Sotatercept for treating pulmonary arterial hypertension [ID6163]

For website - contains no confidential information

Technology appraisal committee A [05 August 2025]

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Sotatercept for treating pulmonary arterial hypertension

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations

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Background on pulmonary arterial hypertension

PAH is a progressive disease impacting daily life

Diagnosis and classification

- PAH is a rare, severe form of PH characterised by high blood pressure leading to thickening of the smaller branches of pulmonary arteries
- Classified by WHO functional class (assesses severity of symptoms and their impact on daily activities) and ESC/ERS classification (predicts outcomes and guides treatment decisions using WHO FC and other factors)

	ESC four-strata risk-assessment tool			
	Low risk	Intermediate-low risk	Intermediate-high risk	High risk
WHO FC	I or II[a]	-	III	IV
[a]WHO FC I and II are assigned 1 point (appendix for more information) and low risk as associated with good long-term survival				

Symptoms and prognosis

- Severe daily impact; breathlessness, extreme fatigue, weakness and chest pain
- PAH is progressive and prognosis is poor - median survival of 6 to 7 years after diagnosis
- People with PAH have a higher risk of hospitalisation and illnesses (pneumonia and heart failure)

Epidemiology

- 4,269 people with PAH in the UK, with 568 new diagnoses each year (2021-2022)
- PAH affects people of all ages but more commonly women between 30 to 60 years

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Abbreviations: ESC/ERS, European society of cardiology/European respiratory society; FC, functional class; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; WHO, world health organisation.

Treatment pathway

Treatment determined by risk status, company positioned sotatercept for intermediate-low risk

People with no cardiopulmonary comorbidities

1. Initial risk stratification at diagnosis

- Low or intermediate → ERA + PDE5i
- High → ERA + PDE5i + PCA

People with cardiopulmonary comorbidities will receive ERA or PDE5i. At follow-up they will be considered for individualised therapies

2. Follow-up with ESC risk stratification after 3 to 6 months

- Low → Continue initial treatment
- Intermediate-low → + PRA (selexipag); + sotatercept; Switch PDE5i to Riociguat
- Intermediate-high or high → PDE5i + ERA + PCA or consider for transplant

EAG: PDE5i + ERA + selexipag is a relevant comparator, but limiting to this excludes intermediate-low risk treated without selexipag

Questions for experts

- Would sotatercept be an option for intermediate-high- or high-risk people? with which treatments?
- What treatments are currently available for intermediate high- or high-risk (key issue 5)
- Is population that is high-risk at diagnosis but intermediate-low at follow-up excluded from decision population?

Questions for committee

- Does this reflect the current treatment pathway in the UK?
- Is the company's positioning of sotatercept appropriate? What are the most appropriate comparators?

Abbreviations: ESC/ERS, European society of cardiology/European respiratory society: ERA: endothelin receptor antagonist; FC: functional class; PAH: pulmonary arterial hypertension; PCA: prostacyclin analogue; PDE5i: phosphodiesterase type 5 inhibitor; PRA: prostacyclin receptor agonist; UK: United Kingdom; WHO: World Health Organization

More information in appendix

Equality considerations

Sotatercept is being considered within its anticipated marketing authorisation

Administration

- Pre-filled injection to be self-administered at home:
    - some people with disabilities may need help to administer (from a healthcare professional)
    - allows some people who have previously not been able to have IV treatment to access at home treatment

Age and sex

- Older patients and people who are menstruating may not be considered for sotatercept because of an increased risk of bleeding and associated complications

Clinical expert submission

Need to attend 5 extra clinic appointments and travel to 1 of 7 specialist centres. Sotatercept accessibility affected by symptom burden, financial burden, mobility and/or time commitments

Abbreviations: IV, intravenous

Patient organisation perspectives

First-in-class drug in PAH, with encouraging clinical trial results

Submissions from Pulmonary Hypertension Association UK

Unmet need

- Recent survey of ~300 people showed high burden of symptoms with current treatment including, breathlessness during daily living activities, fatigue, and poor sleep
- People with PAH consistently place quality of life as their primary goal of treatment
- Sotatercept shows improved QoL beyond current treatments

Use in the NHS

- Early access programme in UK (data not yet published):
  - proportion of participants are expressing improvement in their QoL and ability to engage meaningfully in day-to-day life
  - Reflects what is being seen in clinical trials
- May cause increase bleeding episodes and other common side-effects but organisation does not believe these to be significant

"Unmet need is treatments that fully address the high symptom burden in WHO FC II/III. So, sotatercept is a potential step-change in PAH management"

Abbreviations: FC, functional class; PAH, pulmonary arterial hypertension; QoL, quality of life; WHO, World Health Organization

Clinical perspectives

Trial and clinical experience suggesting improvements in symptoms, risk profile, and QoL

Submissions from Royal Free London NHS Foundation Trust

Benefits of sotatercept

- Benefits of sotatercept include improved QoL and OS beyond current treatments

Use in the NHS

- Used as an add-on therapy but most will stop selexipag to escalate with sotatercept
- Introduction of sotatercept would require centres to have:
  - ~5 extra clinic appointments with full blood count (monitoring phase); accessibility concerns for people needing to travel to additional appointments
  - pharmacy capacity to screen for up-to-date body weight and FBC
  - nurse specialist with training for people on their medication
  - cold chain delivery of medication (kept at 2 to 8 degrees)

"this technology is a step-change in the management of PAH with significant improvements in symptoms and clinical risk profile"

Abbreviations: FC, functional class; FBC, full blood count; MCID, minimal clinically important difference; OS, overall survival; PAH, pulmonary arterial hypertension; QoL, quality of life

Sotatercept (Winrevair, MSD)

Marketing authorisation	• Winrevair, in combination with other PAH therapies, is indicated for the treatment of PAH in adult patients with WHO FC II to III, to improve exercise capacity • Granted by MHRA, 27 December 2024
Mechanism of action	• Sotatercept is a recombinant fusion protein which acts as an activin signalling inhibitor • Helps to balance the proliferative and anti-proliferative signals that control the growth of blood vessel walls, controlling vascular proliferation
Administration	• First dose: 0.3 mg/kg, covers first 21 days of treatment • Following doses: 0.7 mg/kg, every 21 days (subcutaneous) • Note: not possible to vial share as treatment is provided at home
Price	• List price per vial is £5,422.50 (45mg) and £7,230.00 (60mg) • Annual drug acquisition cost of [redacted] • A patient access scheme applies for sotatercept • Company has included wastage in treatment acquisition cost calculations

More information on WHO FC stratification in appendix

Abbreviations: FC, functional class; MHRA, medicines and healthcare products regulatory agency; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; WHO, world health organisation.

Key issues

	Issue	ICER impact
1	Within-trial analyses of PDE5i + ERA + sotatercept vs PDE5i + ERA + selexipag	Unknown
2	Use of relative risks from the post-hoc subgroup analysis of STELLAR to inform transition probabilities for selexipag	Small
3	Ongoing application of a short-term (24 week) RR of deterioration, to generate long-term transition probabilities for selexipag	Large
4	The simplifying assumption of not allowing for clinical improvement following initiation of PGI2 analogues.	Unknown
5	Timing and approach to PGI2 initiation in the sotatercept arm of the model	Large
6	The proportion of PGI2 analogues	Medium
7	Weight-based doses applied to IV PCA preparations	Large
8	Utility	Large

Abbreviations: ERA: endothelin receptor antagonist; FC: functional class; IV: intravenous; PGI2: prostaglandin I2; PAH: pulmonary arterial hypertension; PCA: prostacyclin analogue; PDE5i: phosphodiesterase type 5 inhibitor; PRA: prostacyclin receptor agonist; sGC: soluble guanylate cyclase; RR, relative risk; WHO: World Health Organization

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Key clinical trials – STELLAR and SOTERIA

	STELLAR (NCT04576988) (n=323)	SOTERIA (NCT04796337) (n=426)
Design	Phase 3, multicentre, double-blind, placebo- controlled RCT	Phase 3, open-label, long-term follow-up, interventional study
Population	Adults with PAH with WHO FC II or III Inclusion criteria: Stable background therapy 90 days prior, PVR ≥ 400 dyn·sec·cm−5, PCWP or left ventricular end diastolic pressure ≤ 15 mm Hg, 6MWD ≥ 150 and ≤ 500 metres.	Adults with PAH who have completed 1 of the 7 included studies (different inclusion criteria)
Intervention: Sotatercept	Starting dose of 0.3 mg/kg with a target dose of 0.7 mg/kg Administered SC every 21 days plus background PAH therapy	SC injection at a dose of 0.3 to 0.7 mg/kg
Comparator(s)	Placebo SC every 21 days plus background PAH therapy	N/R
Background	Mono, dual or triple background therapy (ERA, PDE5i, PCA and PRA)	
Duration of study	108 weeks	7 years
Primary outcome	6MWD	Long-term safety and tolerability
Secondary outcomes	MCI, PVR, NT-proBNP, WHO FC	6MWD, PVR. NT-proBNP, WHO FC
Locations	Argentina, Australia, Belgium, Brazil, Canada, Czechia, France, Germany, Israel, Italy, Korea, Republic of, Mexico, Netherlands, New Zealand, Poland, Serbia, Spain, Sweden, Switzerland, **United Kingdom**, United States	STELLAR plus; Austria, Colombia, Croatia, Denmark, Greece, Taiwan
Used in model?	Yes	No

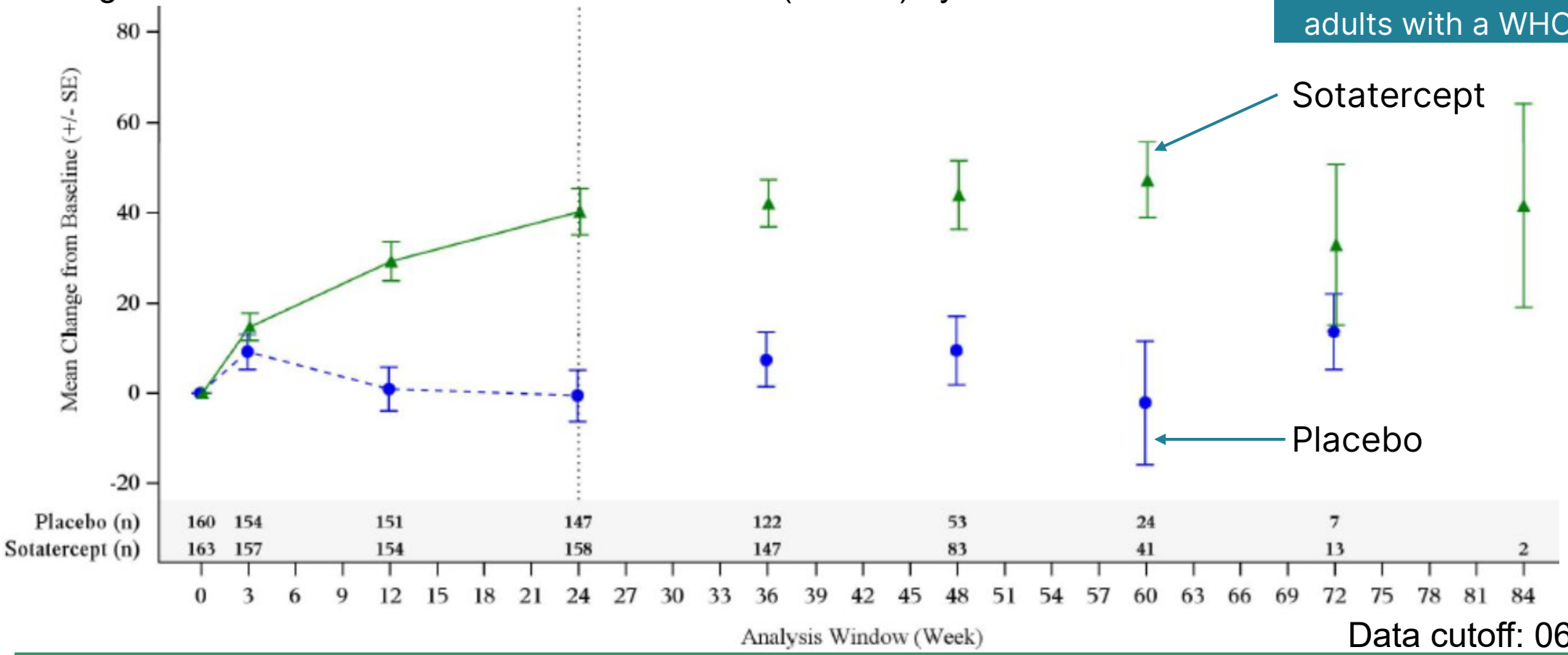
Abbreviations: 6MWD, 6-minute walking distance; ERA, endothelin receptor antagonist; FC, functional class; MCI, multicomponent improvement; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PCA, prostacyclin analogue; PDE5i, phosphodiesterase type 5 inhibitor; PRA (selexipag), prostacyclin receptor agonist; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SC, subcutaneously; WHO, World Health Organization

Key clinical trial results – STELLAR, double-blind, phase 3 RCT

At week 24, sotatercept significantly improves 6MWD compared to placebo

Change from Baseline in 6-Minute Walk Distance (metres) by visit

Results from full trial population: adults with a WHO FC 2 or 3



Data cutoff: 06 Dec 22

Clinical expert submission

6MWD is a common primary endpoint, would consider minimal clinically important difference to be 33 metres

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Abbreviations: 6MWD, 6-minute walking distance; RCT, randomised controlled trial; FC, functional class; WHO, world health organisation

Key clinical trial results – STELLAR

Significantly greater proportion of improvements in 6MWD of at least 30 metres in the sotatercept arm than in the placebo arm

Results from full trial population

Outcome	Sotatercept (n=163)	Placebo (n=160)
Mean change from baseline at week 24 (SD)	40.3 (64.18)	-0.6 (69.54)
Mean change from baseline at week 84 (SD)	41.6 (31.86)	-161.5
Proportion with improvement in 6MWD of at least 30 metres	54%	22%
Hodges-Lehmann location shift (ASE)[a]	40.4 (6.70)	N/A
95% CI of Hodges-Lehmann location shift	(27.28, 53.53); p<.001	N/A

[a]Hodges-Lehmann location shift from placebo estimate (median of all paired differences). Placebo administered every 21 days plus background PAH therapy, may consist of ERA, PDE5i, guanylate cyclase stimulator, and/or a PCA or PRA

- Participants permitted to roll over into SOTERIA if they experienced a clinical worsening event or completed the 24-week treatment period in STELLAR
- SOTERIA reports long-term safety data for sotatercept – see appendix.
- Company did post-hoc, within-trial analysis of STELLAR to assess change from baseline in risk status at week 24 between sotatercept and selexipag – see key issue 1 and results from analysis in appendix

Abbreviations: ASE, asymptomatic standard error; CI: confidence interval; 6MWD, 6-minute walking distance; ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; PCA, prostacyclin analogue; PDE5i, phosphodiesterase type 5 inhibitor; PRA (selexipag), prostacyclin receptor agonist

Indirect treatment comparisons

ITC results significantly favour sotatercept over selexipag for WHO FC worsening, 6MWD and NT-proBNP

	ITC 1	ITC 2	ITC 3
Treatments	sotatercept versus selexipag	sotatercept versus selexipag	sotatercept versus IV PCA
Data type	Trial	Trial and RWE	Lack of an appropriate common comparator from the studies in SLR
Data source	STELLAR (sotatercept), GRIPHON and TRACE (selexipag)	STELLAR (sotatercept), IPD in UK from TRIPHIC database (selexipag)	
		Relevant population from TRIPHIC database was too small to allow for meaningful ITC	Anchored ITCs not feasible due to the lack of common comparator
		Appropriate ITCs not feasible	

Outcome	Point estimates favoured sotatercept	Significant? (based on confidence intervals)
WHO FC improvement	Yes	No
WHO FC worsening	Yes (risk of worsening lower with sotatercept)	Yes
change in 6MWD	Yes	Yes
change in NT-proBNP	Yes	Yes

Abbreviations: 6MWD, 6-minute walking distance; FC, functional class; IPD, individual patient data; ITC, indirect treatment comparison; PCA: prostacyclin analogue; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO, World Health Organization

Key issues 1 and 2: Using relative risks from within-trial analyses (STELLAR) to inform transition probabilities for selexipag (1/2)

Background

- Post-hoc analysis to assess change in risk status included participants from STELLAR that were only treated with:
  A) Sotatercept arm: PDE5i + ERA B) Placebo arm: PDE5i + ERA + selexipag
- RR of ESC/ERS risk strata improvement/deterioration from within trial analysis then used to inform selexipag transition probabilities

Company

- Current treatment is PDE5i + ERA + selexipag so PDE5i + ERA + sotatercept is the relevant regimen → comparison not possible with the ITC using external trial data
- ITC to compare change in risk status from baseline not possible as outcome not included in external trial data
- Transition probabilities for selexipag estimated by applying relative risks of improvement/deterioration to the estimated transition probabilities for sotatercept using a post-hoc subgroup analysis (n=[redacted])
- Results from analysis in appendix

ERA: endothelin receptor antagonist; FC: functional class; ITC, indirect treatment comparison; PCA: prostacyclin analogue; PDE5i: phosphodiesterase type 5 inhibitor; PRA: prostacyclin receptor agonist; TP, trantiion probabilites; RR, relative risk.

Key issues 1 and 2: Using relative risks from within-trial analyses to inform transition probabilities for selexipag (2/2)

EAG comments

- Doesn't allow for a direct comparison of the treatment effects of sotatercept and selexipag because:
  - Placebo arm already receiving PDE5i, ERAs, and selexipag → any treatment effect unobservable
  - Breaks randomisation → comparing double combination to triple combination at baseline
  - Those having triple combination → more heavily treated and doing less well
- EAG suggests: ITC with GRIPHON and TRACE trial of selexipag offers potentially less biased estimates of RR (assumption 3)
- But uses different grouping (WHO FC) - see EAG preferred assumptions and low-high base cases
- Acknowledges challenges in generating this evidence, expert opinion on face validity of modelled projections of progression to intermediate-high and high risks states may be beneficial (Appendix: EAG projections)

	ESC four-strata risk-assessment tool			
Determinants of prognosis	**Low risk**	**Intermediate-low risk**	**Intermediate-high risk**	**High risk**
WHO FC	I or II[a]	-	III	IV
6MWD,m	>440	320-440	165-319	<165
[a]WHO FC I and II are assigned 1 point (appendix for more information) and low risk as associated with good long-term survival				

- Should the within trial analysis or the ITC with GRIPHON/TRACE be used to inform the change in risk status in the model?
- What other analysis would committee need to further understand the impact of using the ITC with GRIPHON/TRACE (less bias but WHO FC stratification) compared to within trial analysis (ESC stratification but bias estimates)?

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ERA: endothelin receptor antagonist; FC: functional class; ITC, indirect treatment comparison; PCA: prostacyclin analogue; PDE5i: phosphodiesterase type 5 inhibitor; PRA: prostacyclin receptor agonist; TP, trantiion probabilites; RR, relative risk.

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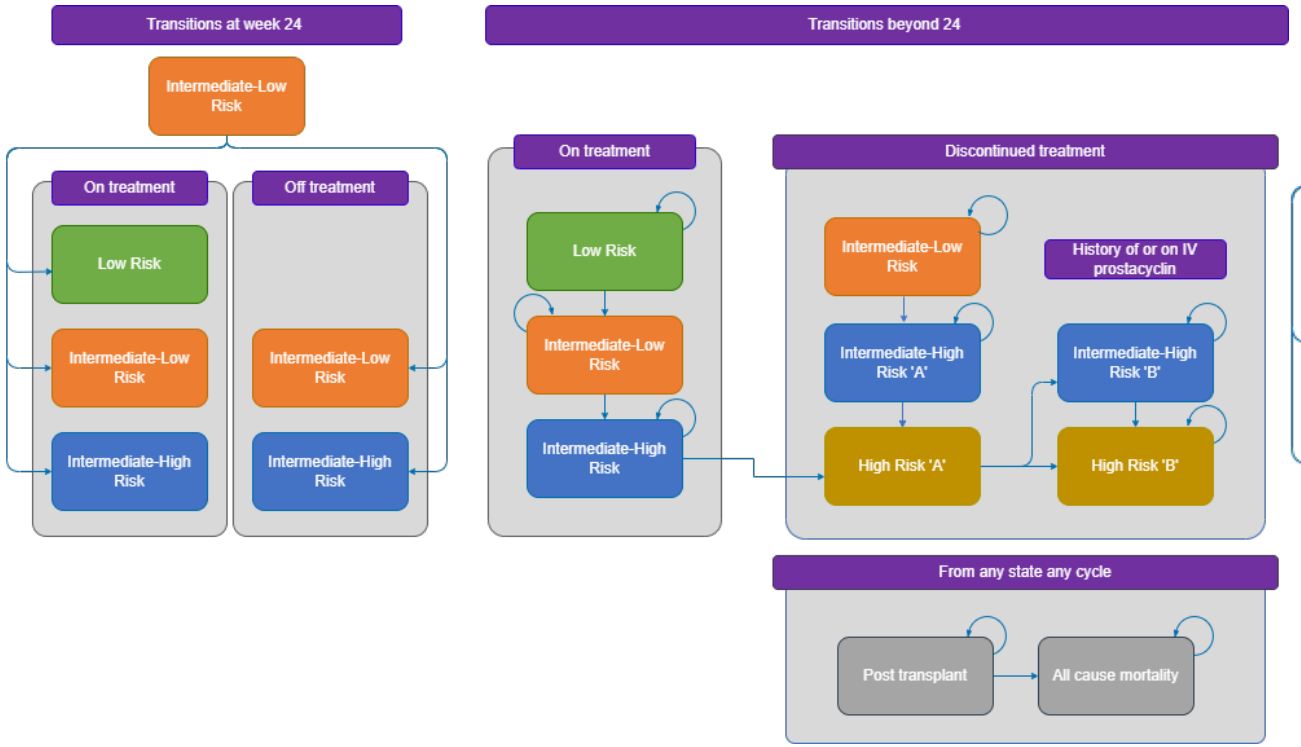
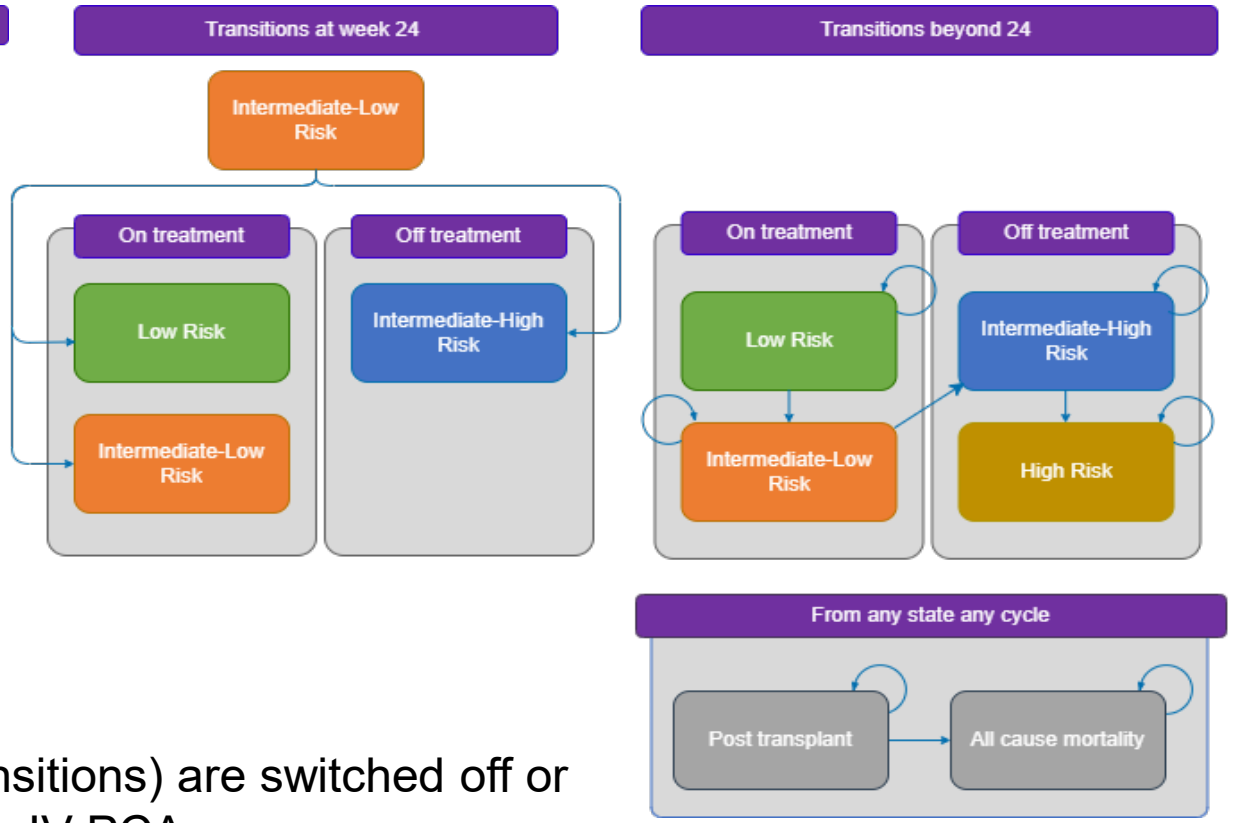
Company's model overview

Model structure: Decision tree (first 24 weeks) with Markov cohort model

Possible movements (sotatercept)



Possible movements (selexipag)



From Company Submission

The possibility for clinical improvements (backwards transitions) are switched off or have not been included in this model after treatment with IV PCA

- Not included in selexipag arm due to uncertain evidence for intermediate-low risk with IV PCA treatment
- Not possible to add the level of complexity needed in the time frame

Company's model overview

Assumptions with greatest **ICER** effect:

- Relative effect of sotatercept versus selexipag on long-term transitions probabilities between health states
- Proportion of patients who have infused PCA treatments upon progression to the higher risk states
- Whether IV PCA is administered with sotatercept or instead of sotatercept in higher risk states
- Assumed weight-based doses of the IV PCA preparations that are applied in the model
- HSUV decrement applied to IV PCA use
- Assumed weight-based dose of sotatercept that is applied

HSUV, health state utility value; ITC, indirect treatment comparison; IV, intravenous; PCA: prostacyclin analogue

Key Issue 3 : Ongoing application of RR for long term transition probabilities

Background

- Short term (24 week) RR of ESC/ERS risk strata improvement/deterioration are used to derive transition probabilities over entire time horizon

Company

- No longer-term RCT evidence → assumption of a constant treatment effect over time (SOTERIA suggests no waning effect)

Alive in progression free states: model output versus GRIPHON (selexipag)

EAG comments

- Lacks clinical face validity → (<1%) on selexipag remain in intermediate-low or low risks states by approximately [redacted] months compared to [redacted] in the sotatercept arm
- EAG suggests, use ITC with GRIPHON/TRACE → more plausible output but reapplications of the same transition probabilities long term may overestimate risk status deterioration in selexipag EAG suggests, reduce the magnitude of these effects when applied to long-term transition probabilities, developed scenario analysis from 100% to 25% of relative treatment effects (Assumption 4)

- Which method is more plausible for the long-term transition probabilities?
- Is risk status expected to change or deteriorate over time and by how much?

Abbreviations: CE, clinical expert; ESC, European Society of Cardiology; European Respiratory Society ; ITC, indirect treatment comparison ; RR, relative risk

Key issue 4: Assuming no clinical improvement following initiation of PGI2 analogues

Background

- On progression to intermediate-high-risk state, people with PAH will be escalated to PGI2 analogues (IV PCA) and discontinue selexipag. But the model does not allow for clinical improvement (transitioning to a lower risk state) with IV PCA. So, the cost but not efficacy of IV PCAs is included in model.

Company

- Including this in the model would add additional complexity to the model structure and the evidence of how the efficacy may differ from the sotatercept arm is uncertain
- Same assumption added to the sotatercept arm of the company's base case at clarification for consistency

EAG comments

- Clinical expert suggests the simplifying assumption lacks clinical validity
- A large proportion of the selexipag arm progress to intermediate-high and high risks states, receiving costly treatment and utility decrement with PGI2 analogues – may bias in favour of sotatercept
- Treatment escalation in progression to intermediate-high risk state for those on sotatercept is not clear
- Expanding model structure for improvement/maintenance of risk status after PGI2 would be beneficial

- Is the model structure suitable for decision making or does it need to be expanded to allow for improvement after PGI2 initiation?

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Abbreviations: IV: intravenous; PCA: prostacyclin analogue; PDE5i: phosphodiesterase type 5 inhibitor; PGI2: prostaglandin I2; PRA: prostacyclin receptor agonist; CE, clinical expert; TTO, time trade-off.

Key issue 5: PGI2 initiation in the sotatercept arm in model

Background

- Progression to intermediate-high risk state on sotatercept: remain on sotatercept and no initiation of PGI2
- Progression to high-risk state on sotatercept: PGI2 analogue treatment instead of sotatercept

Company

- In UK clinical practice, on progression to intermediate-high risk status treatment will be PDE5i + ERA + IV PCA

EAG comments

- CE: progression to intermediate-high or high-risk → some remain on sotatercept with PGI2 analogue initiation
- Recommend including PGI2 costs for a proportion of intermediate-high risk progression
- EAG approach: progression to inter-high risk: treated with ERA+PDE5i+sotatercept+ PGI2 (assumption 9)
- Scenarios for sotatercept + PGI2 (with BGT) on progression to high-risk states - EAG not confident results as can't account for increased efficacy of this compared with less invasive treatment at high-risk in selexipag arm
- Confirmation of treatment escalation approach and data to inform efficacy of different combinations would be beneficial

Clinical expert submission

- Progression to intermediate-high risk state: remain on sotatercept and consider initiation of PGI2 analogue
- Progression to high-risk state: unlikely to stop sotatercept after PGI2 initiation

- Should progression to intermediate-high include the initiation of PGI2 analogues (EAG) or not (company)?
- How should progression to high risk be modelled if there is no way to account for efficacy with sotatercept?

Abbreviations: BGT, background therapy, FC: functional class; ITC, indirect treatment comparison; PCA: prostacyclin analogue; PDE5i: phosphodiesterase type 5 inhibitor; PRA: prostacyclin receptor agonist; PGI2: prostaglandin I2; PRA: prostacyclin receptor agonist; CE, clinical expert; RR, relative risk.

Key issue 6: Proportion treated with PGI2 analogues

Company

- 100% of people are treated with PGI2 analogues when they are initiated following progression
- Consistent across intermediate-high to high-risk states

EAG comments

- CE: treatments may not be suitable for all and of those offered, not all accept it
- CE: In intermediate-high to high-risk states reasonable to assume 85% would have treatment but could be lower in real-world, rest maintain previous treatment (assumption 9)
- Lower proportion than in the data, but counters bias causes by issue 4
- Further CE opinion or RWE could be beneficial

Company and EAG preferred proportions of PGI2 treatments

Risk	Company base case	EAG clinical expert opinion
Intermediate high - sotatercept	0%	39.9%
Intermediate high – sotatercept discontinued	100%	85%
Intermediate high – selexipag	100%	85%
High – sotatercept	100%	85%
High – sotatercept discontinued	100%	85%
High - selexipag	100%	85%
Intermediate low risk not treated with PGI2 analogues		

Which proportions for starting PGI2 analogues are most appropriate?

Abbreviations: IV: intravenous; PCA: prostacyclin analogue; PDE5i: phosphodiesterase type 5 inhibitor; PGI2: prostaglandin I2; PRA: prostacyclin receptor agonist; CE, clinical expert;

Key issue 7: High doses applied to the IV PCA preparations

Background

- IV PCA preparations (epoprostenol and treprostinil) applied in the economic model are administered as weight-based doses by continuous IV infusion. Cost but not efficacy of PCA is included in model (Issue 4)

Company

- Target doses derived from a prior appraisal of selexipag considered by CDA, setting the target dose of epoprostenol at 50ng/kg/min and at 30ng/kg/min for treprostinil

EAG comments

- CE: doses differ (particularly epoprostenol) from NHS practice → overestimation of epoprostenol costs, bias towards sotatercept
- Prefer alignment with ESC/ERS guidelines (assumption 10)
  - Epoprostenol: 23ng/kg/min (midpoint of 16-30ng/kg/min)
  - Treprostinil: 42.5ng/kg/min (midpoint of 25-60ng/kg/min)
- RWE or CE validation of the doses of IV PCA applied in the UK NHS would be beneficial

Clinical expert submission

- PGI2 analogue preparations used by company are applicable to those used in clinical practice

- What doses for IV PCA preparations are most likely to be used in clinical practice?

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Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; IV: intravenous; PCA: prostacyclin analogue; PDE5i: phosphodiesterase type 5 inhibitor; PGI2: prostaglandin I2; PRA: prostacyclin receptor agonist; CE, clinical expert;

QALY weightings for severity

Severity modifier is appropriate in both base cases (x1.2), apart from two scenarios (x1.0)

QALY shortfall in company base case

	QALYs of people without condition (based on trial population characteristics)	QALYs with the condition on current treatment	**Absolute QALY shortfall (has to be >12)**	**Proportional QALY shortfall (has to be >0.85)**
Company base case	16.74	[redacted]	[redacted]	[redacted]

EAG comments

- Case met for a severity weighing of 1.2 on QALY gains, based on the absolute shortfall versus the expected QALYs of the age/sex matched general population
- Approaches that could impact the absolute QALY shortfall include:
  - aligning baseline population characteristics with UK National Audit of Pulmonary Hypertension
  - these baseline population characteristics plus, different mortality modelling approaches

	EAG alternative scenario	EAG base case
Baseline characteristics	Based on UK National Audit of Pulmonary Hypertension	Baseline characteristics of STELLAR
Modelling mortality	Overall survival – Dependent Gompertz model for the four risk strata (with baseline characteristics from UK national audit)	Single gamma model for the low-risk group, with hazard ratios from cox regression applied
Severity modifier	X 1.0	X 1.2

Appendix: baseline characteristics for both populations

- Does committee consider the QALYs presented to be accurate?
- Is additional information needed to assess severity?

Abbreviations: QALY, quality-adjusted life year

Utility

Parameter	Company preferred assumptions	EAG preferred assumptions	EAG rationale
Decrement for IV PCA administration (related to key issue 4)	-0.307, based on difference in TTO values for oral vs IV admin	Remove decrement in inter-high- or high-risk states	Clinical improvement preferred, but unable to modify model structure. Removing decrement compensates for lack of clinical benefit
Increment for carers of people in less severe states	Increments of 0.036,0.023 and 0.013 for low, intermediate-low and intermediate-high risks states	Accepted company approach	-
Decrement of hospitalisation	Decrement of 0.105 per 12-week model cycle	Reduce utility decrement to 0.071, applied for the duration of the cycle in which events occur	McMurray et al. reported 0.105 for hospitalisation within 30 days and 0.054 for hospitalisation within 30-90 days

- Should the utility decrement for IV PCA be removed?
- Should the decrement for hospitalisation be -0.105 or -0.071?

Abbreviations: QALY, quality-adjusted life years; FC, functional class; ITC, indirect treatment comparison; WHO, World Health Organization

Summary of company and EAG base case assumptions (1/2)

Parameter	Company base case assumption	EAG preferred assumptions (applied to company base case)	Issue
Short term selexipag TPs	RR from post-hoc analysis used to inform short term (24 weeks) TPs for selexipag	WHO FC RR from the ITC with GRIPHON/TRACE used to inform TPs for selexipag	2
Long-term selexipag TPs*	Ongoing application of short-term RR over whole time horizon	1. WHO FC RR from the ITC with GRIPHON/TRACE used to inform TPs for selexipag 2. TPs derived by applying [redacted] RR reduction of disease progression at 24 weeks, based on half of RR observed at 24 weeks from ITC with GRIPHON	3
Improvement after PGI2 initiation*	No clinical improvement possible. Decrement of 0.307 applied for IV PCA administration.	Clinical improvement preferred, but unable to modify model structure. Remove decrement in inter-high- or high-risk states (compensate for lack of clinical benefit)	4
Initiation of PGI2 analogues for sotatercept*	Progression to inter-high-risk: no PGI2 Progression to high-risk: PGI2 given in place of sotatercept	Progression to inter-high-risk: PGI2 analogues cost added to sotatercept for 39.9% Progression to high-risk: as company submission	5
Proportion of PGI2 analogues	Selexipag: 100% on progression to the inter-high-risk state. Sotatercept arm: 100% high-risk state.	Selexipag: 85% progression to high- and inter-high Sotatercept: 85% on progression to high-risks state, 39.9% inter-high-risks state.	6
Dosage of PGI2 analogues*	Epoprostenol: 50ng/kg/min Treprostinil: 30ng/kg/min	Epoprostenol: 23ng/Kg/min Treprostinil: 42.5ng/Kg/min	7

*Largest impact as highlighted by the EAG

Abbreviations: FC: functional class; ITC, indirect treatment comparison; PCA: prostacyclin analogue; PGI2: prostaglandin I2; PRA: prostacyclin receptor agonist; CE, clinical expert; RR, relative risk; TP, transition probabilities.

Summary of company and EAG base case assumptions (2/2)

EAG base case	Assumption
Mid	50% of the [redacted] RR reduction from ITC ([redacted]), as proxy to long term effect
Low	Full RR reduction from ITC, as proxy to long term effect
High	25% of the RR reduction from ITC, as proxy to long term effect

Uncertainty in long-term effects of sotatercept versus selexipag on ESC/ERS risk status change.

EAG created mid, low and high base case; RR reduction derived from the ITC between STELLAR and GRIPHON/TRACE for WHO FC and used for the long-term effect risk status deterioration

(Appendix: EAG projected survival in low, mid and high base case)

Remaining assumptions in appendix

Abbreviations: QALY, quality-adjusted life years; FC, functional class; ITC, indirect treatment comparison; WHO, World Health Organization

Cost-effectiveness results: cPAS prices included (1/2)

No.	EAG preferred assumptions (applied to company base case)	Cumulative ICER (£/QALY)*
1	**Company base case**	Under £30,000
2	Hospitalisation QALY loss calculations adjusted to the 12-week cycle length	Under £30,000
3	Selexipag short term (24 week) transition probabilities informed by application of WHO FC relative risks from the ITC with GRIPHON/TRACE (key issue 2)	Under £30,000
4	Selexipag long-term transition probabilities derived by applying half of the [redacted] relative risk reduction of disease progression for sotatercept versus selexipag at 24 weeks, based on the ITC with GRIPHON/TRACE =[redacted] relative risk reduction (key issue 3)	Over £30,000
5	Remove independent effect of sotatercept versus selexipag on hospitalisation in the low and intermediate-low risk state	Over £30,000
6	Remove IV PCA administration disutility - to compensate for the lack of clinical benefit included in the model for these treatments (key issue 8 and related to key issue 4)	Over £30,000
7	Reduce utility decrement associated with hospitalisation from 0.105 to 0.071, applied for the duration of the cycle in which events occur (key issue 8)	Over £30,000

*with and without severity modifier.

Abbreviations: IV: intravenous; PCA: prostacyclin analogue; QALY, quality-adjusted life years; ; FC, functional class; ITC, indirect treatment comparison; WHO, World Health Organization

Cost-effectiveness results: cPAS prices included (2/2)

	EAG preferred assumptions (applied to company base case)	ICER (£/QALY) versus BSC*
1	**Company base case**	Under £30,000
8	PGI2 analogues added to sotatercept for 40% on progression to the intermediate-high risk state (key issue 5)	Over £30,000
9	85% not 100% receive PGI2 analogues following progression to high risk and intermediate high risks state (key issue 6)	Over £30,000
10	Dosing assumptions for epoprostenol and treprostinil based on target maintenance doses in ESC / ERS guidelines: 23ng/Kg/min and 42.5ng/Kg/min, respectively (key issue 7)	Over £30,000
11	Assume consultant led OP appointments to initiate treatment on sotatercept and selexipag but retain company assumptions about number of contacts	Over £30,000
Due to uncertainty in the long-term effects on sotatercept versus selexipag on ESC/ERS risk strata change, the EAG have created a mid, low and high base case where some or all of the RR reduction is derived from the ITC between STELLAR and GRIPHON for WHO FC, is applied as the proxy for the long-term effect of sotatercept versus selexipag on ESC/ERS risk status deterioration		
Mid	EAG base case (50% of [redacted] RR reduction from ITC, applied as proxy to long term effect)	Over £30,000
Low	EAG base case (full ([redacted]) RR reduction from ITC, applied as proxy to long term effect)	Over £30,000
High	EAG base case (25% RR reduction derived from ITC, applied as proxy to long term effect)	Over £30,000

*with and without severity modifier

Sotatercept for treating pulmonary arterial hypertension

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**

NICE National Institute for Health and Care Excellence

Managed access

Company has not submitted a managed access proposal.

Sotatercept for treating pulmonary arterial hypertension [ID6163]

Supplementary appendix

NICE National Institute for Health and Care Excellence

WHO FC and ESC risk stratification

Variables used to calculate the simplified four-strata risk-assessment tool

Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP,[a] ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

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6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO-FC, World Health Organization functional class.
Risk is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer.
[a]WHO-FC I and II are assigned 1 point as both are associated with good long-term survival.

Source: ESC guidelines

- WHO FC is assigned by clinicians asking a series of questions focused on how PAH symptoms affect daily activities and physical exertion
- WHO FC system ranges from Class I (least severe) to Class IV (most severe)
- Classification is based primarily on self-reported symptoms and functional limitations

Abbreviations: 6MWD, 6-minute walking distance; FC, functional class; MCI, multicomponent improvement; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SC, subcutaneously; WHO, World Health Organization

Key issue 1: Within-trial analyses of PDE5i + ERA + sotatercept versus PDE5i + ERA + selexipag

Background

- Post-hoc analysis to assess change in risk status included participants only treated with:
  A) Sotatercept arm: PDE5i + ERA B) Placebo arm: PDE5i + ERA + selexipag

	Sotatercept N =36	Selexipag N =26	p-value
Likelihood of improvement in risk status	[redacted]	[redacted]	[redacted]
Likelihood of worsening in risk status	[redacted]	[redacted]	N/A

Back to key issue 1 and 2

Abbreviations: ERA: endothelin receptor antagonist; IV: intravenous; PCA: prostacyclin analogue; PDE5i: phosphodiesterase type 5 inhibitor; PRA: prostacyclin receptor agonist; PVR: pulmonary vascular resistance

Projected progression: risk status change from baseline

EAG comments

- Key issue 2: acknowledged challenges with generating this evidence, expert opinion on the face validity of the modelled projections of progression to intermediate-high and high risks states may be beneficial

Alive in progression free states (Model output versus GRIPHON Primary Outcome for selexipag)

[redacted]

Percentage survival in low-risk or intermediate-low risk states for the company base case and alternative EAG base case options

[redacted]

Key clinical trial results –SOTERIA

Study shows safety data and effect on long-term treatment with sotatercept. EAG has no concerns about the rates of any AEs in STELLAR or SOTERIA

Cutoff 08-Nov-23		Placebo-Crossed			Continued Sotatercept			Total		
		Baseline	Week 24	Year 1	Baseline	Week 24	Year 1	Baseline	Week 24	**Year 1**
6MWD	n	143	138	130	259	232	214	426	380	347
	Mean (SD)	404.5 (103.3)	448.3 (93.1)	455.3 (91.8)	446.3 (104.6)	455.9 (100.7)	452.8 (106.1)	420.4 (116.4)	449.0 (100.8)	453.1 (100.7)
	Mean (SD) change from baseline	—	41.3 (74.3)	47.3 (80.7)	—	−0.02 (37.2)	−1.7 (47.6)	—	17.4 (59.9)	17.8 (68.7)
	p-value	—	<0.0001	<0.0001	—	0.80	0.75	—	<0.0001	<0.0001
NT-proBNP	**n**	143	128	125	259	226	211	426	363	339
	Mean (SD)	1245.5 (2519.8)	437.9 (1124.7)	339.9 (642.3)	364.8 (1279.1)	314.7 (953.0)	326.6 (981.9)	917.5 (2579.1)	370.9 (1029.7)	330.3 (866.4)
	Mean (SD) change from baseline	—	−828.3 (1861.5)	−826.9 (2099.1)	—	−31.0 (987.4)	−32.8 (1145.3)	—	−396.6 (1620.6)	−341.3 (1620.1)
	p-value	—	<0.0001	<0.0001	—	0.39	0.52	—	<0.0001	<0.0001
WHO FC II/I	**n**	143	140	134	259	250	239	426	400	376
	n (%)	73 (51.0)	108 (77.1)	107 (79.9)	209 (80.7)	205 (82.0)	197 (82.4)	283 (66.4)	316 (79.0)	305 (81.1)

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Abbreviations: ASE, asymptomatic standard error; CI: confidence interval; 6MWD, 6-minute walking distance; RCT, randomised controlled trial

QALY weightings for severity

Severity modifier calculations and components:

QALYs people without the condition (A)

QALYs people with the condition (B)

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

	QALYs of people without condition (based on trial population characteristics)	QALYs with the condition on current treatment	**Absolute QALY shortfall (has to be >12)**	**Proportional QALY shortfall (has to be >0.85)**
Company base case	16.74	[redacted]	[redacted]	[redacted]

Does the committee agree it is appropriate to apply a QALY weighting for severity?

Abbreviations: QALY, quality-adjusted life year

Summary of company and EAG base case assumptions that have a smaller impact on the ICER

Parameter	Company preferred assumptions	EAG preferred assumptions
Hospitalisation QALY loss calculations	Calculation does not appear to account for model cycle length	Hospitalisation QALY loss calculations adjusted to the 12-week cycle length
Utility on hospitalisation	Model captures the utility impact of increasing hospitalisation risk by ESC/ERS risk status, Also include direct effect within the low and intermediate-low risk health states.	Remove independent effect of sotatercept versus selexipag on hospitalisation in the low and intermediate-low risk state – avoid double count
Utility decrement of hospitalisation	Decrement of 0.105 per 12-week model cycle	Reduce utility decrement associated with hospitalisation from 0.105 to 0.071, applied for the duration of the cycle in which events occur
Initiation of selexipag and sotatercept	Initial appointment non consultant led	Initial outpatient appointment consultant led. Remaining uncertainty on if initiation is treated as a day case admission.

Back to assumptions

Abbreviations: QALY, quality-adjusted life years; FC, functional class; ITC, indirect treatment comparison; WHO, World Health Organization

Baseline characterisitcs of UK National Audit of Pulmonary Hypertension compared with STELLAR

	STELLAR		UK NAPH	
	n	%	n	%
Participants in population	323	-	4338	-
Mean starting age	47.9 years	-	58 years	-
Males	-	20.7	-	35
WHO functional classification for symptomatic pulmonary hypertension				
Class I	-	0	-	1
Class II	158	48.9	-	9
Class III	165	51.1	-	76
Class IV	-	0	-	14
Type of background PAH therapy				
Mono	13	4.0	2,144	45
Double	112	34.7	1,945	40
Triple	198	61.3	196	4
No therapy	-	-	513	11

Abbreviations: QALY, quality-adjusted life years; FC, functional class; ITC, indirect treatment comparison; PAH, pulmonary arterial hypertension; WHO, World Health Organization