
Diarrhoea	16 (10.0)	25 (15.3)	41 (12.7)	5.3	(-2.0, 12.8)
Epistaxis	3 (1.9)	36 (22.1)	39 (12.1)	20.2	(13.9, 27.4)
Fatigue	16 (10.0)	23 (14.1)	39 (12.1)	4.1	(-3.1, 11.4)
Dizziness	10 (6.3)	24 (14.7)	34 (10.5)	8.5	(1.9, 15.5)
Telangiectasia	7 (4.4)	27 (16.6)	34 (10.5)	12.2	(5.8, 19.2)
Oedema peripheral	12 (7.5)	14 (8.6)	26 (8.0)	1.1	(-5.1, 7.3)
Nasopharyngitis	13 (8.1)	11 (6.7)	24 (7.4)	-1.4	(-7.5, 4.6)
Dyspnoea	17 (10.6)	5 (3.1)	22 (6.8)	-7.6	(-13.7, -2.2)
Injection site pain	11 (6.9)	11 (6.7)	22 (6.8)	-0.1	(-6.0, 5.7)
Hypokalaemia	6 (3.8)	14 (8.6)	20 (6.2)	4.8	(-0.5, 10.6)
Iron deficiency	9 (5.6)	11 (6.7)	20 (6.2)	1.1	(-4.4, 6.8)
Upper respiratory tract infection	11 (6.9)	9 (5.5)	20 (6.2)	-1.4	(-7.1, 4.2)
Rash	6 (3.8)	13 (8.0)	19 (5.9)	4.2	(-1.0, 9.9)
Thrombocytopenia	3 (1.9)	16 (9.8)	19 (5.9)	7.9	(3.1, 13.7)
Urinary tract infection	6 (3.8)	11 (6.7)	17 (5.3)	3.0	(-2.1, 8.4)
Vomiting	8 (5.0)	8 (4.9)	16 (5.0)	-0.1	(-5.3, 5.0)
Arthralgia	5 (3.1)	9 (5.5)	14 (4.3)	2.4	(-2.3, 7.4)
Flushing	4 (2.5)	10 (6.1)	14 (4.3)	3.6	(-0.9, 8.8)
Pain in extremity	5 (3.1)	9 (5.5)	14 (4.3)	2.4	(-2.3, 7.4)
Vertigo	8 (5.0)	6 (3.7)	14 (4.3)	-1.3	(-6.3, 3.5)
Haemoglobin increased	0 (0.0)	10 (6.1)	10 (3.1)	6.1	(3.4, 10.9)
Nasal congestion	0 (0.0)	10 (6.1)	10 (3.1)	6.1	(3.4, 10.9)

DBPC = double-blind placebo-controlled period; LTDB = long-term double blind period.
N = number of subjects in the treatment group or overall. n = number of subjects in the category. Percentages are calculated as (n/N)*100. NR = Not reported (Incidence <4 in both treatment groups).
For the Sotatercept vs. Placebo comparison, the 95% CI was not provided when the incidence is <4 in both treatment groups.
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 25.0.

Pool A

Overall, incidences of TEAEs in Pool A were generally consistent with those in the DBPC Period of STELLAR. In Pool A, incidences of TEAEs (by PT) were generally similar in the overall sotatercept and overall placebo groups. Frequently reported TEAEs (incidence ≥5%) in the overall sotatercept group that occurred more commonly (incidence ≥2.0 percentage points) than in the overall placebo group in Pool A, respectively, were

- headache (47 [19.8%] vs 30 [15.6%]);
- diarrhea (33 [13.9%] vs 17 [8.9%]);
- epistaxis (29 [12.2%] vs 4 [2.1%]);
- dizziness (26 [11.0%] vs 6 [3.1%]);
- telangiectasia (17 [7.2%] vs 5 [2.6%]);
- hypokalemia (17 [7.2%] vs 9 [4.7%]);
- haemoglobin increased (15 [6.3%] vs 0 [0.0%]);
- thrombocytopenia (15 [6.3%] vs 3 [1.6%]); and
- pain in extremity (13 [5.5%] vs 6 [3.1%])

Pool B

In the SUR1 Cumulative dataset, the most frequently reported TEAEs (incidence ≥15%) in the overall sotatercept group were epistaxis, COVID-19, headache, telangiectasia, and diarrhea. In the SUR2 Cumulative dataset, the same TEAEs were most commonly reported in the overall sotatercept group; each occurred in >20% of participants.

Table 61. Common TEAE (incidence ≥15%) from Pool B

	Overall Sotatercept [1]		
Preferred Term	SUR1 Cumulative (N=431) n (%)	SUR2 (N=400) n (%)	SUR2 Cumulative (N=431) n (%)
Epistaxis	81 (18.8)	74 (18.5)	139 (32.3)
Covid-19	102 (23.7)	43 (10.8)	133 (30.9)
Headache	96 (22.3)	52 (13.0)	131 (30.4)
Telangiectasia	73 (16.9)	56 (14.0)	120 (27.8)
Diarrhoea	72 (16.7)	26 (6.5)	89 (20.6)
Nausea	60 (13.9)	26 (6.5)	82 (19.0)
Fatigue	60 (13.9)	28 (7.0)	79 (18.3)
Dizziness	56 (13.0)	31 (7.8)	78 (18.1)
Oedema Peripheral	58 (13.5)	22 (5.5)	76 (17.6)
Nasopharyngitis	46 (10.7)	34 (8.5)	71 (16.5)
Haemoglobin Increased	37 (8.6)	30 (7.5)	62 (14.4)
Upper Respiratory Tract Infection	38 (8.8)	32 (8.0)	60 (13.9)
Arthralgia	44 (10.2)	16 (4.0)	55 (12.8)
Hypokalaemia	35 (8.1)	28 (7.0)	55 (12.8)
Thrombocytopenia	36 (8.4)	18 (4.5)	51 (11.8)
Iron Deficiency	34 (7.9)	22 (5.5)	50 (11.6)
Urinary Tract Infection	33 (7.7)	23 (5.8)	49 (11.4)
Dyspnoea	29 (6.7)	26 (6.5)	49 (11.4)
Pain In Extremity	37 (8.6)	15 (3.8)	46 (10.7)
Vomiting	34 (7.9)	16 (4.0)	46 (10.7)
Respiratory Tract Infection	25 (5.8)	28 (7.0)	43 (10.0)
Sinusitis	24 (5.6)	23 (5.8)	43 (10.0)
Cough	27 (6.3)	20 (5.0)	42 (9.7)

Adverse drug reactions

The approach to determining ADRs for inclusion in the labelling was as follows:

- Candidate ADRs were identified from STELLAR as PTs, regardless of relationship, with a rate of occurrence in the sotatercept group greater than 5% and greater than placebo, where the lower bound of the 95% confidence intervals around the point estimates excluded 0. Epistaxis, dizziness, and telangiectasia were identified as ADRs using this approach. Based on the magnitudes of the point estimates and the Pool A data, the Applicant acknowledges the request to add Headache and Diarrhoea, noting that for both, the EAIR in Pool B are lower than the respective placebo EAIR.
- Additional candidate ADRs were identified from STELLAR AEOI where the rate of occurrence of PTs regardless of relationship, grouped by SMQ, was greater in sotatercept than placebo, and where the lower bound of the 95% confidence intervals around the point estimates excluded 0. This approach added thrombocytopenia, increased hemoglobin, and increased blood pressure, events with a plausible relationship to sotatercept and supported by laboratory and vital sign data.
- Provisional ADRs thus identified were then compared against AE data from Pool A and Pool B to determine whether additional terms should be added. For Pool B, given the wide disparity in duration of exposure to sotatercept among participants, exposure-adjusted incidence rates assisted evaluation.
- Events with low rates of occurrence were reviewed, but none were included to avoid incorporating events where imbalances may have arisen stochastically, due to low numbers.
- For inclusion of an ADR into the product information, consideration was also given to the biologic plausibility and potential for an event to be nonspecific (i.e. nasal congestion).

The Applicant's approach to determining ADRs was based on AE, regardless of relationship, taking into consideration the well-balanced arms in STELLAR, the relatively low numbers in the treatment arms, and the desire to avoid the introduction of subjectivity from investigator causality assessment.

STELLAR

The overall incidence of TEAEs considered related to study intervention by the investigator was higher in the sotatercept group than in the placebo group. TEAEs considered related to study intervention with a higher incidence in the sotatercept group than in the placebo group, respectively, were telangiectasia (16.6% vs 4.4%), epistaxis (22.1% vs 1.9%), haemoglobin increased (8.6% vs 0.6%), and injection site erythema (3.1% vs 0.6%).

Pool A

Results for TEAEs considered related to study intervention by the investigator in Pool A were generally consistent with those in the DBPC Period of STELLAR. In Pool A, TEAEs considered related to study intervention by the investigator occurred more commonly in the overall sotatercept group (104 [43.9%]) than in the overall placebo group (50 [26.0%]). Frequently reported TEAEs (incidence ≥5%) in the overall sotatercept group that occurred more commonly (incidence ≥2.0 percentage points) than in the overall placebo group, respectively, were headache (47 [19.8%] vs 30 [15.6%]), telangiectasia (17 [7.2%] vs 5 [2.6%]), diarrhea (33 [13.9%] vs 17 [8.9%]), and haemoglobin increased (18 [7.6%] vs 0 [0.0%]). TEAEs considered related to study intervention by the investigator that also occurred more commonly in the overall sotatercept group than in the overall placebo group, respectively, were epistaxis (29 [12.2%] vs 4 [2.1%]) and thrombocytopenia (17 [7.2%] vs 4 [2.1%]).

Pool B

Results for TEAEs considered related to study intervention by the investigator in the overall sotatercept group were generally consistent in the different cumulative pool B datasets. In all of these datasets, the most commonly reported intervention related TEAEs (incidence ≥5%) were thrombocytopenia, haemoglobin increased, dizziness, diarrhoea, headache, epistaxis, and telangiectasia. Results in the SUR dataset were generally consistent with those in the 2 other datasets.

Table 62. ADRs in STELLAR, Pool A, and Cumulative Pool B

Adverse reaction	STELLAR Final CSR			Pool A 24-week data		Pool B Data cuts		
	Placebo N=160 n (%)	Sotatercept N=163 n (%)	Point Estimate (95% CI)	Pool A placebo N=192 n (%) EAIR (95% CI)	Pool A sotatercept N=237 n (%) EAIR (95% CI)	Pool B 26-AUG-2022 N=321 n (%) EAIR (95% CI)	Pool B 06-DEC-2022 N=431 n (%)	Pool B 08-NOV-2023 N=431 n (%) EAIR (95% CI)
Headache	28 (17.5%)	40 (24.5%)	7.0 (-1.9, 15.9)	30 (15.6%) 38.3 (25.8, 54.7)	47 (19.8%) 50.1 (36.8, 66.6)	81 (25.2%) 22.3 (17.7, 27.8)	96 (22.3%)	131 (30.4%) 18.9 (15.8, 22.4)
Epistaxis	3 (1.9%)	36 (22.1%)	20.2 (13.9, 27.4)	4 (2.1%) 4.6 (1.3, 11.9)	29 (12.2%) 28.4 (19.0, 40.7)	65 (20.2%) 16.4 (12.7, 20.9)	81 (18.8%)	139 (32.3%) 19.2 16.1, 22.7
Dizziness	10 (6.3%)	24 (14.7%)	8.5 (1.9, 15.5)	6 (3.1%) 7.0 (2.6, 15.3)	26 (11.0%) 25.5 (16.6, 37.3)	52 (16.2%) 13.1 (9.8, 17.2)	56 (13.0%)	78 (18.1%) 10.0 (7.9, 12.5)
Diarrhoea	16 (10.0%)	25 (15.3%)	5.3 (-2.0, 12.8)	17 (8.9%) 20.5 (11.9, 32.8)	33 (13.9%) 33.4 (23.0, 46.9)	66 (20.6%) 17.8 (13.8, 22.7)	72 (16.7%)	89 (20.6%) 12.1 (9.7, 14.9)
Telangiectasia	7 (4.4%)	27 (16.6%)	12.2 (5.8, 19.2)	5 (2.6%) 5.8 (1.9, 13.4)	17 (7.2%) 16.1 (9.4, 25.8)	55 (17.1%) 12.9 (9.7, 16.8)	73 (16.9%)	120 (27.8%) 15.6 (13.0, 18.7)
Rash†	7 (4.4%)	20 (12.2%)						
Thrombocytopenia*	5 (3.1%)	17 (10.4%)	7.3 (2.0, 13.3)	4 (2.1%) 3.5 (0.7, 10.1)	17 (7.2%) 14.3 (8.0, 23.5)	33 (10.3%) 7.6 (5.2, 10.7)	38 (8.8%) 7.3 (5.2, 10.1)	55 (12.8%) 6.6 (4.9, 8.5)
Increased hemoglobin*	1 (0.6%)	14 (8.6%)	8.0 (4.0, 13.4)	0 0 (NE, NE)	18 (7.6%) 17.4 (10.3, 27.5)	47 (14.6%) 11.6 (8.5, 15.5)	57 (13.2%) 11.8 (8.9, 15.3)	92 (21.3%) 11.9 (9.6, 14.6)

Adverse reaction	STELLAR Final CSR			Pool A 24-week data		Pool B Data cuts		
	Placebo N=160 n (%)	Sotatercept N=163 n (%)	Point Estimate (95% CI)	Pool A placebo N=192 n (%) EAIR (95% CI)	Pool A sotatercept N=237 n (%) EAIR (95% CI)	Pool B 26-AUG-2022 N=321 n (%) EAIR (95% CI)	Pool B 06-DEC-2022 N=431 n (%)	Pool B 08-NOV-2023 N=431 n (%) EAIR (95% CI)
Increased blood pressure*	1 (0.6%)	7 (4.3%)	3.7 (0.4, 8.1)	3 (1.6%)	8 (3.4%)		20 (4.6%) 3.7 (1.7, 4.8)	26 (6.0%) 3.0 (1.2, 3.2)
Erythema†	1 (0.6%)	5 (3.1%)						

*Composites of PT or SMQ. Increased haemoglobin: Haemoglobin increased; Haematocrit increased; Polycythaemia. Thrombocytopenia: SMQ Haematopoietic thrombocytopenia (narrow). Increased blood pressure: SMQ Hypertension (broad). †MedDRA

AE of interest (AEOI)

AEOI of FSH suppression (3 (1.8%) vs 2 (1.3%)), embryo-fetal toxicity (2 (1.2%) vs 3 (1.9%)), thromboembolic events (9 (5.5%) vs 6 (3.8%)), renal toxicity (6 (3.7%) vs 7 (4.4%)), hepatic toxicity (7 (4.3%) vs 7 (4.4%)), cardiac events (5 (3.1%) vs 11 (6.9%)), leukopenia (1 (0.6%) vs 6 (3.8%)), and neutropenia (1 (0.6%) vs 3 (1.9%)) did not occur more often in the sotatercept arm as compared to the placebo arm, and therefore did not emerge as safety concerns for sotatercept. Imbalances in immunogenicity-related TEAEs were mostly accounted for by rashes, dermatitis, and other nonserious cutaneous events. The occurrences of drug hypersensitivity were attributed to other medications, not study intervention, and immunogenicity-related TEAEs considered related to study intervention by the investigator were low (≤3.7% in both groups). Therefore, immunogenicity related TEAE did not emerge as a safety concern for sotatercept. No participants met the Hy's Law criteria for drug-induced liver injury. The other AE of (special) interest with imbalances between the treatment arms are described below.

Table 63. Summary table of AE of interest in STELLAR

AESI/AEOI Preferred Term	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)	Sotatercept vs. Placebo Comparison: Point Estimate (%)	Sotatercept vs. Placebo Comparison: 95% CI [1]
Subjects with events	77 (48.1)	108 (66.3)	185 (57.3)	18.1	(7.4, 28.5)
AESI:					
Telangiectasia	7 (4.4)	27 (16.6)	34 (10.5)	12.2	(5.8, 19.2)
Telangiectasia	7 (4.4)	27 (16.6)	34 (10.5)	12.2	(5.8, 19.2)
AEOI:					
Bleeding events	25 (15.6)	57 (35.0)	82 (25.4)	19.3	(10.0, 28.5)
Epistaxis	3 (1.9)	36 (22.1)	39 (12.1)	20.2	(13.9, 27.4)
Anaemia	7 (4.4)	3 (1.8)	10 (3.1)	-2.5	(-7.2, 1.5)
Gingival bleeding	1 (0.6)	7 (4.3)	8 (2.5)	3.7	(0.4, 8.1)
Haemoptysis	3 (1.9)	4 (2.5)	7 (2.2)	0.6	(-3.2, 4.5)
Cardiac events	11 (6.9)	5 (3.1)	16 (5.0)	-3.8	(-9.2, 1.0)
Angina pectoris	5 (3.1)	1 (0.6)	6 (1.9)	-2.5	(-6.6, 0.6)
Right ventricular failure	3 (1.9)	0 (0.0)	3 (0.9)	-1.9	NR
Embryo-fetal toxicity	3 (1.9)	2 (1.2)	5 (1.5)	-0.6	NR
Abortion	1 (0.6)	0 (0.0)	1 (0.3)	-0.6	NR
Hepatic toxicity	7 (4.4)	7 (4.3)	14 (4.3)	-0.1	(-5.0, 4.8)
Aspartate aminotransferase increased	2 (1.3)	4 (2.5)	6 (1.9)	1.2	(-2.3, 5.1)
Alanine aminotransferase increased	2 (1.3)	3 (1.8)	5 (1.5)	0.6	NR
Immunogenicity	18 (11.3)	36 (22.1)	54 (16.7)	10.8	(2.7, 19.0)
Rash	6 (3.8)	13 (8.0)	19 (5.9)	4.2	(-1.0, 9.9)
Dermatitis contact	1 (0.6)	5 (3.1)	6 (1.9)	2.4	(-0.7, 6.4)
Drug hypersensitivity	2 (1.3)	4 (2.5)	6 (1.9)	1.2	(-2.3, 5.1)
Urticaria	2 (1.3)	3 (1.8)	5 (1.5)	0.6	NR
Increased blood pressure	1 (0.6)	7 (4.3)	8 (2.5)	3.7	(0.4, 8.1)
Hypertension	1 (0.6)	5 (3.1)	6 (1.9)	2.4	(-0.7, 6.4)
Blood pressure diastolic increased	0 (0.0)	1 (0.6)	1 (0.3)	0.6	NR
Blood pressure increased	0 (0.0)	1 (0.6)	1 (0.3)	0.6	NR
Increased hemoglobin (increased hematocrit, increased RBC count)	1 (0.6)	14 (8.6)	15 (4.6)	8.0	(4.0, 13.4)
Haemoglobin increased	0 (0.0)	10 (6.1)	10 (3.1)	6.1	(3.4, 10.9)
Polycythaemia	0 (0.0)	4 (2.5)	4 (1.2)	2.5	(0.1, 6.1)
Haematocrit increased	1 (0.6)	0 (0.0)	1 (0.3)	-0.6	NR
Leukopenia	6 (3.8)	1 (0.6)	7 (2.2)	-3.1	(-7.4, 0.1)
Neutropenia	3 (1.9)	1 (0.6)	4 (1.2)	-1.3	NR
Leukopenia	2 (1.3)	0 (0.0)	2 (0.6)	-1.3	NR
Lymphopenia	1 (0.6)	0 (0.0)	1 (0.3)	-0.6	NR
Neutropenia (including febrile neutropenia)	3 (1.9)	1 (0.6)	4 (1.2)	-1.3	NR
Neutropenia	3 (1.9)	1 (0.6)	4 (1.2)	-1.3	NR
Renal toxicity	7 (4.4)	6 (3.7)	13 (4.0)	-0.7	(-5.5, 4.0)
Acute kidney injury	4 (2.5)	3 (1.8)	7 (2.2)	-0.7	(-4.6, 3.1)
Renal impairment	2 (1.3)	2 (1.2)	4 (1.2)	-0.0	NR
Chronic kidney disease	0 (0.0)	1 (0.6)	1 (0.3)	0.6	NR
Renal failure	1 (0.6)	0 (0.0)	1 (0.3)	-0.6	NR
Suppression of FSH	2 (1.3)	3 (1.8)	5 (1.5)	0.6	NR
Amenorrhoea	0 (0.0)	2 (1.2)	2 (0.6)	1.2	NR
Menstruation irregular	2 (1.3)	0 (0.0)	2 (0.6)	-1.3	NR
Menstruation delayed	0 (0.0)	1 (0.6)	1 (0.3)	0.6	NR
Thrombocytopenia	5 (3.1)	17 (10.4)	22 (6.8)	7.3	(2.0, 13.3)
Thrombocytopenia	3 (1.9)	16 (9.8)	19 (5.9)	7.9	(3.1, 13.7)
Platelet count decreased	2 (1.3)	1 (0.6)	3 (0.9)	-0.6	NR
Thromboembolic events	6 (3.8)	9 (5.5)	15 (4.6)	1.8	(-3.1, 6.9)
Pulmonary embolism	1 (0.6)	2 (1.2)	3 (0.9)	0.6	NR
Superficial vein thrombosis	0 (0.0)	2 (1.2)	2 (0.6)	1.2	NR

Telangiectasia (AESI)

STELLAR

In STELLAR, the incidence of the AESI telangiectasia was higher in the sotatercept group than in the placebo group in the cumulative dataset (27 (16.6% vs 7 (4.4%)). Most events were considered by the investigator to be related to study intervention. In the sotatercept group, none of these events were serious or severe, and only 1 led to discontinuation of study intervention. This participant was also reported to have discontinued study intervention due to epistaxis. No participant with the AESI telangiectasia was reported with a serious bleeding event. The risk of first onset of telangiectasia in the sotatercept group was approximately 3.6 times higher than the risk in the placebo group (HR 3.617; 95% CI, 1.573, 8.316). Kaplan-Meier curves for time to first onset of telangiectasia showed an early separation (approximately Week 10) of the sotatercept and placebo curves that continued for the remainder of the study.

Pool A

In Pool A, the number of participants with the AESI telangiectasia (PT telangiectasia) and the median onset of this event was the same as in STELLAR, since no events were reported in the initial 24-week treatment period of PULSAR.

Pool B

In the SUR2 cumulative Pool B dataset, the AESI telangiectasia was reported in 120 (27.8%) participants. No events of the AESI telangiectasia were serious, and 2 led to discontinuation of study intervention. The TAR-EAIRs for this event were similar in both SUR1 and SUR 2 cumulative datasets, suggesting that the risk did not increase over time. Of the 120 participants with the AESI telangiectasia, 63 (52.5%) also had a TEAE of epistaxis, and 5 (4.2%) experienced a serious bleeding event.

Haemoglobin increase

STELLAR

In STELLAR, the incidence of the AEOI increased haemoglobin (PTs reported: haemoglobin increased, polycythemia, hematocrit increased) in the cumulative dataset was higher in the sotatercept group than in the placebo group (14 (8.6% vs 1 (0.6%)). None of these events were serious or severe, and none led to discontinuation of study intervention. Haemoglobin increase led to the modification (interruption) of study intervention, per protocol, in 5 participants. There were no increases in haemoglobin greater than 4 g/dL above the ULN (CTCAE Grade 3 as predefined) and no participant required phlebotomy. Mean increases from baseline in haemoglobin were observed in the sotatercept group compared with no notable changes from baseline in the placebo group over time.

Pool A

In Pool A, results for the AEOI increased haemoglobin (PTs reported: haemoglobin increased, polycythemia, and RBC count increased) were consistent with the results in STELLAR (18 (7.6%) vs 0 (0%)).

Pool B

In the SUR2 cumulative Pool B dataset, the AEOI increased haemoglobin in the sotatercept arm was higher than in STELLAR (92 (21.3%)). The TAR-EAIRs for this event were similar in both SUR1 and SUR 2 cumulative datasets, suggesting that the risk did not increase over time. One participant had a serious event of the AEOI increased hemoglobin (red blood cell count increased). Three participants, including the participant with the serious event, had an AEOI increased hemoglobin (hemoglobin increased, polycythemia, red blood cell count increased) that led to discontinuation of study intervention.

Laboratory data on the number of participants in the overall sotatercept group with at least 1 increase >2.0 g/dL in hemoglobin from baseline in the SUR2 (251 [58.2%]) and SUR1 (163 [37.8%]). Cumulative datasets suggest that hemoglobin levels may increase with sotatercept treatment.

Bleeding events

STELLAR

The incidence of the AEOI bleeding events (SMQ Hemorrhages), the most commonly reported AEOI, was higher in the sotatercept group than in the placebo group (57 (35.0%) vs 25 (15.6%)). The most commonly reported bleeding events in the sotatercept group were epistaxis followed by gingival bleeding. Participants with epistaxis, and to a lesser extent gingival bleeding, accounted almost entirely for the imbalance between sotatercept and placebo groups. In the sotatercept group, 1 event of epistaxis was serious and none of the gingival bleeding events were serious or severe. Another participant in the sotatercept group discontinued study intervention due to epistaxis. Among participants with epistaxis treated with sotatercept, telangiectasia was reported nearly twice as frequent relative to all sotatercept treated participants.

Nine participants (7 in the sotatercept group and 2 in the placebo group) experienced serious bleeding events. Several factors predisposing to bleeding were present; most were on both anticoagulants and prostacyclin analogues. Of these 8 participants, 2 were not on prostacyclin analogues and 1 was not on any oral anticoagulants; all 3 were in the sotatercept group. The non-user of anticoagulants had a history of chronic thrombocytopenia. One participant in the sotatercept group died due to a serious intracranial hemorrhage associated with supratherapeutic INR. Two participants in the sotatercept group had serious events of hemoptysis. One event of hemoptysis was considered by the investigator to be related to study intervention and led to the discontinuation of study intervention and withdrawal from the study. No other serious bleeding events were considered by the investigator to be related to study intervention or led to discontinuation of study intervention.

Table 64. Overview of adverse events of interest (AEOI) of bleeding events- Safety Set STELLAR- Cumulative results (DBPC+LTDB)

	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)
Number of subjects with bleeding events	25 (15.6)	57 (35.0)	82 (25.4)
Number of subjects with serious bleeding events	2 (1.3)	7 (4.3)	9 (2.8)
Number of subjects with severe bleeding events	2 (1.3)	5 (3.1)	7 (2.2)
Number of subjects with bleeding events leading to dose delay	0 (0.0)	0 (0.0)	0 (0.0)
Number of subjects with bleeding events leading to dose reduction	0 (0.0)	2 (1.2)	2 (0.6)
Number of subjects with bleeding events leading to treatment discontinuation	0 (0.0)	3 (1.8)	3 (0.9)
Number of subjects with bleeding events leading to study discontinuation	0 (0.0)	2 (1.2)	2 (0.6)
Number of subjects with bleeding events leading to death	0 (0.0)	1 (0.6)	1 (0.3)

Pool A

Results for the AEOI increased bleeding events in Pool A were somewhat lower for the Sotatercept arm, yet comparable for the placebo arm (49 (20.7%) vs 28 (14.6%)).

Pool B

In the SUR2 cumulative Pool B dataset, the AEOI bleeding events were reported for 215 (49.9%) participants in the overall sotatercept group. The TAR-EAIRs for this event were similar in both SUR1

and SUR 2 cumulative datasets, suggesting that the risk did not increase over time. Epistaxis was the most commonly reported bleeding event in the SUR2 (139 [32.3%]). The incidence of serious AEOI bleeding events (30 [7.0%]). Five (1.2%) participants discontinued study intervention because of the AEOI bleeding events. Of these 5 participants, 2 had fatal bleeding events, 1 had hemoptysis, 1 had epistaxis, and 1 had a gastrointestinal hemorrhage.

Gingival bleeding

In STELLAR (through 06-DEC-2022), gingival bleeding was reported in 7 (4.3%) participants in the sotatercept group and 1 (0.6%) participant in the placebo group.

In Pool A, gingival bleeding was reported in 5 (2.1%) participants in the sotatercept group and 1 (0.5%) in the placebo group. Pool A data are included as the duration of exposure to sotatercept is closer to the duration of exposure on placebo, as the data were cut at 24 weeks. In the STELLAR final CSR, the duration of exposure was greater for participants on sotatercept (44.7 weeks) compared with those on placebo (39.0 weeks), favoring the accumulation of more events on sotatercept.

Increased blood pressure

STELLAR

The AEOI of increased blood pressure (preferred terms of hypertension, blood pressure diastolic increased, and blood pressure increased) was more commonly reported in the sotatercept group than in the placebo group (7 (4.3%) vs 1 (0.6%). In the sotatercept group, none of these events were serious or severe, and none led to discontinuation of study intervention. At Week 24 (Visit 9) in the sotatercept group, the mean increase from baseline in systolic blood pressure was 2.2 mmHg and in diastolic blood pressure was 4.9 mmHg. Mean changes from baseline in systolic and diastolic blood pressure in the placebo group were minimal relative to baseline over time.

Pool A

Results for the AEOI increased blood pressure (PTs reported: hypertension, blood pressure increased, labile hypertension, and blood pressure diastolic increased) in Pool A were generally consistent with those in the DBPC Period of STELLAR (8 (3.4% vs 3 (1.6%)).

Pool B

In the SUR2 cumulative Pool B dataset, the AEOI increased blood pressure was reported for 26 (6.0%) participants in the overall sotatercept group. The TAR-EAIRs for this event were similar in both SUR1 and SUR 2 cumulative datasets, suggesting that the risk did not increase over time.

Thrombocytopenia

STELLAR

The AEOI of thrombocytopenia (preferred terms of thrombocytopenia and platelet count decreased) was more commonly reported in the sotatercept group than in the placebo group (17 (10.4%) vs 5 (3.1%)). In the sotatercept group, 1 event of the AEOI thrombocytopenia was serious and another was severe; both events led to the interruption of study intervention. None of the thrombocytopenia events in the sotatercept group led to discontinuation of study intervention. Mean decreases from baseline in platelet counts were observed in the sotatercept group compared with no notable changes from baseline in the placebo group over time. Of the 17 participants treated with sotatercept who developed thrombocytopenia, 2 also had events of epistaxis reported at any time in the study. The platelet counts

in these 2 participants were generally above 100×10^9/L and no temporal associations with epistaxis and thrombocytopenia were apparent. Based on these observations, the imbalance of epistaxis in the sotatercept group does not appear to be explained solely by thrombocytopenia.

Of the 7 participants in the sotatercept group with serious bleeding events, 2 were reported with thrombocytopenia. One participant with a history of chronic thrombocytopenia had multiple bleeding episodes with declines in platelet counts $<25\times10^9$/L (CTCAE Grade 4 as predefined but with no consistent temporal association with bleeding episodes. The other participant had multiple bleeding episodes and consistently low platelet counts (all above 50×10^9/L). Four other participants, in the sotatercept group, had shifts to platelet counts $<50\times10^9$/L (CTCAE Grade 3 as predefined), but no reports of bleeding events. Two of these 4 participants were reported with nonserious adverse events of thrombocytopenia. No participant required platelet replacement therapy.

A total of 33 participants in the STELLAR sotatercept group experienced a platelet count $<100\times10^9$/L. Among these 33 participants, 10 participants (30.3%) experienced a bleeding event after a platelet count $<100\times10^9$/L.

A total of 56 participants in the STELLAR sotatercept group experienced a platelet count decrease from baseline $\geq65\times10^9$/L. Among these 56 participants, 20 participants (35.7%) experienced a bleeding event after reduction in platelet count from baseline $\geq65\times10^9$/L.

Pool A

Results for the AEOI thrombocytopenia (PTs reported: thrombocytopenia and platelet count decreased) in Pool A were generally consistent with those in STELLAR (17 (7.2%) vs 4 (2.1%)).

Pool B

In the SUR2 cumulative Pool B dataset, the AEOI thrombocytopenia was reported for 55 (12.8%) participants in the overall sotatercept group. The TAR-EAIRs for this event were similar in both SUR1 and SUR 2 cumulative datasets, suggesting that the risk did not increase over time. Five participants had a serious event of the AEOI thrombocytopenia of whom 3 required hospitalization. Only 1 participant, who had a moderate event, discontinued study intervention due to the AEOI thrombocytopenia.

Injection site Pruritus

In STELLAR (through 06-DEC-2022), injection site pruritus was reported in 3 (1.8%) participants in the sotatercept group (2 of which [1.2%] had events considered related to study drug) and 0 (0.0%) participants in the placebo group. Causal relationship is included for injection site AEs to distinguish them from events caused by other parenteral medications. In Pool A, injection site pruritus was reported in 4 (1.7%) participants in the sotatercept group (2 of which [0.8%] had events considered related to study drug) and 0 participants in the placebo group.

After 923.7 person-years of exposure across all sotatercept-treated participants in Pool B (N=431) through 08-NOV-2023, the cumulative incidence of injection site pruritus remained similar to that in STELLAR (6 participants [1.4%]); of these, 4 (0.9%) participants had events considered related to sotatercept.

2.7.8.3. Serious adverse event/deaths/other significant events

STELLAR

Severe TEAEs (24 (14.7%) vs 33 (20.6%)), serious TEAEs (40 (24.5%) vs 47 (29.4%)) and serious TEAEs leading to treatment discontinuation (4 (2.5%) vs 9 (5.6%)) occurred less commonly in the

sotatercept group than in the placebo group. The number of serious TEAEs related to treatment was comparable between the sotatercept and placebo group (3 (1.8%) vs 2 (1.3%)).

No notable pattern of serious TEAEs was observed in the sotatercept group relative to the placebo group. The serious TEAE of pneumonia was reported in 3 participants in the sotatercept group; no other serious TEAEs were reported in >2 participants in this group. One event each of fall, hemoptysis and sarcoidosis were the only serious TEAEs in the sotatercept group considered related to study intervention by the investigator, of which hemoptysis and sarcoidosis were the only serious events in the sotatercept group that led to discontinuation of study intervention and study withdrawal.

Serious TEAEs associated with PAH disease progression (e.g. dyspnea, right ventricular failure, cardiac failure, cardiac failure acute, cardiogenic shock, fluid retention, and hypervolemia) occurred more commonly in the placebo group than in the sotatercept group. Nine participants in the placebo group discontinued study intervention due to serious TEAEs.

Pool A

In Pool A, serious TEAEs occurred less commonly in the overall sotatercept group (35 [14.8%]) than in the overall placebo group (39 [20.3%]).

Pool B

In Pool B, the number of serious TEAE was 107 (40.1%) and the number of serious TEAEs related to treatment was 20 (4.6%). In the SUR2 cumulative dataset, 3 participants had serious TEAEs of thrombocytopenia that were considered related to study intervention by the investigator; no other serious TEAEs considered related to study intervention by the investigator were reported in >1 participant.

Deaths

STELLAR

Overall, 2 deaths were reported in the sotatercept group compared with 7 in the placebo group. No deaths were considered causally related to sotatercept treatment.

Table 65. Treatment-emergent Adverse Events Leading to Death by System Organ Class and Preferred Term Safety Set STELLAR Cumulative Results

	Placebo			Sotatercept		
System Organ Class Preferred Term	Application (N=160) n (%)	SUR (N=117) n (%)	Cumulative (N=160) n (%)	Application (N=163) n (%)	SUR (N=152) n (%)	Cumulative (N=163) n (%)
Subjects with events	7 (4.4)	0 (0.0)	7 (4.4)	2 (1.2)	0 (0.0)	2 (1.2)
Cardiac disorders	4 (2.5)	0 (0.0)	4 (2.5)	1 (0.6)	0 (0.0)	1 (0.6)
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)
Cardiac arrest	2 (1.3)	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiogenic shock	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Right ventricular failure	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	2 (1.3)	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 pneumonia	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)
Haemorrhage intracranial	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary arterial hypertension	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)

DBPC = double-blind placebo-controlled period; LTDB = long-term double-blind period.
N = number of subjects in the treatment group or overall. n = number of subjects in the category.
Percentages are calculated as (n/N)*100.
A treatment-emergent adverse event 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 25.0. System organ class were ordered alphabetically and Preferred Terms were ordered by descending frequency based on Sotatercept for the cumulative column.

Pool A

In Pool A, 1 death was reported in the overall sotatercept group (PULSAR) compared with the 6 deaths in the overall placebo group (STELLAR). The death in the overall sotatercept group (cardiac arrest) was not considered related to study intervention by the investigator. No post-treatment deaths occurred.

Table 66. Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term Safety Set Pool A - Sotatercept Treatment for First 6 Months

	STELLAR (MK-7962-003)		PULSAR (MK-7962-001)		Overall	
System Organ Class Preferred Term	Placebo (N=160) n (%)	Sotatercept 0.3mg/kg then 0.7mg/kg (N=163) n (%)	Placebo (N=32) n (%)	Combined Sotatercept (N=74) n (%)	Placebo (N=192) n (%)	Sotatercept (N=237) n (%)
Total number of participant with events	6 (3.8)	0	0	1 (1.4)	6 (3.1)	1 (0.4)
Cardiac Disorders	4 (2.5)	0	0	1 (1.4)	4 (2.1)	1 (0.4)
Cardiac Arrest	2 (1.3)	0	0	1 (1.4)	2 (1.0)	1 (0.4)
Cardiogenic Shock	1 (0.6)	0	0	0	1 (0.5)	0
Right Ventricular Failure	1 (0.6)	0	0	0	1 (0.5)	0
Infections And Infestations	1 (0.6)	0	0	0	1 (0.5)	0
Sepsis	1 (0.6)	0	0	0	1 (0.5)	0
Respiratory, Thoracic And Mediastinal Disorders	1 (0.6)	0	0	0	1 (0.5)	0
Pulmonary Arterial Hypertension	1 (0.6)	0	0	0	1 (0.5)	0

Participants from PULSAR and STELLAR are included.
All participants received standard of care in addition to receiving study drug.
The Combined Sotatercept group from PULSAR includes participants treated with sotatercept during the first 6 months (Placebo-controlled Period).
Adverse Events were coded using MedDRA Version 25.0. System organ class were ordered alphabetically and Preferred Terms were ordered by descending frequency based on overall Sotatercept.

Pool B

A total of 16 (3.7%) deaths were reported in the overall sotatercept group. Six (1.5%) additional deaths were reported in the SUR2 Cumulative dataset compared with the SUR1 Cumulative dataset.

In the SUR2 Cumulative dataset, 2 deaths were due to cardiac arrest, 2 were due to pneumonia, and 3 were due to bleeding events (2 participants with gastrointestinal hemorrhage and 1 with intracranial hemorrhage). No other causes of death occurred in >1 participant in the overall sotatercept group.

Two participants had fatal TEAEs considered related to study intervention by the investigator. One of these 2 participants had a non-serious TEAE of neutropenia that led to a dose reduction from 0.3 mg/kg to 0.1 mg/kg. The participant later died because of worsening PAH, which was considered related to study intervention as a result of the dose reduction. However, given the patient narrative, the fatal event was more likely due to progressive clinical worsening instead of associated with sotatercept. The other participant had a fatal TEAE of adenocarcinoma of the colon that was initially reported as related to study intervention by the investigator but later updated to not related after the data cutoff for this report (08-NOV-2023).

Table 67. Treatment-emergent Adverse Events Leading to Death by System Organ Class and Preferred Term Safety Set

	Overall Sotatercept [1]		
System Organ Class Preferred Term	SUR1 Cumulative (N=431) n (%)	SUR2 (N=400) n (%)	SUR2 Cumulative (N=431) n (%)
Total number of participants with events	10 (2.3)	6 (1.5)	16 (3.7)
Cardiac Disorders	4 (0.9)	0	4 (0.9)
Cardiac Arrest	2 (0.5)	0	2 (0.5)
Acute Myocardial Infarction	1 (0.2)	0	1 (0.2)
Right Ventricular Failure	1 (0.2)	0	1 (0.2)
Gastrointestinal Disorders	1 (0.2)	1 (0.3)	2 (0.5)
Gastrointestinal Haemorrhage	1 (0.2)	1 (0.3)	2 (0.5)
General Disorders And Administration Site Conditions	0	1 (0.3)	1 (0.2)
Multiple Organ Dysfunction Syndrome	0	1 (0.3)	1 (0.2)
Infections And Infestations	3 (0.7)	2 (0.5)	5 (1.2)
Pneumonia	2 (0.5)	0	2 (0.5)
Brain Abscess	1 (0.2)	0	1 (0.2)
Bronchopulmonary Aspergillosis	0	1 (0.3)	1 (0.2)
Sepsis	0	1 (0.3)	1 (0.2)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	0	2 (0.5)	2 (0.5)
Adenocarcinoma Of Colon	0	1 (0.3)	1 (0.2)
Brain Neoplasm Malignant	0	1 (0.3)	1 (0.2)
Nervous System Disorders	1 (0.2)	0	1 (0.2)
Haemorrhage Intracranial	1 (0.2)	0	1 (0.2)
Respiratory, Thoracic And Mediastinal Disorders	1 (0.2)	0	1 (0.2)
Pulmonary Hypertension	1 (0.2)	0	1 (0.2)

N = total number of participants randomized. n = number of participants in the category. Percentages are calculated as (n/N)*100, except where noted.
Note: Column SUR1 Cumulative includes completed studies PULSAR, SPECTRA, STELLAR and the ongoing SOTERIA study with data cut of 6-Dec-2022. Column SUR2 Cumulative includes the same set of completed studies as SUR1 Cumulative but with new data cut from SOTERIA of 8-Nov-2023.
[1] Overall Sotatercept includes all participants who were treated with at least one dose of Sotatercept.
Adverse Events were coded using MedDRA Version 25.0. System organ class were ordered alphabetically and Preferred Terms were ordered by descending frequency based on overall Sotatercept for the SUR2 Cumulative column.

MACE

It is important to note that STELLAR, PULSAR, and SPECTRA studies were not designed as cardiovascular outcomes studies, and as such, MACE were not adjudicated. Analyses of MACE from the individual studies and cumulative sotatercept treatment through 08-NOV-2023 are provided. The

numbers of participants with MACE are low, and the information yielded from the analyses are limited. No new safety signals were identified for sotatercept based on the analyses.

In STELLAR, the number of participants with any MACE composite endpoint in the sotatercept group (2 [1.2%]) was comparable with the placebo group (5 [3.1%]). The TAR-EAIRs for participants from PULSAR and SPECTRA who continued into SOTERIA and have the longest duration of exposure, as well as the overall sotatercept EAIR, also remain low. There is no evidence of increased accrual of MACE to suggest that sotatercept has undesirable cardiovascular effects over time. There have been no non-fatal myocardial infarctions in Pool B through 08-NOV-2023; non-fatal stroke has occurred infrequently. Cardiovascular deaths, anticipated events in the PAH population, are relatively low in number and remain low when the overall sotatercept Pool B EAIRs are compared with the STELLAR placebo EAIRs. Considering the limitations imposed by the low numbers of events, this observation appears to be consistent with a sustained effect of sotatercept to lower mortality.

The Applicant focused on analysis of MACE, rather than MACE+, to avoid the potential of confounding because of the beneficial effects of sotatercept in reducing events associated with cor pulmonale / right heart failure. STELLAR participants followed through 08-NOV-2023 showed similar rates of events in the Cardiac disorders SOC when adjusted for exposure (EAIR of 17.0 /100 PYAR in the sotatercept group and 26.6 /100 PYAR in the placebo group). Of note, EAIRs in the Cardiac disorders SOC by study and for the overall sotatercept group in Pool B, 08-NOV-2023 data cut, show a pattern of lower rates over time.

Thrombotic and thromboembolic events

In STELLAR the numbers of occurrences of thrombotic and thromboembolic events were too low to determine a possible contribution from sotatercept. Furthermore, the nature of events returned by the search strategy include occlusions of devices (central lines) that reflect technical issues with the device, rather than systemic changes that predispose to thrombosis. When SAEs for the AEOI thrombotic events were compared from the 06 DEC-2022 data cut (N=431) with those from the 08-NOV-2023 data cut (N=431), the numbers of participants with events have risen from 9 (2.1%) to 13 (3.0%); however the EAIRs (95% CI) are steady at 1.6 (0.7, 3.1) and 1.4 (0.8, 2.5) per 100 p-y at risk, respectively. The 13 participants with AEOI thrombotic events include 4 participants with the following thrombotic events: device occlusion (2), thrombosis in device, or vascular device occlusion. Epidemiological data on thromboembolic events from a retrospective cohort study conducted by the Applicant show a background rate of 6.6 (6.3, 6.8). In view of the increased risk of thromboembolic events in patients with PAH and corresponding background rates, the Applicant’s position is that the rates of thrombotic and thromboembolic events observed in the PAH pool B data cuts are lower than the background rates in patients with PAH and do not show an increase over time.

2.7.8.4. Laboratory findings

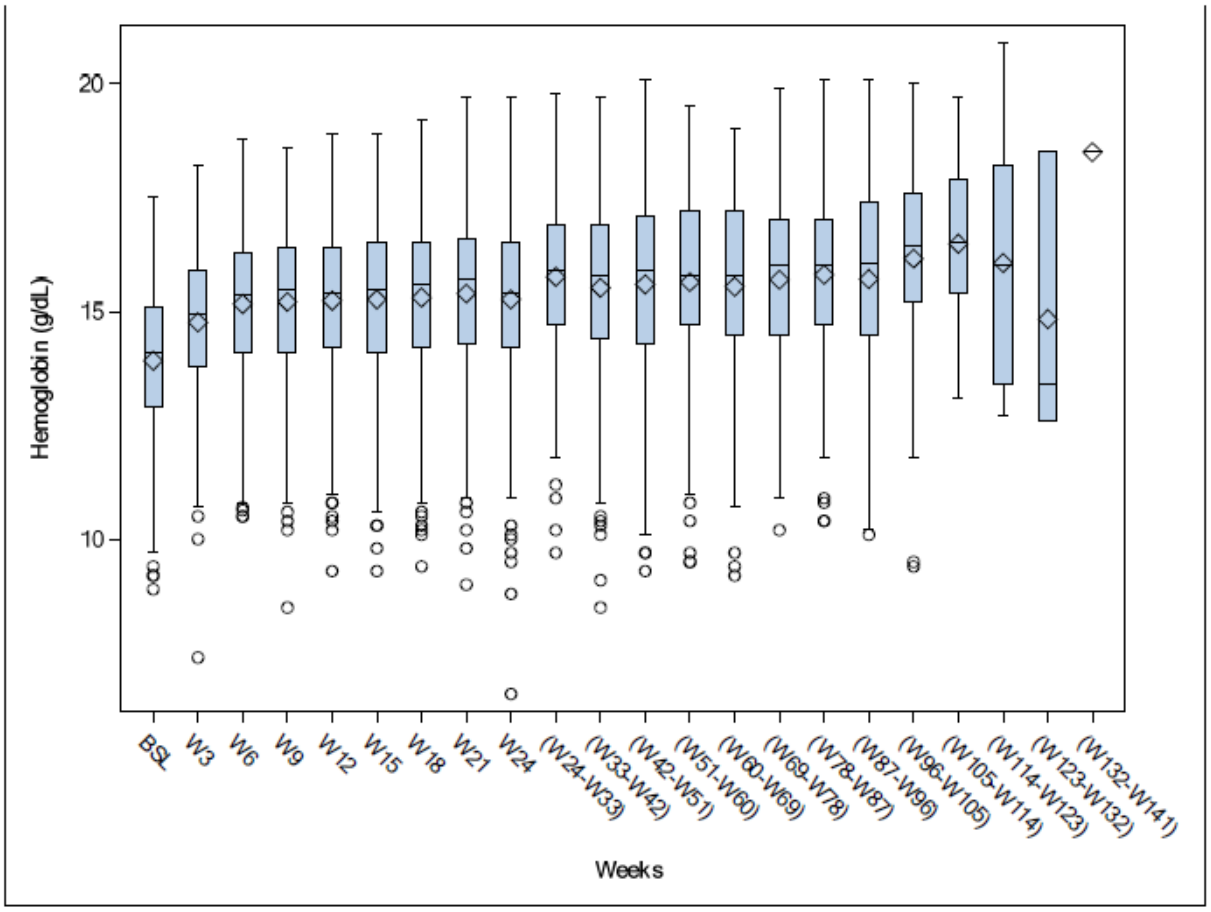
Laboratory findings were presented for STELLAR.

Hematology

Haemoglobin

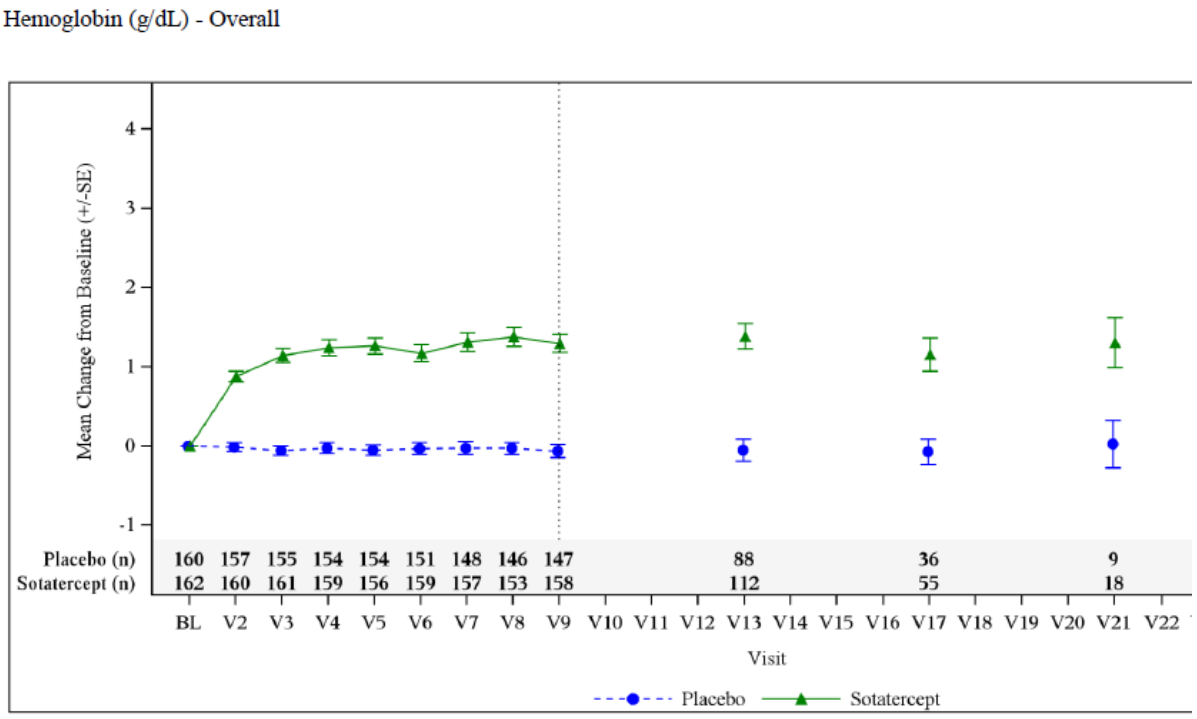
Mean increases from baseline over time in haemoglobin were observed in the sotatercept group. The mean increase from baseline at Week 24 (Visit 9) was 0.81 mmol/L (1.3 g/dL); this mean increase remained consistent at visits after Week 24.

Figure 26. Absolute haemoglobin change from baseline in STELLAR



Note: Only timepoints with at least 2 subjects are shown. Weeks are relative to the first dose of sotatercept. Beyond 24 weeks, the maximum value is shown in the 9-week time interval. Data from participants receiving sotatercept in STELLAR and their participation in SOTERIA is shown. For participants receiving placebo in STELLAR, only data following their rollover to SOTERIA is shown.

Figure 27. Haemoglobin change from baseline in STELLAR



Hematocrit

Mean increases from baseline over time in hematocrit were observed in the sotatercept group. The mean increase from baseline at Week 24 (Visit 9) was 4.20%; this mean increase remained consistent at visits after Week 24.

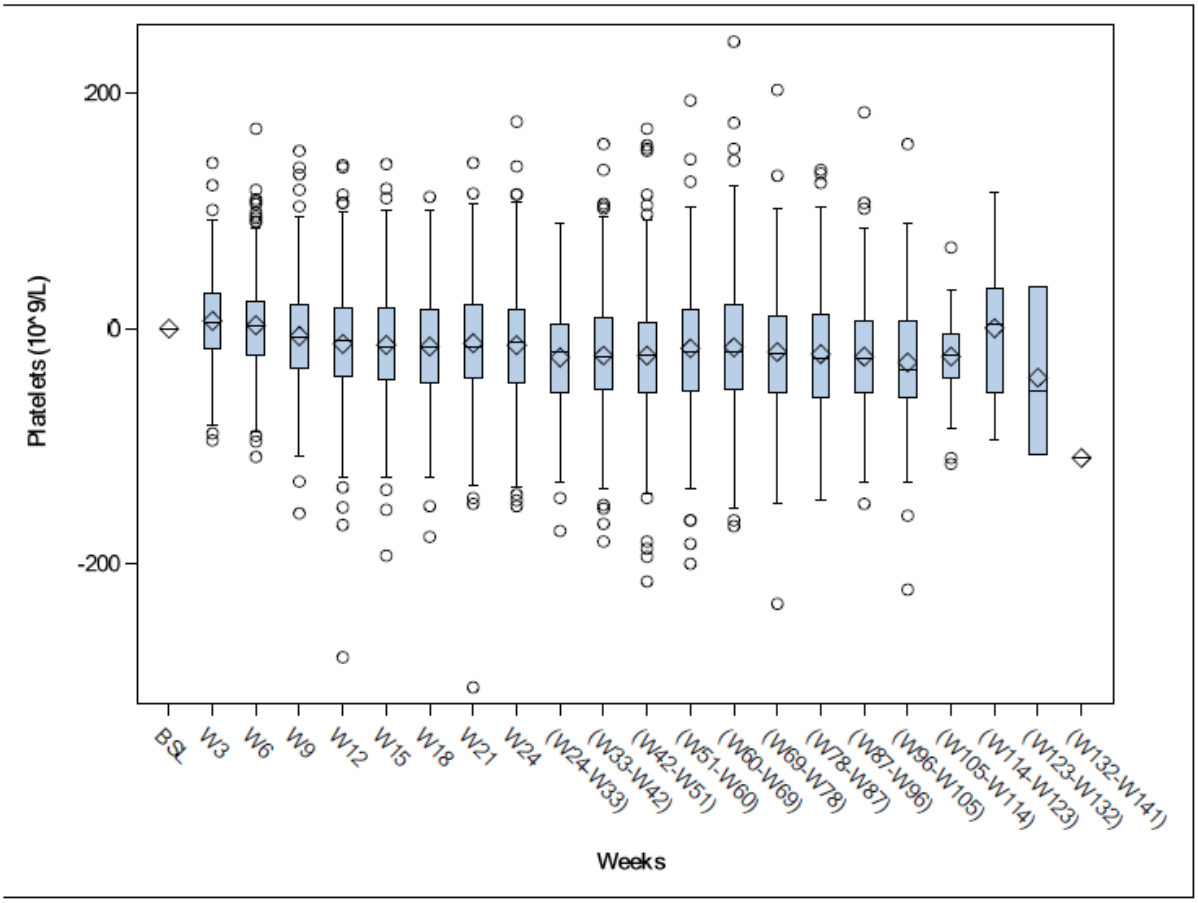
Erythrocytes

Mean increases from baseline over time in erythrocytes were observed in the sotatercept group. The mean increase from baseline at Week 24 (Visit 9) was 0.4×10^{12}/L; this mean increase remained consistent at visits after Week 24.

Platelets

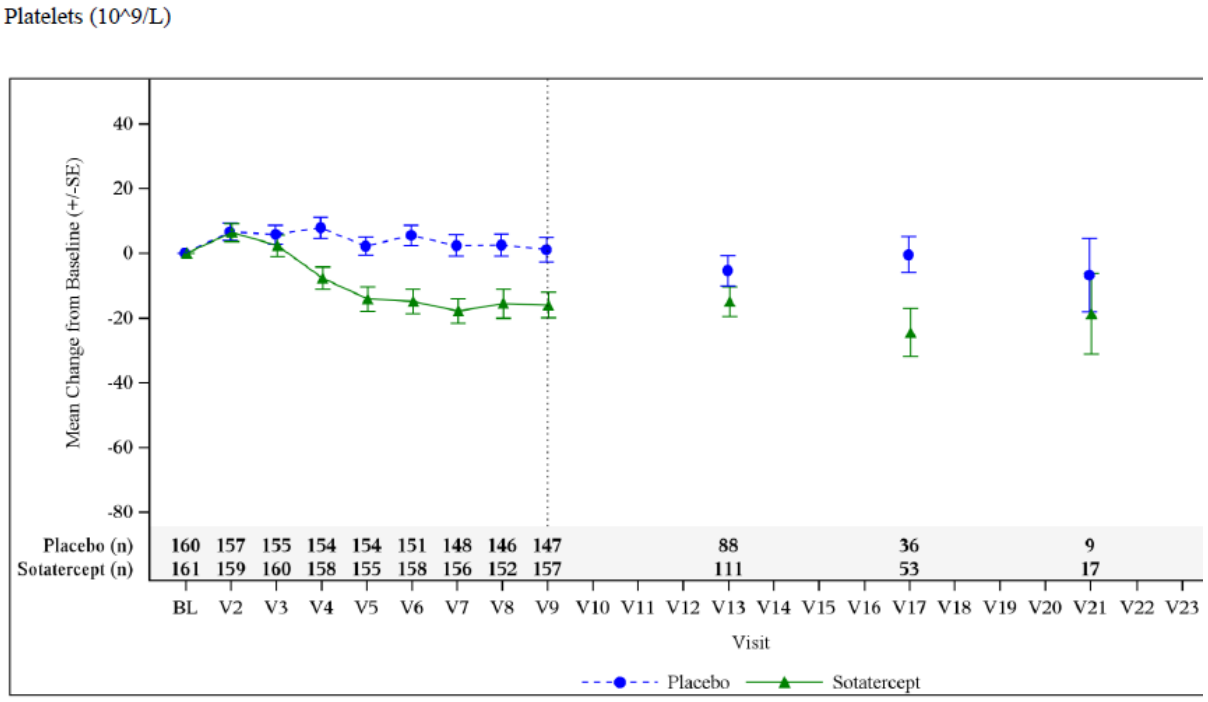
Mean decreases from baseline over time in platelet counts were observed in the sotatercept group. The mean decrease from baseline at Week 24 (Visit 9) was -15.9×10^{9}/L; this mean decrease remained consistent at visits after Week 24.

Figure 28. Platelets absolute change from baseline in STELLAR



Note: Only timepoints with at least 2 subjects are shown. Weeks are relative to the first dose of sotatercept. Beyond 24 weeks, the maximum value is shown in the 9-week time interval. Data from participants receiving sotatercept in STELLAR and their participation in SOTERIA is shown. For participants receiving placebo in STELLAR, only data following their rollover to SOTERIA is shown.

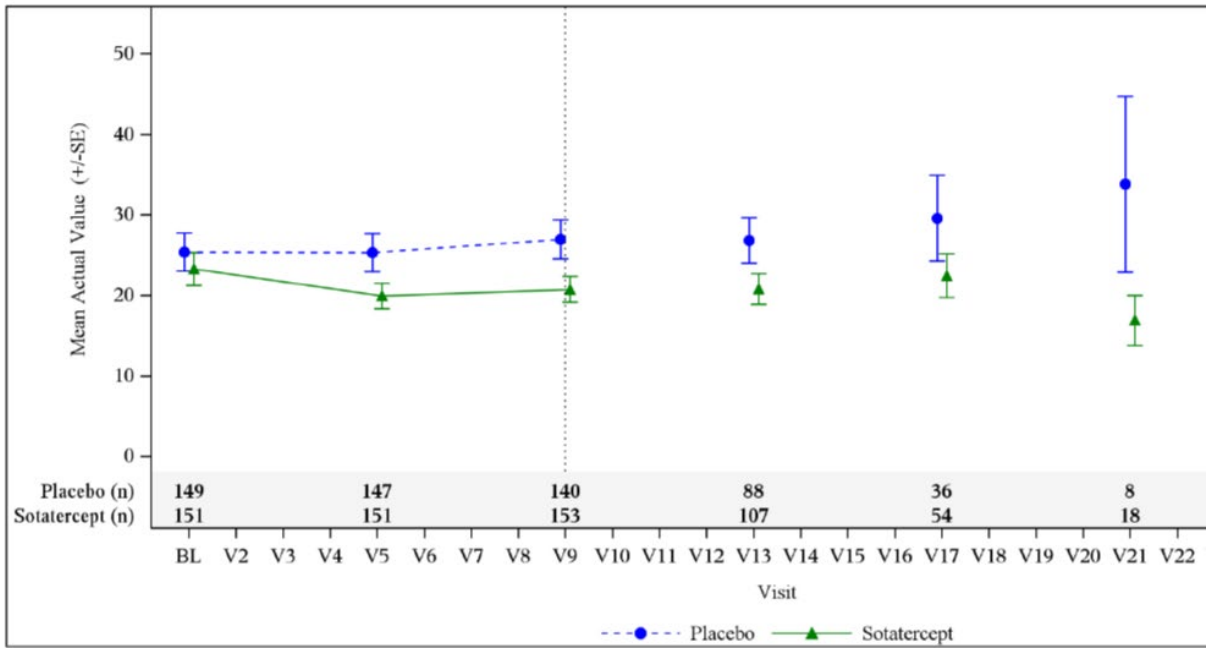
Figure 29. Platelet change (%) from baseline in STELLAR



Chemistry

In STELLAR, there were no notable differences in mean changes from baseline over time in chemistry parameters alkaline phosphatase, ALAT, ASAT, bicarbonate, calcium, chloride, creatinine, glucose, potassium, magnesium, phosphorus, sodium, urea and follicle stimulating hormone. In the sotatercept arm, small decreases were noted for direct and total bilirubin at week 9 (-0.9 and -1.3 umol/L). No participants met the Hy's Law laboratory criteria for drug-induced liver injury.

Figure 30. Follicle Stimulating Hormone (IU/L) changes in STELLAR



Urinalysis

No notable changes from baseline in urinalysis parameters were observed in either group.

Blood pressure

At week 24 (Visit 9) in the sotatercept group, the mean increase from baseline in systolic blood pressure was 2.2 mmHg and in diastolic blood pressure was 4.9 mmHg; similar results were also observed at visits after Week 24. At week 24 the mean changes from baseline in systolic and diastolic blood pressure in the placebo group were -1.6 mmHg and -0.6 mmHg, respectively.

Figure 31. Systolic blood pressure in STELLAR

Systolic Blood Pressure (mmHg)

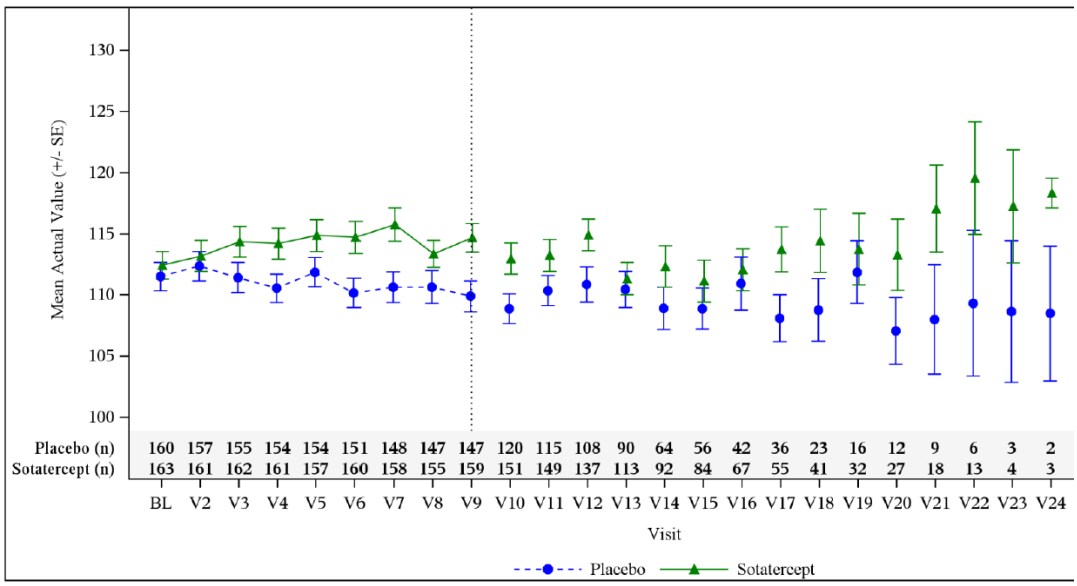
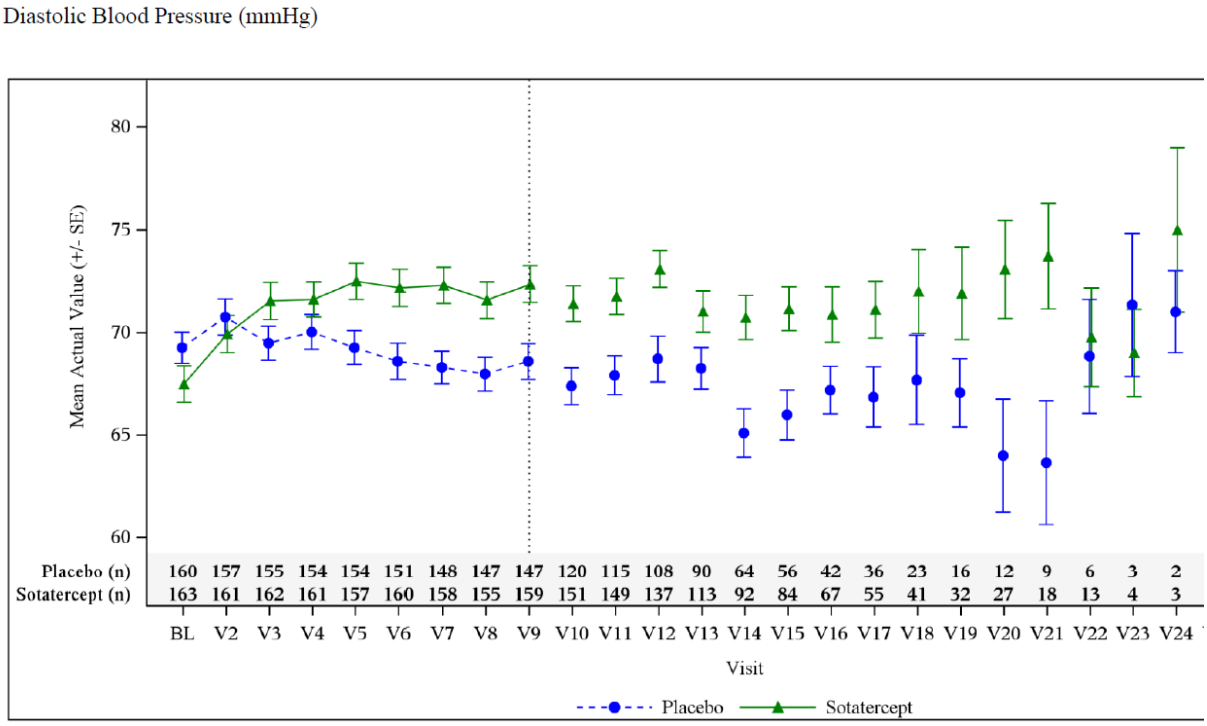


Figure 32. Diastolic blood pressure in STELLAR



Electrocardiogram

There were no notable findings in ECG results. The proportions of participants with abnormal findings were similar in both groups over time. No specific data is provided beyond the differentiation normal and abnormal.

2.7.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.7.8.6. Safety in special populations

Intrinsic factors (age, sex, race, and BMI) were evaluated for sotatercept in Pools A and B only. The safety evaluation for each intrinsic factor included review of TEAEs, serious TEAEs, TEAEs leading to discontinuation of study intervention, AEOIs, the AESI, and selected hematology parameters. Extrinsic factors other than use of other PAH therapy (see section safety related to drug-drug interactions) have not been evaluated.

Age

In Pool A, serious TEAEs occurred less commonly in the <65-year-old subgroup than in ≥65-year-old subgroup in the overall sotatercept group (23 [11.8%] vs 12 [28.6%]) and the overall placebo group (26 [16.1%] vs 13 [41.9%]); however, the relationship of sotatercept compared with placebo was preserved in the ≥65-year-old subgroup.

The AEOI bleeding events occurred less commonly in the <65-year-old subgroup than in ≥65-year-old subgroup in the overall sotatercept group (36 [18.5%] vs 13 [31.0%]) compared with no notable difference between age subgroups in the overall placebo group (23 [14.3%] vs 5 [16.1%]). In the

overall sotatercept group, there was no notable imbalance between age categories for any specific PT, including epistaxis, hemoptysis, and gingival bleeding, although at the PT level, event numbers were few. In Pool B, 371 participants were ≥18 to <65 years of age and 77 were ≥65 years of age. The safety evaluation of sotatercept by age subgroups with longer-term exposure to sotatercept in Pool B were generally consistent with those observed in Pool A.

Table 68. AE categories by Age (STELLAR through 06-DECF-2022)

	Sotatercept				Placebo			
	Age <65 (N= 138)	Age 65-74 (N= 20)	Age 75-84 (N= 5)	Age 85+ (N=0)	Age <65 (N= 131)	Age 65-74 (N=24)	Age 75-84 (N=5)	Age 85+ (N=0)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total AEs	129 (93.5)	19 (95.0)	3 (60.0)	NA	122 (93.1)	22 (91.7)	5 (100.0)	NA
Serious AEs – Total	28 (20.3)	11 (55.0)	1 (20.0)	NA	32 (24.4)	12 (50.0)	3 (60.0)	NA
Fatal	1 (0.7)	1 (5.0)	0 (0.0)	NA	3 (2.3)	3 (12.5)	1 (20.0)	NA
Hospitalization/ prolong existing hospitalization	27 (19.6)	9 (45.0)	1 (20.0)	NA	26 (19.8)	10 (41.7)	3 (60.0)	NA
Life-threatening	1 (0.7)	2 (10.0)	0 (0.0)	NA	2 (1.5)	0 (0.0)	0 (0.0)	NA
Disability/ incapacity	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	NA
Other (medically significant)	2 (1.4)	2 (10.0)	0 (0.0)	NA	9 (6.9)	1 (4.2)	0 (0.0)	NA
AE leading to drop-out[1]	5 (3.6)	1 (5.0)	0 (0.0)	NA	4 (3.1)	5 (20.8)	0 (0.0)	NA
Psychiatric disorders	7 (5.1)	4 (20.0)	2 (40.0)	NA	7 (5.3)	0 (0.0)	1 (20.0)	NA
Nervous system disorders	50 (36.2)	11 (55.0)	1 (20.0)	NA	33 (25.2)	5 (20.8)	2 (40.0)	NA
Accidents and injuries[2]	18 (13.0)	7 (35.0)	2 (40.0)	NA	18 (13.7)	1 (4.2)	0 (0.0)	NA
Cardiac disorders	23 (16.7)	6 (30.0)	1 (20.0)	NA	19 (14.5)	7 (29.2)	4 (80.0)	NA
Vascular disorders	22 (15.9)	5 (25.0)	0 (0.0)	NA	11 (8.4)	3 (12.5)	2 (40.0)	NA
Cerebrovascular disorders	1 (0.7)	1 (5.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	NA
Infections and infestations	91 (65.9)	11 (55.0)	3 (60.0)	NA	75 (57.3)	12 (50.0)	2 (40.0)	NA

	Sotatercept				Placebo			
	Age <65 (N= 138)	Age 65-74 (N= 20)	Age 75-84 (N= 5)	Age 85+ (N=0)	Age <65 (N= 131)	Age 65-74 (N=24)	Age 75-84 (N=5)	Age 85+ (N=0)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Anticholinergic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	NA
Quality of life decreased	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	NA
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[3]	24 (17.4)	9 (45.0)	3 (60.0)	NA	23 (17.6)	1 (4.2)	2 (40.0	NA

Sex

In Pool A, 348 participants were female and 81 were male. No notable findings were observed in the safety evaluation of sotatercept by sex. In Pool B, 363 participants were female and 85 were male. The safety evaluation of sotatercept by sex subgroups with longer-term exposure to sotatercept in Pool B were generally consistent with those observed in Pool A. In Pool B, 363 participants were female and 85 were male. The safety evaluation of sotatercept by sex subgroups with longer-term exposure to sotatercept in Pool B were generally consistent with those observed in Pool A.

Race

In Pool A, 386 participants were White and 35 were Non-White. The disproportionate numbers of participants within each race category limit the interpretation of results for these subgroups. In Pool B, 401 participants were White and 39 were Non-White. The disproportionate numbers of participants within each race category limit the interpretation of results for these subgroups.

BMI

In Pool A:

- 15 participants had a BMI <18.5 kg/m^2;
- 186 had a BMI of 18.5 to <25 kg/m^2;
- 129 had a BMI of 25 to <30 kg/m^2;
- 86 had a BMI of 30 to <40 kg/m^2; and
- 13 had a BMI of ≥40 kg/m^2

Disproportionate numbers of participants within the lowest (<18.5 kg/m^2) and highest (≥40 kg/m^2) BMI subgroups limit the interpretation of results for these subgroups. No notable findings were observed in the safety evaluation of sotatercept in the other BMI subgroups. Similar findings were found in Pool B.

Pregnancy

There are no available data on sotatercept use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. However, based on animal embryofetal toxicity studies, sotatercept may cause post-implantation loss or fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

There are no data on the presence of sotatercept in human milk, the effects on the breastfed infant, or the effects on milk production. Since it is not known if sotatercept is excreted in breast milk, the use of sotatercept in nursing mothers should be avoided.

At the time of data cut-off, 1 positive pregnancy test, in the placebo group in STELLAR, was reported. Study intervention was discontinued due to the pregnancy.

Overdose

There is no specific experience in the management of sotatercept overdose.

In P010, at the maximum dose level of sotatercept studied (1.0 mg/kg, n=8), an SAE of persistent and progressive hypertension in conjunction with elevated haemoglobin and hematocrit was reported in 1 participant. The SAE of hypertension resulted in the discontinuation of dosing in all study participants, and further dose escalation was suspended.

There is no specific antidote for overdose with sotatercept. In the event of overdose, increases in haemoglobin/hematocrit and blood pressure should be monitored closely, and supportive care should be provided as indicated.

Special populations

Table below presents the AE overview of the special populations.

Table 69. AE in patients with renal impairment

	Sotatercept				Placebo			
MedDRA Terms	Hepati-cally impaired n (%)	Renally impaired n (%)	Preg-nant n (%)	Other n (%)	Hepati-cally impaired n (%)	Renally impaired n (%)	Preg-nant n (%)	Other n (%)
Total AEs	NA	87 (93.5)	NA	63 (91.3)	NA	93 (92.1)	NA	55 (94.8)
Serious AEs – Total	NA	28 (30.1)	NA	11 (15.9)	NA	35 (34.7)	NA	12 (20.7)
Fatal	NA	2 (2.2)	NA	0 (0.0)	NA	6 (5.9)	NA	1 (1.7)
Hospitalization/ prolong existing hospitalization	NA	25 (26.9)	NA	11 (15.9)	NA	29 (28.7)	NA	10 (17.2)
Life-threatening	NA	1 (1.1)	NA	0 (0.0)	NA	2 (2.0)	NA	0 (0.0)
Disability/ incapacity	NA	0 (0.0)	NA	0 (0.0)	NA	0 (0.0)	NA	0 (0.0)
Other (medically significant)	NA	3 (3.2)	NA	1 (1.4)	NA	7 (6.9)	NA	3 (5.2)

AE leading to drop-out[1]	NA	3 (3.2)	NA	3 (4.3)	NA	8 (7.9)	NA	1 (1.7)

NA=not applicable
1. TEAEs leading to study discontinuation.

2.7.8.7. Immunological events

In STELLAR, 46 (28%) participants tested positive for sotatercept ADAs, which comprised 2 (1.2%) non-treatment emergent positive, 2 (1.2%) treatment boosted positive, and 42 (25.8%) treatment-emergent positive participants. Of these participants, 13 (8.0%) tested positive for neutralizing antibodies. There were no clinically meaningful safety findings attributable to ADA and no serious TEAEs attributable to immunogenicity in participants who were ADA positive.

The ADA response was transient in 56.8% of ADA positive participants and remained undetermined for only 2 (4.5%) participants. The NAb response was transient in 16.7% of participants with NAb positive response.

Table 70. ADA and NAb in STELLAR

Immunogenicity Status – ADA and Nab	Sotatercept (N=163)
ADA Status, n (%)	
Negative	117 (71.8)
Inconclusive	0 (0.0)
Non-treatment emergent positive	2 (1.2)
Positive response to Sotatercept	44 (27.0)
Treatment emergent positive	42 (25.8)
Treatment boosted positive	2 (1.2)
Maximum post dose Titer	
Median (Min, Max)	40 (<20, 2560)
Neutralizing Antibody (NAb) status, n (%)	
NAb positive	13 (8.0)

N = number of subjects in the treatment group. n = number of subjects in the category. Percentages are calculated as (n/N)*100.
Negative: All pre-treatment and post-dose samples were negative in the ADA assay and the drug concentration in the last post-dose sample was equal to or below the respective DTL (20 µg/ml) for the ADA assay.
Inconclusive: All pre-treatment and post-dose samples were negative in the ADA assay and the drug concentration in the last post-dose sample was above the respective DTL (20 µg/ml) for the ADA assay.
Treatment emergent Positive: Pre-treatment sample was negative and at least one post-dose sample was positive in the ADA assay.
Treatment Boosted Positive: Pre-treatment and post-dose samples were both positive in the ADA assay and the titer increased >=-2-fold post-dose.
Non-treatment emergent positive: Pre-treatment sample was positive and post-dose samples were negative in the ADA confirmatory assay or no increase in magnitude (< 2-fold) post-dose.

Table 71. ADA persistency

ADA Persistency [a]	NAb Positive (N=12)	NAb Negative (N=32)	Total (N=44)
Transient, n (%)	2 (16.7)	23 (71.9)	25 (56.8)
Persistent, n (%)	10 (83.3)	7 (21.9)	17 (38.6)
Undetermined, n (%)	0 (0.0)	2 (6.3)	2 (4.5)

DBPC = double-blind placebo-controlled period; LTDB = long-term double-blind period.
N = Total number of evaluable participants. n = number of participants in the category. Percentages are calculated as (n/N)*100.
Note: Only participants with Treatment emergent (TE) positive and Treatment boosted (TB) positive were included. One non-treatment emergent positive participant with NAb positive was excluded.
[a] ADA Persistency is defined as if the ADA Positive Status from onset to the last time point where it met the criteria for the ADA Positive Status is higher than or equal to 16 Weeks then it is "Persistent", else if the last time point for the ADA.
Positive Status is the last time point for which the ADA status is available then it is "Undetermined", otherwise it is "Transient". ADA Positive Status refers to either TE Positive or TB Positive.

Table 72. Summary of Selected Safety Events Observed by ADA Status

			Non-treatment emergent positive			ADA Positive [a]		
Selected Safety Events	Placebo (N=160)	Negative (N=117)	NAb negative (N=1)	NAb positive (N=1)	Total (N=2)	NAb negative (N=32)	NAb positive (N=12)	Total (N=44)
Total number of participants with selected safety events	18 (11.3)	30 (25.6)	0 (0.0)	1 (100.0)	1 (50.0)	9 (28.1)	5 (41.7)	14 (31.8)
Hypersensitivity-like reactions	18 (11.3)	23 (19.7)	0 (0.0)	1 (100.0)	1 (50.0)	9 (28.1)	3 (25.0)	12 (27.3)
Anaphylactic reactions SMQ	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypersensitivity SMQ	18 (11.3)	23 (19.7)	0 (0.0)	1 (100.0)	1 (50.0)	9 (28.1)	3 (25.0)	12 (27.3)
HLGT: Administration site reactions (related to sotatercept)	0 (0.0)	12 (10.3)	0 (0.0)	1 (100.0)	1 (50.0)	2 (6.3)	3 (25.0)	5 (11.4)

DBPC = double-blind placebo-controlled period; LTDB = long-term double-blind period.
N = Total number of evaluable participants. n = number of participants in the category. Percentages are calculated as (n/N)*100. SMQ = Standardized MedDRA query
[a] ADA positive includes both Treatment emergent positive and Treatment boosted positive.
STELLAR Placebo participants were excluded from all ADA categories: Negative, Non-treatment emergent positive, and ADA Positive.

The number of patients with a hypersensitivity like reaction or administration site reaction did not differ across those with or without ADA.

2.7.8.8. Safety related to drug-drug interactions and other interactions

TEAEs by background PAH therapy.

TEAEs by standard of care combination therapy were evaluated in STELLAR only. In the sotatercept group, flushing, nasal congestion, thrombocytopenia, atrial fibrillation, pyrexia, and joint swelling were more commonly reported in participants on triple therapy than on double therapy.

Table 73. TEAEs by background therapy

	Triple Background PAH Therapy		Double Background PAH Therapy	
Preferred Term	**Placebo (N=100)**	**Sotatercept (N=98)**	**Placebo (N=56)**	**Sotatercept (N=56)**
Epistaxis	1 (1.0%)	22 (22.4%)	2 (3.6%)	14 (25.0%)
Telangiectasia	2 (2.0%)	15 (15.3)	5 (8.9%)	11 (19.6%)
Flushing	3 (3.0%)	10 (10.2%)	1 (1.8%)	0 (0.0%)
Nasal congestion	0 (0.0%)	9 (9.2%)	0 (0.0%)	1 (1.8%)
Thrombocytopenia	2 (2.0%)	13 (13.3%)	1 (1.8%)	3 (5.4%)
Atrial fibrillation	0 (0.0%)	6 (6.1%)	1 (1.8%)	0 (0.0%)
Gingival bleeding	0 (0.0%)	4 (4.1%)	1 (1.8%)	3 (5.4%)
Injection site erythema	0 (0.0%)	4 (4.1%)	0 (0.0%)	1 (1.8%)
Pyrexia	2 (2.0%)	8 (8.2%)	1 (1.8%)	0 (0.0%)
Hemoglobin increased	0 (0.0%)	5 (5.1%)	0 (0.0%)	5 (8.9%)
Joint swelling	0 (0.0%)	4 (4.1%)	2 (3.6%)	0 (0.0%)

DBPC=double-blind placebo-controlled; LTDB=long-term double-blind; N=number; TEAE=treatment-emergent adverse event; PAH=pulmonary arterial hypertension

TEAEs by prostacyclin infusion

The proportions of participants who used prostacyclin infusion therapy were similar in the sotatercept and placebo groups. Overall, the proportions of participants with TEAEs by prostacyclin infusion therapy usage were similar in both groups. The incidence of TEAEs of interest was higher in the sotatercept group than the placebo group among participants who used prostacyclin infusion therapy; the incidence was comparable in the 2 groups among those who did not use prostacyclin infusion therapy. In the sotatercept group, thrombocytopenia was more commonly reported in users versus non-users of prostacyclin infusion therapy. The pattern of TEAEs observed for users versus non-users of prostacyclin infusion therapy is similar to that observed for participants on triple versus double therapy.

Table 74. TEAE by prostacyclin infusion therapy

	Use of Prostacyclin Infusion Therapy		Non-Use of Prostacyclin Infusion Therapy	
Preferred Term	**Placebo (N=65)**	**Sotatercept (N=65)**	**Placebo (N=95)**	**Sotatercept (N=98)**
Epistaxis	0 (0.0%)	16 (24.6%)	3 (3.2%)	20 (20.4%)
Telangiectasia	2 (3.1%)	10 (15.4%)	5 (5.3%)	17 (17.3%)
Nasal congestion	0 (0.0%)	5 (7.7%)	0 (0.0%)	5 (5.1%)
Thrombocytopenia	0 (0.0%)	13 (20.0%)	3 (3.2%)	3 (3.1%)
Atrial fibrillation	0 (0.0%)	4 (6.2%)	1 (1.0%)	2 (2.0%)
Injection site erythema	0 (0.0%)	4 (6.2%)	0 (0.0%)	1 (1.0%)
Abdominal pain upper	0 (0.0%)	5 (7.7%)	1 (1.0%)	2 (2.0%)
Dermatitis contact	0 (0.0%)	4 (6.2%)	1 (1.1%)	1 (1.0%)
Gastritis	0 (0.0%)	4 (6.2%)	1 (1.1%)	1 (1.0%)

DBPC=double-blind placebo-controlled; LTDB=long-term double-blind; N=number; TEAE=treatment-emergent adverse event

2.7.8.9. Discontinuation due to adverse events

Resolution status of events

In participants receiving sotatercept in STELLAR, a majority of occurrences of AEOI increased hemoglobin and AEOI thrombocytopenia leading to dose modification (dose delay or dose reduction) subsequently resolved. Of 7 AEOI increased hemoglobin leading to dose delay, 6 resolved; there were no AEs leading to dose reduction or discontinuation. Of 7 AEs of thrombocytopenia leading to dose delay, all 7 resolved; there were no AEs leading to dose reduction or discontinuation. By contrast, 2 AESIs of telangiectasia led to dose delay and 1 event led to dose reduction. None of these AEs resolved, and 1 participant discontinued sotatercept.

For telangiectasia, lack of resolution in response to dose modification is an expected finding based on the nature of the event, the lack of clear dose relationship of sotatercept with telangiectasia, and the intention behind dose modification for telangiectasia. Because telangiectasia was not reported during the placebo-controlled portion of PULSAR, a relationship with dose was not established. When reports of telangiectasia were received from PULSAR, dose adjustments for telangiectasia were included in the STELLAR clinical study protocol as a precautionary measure to address telangiectasia that were expanding in size or with increasing extent of distribution. Dose modifications were envisaged to limit this process and not expected to make telangiectasia regress or disappear. There is no information on regression of telangiectasia following treatment discontinuation.

Table 75. 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 (STELLAR)- Cumulative Results (DBPC+LTDB)

	Placebo N=160	Sotatercept N=163	Total N=323
AESI: Telangiectasia			
Number of events	9	37	46
Resolved	5	10	15
Not resolved	4	27	31
Number of events leading to dose delay	0	2	2
Resolved	0	0	0
Not resolved	0	2	2
Number of events leading to dose reduction	0	1	1
Resolved	0	0	0
Not resolved	0	1	1
Number of events leading to treatment discontinuation	0	1	1
Resolved	0	0	0
Not resolved	0	1	1
AEOI: Increased hemoglobin (increased hematocrit, increased RBC count)			
Number of events	2	15	17
Resolved	2	11	13
Not resolved	0	4	4
Number of events leading to dose delay	1	7	8
Resolved	1	6	7
Not resolved	0	1	1
Number of events leading to dose reduction	0	0	0
Resolved	0	0	0
Not resolved	0	0	0
Number of events leading to treatment discontinuation	0	0	0
Resolved	0	0	0
Not resolved	0	0	0

	Placebo N=160	Sotatercept N=163	Total N=323
AEOI: Thrombocytopenia			
Number of events	5	20	25
Resolved	1	16	17
Not resolved	4	4	8
Number of events leading to dose delay	0	7	7
Resolved	0	7	7
Not resolved	0	0	0
Number of events leading to dose reduction	1	0	1
Resolved	0	0	0
Not resolved	1	0	1
Number of events leading to treatment discontinuation	0	0	0
Resolved	0	0	0
Not resolved	0	0	0

DBPC = double-blind placebo-controlled period; LTDB = long-term double blind period.

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 25.0.

Note: Includes updated resolution status from SOTERIA (cutoff 06DEC2022) for AEs that started in STELLAR and where ongoing into SOTERIA

Source: [P003MK7962: adam-adsl; adae]

Discontinuation due to adverse events

STELLAR

TEAEs that led to discontinuation of study intervention (6 (3.7% vs 11 (6.9%)) and/or study withdrawal (6 (3.7%) vs 9 (5.6%)) occurred less commonly in the sotatercept group than the placebo group. This imbalance was primarily due to the higher incidence of fatal TEAEs in the placebo group (2 (1.2% vs 7 (4.4%)). No notable pattern of TEAEs leading to discontinuation of study intervention or study withdrawal were observed in the sotatercept group; no TEAE leading to discontinuation of study intervention or study withdrawal was reported in >1 participant in this group.

Pool A

Results for TEAEs leading to discontinuation of study intervention in Pool A were generally consistent with those in the DBPC Period of STELLAR. In Pool A, discontinuation of study intervention due to a TEAE occurred less commonly in the overall sotatercept group (9 [3.8%]) than in the overall placebo group (11 [5.7%]). In the overall sotatercept group, no TEAE leading to discontinuation of study intervention was reported in >1 participant.

Pool B

In the SUR2 cumulative Pool B dataset, the proportion of participants who discontinued study intervention in the cumulative dataset due to a TEAE was 31 (7.2%). TEAEs of gastrointestinal hemorrhage, pleural effusion, respiratory failure, PAH, and telangiectasia each led to discontinuation of study intervention in 2 participants in the overall sotatercept group; no other TEAEs led to discontinuation of study intervention in >1 participant.

2.7.8.10. Post marketing experience

Not applicable.

2.7.9. Discussion on clinical safety

Data collection and exposure

The safety data set for sotatercept is primarily based on the results from STELLAR, supported by the pooled data from Pool A and Pool B. The STELLAR had a 24-week DBPC period. Participants who completed the DBPC Treatment Period entered the long-term double-blind (LTDB) Treatment Period, which was up to 72 weeks. The last-participant-last-visit date for the DBPC Treatment Period was 26-AUG-2022. An additional safety update report was submitted by the Applicant which included updated data for longer-term follow-up with a cut-off date of 6-DEC-2022. The LTDB period could last up to 72 weeks or until the last participant completed the 24-week DBPC period. After the last subject's completion of the 24-week DBPC period (26-AUG-2022), all remaining STELLAR participants (who were all then in the LTDB period) began to rollover into the open-label SOTERIA study. After this information was communicated to the study sites, each active subject underwent an end-of-study visit in STELLAR before being invited to enter SOTERIA. The final STELLAR participant had their last STELLAR visit on 06-DEC-2022, which was the end of study (EOS) date. For the current safety assessment, the main focus was on the cumulative (DBPC+ LTDB) placebo-controlled safety data from STELLAR (CSR 06-DEC-2022). Safety data was further supplemented with two safety pools (Pool A and B). Pool A consists of short-term safety data from the 24-week placebo-controlled periods of STELLAR and PULSAR (data cut-off 26-AUG-2022). Pool B consists of cumulative data from STELLAR, PULSAR,

SPECTRA, and SOTERIA and therefore contains the most long-term safety data, but lacks a control arm (data cut-off 8-NOV-2023).

AEs were coded using MedDRA version 25.0 and TEAEs were defined as any AE with onset after the first dose of study intervention, or any AE with onset before the first dose of study intervention that worsened in severity after the first dose of study intervention. AEs were categorized by system organ class and PT.

In STELLAR, the median exposure in the sotatercept and placebo arms was 313 and 273 days, with a cumulative drug exposure of 644 mg in the sotatercept arm. A total of 95.1% and 88.8% of participants completed the study in the sotatercept and placebo arm. Two (1.2%) participants in the sotatercept group discontinued study intervention due to death and 4 (2.5%) discontinued due to an AE. No other discontinuation category had >1 participant in the sotatercept group. In Pool A, the proportion of participants who completed Visit 9 (Week 24) was higher in the overall sotatercept group (95.8%) than in the overall placebo group (92.7%). Consequently, in Pool A, the proportion of participants who discontinued study intervention was lower in the overall sotatercept group (4.2%) than in the placebo group (7.3%). In Pool B, the majority of participants (>90%) in the overall sotatercept group completed a parent study (STELLAR, PULSAR, or SPECTRA) and rolled over to SOTERIA. A total of 343 subjects have at least 52 weeks of exposure to sotatercept (Pool B) at the data cut-off of 08-Nov-2023, which is acceptable in terms of short-term safety (up to 1 year). With regard to long-term safety, the median duration of exposure of 431 subjects in the overall sotatercept group was 657 days and the median number of doses received was 30, which is 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, as well as from the ongoing clinical outcome studies HYPERION (MK-7962-005) and ZENITH (MK-7962-006).

Treatment-emergent adverse events

During STELLAR, the number of treatment-emergent adverse events (TEAEs) was 149 (93.1%) and 151 (92.6%) in the placebo and sotatercept arm, respectively. The number of serious TEAEs was 47 (29.4%) and 40 (24.5%) in the placebo and sotatercept arm, respectively. The number of TEAE leading to treatment discontinuation was 11 (6.9%) and 6 (3.7%) in the placebo and sotatercept arm, respectively. It is reassuring that the number of serious TEAEs and TEAEs leading to treatment discontinuation were lower in the sotatercept arm than the placebo arm, which is likely due to the efficacy of sotatercept. It is also reassuring that the results of Pool A and B were in line with the findings from STELLAR. In STELLAR, the incidences of TEAEs by preferred term were generally similar in both treatment arms. Frequently reported TEAEs (incidence ≥5%) with a higher incidence in the sotatercept group than in the placebo group were epistaxis (22%), telangiectasia (17%), dizziness (15%), nasal congestion (6%), thrombocytopenia (10%), and haemoglobin increased (6%). The majority of these TEAE were also identified as AEs of (special) interest, discussed further below. Pool A also indicated higher frequencies in the sotatercept arm for diarrhea (14%), headache (20%), hypokalemia (7%), and pain in the extremity (6%). These adverse events were also found in STELLAR itself, albeit with a somewhat lower incidence difference between treatment arms. Pool B did not include a control arm, but found comparable results in the sotatercept arm.

In STELLAR, the overall incidence of TEAEs considered related to study intervention by the investigator was higher in the sotatercept group (50.9%) than in the placebo group (28.1%). TEAEs considered related to study intervention with a higher incidence in the sotatercept group than in the placebo group, respectively, were telangiectasia (15.3% vs 2.5%), epistaxis (9.2% vs 0.6%), haemoglobin increased (5.5% vs 0.0%), and injection site erythema (2.5% vs 0.0%). The AEs which were

considered adverse drug reactions based on the ADR identification approach as outline in this overview were headache, epistaxis, dizziness, telangiectasia, rash, thrombocytopenia, increased hemoglobin, increased blood pressure and erythema. However, based on low numbers of events of TEAEs related to study intervention in the cumulative safety set of STELLAR, the Applicant's position was that gingival bleeding and injection site pruritus do not warrant inclusion as ADRs. However, the low numbers cannot be the only reason not to include these AEs as ADRs. In this respect, a higher incidence in gingival bleeding in the sotatercept group compared with the placebo group was observed in STELLAR (4.3% and 0.6%), Pool A (2.1% and 0.5%). Additionally, considering the mechanistic plausibility and the fact that causality of sotatercept in the events of gingival bleeding has still not been sufficiently excluded, the Applicant has added gingival bleeding as an ADR in the SmPC. Similarly, a higher incidence in injection site pruritus in the sotatercept group compared with the placebo group was observed in STELLAR (3 (1.8%) of which 2 (1.2%) were considered related compared with 0 participants in the placebo group) and in Pool A (4 (1.7%) of which 2 (0.8%) were considered related compared with 0 in the placebo group). Based on these findings, the Applicant has added injection site pruritus as an ADR in section 4.8 of the SmPC.

AE of (special) interest

Based on non-clinical observations, the mechanism of action and early clinical findings, the Applicant had identified the following adverse events of interest (AEOIs) for STELLAR: Increased haemoglobin, immunogenicity, thrombocytopenia, neutropenia (including febrile neutropenia), embryo-fetal toxicity, hepatic toxicity, cardiac events, thrombotic events, renal toxicity, bleeding events, increased blood pressure, and suppression of FSH. The occurrence of FSH suppression (1.8% vs 1.3%), embryo-fetal toxicity (1.2% vs 1.9%), thromboembolic events (5.5% vs 3.8%), renal toxicity (3.7% vs 4.4%), hepatic toxicity (4.3% vs 4.4%), cardiac events (3.1% vs 11 6.9%), leukopenia (0.6% vs 3.8%), and neutropenia (0.6% vs 3 1.9%) did not occur more often in the sotatercept arm as compared to the placebo arm, and therefore did not emerge as safety concerns for sotatercept. Imbalances in immunogenicity-related TEAEs were mostly accounted for by rashes, dermatitis, and other nonserious cutaneous events. Therefore immunogenicity related TEAE did not emerge as a safety concern for sotatercept. Nonetheless, erythema and rash has been identified as ADRs and as such included in the product information. No participants met the Hy's Law criteria for drug-induced liver injury.

In STELLAR, the incidence of the adverse events of special interest (AESI) telangiectasia was higher in the sotatercept group than in the placebo group in the cumulative dataset (16.6% vs 4.4%). Most events were considered by the investigator to be related to study intervention. In the sotatercept group, none of these events were serious or severe, and only 1 led to discontinuation of study intervention. The underlying mechanisms is not known. The location of telangiectasia varies across the body and does not seems to develop in a specific area, although it is more commonly observed on the upper body. According to the analysis of 237 events from SOTERIA, the frequency of telangiectasia occurrence in different locations: chest (25.7%), face (19.8%), leg (11.0%), arm (10.5%), back (7.6%), neck (5.5%), shoulder (4.2%), trunk (4.2%), hand (4.2%), nose (2.1%), abdomen (1.3%), feet (0.8%), and unknown (3.0%). The data also indicate that the diameter of telangiectasia varies, with 75.1% having a size of less than 5 mm, 18.1% between 5-10 mm, 1.3% larger than 10.0 mm, and 5.5% unknown.

The incidence of the AEOI increased haemoglobin in the cumulative dataset was higher in the sotatercept group than in the placebo group (8.6% vs 0.6%). None of these events were serious or severe, and none led to discontinuation of study intervention. The mean increase from baseline at Week 24 (Visit 9) was 0.81 mmol/L and this mean increase remained consistent at visits after Week 24. Similarly, hematocrit increased by 4.20% and erythrocytes by $0.4*10^{12}$/L. Of interest, the

incidence of increased haemoglobin was higher in Pool B, indicating that this AE can also occur later during treatment.

The incidence of the AEOI bleeding events, was higher in the sotatercept group than in the placebo group (35.0% vs 15.6%). The most commonly reported bleeding events in the sotatercept group were epistaxis followed by gingival bleeding. Participants with epistaxis, and to a lesser extent gingival bleeding, accounted almost entirely for the imbalance between sotatercept and placebo groups. Nine participants (7 in the sotatercept group and 2 in the placebo group) experienced serious bleeding events. Several factors predisposing to bleeding were present; most were on both anticoagulants and prostacyclin analogues and those >65 year also had an increased risk, which is reflected in the SmPC.

The AEOI of thrombocytopenia was more commonly reported in the sotatercept group than in the placebo group (10.4% vs 3.1%). In the sotatercept group, 1 event of the AEOI thrombocytopenia was serious and another was severe; both events led to the interruption of study intervention. Mean decreases from baseline over time in platelet counts were observed in the sotatercept group. The mean decrease from baseline at Week 24 (Visit 9) was -15.9×10^9/L; this mean decrease remained consistent at visits after Week 24. The median time to onset of thrombocytopenia in STELLAR was 81 days (range 22-338 days) in the sotatercept group and 86 days (range 64-253 days) in the placebo group. Based on the magnitude, time course, and reversibility of reductions in platelet counts, there is a low probability that an immune-mediated mechanism is implicated. Further, of the 33 subjects with a platelet count < 100×10^9/L, 10 subjects (30.3%) experienced a bleeding event and of the 56 subjects who experienced a platelet decrease from baseline of ≥65×10^9/L, 20 participants (35.7%) experienced a bleeding event. Considering that these incidences are comparable to the overall bleeding rate in STELLAR (35.0%), it is considered that there appears no clear causal relationship between thrombocytopenia and bleeding events. Furthermore, if there is no relationship between platelets and bleeding events, it is of interest to investigate whether sotatercept affects other parts of the coagulation pathway. However, no effects on intrinsic, extrinsic, and common coagulation pathways by assessing activated partial thromboplastin time (APTT) and prothrombin time (PT) were observed in pre-clinical nonhuman primate toxicity studies. Since these pathways are well conserved between nonhuman primates and humans, no effects of sotatercept on parameters in the intrinsic, extrinsic, or common coagulation pathway are expected.

The AEOI of increased blood pressure was more commonly reported in the sotatercept group than in the placebo group (4.3% vs 0.6%). In the sotatercept group, none of these events were serious or severe, and none led to discontinuation of study intervention. At Week 24 (Visit 9) in the sotatercept group, the mean increase from baseline in systolic blood pressure was 2.2 mmHg and in diastolic blood pressure was 4.9 mmHg, which remained comparable in longer term follow-up. Mean changes from baseline in systolic and diastolic blood pressure in the placebo group were minimal relative to baseline over time. In this respect, patients with uncontrolled hypertension were excluded and it is currently unclear how this affects safety on the long-term. Nevertheless, 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.

Overall, sotatercept is associated with the AE of interest telangiectasia, increased haemoglobin, bleedings events, thrombocytopenia and increased blood pressure. These adverse events of interest are reflected in the product information and increased haemoglobin and severe thrombocytopenia have been included in the risk management plan safety specification.
However, it is unknown whether the combined risk of increased haemoglobin, decreased platelet counts, bleeding events, and hypertension adversely affects long-term cardiovascular safety. Therefore, additional MACE (i.e. cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) and MACE+ (also including transient ischemic attack, sudden death and hospitalization for

cardiovascular causes, like those due to unstable angina, need for revascularization, acute heart failure/worsening of existent heart failure, and also deep vein thrombosis and pulmonary embolism that could be related to erythrocytosis) 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 Applicant clarified that the STELLAR, PULSAR, and SPECTRA study were not designed as cardiovascular outcome studies, and as such, MACE were not adjudicated. Nevertheless, MACE events from these studies and cumulative sotatercept treatment up to data cut-off 08-NOV-2023 have been provided. In STELLAR, the number of subjects with any MACE composite endpoint was slightly lower in the sotatercept group compared with the placebo group (n=2 (1.2%) and n= 5 (3.1%), respectively). Further, it is acknowledged that the time-at-risk exposure adjusted incidence rate (TAR-EAIR) for subjects from PULSAR (1.5) and SPECTRA (1.6) who continued into SOTERIA and have the longest duration of exposure, as well as the overall sotatercept EAIR (1.0) remained low, indicating that there appears not to be an increased risk for MACE event over time. There were no events of fatal myocardial infarctions and only one non-fatal stroke event in all these studies, therefore, the results on MACE are mainly driven by cardiovascular deaths. Cardiovascular deaths are anticipated events in the PAH population, as such, this observation is consistent to anticipated effect of sotatercept to lower mortality, as also indicated by the preliminary TTCW results. Nevertheless, the number of events were too low to draw firm conclusions.

Furthermore, the focus of the Applicant was on MACE analysis rather than MACE+ to avoid the potential of confounding because of the beneficial effects of sotatercept is reducing events associated with pulmonale/ right heart failure. Although this reasoning can be followed, considering that the MACE events are very low, additional analyses using MACE+ in order to exclude a detrimental effect on cardiovascular safety were preferred. Instead, the Applicant provided exposure adjusted rates of events in the Cardiac disorders SOC (EAIR of 17.0 /100 PYAR in the sotatercept group and 27 /100 PYAR in the placebo group). The EAIRs by study and for the overall sotatercept group in Pool B showed a pattern of lower rates over time and therefore did not identify a new safety signal in terms of cardiac disorders, with the exception of tachycardia.

Overall, the number of MACE events is limited and consequently these results can not preclude a detrimental effect on cardiovascular safety. However, the positive trend towards a lower adjusted rate of "cardiac disorders" in the sotatercept group (17%/yr; 95%CI: 13 to 22%/yr) compared with the placebo group (27%/yr; 95%CI: 18 to 38%/yr) suggests a low probability of sotatercept to have a detrimental effect on CV safety. According to the 'Reflection paper on assessment of cardiovascular safety profile of medicinal products' (EMA/CHMP/50549/2015) two approaches are generally conceivable with respect to the presentation of clinical outcome data enabling an evaluation of the cardiovascular safety profile: a meta-analytic approach and a dedicated cardiovascular outcome study. Therefore, in line with the guideline, conducting a meta-analysis post-marketing with continuous monitoring of the cardiovascular safety of sotatercept by routine pharmacovigilance based on the completed STELLAR and the ongoing HYPERION and ZENITH studies and continuous monitoring of the cardiovascular safety of sotatercept by routine pharmacovigilance is an acceptable alternative approach. The Applicant has made a commitment to submit a post-marketing meta-analytic plan within 3 months after approval and to perform the requested meta-analyses once data from the other clinical trials is available.

Regarding thrombotic and thromboembolic events, when SAEs for the thrombotic events of the data cut-off the 06-DEC-2022 data cut (N=431) were compared with those from the 08-NOV-2023 data cut (N=431), the numbers of participants with events have risen from 9 (2.1%) to 13 (3.0%); however the EAIRs (95% CI) are steady at 1.6 (0.7, 3.1) and 1.4 (0.8, 2.5) per 100 p-y at risk, respectively,

which is reassuring. Moreover, the background rate of thromboembolic events in patients with PAH (6.6 (6.3, 6.8) per 110 p-y) from a retrospective cohort study conducted by the Applicant has been provided, which were lower than the rates of thrombotic and thromboembolic events observed in pool B, which is reassuring.

An overview table on resolution status of events leading to dose modifications showed that in almost all subjects who received a dose delay due to an event of increased hemoglobin, the event resolved (6 resolved and 1 not resolved). There were no dose reductions or discontinuations due to an increased hemoglobin event. Of 7 AEs of thrombocytopenia leading to dose delay, all 7 resolved; there were no Aes leading to dose reduction or discontinuation. Furthermore , of the 35 subjects (21.5%) who had dose delays or dose reductions for increased hemoglobin or thrombocytopenia, none led to treatment discontinuation. These results indicate that the increase in hemoglobin levels and decreases in platelet counts are manageable. However, only a few dose modifications have been performed due to telangiectasia events (3 out of 37 events). Two AESIs of telangiectasia led to dose delay and 1 event led to dose reduction. None of these Aes resolved, and 1 participant discontinued sotatercept. As a lack of resolution in response to dose modification is an expected finding based on the nature of the telangiectasia event and there are no indications that telangiectasia incidence is dose related, it is considered acceptable not to include telangiectasia as part of the dose modification rules.

Serious TEAEs, deaths and dose modifications

Serious TEAEs (24.5% vs 29.4%) and serious TEAEs leading to treatment discontinuation (2.5% vs 5.6%) occurred less commonly in the sotatercept group than in the placebo group. No notable pattern of serious TEAEs was observed in the sotatercept group relative to the placebo group. The serious TEAE of pneumonia was reported in 3 participants in the sotatercept group; no other serious TEAEs were reported in >2 participants in this group. Serious TEAEs associated with PAH disease progression (e.g. dyspnea, right ventricular failure, cardiac failure, cardiac failure acute, cardiogenic shock, fluid retention, and hypervolemia) occurred more commonly in the placebo group than in the sotatercept group. It is considered reassuring that serious TEAEs occurred less often in the sotatercept group and that no clear pattern of serious TEAEs was observed.

In STELLAR a total of 2 deaths were reported in the sotatercept group compared with 7 in the placebo group. None were considered related to study drug. In Pool A, there was 1 death in the sotatercept group (not related to treatment) and 6 deaths in the placebo group. In Pool B (8-NOV-2023), there were 16 deaths in total in the overall sotatercept group, 4 deaths were due to cardiac arrest and 4 were due to pneumonia and 3 due to bleeding events (2 participants with gastrointestinal hemorrhage and 1 with intracranial hemorrhage (see above for discussion on the bleeding events). No other causes of death occurred in >1 participant in the overall sotatercept group. None of the deaths were considered related to study drug.

Overall, the lower number of deaths on sotatercept is reassuring and likely reflects the efficacy, most of the deaths in the placebo group were cardiac related (and right ventricular failure is an end-stage of PAH).

Special populations

Intrinsic factors (age, sex, race, and BMI) were evaluated for sotatercept in Pools A and B only. The AEOI bleeding events occurred less commonly in the <65-year-old subgroup than in ≥65-year-old subgroup in the overall sotatercept group (18.5% vs 31.0%), yet no notable imbalance between age categories for any specific PT was found within this AEOI bleeding events. Nevertheless, the Applicant has included age >65 years old as a risk factor for serious bleeding in the SmPC. No other notable

findings were observed in the safety evaluation of sotatercept by sex, race, BMI or age categories or in patients with renal impairment.

No specific interaction study was conducted. However, in STELLAR, in the sotatercept group, flushing, nasal congestion, thrombocytopenia, atrial fibrillation, pyrexia, and joint swelling were more commonly reported in participants on triple PAH background therapy than on double therapy. The most evident difference was found for thrombocytopenia (13.2% vs 5.4%). When evaluating the TEAEs by prostacyclin infusion therapy, this imbalance was further increased (20.0% vs 3.1%), strongly suggestive of a pharmacodynamic interaction of prostacyclin infusion therapy and sotatercept (see discussion above under bleeding events).

Immunogenicity

In STELLAR, 46 (28%) patients tested positive for sotatercept ADAs, which comprised 2 (1.2%) non-treatment emergent positive, 2 (1.2%) treatment boosted positive, and 42 (25.8%) treatment-emergent positive patients. Of these patients, 13 (8.0%) tested positive for neutralizing antibodies. The ADA response was transient in 56.8% of ADA positive patients and remained undetermined for only 2 (4.5%) patients. The Nab response was transient in 16.7% of patients with Nab positive response. There were no clinically meaningful safety findings attributable to ADA. Overall, it is reassuring that the number of hypersensitivity-like reactions did not differ for those with and without ADA and that no anaphylactic reactions were reported for the entire sotatercept arm.

2.7.10. Conclusions on the clinical safety

Sotatercept was generally well-tolerated and had a manageable safety profile in participants with PAH (WHO Group 1, FC II or III). Treatment with sotatercept was associated with increased haemoglobin and thrombocytopenia, both of which were manageable by dose modification. The incidences of telangiectasia, bleeding events (mostly epistaxis), and increased blood pressure were higher in participants treated with sotatercept than in those treated with placebo. Fewer deaths occurred in participants treated with sotatercept than in those treated with placebo in STELLAR and Pool A. No differences in the occurrence of anaphylactic reactions, hypersensitivity reactions, or administration site reactions were found based on ADA status. The longer-term safety profile of sotatercept from Pool B was generally consistent with safety findings observed in STELLAR and Pool A. Regarding cardiovascular safety, based on the provided MACE analyses, a detrimental effect on the cardiovascular system could still not be excluded due to the low numbers of events. However, the positive trend towards a lower adjusted rate of "cardiac disorders" in the sotatercept group compared with the placebo group suggests a low probability of sotatercept to have a detrimental effect on CV safety. Therefore, the Applicant has made the commitment to submit a post-marketing meta-analytic plan within 3 months after approval and to perform the meta-analysis post-marketing once data from the other clinical trials is available in line with the Reflection paper on assessment of cardiovascular safety profile of medicinal products' (EMA/CHMP/50549/2015).

2.8. Risk Management Plan

2.8.1. Safety concerns

Table 76. 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

2.8.2. Pharmacovigilance plan

Table 77. 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

2.8.3. Risk minimisation measures

Table 78. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

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

	Additional risk minimisation measures: None.	**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.

2.8.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.9. Pharmacovigilance

2.9.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 26 March 2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Winrevair (sotatercept) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

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 and ActRIIB 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, to improve exercise capacity (see section 5.1)."

3.1.2. Available therapies and unmet medical need

In the EU, multiple medicinal products have gained approval for PAH treatment. These products 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 compounds 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 products, 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 products, 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 has been associated with hepatotoxicity.

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.

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 benefit risk is primarily based on data from the pivotal phase 3 trial STELLAR. STELLAR was a randomized, double-blind, parallel group study designed to evaluate the efficacy and safety of sotatercept in adults ⩾18 years old with PAH (WHO Group 1, FC II or III) on stable treatment (⩾90 days) with background PAH therapy (monotherapy or combination therapy with ERA, PDE5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists). Randomization was stratified by baseline WHO FC (II or III) and background PAH therapy (mono/double or triple therapy). The study consisted of a 24-week placebo-controlled double-blind primary treatment period (referred to as DBPC Treatment Period) and an extension period (referred to as LTDB Treatment Period) up to 72 weeks. Subjects were randomized (1:1) to receive either sotatercept or placebo subcutaneous Q3W. The starting dose of sotatercept was 0.3 mg/kg at Visit 1, followed by 0.7 mg/kg Q3W for the remainder of the study, unless dose modifications were required.

Pooled data is presented as supportive evidence. Pool A consists of safety data from the 24-week placebo-controlled periods of STELLAR and PULSAR. Pool B consists of cumulative data from STELLAR, PULSAR, SPECTRA, and SOTERIA, which contains the most long-term safety data, but lacks a control arm.

3.2. Favourable effects

Primary endpoint - In the pivotal study STELLAR, treatment with sotatercept resulted in a significant improvement in 6MWD from baseline to week 24 as compared to placebo in patients with PAH (WHO

Group 1) on background PAH therapy (median: 34.4 m vs. 1.0 m, respectively; median treatment difference (Hodges-Lehmann location shift) of 40.8m (95% CI : 27.53, 54.14); p< 0.001) from baseline levels of 397.6 m and 404.7 m for the sotatercept and placebo group, respectively. The effect was consistent in the prespecified sensitivity analyses using alternative methods of imputation for the 6MWD.

The beneficial effect was supported by the phase 2 dose-finding study PULSAR.

Subgroups - The treatment effect was a consistent across all prespecified subgroups, including background therapy at baseline (monotherapy, double or triple therapy), baseline PVR (≤ 800, > 800 dynes*sec/cm^5, prostacyclin infusion therapy (y/n).

Secondary endpoint TTCW (post-hoc analyses using CHMP definition; data cut-off 06-DEC-2022) -The results of the post-hoc analysis of TTCW using the CHMP definition corroborate the results of the primary TTCW analysis; Treatment with sotatercept resulted in a significant improvement 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; Logrank test p-value < 0.001). All components contributed to this effect.

Other secondary endpoints - Significant improvements were seen in PVR (median treatment difference of -234.6 dynes*sec/cm5; p< 0.001), NT-proBNP (median treatment difference of -441.6 pg/ml; p< 0.001) dynes*sec/cm5; p< 0.001), WHO FC (improvement in 29.4% vs. 13.8% subjects in the sotatercept and placebo group, respectively; p< 0.001). A consistent treatment effect in terms of PVR and NT-proBNP was observed across all prespecified subgroups. The percentage of subjects who maintained or achieved a low-risk score (French Risk score calculator) relative to baseline was significantly greater in the sotatercept group (39.5% vs. 18.2%; p<0.001). Regarding the QoL PAH-SYMPACT score, significant improvements of treatment with sotatercept compared with placebo was observed for the physical impacts (median treatment difference of -0.26; p=0.010) and the cardiopulmonary symptoms (treatment difference of -0.13; p=0.028) domain score of PAH-SYMPACT, but not for the cognitive/emotional impacts domain score of PAH-SYMPACT (treatment difference of -0.16 ; p=0.156).

The beneficial effects in terms of 6MWD, PVR, NT-proBNP, WHO FC improvement, and simplified French risk score was consistent with those observed in the phase 2 dose-finding study PULSAR and the exploratory phase 2 study SPECTRA.

3.3. Uncertainties and limitations about favourable effects

Mechanism of action - The MoA could not be fully elucidated. Biological processes of activin-A other than vascular remodeling 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.

Maintenance of effect - The increases in 6MWD were maintained through at least Week 60 (median: 47.4 m vs. 4.3 m for the sotatercept and placebo group, respectively), after which the results were more variable, which may have been due to the small patient numbers. No efficacy results from the extension study SOTERIA have been provided yet.

3.4. Unfavourable effects

Deaths - Two deaths were reported in the sotatercept group compared with seven in the placebo group. Severe TEAEs (24 (14.7%) vs 33 (20.6%)), serious TEAEs (40 (24.5%) vs 47 (29.4%)) and

serious TEAEs leading to treatment discontinuation (4 (2.5%) vs 9 (5.6%)) occurred less commonly in the sotatercept group than in the placebo group. No notable pattern of serious TEAEs was observed in the sotatercept group relative to the placebo group.

AEOI - The key unfavourable effects of sotatercept were the adverse events of (special) interest bleeding events, thrombocytopenia, telangiectasia, increased haemoglobin and increased blood pressure.

Bleeding events - In the completed STELLAR study, bleeding events occurred in 35.0% of the patients treated with sotatercept and 15.6% of patients treated with placebo. The imbalance was driven primarily by epistaxis and gingival bleeding, which occurred in 22.1% and 4.3% of patients treated with sotatercept and 1.9% and 0.6% of patients with treated with placebo, respectively. In the sotatercept arm, seven patients experienced serious bleeding events and three participants discontinued treatment due to bleeding events.

Thrombocytopenia - Thrombocytopenia occurred in 10.0% of the patients treated with sotatercept and 3.1% of patients treated with placebo in STELLAR. In the sotatercept arm, the mean decrease from baseline at 24 weeks was -15.9×10^9/L, with no change in the placebo arm. In the sotatercept arm, one of the events was serious, one event was severe, and none led to treatment discontinuation.

Telangiectasia - Telangiectasia refers to small, dilated blood vessels that can occur near the surface of the skin or mucous membranes and occurred in 16.6% of the patients treated with sotatercept and 4.4% of the patients treated with placebo in STELLAR. In the sotatercept arm, none of the events were serious, severe or led to treatment discontinuation.

Increased haemoglobin - Increased haemoglobin occurred in 8.6% of patients treated with sotatercept and 0.6% of patients treated with placebo. In the sotatercept arm, the mean haemoglobin increase from baseline at week 24 was 0.8 mmol/L (1.3 g/dL), the mean hematocrit increase was 4.20% and the mean erythrocyte increase was 0.4×10^{12}/L, with no changes in the placebo arm. In the sotatercept arm, none of the events were serious, severe or led to treatment discontinuation.

Increased blood pressure - Increased blood pressure occurred in 4.3% of patients treated with sotatercept and 0.6% of patients treated with placebo. In the sotatercept arm, the mean increase from baseline at week 24 in systolic blood pressure was 2.2 mmHg and in diastolic blood pressure was 4.9 mmHg. In the placebo arm, the mean change from baseline in systolic blood pressure was -1.6 mmHg and in diastolic blood pressure was -0.6 mmHg. In the sotatercept arm, none of the events were serious, severe or led to treatment discontinuation.

Long-term safety - In Pool B (data cut-off 08-NOV-2023), a total of 343 subjects had at least 52 weeks of exposure to sotatercept. Further, the median duration of exposure of 431 subjects in the overall sotatercept group of Pool B was 657 days and the median number of doses received was 30. The longer-term safety profile of sotatercept from Pool B was generally consistent with safety findings observed in STELLAR and Pool A. 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, as well as, from the ongoing clinical outcome studies HYPERION (MK-7962-005) and ZENITH (MK-7962-006).

Dose modification rules - Thirty-five (21.5%) participants in the STELLAR sotatercept group experienced dose modifications (dose reduction or delay). Only 10 subjects of the 35 subjects with dose modifications (dose reduction or delay) in the sotatercept group of STELLAR experienced a subsequent AESI/AEOI after a dose modification. The most common reported AESI/AEOI were increased hemoglobin (n=6), telangiectasia (n=4) and bleeding events (n=3). Nevertheless, 9 of the 10 subjects completed the STELLAR study and continued sotatercept treatment in SOTERIA, whereas

one subjects with multiple comorbidities died from an acute myocardial infarction ~4 months after the dose hold/reduction.

3.5. Uncertainties and limitations about unfavourable effects

Cardiovascular safety - The safety data package does not fulfil the requirements of the "reflection paper on assessment of cardiovascular safety profile of medicinal products". In STELLAR, the number of subjects with any MACE composite endpoint was slightly lower in the sotatercept group compared with the placebo group (n=2 (1.2%) and n= 5 (3.1%), respectively). The time-at-risk exposure adjusted incidence rate (TAR-EAIR) for subjects from PULSAR (1.5) and SPECTRA (1.6) who continued into SOTERIA and have the longest duration of exposure, as well as the overall sotatercept EAIR (1.0), remained low. However, the number of events were too low to draw firm conclusions. Nevertheless, the positive trend towards a lower adjusted rate of "cardiac disorders" in the sotatercept group (17%/yr; 95%CI: 13 to 22%/yr) compared with the placebo group (27%/yr; 95%CI: 18 to 38%/yr) suggests a low probability of sotatercept to have a detrimental effect on CV safety.

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, however there was neither a trend observed in exposure-platelet relationship stratified by use of prostacyclin infusion therapy, nor a mechanistical explanation.

Telangiectasia - The location of telangiectasia varies across the body and does not seem to develop in a specific area, although it is more commonly observed on the upper body. In this respect, it is uncertain how big an impact telangiectasis had for patients. Moreover, the pathophysiological mechanism behind telangiectasia in sotatercept treated patients remains ununderstood.

3.6. Effects Table

Table 79*.* Effects Table for sotatercept for the proposed indication of treatment of PAH in adult patients with WHO FC II to III for the full analysis set, based on STELLAR (data cut-off: 06-DEC-2022).

Effect	Short Description	Treatment n=163	Control n=160	Uncertainties/ Strength of evidence
Favourable Effects				
6MWD	Median change from baseline at week 24 [m]	34.4	1.0	**Primary endpoint** **SoE:** median treatment difference (Hodges-Lehnmann location shift): 40.8 m (95% CI: 27.3, 54.1; p<0.001). Consistent effect across subgroups and in the prespecified sensitivity analyses. Maintenance of effect through at least week 60 (47.4 m vs. 4.3 m, respectively).
PVR	Mean change from baseline at week 24 [dyn*s/cm^5]	-234.5	42.4	**2nd secondary endpoint** **SoE:** median treatment difference (Hodges-Lehnmann location shift): -234.6; 95%CI: -288.4, -180.8; p<0.001. Consistent effect across subgroups.
NT-proBNP	Mean change from baseline at week 24 [pg/mL]	-722.3	-355.6	**3rd secondary endpoint** **SoE:** median treatment difference (Hodges-Lehnmann location shift): -441.6; 95% CI: -573.4, -309.6; p<0.001. Consistent effect across subgroups.
WHO FC	improvement from baseline at week 24 [%]	29.4	13.8	**4th secondary endpoint** **SoE:** p< 0.001
Time to clinical worsening (TTCW) [1]	Total number of TTCW events (**CHMP definition; 06-DEC-2022**) [N (%)]	9 (5.5)	29 (18.1)	**5th secondary endpoint** Data cut-off: 06-DEC-2022 **SoE:** HR 0.274 (95% CI: 0.129, 0.582; p<0.01). Consistent with the results of the primary TTCW analysis. **Unc:** not consistent with the results observed in the phase 2 PULSAR study
	Death	2 (1.2)	6 (3.8)	
	worsening related listing for lung and/or heart transplant	1 (0.6)	1 (0.6)	
	need for atrial septostomy	0 (0.0)	0 (0.0)	
	PAH-specific hospitalization	1 (0.6)	8 (5.0)	
	Deterioration of PAH	5 (3.1)	15 (9.4)	
PAH-SYMPACT	Mean change from baseline at week 24			**7, 8, 9th secondary endpoint** **SoE:** median treatment differences:
	Physical impacts	-0.3	0	-0.26; 95% CI: -0.49, -0.04; p=0.010).
	Cardiopulmonary symptoms	-0.1	0	-0.13; 95% CI: -0.25, -0.014; p=0.028)
	Cognitive/emotional impacts	-0.1	0.1	-0.16; 95% CI: -0.40, 0.084; p=0.156
Unfavourable Effects				
AEOI	Bleeding events (mostly epistaxis) [n (%)]	57 (35.0%)	25 (15.6%)	**SoE**: Similar in long-term Pool B. 7 SAE in sotatercept arm (1 died)
AEOI	Thrombocytopenia [n (%)]	17 (10.0%)	5 (3.1%)	**SoE**: Similar results in long-term Pool B Lab STELLAR: mean decrease from baseline at 24 weeks: -15.9×10^9/L
AESI	Telangiectasia (dilated blood vessels under skin) [n (%)]	27 (16.6%)	7 (4.4%)	**SoE**: Similar results in long-term Pool B
AEOI	Increased haemoglobin [n (%)]	14 (8.6%)	1 (0.6%)	**SoE**: Lab STELLAR: mean increase from baseline at Week 24 was 1.3 g/dL **Unc**: Incidence higher in Pool B (57 (13.2%))
AEOI	Increased Blood Pressure [n (%)]	7 (4.3%)	1 (0.6)	**SoE**: Similar in long-term Pool B.

Note: [1] Deterioration of PAH therapy is defined by both of the following events occurring at any time, even if they began at different times, as compared to their baseline values: a) worsened WHO functional class b) Decrease in 6MWD by ⩾ 15% (confirmed by 2 6MWTs 4-168 hours apart).

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 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. Therefore, there is an unmet medical need for additional PAH therapy.

The current application is based on the results of a single pivotal study STELLAR, which can be considered acceptable provided that the results are consistent and compelling (CHMP guideline "Point to consider on application with 1. Meta-analyses; 2 One pivotal study"; CHMP/EWP/2330/99). Supportive data are obtained from phase 2 dose-finding study PULSAR, the exploratory Phase 2 study SPECTRA (P002MK7962) and the open-label extension study SOTERIA.

Results show a significant improvement in exercise capacity measured by 6MWD from baseline to week 24 in patients with PAH (WHO Group 1) on background PAH therapy (median: 47.4 m vs. 4.3 m, respectively; median treatment difference (Hodges-Lehmann location shift) of 40.8 m (95% CI : 27.5, 54.1); p< 0.001) from a baseline levels of 397.6 m and 404.7 m for the sotatercept and placebo group, respectively. This increase is considered clinically relevant as it compares to the results of the pivotal study of already authorised products for PAH, e.g. Adempas (riociguat), which showed a mean increase of 36 m compared with placebo in PAH patients on background PAH therapy. The primary result was robust to sensitivity analyses, consistent in subgroup analyses and consistent to results observed in the Phase 2 PULSAR study and therefore supports the indication "to improve exercise capacity" in line with the relevant CHMP guideline (EMEA/CHMP/EWP/356954/2008).

The secondary efficacy results further support the primary efficacy endpoint. Significant improvements were also seen in PVR (median treatment difference of -234.6 dynes*sec/cm5 (95% CI: -288.4, -180.8; p< 0.001), NT-proBNP (median treatment difference of -441.6 pg/ml (95% CI: -573.5, -309.6; p< 0.001), WHO FC (improvement in 29.4% vs. 13.8% subjects in the sotatercept and placebo group, respectively; p< 0.001). The magnitude of effect in terms of PVR and NT-proBNP and WHO FC improvement is consistent with that observed in the pivotal study of another approved PAH medicinal product, i.e. Adempas (riociguat). Moreover, a consistent treatment effect in terms of PVR and NT-proBNP was also observed across all prespecified subgroups. Regarding the QoL PAH-SYMPACT score, significant improvements of treatment with sotatercept compared with placebo was observed for the physical impacts (median treatment difference of -0.26; p=0.010) and the cardiopulmonary symptoms (treatment difference of -0.13; p=0.028) domain score of PAH-SYMPACT, but not for the cognitive/emotional impacts domain score of PAH-SYMPACT (treatment difference of -0.16 ; p=0.156).

The 6MWD is acceptable as primary endpoint provided that the indication is restricted to an improvement in exercise capacity. For the broader treatment of PAH indication, "hard" clinical outcomes are required, such as time to clinical worsening (TTCW). In the STELLAR study, TTCW has been evaluated as a secondary endpoint, however, the components of the definition TTCW are not all equally robust. Therefore, a post-hoc analysis of TTCW using the CHMP definition (06-DEC-2022) has been provided, which corroborate the results of the primary TTCW analysis. Treatment with sotatercept resulted in a significant improvement 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; Logrank test p-value < 0.001). All components contributed to this effect. In comparison, the pivotal study GRIPHON of Uptravi (selexipag) conducted in 1156 subjects with WHO FC I-IV PAH,

showed a risk reduction of 40% (hazard ratio [HR] 0.60; 99% CI: 0.46, 0.78; one-sided log-rank p value < 0.0001) in TTCW using approximately the same TTCW definition as used in STELLAR. As mentioned above, in cases where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency. In this respect, the findings are not consistent to those observed in the phase 2 PULSAR study, even though the mean duration of exposure (~160 days) and the population studied in PULSAR is comparable to STELLAR, with the side note that the number of patients in the PULSAR study were limited (n= 100). Therefore, the external validity could not be justified and consequently, the broader long-term PAH treatment indication is not acceptable. The ongoing studies HYPERION (MK-7962-005) and ZENITH (MK-7962-006) will provide further insights on the effect of sotatercept on clinical worsening and might potentially result in a modification of the indication in the future.

Sotatercept was generally well-tolerated, however, associated with increased haemoglobin and thrombocytopenia, both of which are considered manageable by dose modification. Most thrombocytopenia events were non-serious, mild, reversible, and were not associated with discontinuation of treatment. Nonetheless, the development of severe thrombocytopenia is a risk and may lead to serious or life-threatening haemorrhage. Increased haemoglobin may be asymptomatic or may be associated with vague symptoms such as headache, dizziness, myalgia, but may also predispose to potentially serious adverse consequences including hyper viscosity syndrome, hypertension, and thromboembolic events. However, in the clinical development program it was not severe or serious in any of the patients and did not lead to study discontinuations. Bleeding events is another important unfavourable effect. Although most of these events were epistaxis and non-serious, there were more serious bleeding events in the sotatercept arm. The risk of bleeding events may also be increased by severe thrombocytopenia and underlying risks factors including age, concomitant anticoagulants and concomitant prostacyclin infusion, factors which are sufficiently reflected in the product information. The incidences of telangiectasia and increased blood pressure were also both higher in the sotatercept group compared with placebo, however, none were deemed serious. Nevertheless, increased blood pressure may potentially predispose to adverse cardiovascular outcomes in the long-term. Given the high morbidity and mortality of PAH, the importance of this uncertainty is limited.

Overall, the safety exposure is considered sufficient. In Pool B (08-NOV-2023), a total of 343 subjects have at least 52 weeks of exposure to sotatercept and the median duration of exposure of 431 subjects in the overall sotatercept group was 657 days. 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, as well as, from the ongoing clinical outcome studies HYPERION (MK-7962-005) and ZENITH (MK-7962-006). Nevertheless, the safety data package does not fulfil the requirements of the "reflection paper on assessment of cardiovascular safety profile of medicinal products" (EMA/CHMP/50549/2015). In STELLAR, the number of subjects with any (non-adjudicated) MACE composite endpoint was slightly lower in the sotatercept group compared with the placebo group (n=2 (1.2%) and n= 5 (3.1%), respectively), but the number of events were too low to draw firm conclusions. Nevertheless, the positive trend towards a lower adjusted rate of "cardiac disorders" in the sotatercept group compared with the placebo group suggests a low probability of sotatercept to have a detrimental effect on CV safety. The Applicant has made a commitment to conduct a meta-analysis post-marketing in line with the EMA reflection paper on cardiovascular safety.

3.7.2. Balance of benefits and risks

The benefits of sotatercept in terms of significant improvement in exercise capacity as measured by an improvement in 6MWD compared to placebo are accompanied by manageable risks. However, available safety data does not fulfil the requirements of the "reflection paper on assessment of cardiovascular safety profile of medicinal products". Therefore, the Applicant has 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

3.8. Conclusions

The overall benefit/risk balance of Winrevair is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Winrevair is not similar to Opsumit within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Winrevair is favourable in the following indication(s):

"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)."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Sotatercept is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0414/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.