Unit: Technical Assessment Unit

Public assessment report for biological products

Winrevair

Administrative information:

Trade name of the medicinal product:	Winrevair
INN (or common name) of the active substance(s):	Sotatercept
Manufacturer of the finished product	Patheon Italia S.p.A, Italy
Marketing Authorization holder	Merck Sharp & Dohme B.V., the Netherlands
Applied 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
Pharmaceutical form(s) and strength(s):	Powder and solvent for solution for injection & 45 mg/vial or 60 mg/vial
Route of administration	by subcutaneous (SC) injection
Type of registration (EMA/FDA – Local)	EMA

List of abbreviations

ACE-011	sotatercept
ActRIIA	Activin receptor type IIA
ADA	Antidrug antibody
AESI	Adverse Events of Special Interest
AEOIs	Adverse Events of Interest
AUC	Area under the concentration-time curve
$AUC_{0\text{-}inf}$	Total AUC after extrapolation from time t (the last time point with a concentration above LLOQ) to infinity
BBB	Blood brain barrier
BMP	Bone morphogenetic protein
CHO	Chinese hamster ovary
CL	Clearance
C_{max}	Maximum concentration observed

CV	Cardiovascular
D	Day
ECD	Extracellular domain
EMA	European Medicines Agency
EPO	Erythropoietin
FC	Function class
fc	fragment crystallizable
FDA	US Food and Drug Administration
GDF	Growth and differentiation factor
GLP	Good laboratory practice
HCT	Hematocrit
hERG	Human Ether-a-go-go Related Gene, encodes the pore-forming subunit of the rapidly activating delayed-rectifier K^+ channel, Kv11.1, which is important for cardiac repolarization
Hgb	Hemoglobin
IC_{50}	Half maximal inhibitory concentration
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IP	Intraperitoneal(ly)
IV	Intravenous(ly)
kDa	kilodalton
MCT	Monocrotaline
MK-7962	Sotatercept or ACE-011, also known as ActRIIA-IgG1Fc
MRHD	Maximum recommended human dose
NOAEL	No observed adverse effect level
NT-proBNP	N-terminal pro b-type natriuretic peptide
PAH	Pulmonary arterial hypertension
PFS	Prefilled syringe
PK	Pharmacokinetics
PVR	Pulmonary Vascular Resistance
QTc	Corrected QT interval
RAP-011	Murine surrogate for sotatercept, constructed by exchanging the human IgG Fc of sotatercept with a murine IgG Fc
QxW	Every x week
RBC	Red blood cell
RGA	Reporter gene assay
SC	Subcutaneous(ly)
Smad	Small Mothers Against Decapentaplegic, a group of related intracellular proteins critical for transmitting to the nucleus signals from the TGF- β superfamily at the cell surface

t1/2	Half-life
TEAEs	Treatment-Emergent Adverse Events
TGF-β	Transforming growth factor- β
TTCW	Time to Clinical Worsening
UUL	Unilateral ureteral ligation
Vd	Apparent volume of distribution
VEGF	Vascular Endothelial Growth Factor
WBCs	White blood cells
WHO	World Health Organization
6MWD	6-Minute Walk Distance

Table of contents

1. Introduction

The file evaluated according to EDA Reliance Model & the company submitted data which are the following:

1. Quality module-3 from the CTD file.
2. EMA Unredacted Assessment.

2. Quality aspects:

Manufacturer(s):

- **Drug Substance**

- The Active substance is manufactured at Abbvie Bioresearch Center, 100 Research Drive, Worcester, MA 01605, USA.

- **Drug product**

(Winrevair 45 mg & 60mg)

- The Finished product is manufactured at Patheon Italia S.p.A, Viale Gian Battista Stucchi 110 Monza 20900, Italy.

Stability

- **Approved Shelf Life for**
  Drug Substance: 60 months
  Finished Product (Unopened vial): 36 months
- **Approved Storage Conditions:**
  Drug Substance: -80 ± 10 °C, Diluent: 2 to 8 °C / Ambient RH and 30 °C ± 2 °C / 65% ± 5%RH

  Finished Product: Store in a refrigerator (2– 8 °C). Do not freeze.
  Store 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.

3. **Non –clinical aspect:**

➢ **Sotatercept (MK-7962** or **ACE-011)** is a homodimeric recombinant fusion protein expressed in Chinese hamster ovary (CHO) cells and consisting of the extracellular domain (ECD) of the human activin receptor type IIA (ActRIIA) linked to the human IgG1 Fc domain. The observed size is ~ 92 kDa. Each monomer consists of 344 amino acids. Sotatercept is a highly selective activin signalling inhibitor that binds to the human ActRIIA, regulating key signalling for inflammation, cell proliferation, apoptosis, and tissue homeostasis and is indicated for the treatment of PAH in adult patients with WHO Functional Class (FC) II to III, to improve exercise capacity, in combination with other PAH therapies. This product was granted EMA and FDA approvals on 22 August 2024 and 26 March 2024, respectively.

➢ **Pharmacology:** 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. *In vitro* pharmacology studies showed that sotatercept and endogenous cell membrane ActRIIA bind with comparable affinity to the human ActRIIA ligands activin A and B, GDF-11, GDF-8, and BMP-10. The results of the cell-based RGAs assay demonstrate that sotatercept potently inhibited GDF11, Activin A, and Activin B and to a lesser extent GDF8, that signal through the Smad 2/3 pathway. In contrast, minimal inhibition was detected for BMP6, BMP9, and BMP10 that signal through the Smad 1/5/8 pathway. The sotatercept murine surrogate RAP-011 showed anti-remodelling effects in the pulmonary vascular wall in animal models of PAH, including pressure overload or drug-induced and genetic PAH models. RAP-011 also suppressed pulmonary inflammation and prevented macrophage infiltration in the MCT-induced PAH model. In a secondary pharmacological study evaluating hematologic endpoints, administration of RAP-011 (for 3-14 days) in C57BL/6 mice resulted in significant increases in the numbers of RBCs, Hgb, and HCT as well as a significant increase in erythropoietin protein. RAP-011 is a suitable alternative to Erythropoietin (EPO) therapy, and its effect is independent of EPO, at least in the short termIncreases in erythroid parameters in animals were of small magnitude and were not considered adverse. Safety pharmacology studies revealed no sotatercept-related abnormalities at neurological, CV or respiratory endpoints in monkey (9-month repeat-dose toxicity study), nor

any concerns regarding hERG inhibition (IC_{50} >1000 ug/mL *in vitro*) as expected from recombinant protein. Taken together the nonclinical primary, secondary, and safety pharmacology studies support sotatercept for the treatment of adults with PAH.

➢ **Pharmacokinetics:** The sotatercept PK profile in rats, rabbits, and monkeys was characterized by a biphasic distribution and elimination pattern with a low Vd (2 to 5-fold plasma volume), which is consistent with the known biodistribution of Antibodies, and a low CL resulting in a long terminal elimination t1/2 (SC) ranging from 2 to 3 days in rabbit, 4 to 8 days in rats, and 7 to 9 days in monkey, which is typical for a fusion protein and lower than in human (20 to 30 days). Systemic exposure (C_{max}, AUC) was found to be roughly proportional to the dose with no sex differences observed. Accumulation upon multiple dosing is generally absent or low. Following single-dose IV administration to rats, sotatercept exhibited linear PK, with mean t1/2 ranging from 6 to 9 days across the dose range of 1 mg/kg to 30 mg/kg. The exposure ($AUC_{0\text{-}inf}$) increased in a dose-proportional manner over the dose range. The mean CL and Vd were ~0.12 mL/h/kg and ~35 mL/kg, respectively. Following single dose IV administrations to cynomolgus monkeys, sotatercept exhibited slightly less than dose proportional increase in exposures from 1 to 30 mg/kg dose with a t1/2 ranging between 9 to 11 days. In toxicology studies, sotatercept was observed in fetal rabbit serum, and sotatercept-related effects occurred in suckling offspring from maternal rats dosed during lactation, suggesting that sotatercept can cross the placental barrier and is distributed into rat milk.

➢ **Toxicology:** In all repeat-dose toxicity studies, in both rats and monkeys, sotatercept caused an anticipated non-adverse increase in erythroid parameters and kidney toxicity at exposure margins within the clinical exposure window. The kidney toxicity has not been translated to human to date. 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. 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. Testis/epididymis toxicity observed in rats was considered to be pharmacologically driven. The microscopic features noted in the efferent ducts, the low incidence of these changes, and the predominately unilateral presentation of these effects, are all consistent with altered fluid dynamics secondary to efferent duct obstruction. Because of anatomical differences between the efferent ducts of rats and humans, the Applicant argues that the risk of testicular toxicity is species-specific and unlikely to translate to humans. 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 this finding was considered non-adverse based on the lack of structural changes in the adrenal cortex and the reversibility of the changes. The cause of the inflammatory infiltrates observed in the monkey choroid plexus is unknown. IHC data indicate that these changes are unlikely the result of ADA/immune complex deposition and could therefore be directly mediated by sotatercept. Given that sotatercept is considered unlikely to cross the blood-brain-barrier, the Applicant hypothesised based on literature that reduced Activin A activity in endothelial cells that form part of the BBB results in increased VEGF activity, which has been linked to tissue inflammation. Inflammatory infiltrates were observed in liver at clinical exposure margins in monkeys. Translation of inflammatory infiltrates in choroid plexus or liver to human is uncertain, though the Applicant noted that so far, no related adverse events have been found. Non-inflammatory perivascular basophilic deposits were observed in the aorta/heart/pancreas. Although the cause and content of the basophilic deposits are

unknown, their toxicological significance is agreed to be low as there was no corresponding tissue injury, and the findings were reversible. Developmental and reproductive toxicity studies in rats and rabbits showed efferent duct/testes toxicity, ↓ in male and female fertility, ↑ in pre- and post-implantation loss, and delays in fetal/postnatal growth and maturation, consistent with decreased ActRIIA signalling. While male fertility findings are unlikely to translate to humans due to anatomical differences between rat and human efferent ducts, this cannot be fully ruled out. As the rat is rapidly growing at a rate not seen in humans, the observed heart weight effects in juvenile animals are unlikely to be relevant. Sotatercept-mediated toxicities were similar in juvenile and adult rats but generally occurred at higher severity and at lower dosages in juvenile animals, which suggests that sotatercept may have more pronounced effects on organ systems that have not reached maturity. Sotatercept was well-tolerated locally after SC and IV administration in rats & monkeys. 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 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 UUL model, though ADA complex formation did not seem a primary mechanism, similar to observations in the GLP repeat-dose studies. Sotatercept resulted in lymphoid depletion in thymus & spleen in the 6-month and 9-month monkey studies respectively, but these findings were reversible and not associated with changes in circulating WBCs. Therefore, immunotoxicity by sotatercept is not expected.

- **Overall conclusion:** The nonclinical toxicology studies conducted with sotatercept identified adverse kidney changes in rats and monkeys that have not translated to the clinic to date, and adverse developmental and reproductive effects in female rats and rabbits that generally occurred at low exposure multiples over the exposure at the MRHD. The nonclinical profile of sotatercept supports its safe use at the proposed clinical dose for the treatment of adults with PAH.

4. Clinical aspect:

- **Clinical overview:**

The clinical pharmacology program for sotatercept consisted of:

- Two completed Phase I clinical studies conducted in healthy postmenopausal women:
  - One single-dose intravenous/subcutaneous dose-escalation study (P009),
  - And one multiple-dose subcutaneous dose-escalation study (P010).
- Three completed clinical studies in patients with pulmonary arterial hypertension (PAH):
  - Two Phase II studies (PULSAR and SPECTRA),
  - And one pivotal Phase III study (STELLAR).
- One ongoing Phase III clinical study (SOTERIA).

- **Clinical pharmacology:**

- PK of sotatercept were dose proportional and not time-dependent.
- No clinically significant effect on QTc interval was observed after administration of WINREVAIR™.
- Both 6MWD and PVR are estimated to **be flat in the dose range 0.3-0.7 mg/kg.**

➢ **Clinical Efficacy:**

The pivotal study STELLAR demonstrated that treatment with sotatercept resulted in a significant improvement in 6MWD from baseline to week 24. This improvement is considered clinically relevant and, in the range, observed with other approved PAH therapies. In addition, 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.

Overall:

WINREVAIR™

➢ **Clinical Safety:**

Across clinical studies, WINREVAIR™ demonstrated an acceptable safety profile:

- Incidences of TEAEs, serious TEAEs and severe TEAEs were low.
- No death related to WINREVAIR™ treatment.
- Telangiectasia is common AESI.
- AEOIs including increased hemoglobin, thrombocytopenia and epistaxis are commonly reported.
  - None of the events of increased haemoglobin were serious or severe.

Overall:

WINREVAIR™ was generally well-tolerated and had a manageable safety profile in participants with PAH (WHO Group 1, FC II or III).

➢ **Clinical Immunogenicity:** WINREVAIR™ is immunogenic. Although the incidence in antibodies positive and neutralizing antibodies positive was relatively high in treated subjects with PAH in Phase 2 and 3 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.

Overall: the formation of antibodies and neutralizing antibodies did not meaningfully affect PK, PD, or efficacy.

➢ **Benefit-Risk:**

Based on the totality of submitted evidence, the overall benefit-risk balance of WINREVAIR™ (45 mg/vial and 60 mg/1.3 mL) is considered favorable when used in combination with other pulmonary arterial hypertension therapies for the treatment of adult patients with pulmonary arterial hypertension (PAH) classified as WHO Functional Class II–III.

5. **General Conclusion and Recommendations if any:**

Based on the review of CTD modules and other supplementary documents, the product is approved.

For more information, please visit EMA published assessment report link:

https://www.ema.europa.eu/en/documents/assessment-report/winrevair-epar-public-assessment-report_en.pdf