Sotatercept for treating pulmonary arterial hypertension [ID6163]

Confidential information redacted

Technology appraisal committee A [2 December 2025]

Chair: James Fotheringham

External assessment group: Aberdeen HTA Group

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Company: Merck Sharp & Dohme (UK) Limited

Sotatercept for treating pulmonary arterial hypertension [ID6163]

- ✓ **Background and ACM1 recap**
- ❑ Consultation responses and key issues
- ❑ Cost effectiveness results
- ❑ Summary

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Draft guidance recommendation

Preliminary recommendation: Sotatercept, with other pulmonary arterial hypertension (PAH) treatments, should not be used to treat PAH in adults with World Health Organization functional class (WHO FC) 2 to 3, to improve exercise capacity.

Key uncertainties around:

- Company's ITC and STELLAR post-hoc analysis assessing treatment effect of sotatercept vs. selexipag
- Long-term treatment effects of sotatercept vs. selexipag; short-term relative risk applied to lifetime horizon;
- Initiation of PCA (PGI2) upon PAH progression
- Lack of clinical improvement after PCA initiation in model
- Potential overestimation of IV PCA costs because of high dosing assumption

Requested analyses:

- Comparison of sotatercept with PCA analogues in *intermediate-high and high-risk populations*
- MAIC for the ITC
- Propensity score matching for STELLAR post-hoc analysis
- Validation of relative risk reduction from the ITC in the longer term, using alternative data sets
- Changes to model structure to allow clinical improvement after starting PCA
- Scenario analyses aligned with UK NAPH audit and alternative OS modelling

PAH: Pulmonary arterial hypertension; ITC, indirect treatment comparison; PGI2, prostaglandin I2; PCA, prostacyclin analogue; IV, intravenous; MAIC, matching adjusted indirect comparison; NAPH; National Audit of Pulmonary Hypertension; OS, overall survival

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

Information on WHO FC stratification

FC, functional class; MHRA, Medicines and Healthcare Products Regulatory Agency; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; WHO, World Health Organisation.

STELLAR within-trial post-hoc analysis and ITC

Post-hoc within-trial analysis results for change in baseline risk status at week 24:

	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

Based on people having PDE5i + ERA in sotatercept arm and PDE5i + ERA + selexipag in placebo arm in STELLAR

ACM1 committee conclusion: post-hoc analysis potentially biased in favour of sotatercept – ITC should be used in decision making

Original ITC results comparing sotatercept vs selexipag - based on STELLAR (sotatercept), GRIPHON and TRACE (selexipag):

Outcome	Point estimate (95% CI)	Significant? (based on CIs)
WHO FC improvement*	RR[redacted]	No
WHO FC worsening*	RR: [redacted] (risk of worsening lower with sotatercept)	Yes
Change in 6MWD	GRIPHON: [redacted] TRACE[redacted]	Yes
Change in NT-proBNP	GRIPHON: [redacted] TRACE: [redacted]	Yes

*WHO FC improvement and worsening use pooled GRIPHON and TRACE data):

ACM1 committee conclusion: ITC not adjusted for differences in baseline characteristics – using a MAIC could address this

FC, functional class; ITC, indirect treatment comparison; 6WMD, 6 minute walking distance;; WHO, World Health Organisation; NT-proBNP, N-terminal pro-brain natriuretic peptide; CI, confidence interval; PDE5i: phosphodiesterase type 5 inhibitor; ERA: endothelin receptor antagonist; MAIC, matching-adjusted indirect comparison; RR, relative risk

SOTERIA: risk status improvement in longer term

Company: evidence from SOTERIA shows treatment effect (in terms of WHO FC improvement or maintenance) persists into long term with continued use of sotatercept

- **SOTERIA**: open label single-arm study evaluating safety and efficacy of sotatercept in participants with PAH previously treated with sotatercept, follow up time 7 years
  - STELLAR participants permitted to roll over into SOTERIA if they experienced a clinical worsening event or completed the 24-week treatment period in STELLAR

Results for n=[redacted]

- based on people who enrolled to SOTERIA from STELLAR sotatercept arm and continued receiving sotatercept

Proportion of risk status improvement or maintenance relative to STELLAR Week 24 (DCO August 2024):

Time point	Sotatercept (N = [redacted])	
	n/N	Percentage of STELLAR week 24 cohort with risk status improvement or maintenance (95% CI)
Week 36	[redacted]	[redacted]
Week 52 (Year 1)	[redacted]	[redacted]
Week 108 (Year 2)	[redacted]	[redacted]

DCO, data cut off; CI, confidence interval

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- ✓ **Consultation responses and key issues**
- ❑ Cost effectiveness results
- ❑ Summary

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Summary of consultation responses

Consultation responses received from:

- MSD (company)
- Clinical expert
- Web comments (n=3)

Key comment themes:

- **Company, clinical expert and web comments**: Positioning of sotatercept and unmet need in intermediate-high- and high-risk populations – supported by new clinical evidence (PULSAR, STELLAR, ZENITH, HYPERION)
  - **Web comments** - Specialist centres should have discretion to identify suitable patients
- **Web comments**: Uncertainty in current evidence – differences in baseline characteristics between key trials make ITC methods and results uncertain, but adjustments also carry uncertainty due to available populations
  - RWE (COMPERA and ASPIRE registries) shows UK PAH patients are typically older with comorbidities → evidence needed from broad, diverse patient populations that reflect the NHS
- **Clinical expert**: Use of IV PCA as subsequent treatment – safety concerns (potential infection risk associated with indwelling venous catheter) and suitability (training needed to reconstitute, administer and manage the treatment)
  - Benefits of IV PCA → reduced PAH mortality with clinical improvement (whereas selexipag improves disease stability in intermediate-low risk state)
- **Company and web comments -** economic model may not fully capture benefits of sotatercept

RWE; real world evidence; PAH, pulmonary arterial hypertension

Company response and key issues for discussion

Issue	Updated analysis by company (Y/N)	ICER impact
Positioning of sotatercept: • Comparative efficacy of sotatercept vs PCA in intermediate-high and high-risk populations	N	Unknown
New MAIC between STELLAR and GRIPHON	Y	Large
Long term transition probabilities from MAIC	Y	Large
Clinical improvement after PGI2 initiation	Y	Large
Weight-based dosing of intravenous PCA	Y	Large
Administration disutility in the economic model	Y	Small
Severity	Y	Large

Abbreviations: PCA: prostacyclin analogue; MAIC, matching adjusted indirect comparison

Equality issues and other considerations

- Consultation comments highlighted that PAH is a rare, orphan disease with underserved populations, reinforcing the need for access to innovative treatments
- Other considerations and uncaptured benefits proposed by company at consultation are identical to ACM1

Are there any additional equalities issues that need to be considered?

PAH: Pulmonary arterial hypertension

Other considerations from ACM1

Key issue: Positioning of sotatercept

Sotatercept MA	STELLAR trial population	Company positioning
Adults with WHO FC II to III*	Inclusion criteria: adults with WHO FC II to III* at baseline receiving stable background therapy STELLAR population also included [redacted] baseline high risk patients [redacted]	Initiation in intermediate-low risk population (narrower than MA)

*covers ESC/ERS **low risk**, **intermediate-low** risk, **intermediate high** risk and high risk

Company: positioning for initiation in intermediate-low risk, not restricted to intermediate-low risk population

- Evidence from STELLAR across risk status groups for clinical benefit in intermediate-high risk and low risk – so proposed population includes people continuing sotatercept when moving into these risk states
- Evidence for high-risk population in STELLAR [redacted] and new evidence for high-risk patients in relevant population (e.g. from ZENITH) is small – people discontinue sotatercept in model on progression to high risk
- Initiation only at intermediate-low risk because low-risk population needs already met with SoC, and intermediate-high risk start IV PCA in current practice, but no comparative evidence in STELLAR for initiating PCA with sotatercept

EAG comments – company did not provide new analysis for comparing sotatercept with PCA in other risk groups in MA (intermediate-high and high risk)

- Agrees that comparative evidence for initiating sotatercept as add on to background treatments (including PCA) in high-risk state from ZENITH is very limited
- People in relevant risk groups in ZENITH already on PCA at baseline. Evidence required.

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Would people be expected to discontinue sotatercept on progression to high risk in practice? Is the company's positioning for sotatercept (initiating in intermediate-low risk group and continuing in intermediate-high or low risk groups) appropriate?

MA, marketing authorisation; SoC, standard of care; PCA, prostacyclin analogue

Key issue: New MAIC between STELLAR and GRIPHON (1)

Consideration/conclusion at ACM1

- EAG's BUCHER ITC approach should be used in decision making because of potential bias in the company's within-trial post-hoc analysis – suggested MAIC
  - Propensity score matching may help to account for differences in subgroup baseline characteristics and determine to what extent the STELLAR within-trial data can be used

Company

- PSM for STELLAR post-hoc analysis not feasible sample sizes too small (sotatercept, [redacted], selexipag [redacted])
- Conducted MAIC: data from a subpopulation of STELLAR having PAH background monotherapy or dual therapy (n=125) for sotatercept vs. GRIPHON for selexipag (n=1,156 with PAH receiving background monotherapy or dual therapy only)
  - TRACE not used given lack of reported baseline data for pooled GRIPHON/TRACE group
- Treatment effect modifiers included WHO diagnostic group, WHO FC, age and 6MWD – adjusting for further modifiers would reduce statistical power, and baseline data not available for all factors in GRIPHON
- MAIC results used to derive short-term transition probabilities for selexipag relative to sotatercept in model

EAG comments on MAIC methodology

- Matching only on selected characteristics instead of all potential modifiers may bias ITC estimates
- **Analysis restricted to subpopulations on mono or dual therapy at baseline in STELLAR:** excludes a large proportion of people (61%) from sample, which may further confound comparison
- STELLAR subgroup analysis does not support background triple combination therapy as effect modifier of sotatercept

ITC, indirect treatment comparison; ESC/ERS, European society of Cardiology/European Respiratory Society; PAH, pulmonary arterial hypertension; PSM, propensity score matching; MAIC: matching-adjusted indirect comparison

Key issue: New MAIC between STELLAR and GRIPHON (2)

Company: MAIC results significantly favour sotatercept over selexipag for WHO FC worsening

Key outcomes at Week 24 (STELLAR)/Week 26 (GRIPHON) of sotatercept + background therapy versus selexipag + background therapy:

Outcome	MAIC, RR (95% CI); p-value
WHO FC improvement	[redacted]
WHO FC maintenance	[redacted]
WHO FC worsening	[redacted]*

* = statistically significant based on confidence intervals

Company

- Precision of MAIC is lower than previous Bucher ITC, but addresses previous issues with population comparability by adjusting for differences in selected baseline characteristics
- Used MAIC estimates for selexipag short term transition probabilities in model

EAG comments (continued)

- Highly uncertain if the MAIC **based on subpopulations on mono or dual therapy** has improved validity of ITC with selexipag, particularly in the longer term;
- Also used MAIC estimates for selexipag short term transition probabilities in model

Does the committee consider that the MAIC improves the validity of ITC? Is it appropriate to use the MAIC estimates to inform short term probabilities in the model?

FC, functional class; ITC, indirect treatment comparison; WHO, World Health Organization; MAIC, matching adjusted indirect comparison; HR, hazard ratio; CI, confidence interval; TP, transition probabilities; RR, relative risk

Key issue: Long term transition probabilities from MAIC (1)

Conclusion at ACM1 – Long-term transition probabilities derived by applying half of relative risk reduction of disease progression observed for sotatercept versus selexipag at 24 weeks (based on the ITC with GRIPHON and TRACE); further analysis requested using alternative datasets to validate relative risk reduction

Company

- Revised long-term transition probabilities for disease progression, based on relative risks of WHO FC status improvement/worsening at 24/26 weeks from company MAIC (RR for WHO FC deterioration = [redacted])
- No change to relative risk reduction of disease progression after week 24 – no extra data but explored in scenarios
- Time for improvement to low risk state: increased from 24 weeks to 108 weeks in both arms, based on data from SOTERIA extension (n=[redacted] at 108 weeks, slide 6)
- 50% reduction in treatment effect (informed by clinical experts at ACM1) arbitrary and implies waning, but reduction in sotatercept's treatment effect not observed in SOTERIA extension

EAG comments: concerned with applying 24-week relative risk over lifetime because it

- Underestimates selexipag benefit - inconsistent with clinical expert opinion;
- Predicts [redacted] remain controlled at 3 years on selexipag vs ~60% in GRIPHON
- Assumes selexipag is no better than placebo in preventing risk status deterioration (RR vs. placebo in GRIPHON at 26 weeks: [redacted]).Good evidence from GRIPHON supporting selexipag treatment effect on mortality and complications over 3-year follow up
- Accepts increase to time frame for risk status improvement despite uncertainty – sotatercept risk maintenance projections more in line with SOTERIA data and extrapolated selexipag outcomes slightly more optimistic

Prefers to calibrate MAIC relative risks applied to long term transition probabilities, so implied weighted HR between treatment arms for time to progression to intermediate-high risk or death, aligns with estimated HR from company's original ITC ([redacted]) – 63% of estimated relative risk reductions applied

ITC, indirect treatment comparison; ESC/ERS, European society of Cardiology/European Respiratory Society; PAH, pulmonary arterial hypertension; PSM, propensity score matching; RR, relative risk; HR, hazard ratio

Key issue: Long term transition probabilities from MAIC (2)

EAG: company revised long-term projections based on MAIC at 24/26 weeks leads to overly pessimistic projections of progression and survival in selexipag arm

Company revised base case projections for OS and progression to higher risk states:

EAG revised base case projections for OS and progression to higher risk states:

Primary outcome of GRIPHON = composite of death from any cause or complication related to PAH

- Does the company's approach overestimate sotatercept benefit and underestimate selexipag benefit?
- Does the committee prefer to apply full short-term relative risks over the lifetime horizon for long-term transition probabilities, or calibrate long-term probabilities in line with the EAG's approach?
- Is extending the improvement window from 24 to 108 weeks in both arms reasonable?

HR, hazard ratio; PO, primary outcome; OS, overall survival; MAIC, matching adjusted indirect comparison; PAH, pulmonary arterial hypertension

Key issue: Clinical improvement after PGI2 initiation

Conclusion at ACM1

- Including IV PCA utility decrement and costs but not utility increments in modelling is not reasonable
- Model structure should reflect improvements in risk status after starting IV PCA;
- Requested further analysis exploring other data sources around sotatercept with PCA analogues

Company

- Revised base case includes additional intermediate-high tunnel state that allows for improvement in risk status in first 12-week cycle following initiation of PCA
  - Company's clinical experts – most people improve on PCA within 12 weeks of initiation
- Transition probabilities for risk status improvement in intermediate-high risk state:
  - **For selexipag arm:** informed by observed transitions between risk states from 12-24 weeks in placebo arm of STELLAR trial
  - **For sotatercept arm:** company applies chance of improvement to people starting PCA in intermediate-high risk
    - For progressors to intermediate-high risk, the same transitions between risk status (based on transition data from 12-24 weeks in sotatercept arm of STELLAR) are used to inform probabilities for those starting treatment with PCA and those who do not
    - For people not starting PCA (60.1%), transitions restricted so that any % chance of improvement according to STELLAR transitions is instead applied as maintenance of risk status
- Proportion of people starting PCA on progression in line with committee preference for both model arms (selexipag = 85% in intermediate-high and high risk states, sotatercept = 39.9% in intermediate-high risk)

IV, intravenous; PCA; prostacyclin analogue; PGI2; prostaglandin I2

Key issue: Clinical improvement after PGI2 initiation (2)

EAG comments

- Model restructuring is appropriate, but source of transition probabilities is from STELLAR at 12-24 weeks, with cohort already on background therapy including PCA for months prior to trial – so transitions from STELLAR do not represent effect of starting PCA after progression
- **For selexipag**:
  - Transitions from STELLAR likely not applicable to selexipag arm when assuming that 85% of people in model arm are newly initiated on PCA upon progression
  - Model suggests [redacted] on selexipag improve risk status after progression to intermediate-high risk, but EAG's clinical experts state around 60% expected improvement after starting PCA
  - Prefers to use data from Roman et al. (previously used in company model), to inform transition probabilities for people starting PCA in intermediate-high risk in selexipag arm
- **For sotatercept**:
  - Transition probabilities for 39.9% starting PCA in model reflect patients already on sotatercept/already in intermediate-high risk state at baseline, not those adding PCA upon progression
  - Retains company transition probabilities in this arm despite uncertainty, but with adjustment assuming probability of risk status improvement for people starting PCA is no worse than in selexipag arm
    - In long-term, lower risk of further progression related to PCA in sotatercept arm versus selexipag

How should clinical improvement after PGI2 initiation be modelled?
Is it more appropriate to use the STELLAR placebo arm transitions between 12 and 24 weeks or the Roman et al. data to estimate the transition probabilities for people starting PCA in the intermediate-high risk state in selexipag arm?

N

IV, intravenous; PCA; prostacyclin analogue; PGI2; prostaglandin I2

Key issue: Weight-based dosing of intravenous PCA

Conclusion at ACM1

- EAG approach, with assumed dosing of 23 ng/kg/min for epoprostenol and 42.5 ng/kg/min for treprostinil, (based on target maintenance doses in ESC/ERS guidelines), should be used in model

Company

- Revised base case assumes dosing assumptions in line with committee preference for progression to intermediate-high risk state in sotatercept arm, based on clinical opinion
- Higher dosages assumed for intermediate-high risk in selexipag arm, and progression to high-risk state in both sotatercept and selexipag model arms (35 ng/kg/min for epoprostenol and 70 ng/kg/min for treprostin), based on clinical expert panel opinion (n=4)
- Company's clinical experts - people in intermediate-high risk state after previous treatments targeting the prostacyclin receptor (such as selexipag) can be suitable for higher target doses
    - Reduced likelihood of tolerance issues for person who has previously had prostacyclin receptor targeting treatments
    - Range of 30-40 ng/kg/min for epoprostenol proposed by panel, with dosing of treprostinil usually twice that of epoprostenol

ESC/ERS, European society of Cardiology/European Respiratory Society; IV, intravenous; PCA, prostacyclin analogue

Key issue: Weight-based dosing of intravenous PCA

	Committee preference at ACM1/ EAG base case (both model arms)	Revised company base case (sotatercept arm)	Revised company base case (selexipag arm)
Intermediate -high risk	Epoprostenol: 23 ng/kg/min Treprostinil: 42.5 ng/kg/min	Epoprostenol: 23 ng/kg/min Treprostinil: 42.5 ng/kg/min	Epoprostenol: 35 ng/kg/min Treprostinil: 70 ng/kg/min
High risk	Epoprostenol: 23 ng/kg/min Treprostinil: 42.5 ng/kg/min	Epoprostenol: 35 ng/kg/min Treprostinil: 70 ng/kg/min	Epoprostenol: 35 ng/kg/min Treprostinil: 70 ng/kg/min

EAG comments

- EAG's clinical experts – did not agree with assuming higher target dose of IV PCA in those switching from selexipag (though titration may be quicker and better tolerated)
  - EAG prefers to retain original dosing assumptions and align with EAG's clinical expert opinion

What dosages of intravenous PCA should be used in the intermediate-high risk state?
What dosages of intravenous PCA should be used in the high risk state?

ESC/ERS, European society of Cardiology/European Respiratory Society; IV, intravenous; PCA, prostacyclin analogue

Key issue: Administration disutility in the economic model

	Company base case, ACM1	Source	Conclusion at ACM1
Disutility, IV PCA administration	-0.307	Vignette study, Davies 2018	Remove decrement if no possibility of clinical improvement after starting PGI2
Decrement for hospitalisation	-0.105 per 12 week model cycle	Hospitalisation disutility in heart failure, McMurray 2018	Reduced to 0.071, applied in cycle in which events occur
Increment for carers of people in less severe risk state	0.036,0.023 and 0.013 for low, intermediate-low and intermediate-high risk states	Calculation based on Pennington (2024)	Included in preferred base case

Company

- Retains utility decrement of -0.307 in revised base case since model now also includes clinical benefit for PCA through risk status improvement in people initiating PCA – aligns with clinical and patient expert input from ACM1

EAG comments

- Agrees that including utility decrement is appropriate in revised model – included in EAG base case
- Methodology of obtaining utility decrements not aligned with NICE reference case (since health states developed with clinical experts and not patient reported) so magnitude of decrement still uncertain
  - Additional sensitivity analysis around size of utility decrement in addition to company scenario analysis

Should an administration disutility be applied in the economic model?

QALY weightings for severity

ACM1 conclusion

- In some scenarios, such as aligning population age and sex to UK NAPH cohort and different methods of modelling mortality, 1.2x QALY weighting may not hold
- Severity to be reassessed following updates to model structure and alignment with UK NAPH population

Company

- Data reported for NAPH is broad and not generalisable to appraisal population
- Maintains appropriate baseline characteristics for calculation of QALY shortfall should be based on STELLAR cohort (with 1.2x QALY weighting), but scenario using NAPH baseline characteristics also meets threshold for 1.2x modifier
- Mortality modelling explored in scenario analysis using dependent mortality approach with Gompertz extrapolation, but company maintains preference for using hazard ratios relative to low risk

EAG

- Maintains hazard ratios relative to low-risk approach for modelling mortality in base case, with scenarios provided based on UK NAPH baseline characteristics and overall survival modelling with dependent mortality approach (see appendix)
- Updated QALY shortfall calculations show 1.2x modifier threshold not met in scenario of revised EAG base case with baseline characteristics align with UK NAPH population
    - No ESC/ERS risk status data provided for NAPH cohort (WHO FC only)

QALY, quality adjusted life year; NAPH, National Audit of Pulmonary Hypertension; PAH, pulmonary arterial hypertension

Baseline characteristics, STELLAR and NAPH populations

QALY weightings for severity

Source of baseline characteristics	Age and sex proportion	General population QALYs		Company	EAG
STELLAR (company & EAG base case)	Mean age = 47.9 % male = 20.7	16.74	QALYs on current treatment	[redacted]	[redacted]
			Absolute QALY shortfall	[redacted]	[redacted]
			Proportional QALY shortfall	[redacted]	[redacted]
			QALY weight	**x1.2**	**x1.2**
UK NAPH (scenario analysis)	Mean age = 58 % male = 32	13.35	QALYs on current treatment	[redacted]	[redacted]
			Absolute QALY shortfall	[redacted]	[redacted]
			Proportional QALY shortfall	[redacted]	[redacted]
			QALY weight	**x1.2**	**x1**

Consultation response

- RWE (COMPERA and ASPIRE registries) shows UK PAH patients are typically older with comorbidities

Does the committee agree it is appropriate to apply a QALY weighting for severity? On what baseline characteristics should the QALY shortfall be calculated?

Baseline characteristics, STELLAR and NAPH populations

QALY, quality adjusted life year; NAPH, National Audit of Pulmonary Hypertension; PAH, pulmonary arterial hypertension

Summary of key company and EAG base case assumptions

Assumption	Company base case ACM1	Revised company base case	EAG base case
Source of transition probabilities	RR of ESC/ERS risk status improvement or deterioration from STELLAR post-hoc within-trial analysis	RR from MAIC with STELLAR and GRIPHON using WHO FC states	RR from MAIC with STELLAR and GRIPHON using WHO FC states
Reduction in RR of deterioration for long term transition probabilities	No reduction	No reduction	63% of estimated RR applied
Time frame for of improvement in risk status	24 weeks	108 weeks	108 weeks
Clinical improvement following PGI2 initiation	No clinical improvement	Some clinical improvement Observed transitions from 12-24 weeks in sotatercept and placebo arm of STELLAR trial respectively (sotatercept and selexipag)	Some clinical improvement Selexipag transitions based on data from Roman et. al Sotatercept transitions based on data from 12-24 weeks in sotatercept arm of STELLAR

ESC/ERS, European society of Cardiology/European Respiratory Society; IV, intravenous; PCA, prostacyclin analogue; RR, relative risk; MAIC, matching adjusted indirect comparison; FC: functional class; WHO: World Health Organization

Summary of key company and EAG base case assumptions

Assumption	Company base case ACM1	Revised company base case	EAG base case
PCA dosing assumptions	Epoprostenol: 50 ng/kg/min Treprostinil: 30 ng/kg/min	Selexipag intermediate-high risk and high risk, sotatercept high risk: Epoprostenol: 35 ng/kg/min Treprostinil: 70 ng/kg/min Sotatercept intermediate-high risk: Epoprostenol: 23 ng/kg/min Treprostinil: 42.5 ng/kg/min	Epoprostenol: 23 ng/kg/min Treprostinil: 42.5 ng/kg/min
Administration disutility for PCA	Included	Included	Included

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PCA, prostacyclin analogue;

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Cost effectiveness results

All ICERs are reported in Part 2 slides because they include confidential discounts

- Company base case ICERs >£30,000 per QALY gained with no severity modifier and 1.2x severity modifier applied
- EAG base case ICERs >£30,000 per QALY gained with no severity modifier and 1.2x severity modifier applied

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Summary of issues for discussion

Issue	Updated analysis by company (Y/N)	ICER impact	Slide
Positioning of sotatercept: • Comparative efficacy of sotatercept vs PCA in intermediate-high and high-risk populations	N	Unknown	11
New MAIC between STELLAR and GRIPHON	Y	Large	12-13
Long term transition probabilities from MAIC	Y	Large	14-15
Clinical improvement after PGI2 initiation	Y	Large	16-17
Weight-based dosing of intravenous PCA	Y	Large	18-19
Administration disutility in the economic model	Y	Small	20
Severity	Y	Large	21-22

Abbreviations: PCA: prostacyclin analogue; MAIC, matching adjusted indirect comparison

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Supplementary appendix

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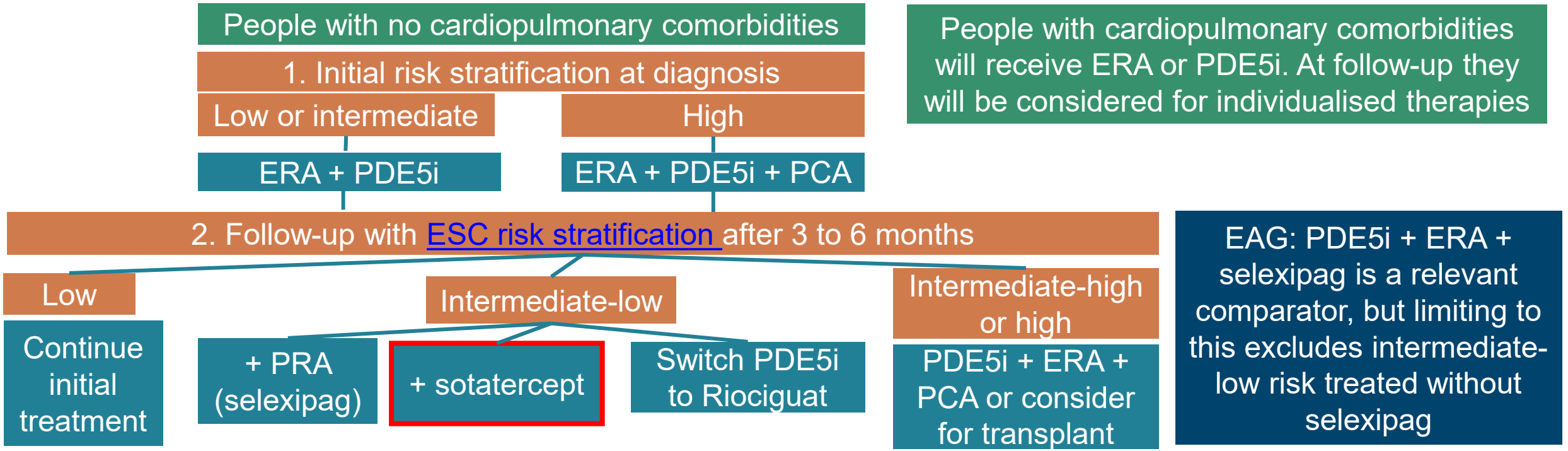
Treatment pathway

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



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

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 long-term extension study (SOTERIA) if they experienced a clinical worsening event or completed the 24-week treatment period in STELLAR

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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

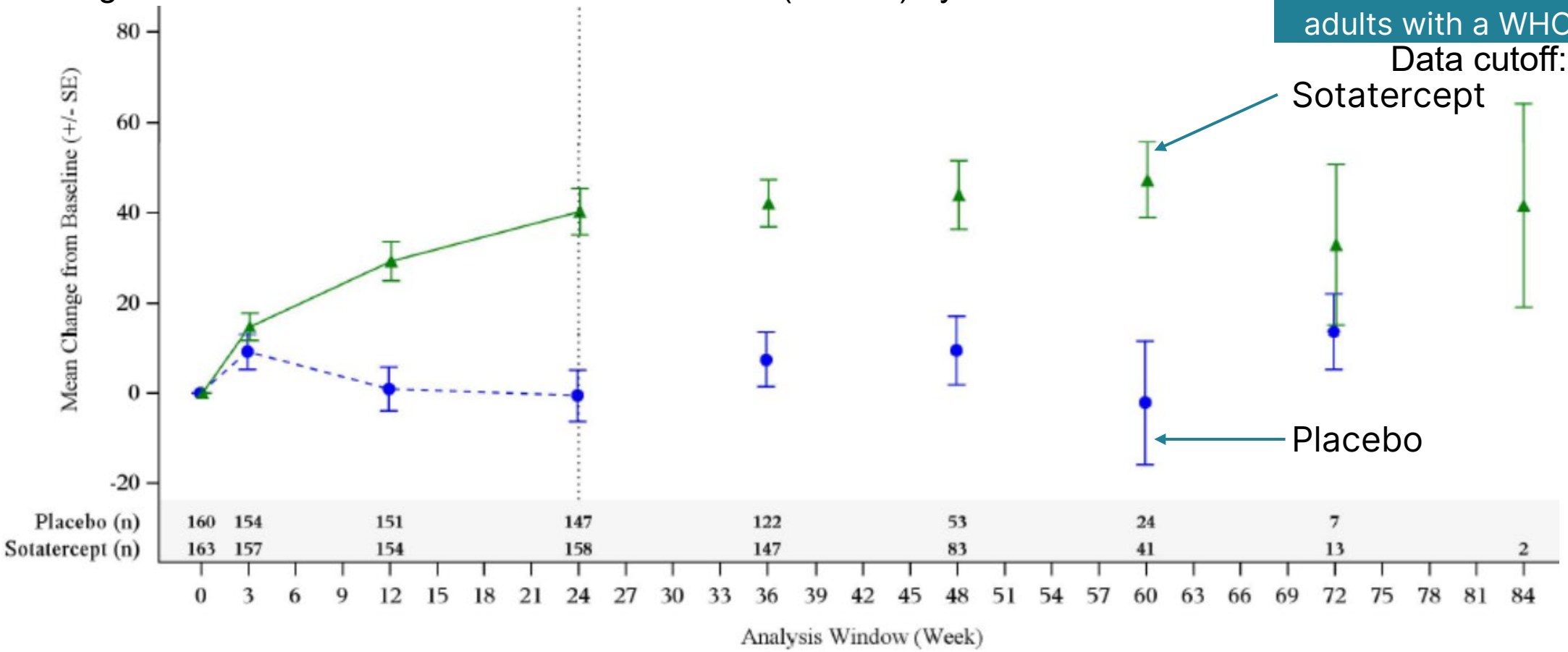
Key clinical trial results – STELLAR, double-blind, phase 3 RCT

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

NICE

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

Committee conclusions at ACM1

Issue	Committee consideration/conclusion at ACM1
Positioning of sotatercept	• Understood company's positioning of sotatercept for ESC/ERC intermediate-low-risk PAH narrower than its MA; noted other risk groups within the MA could benefit from sotatercept • Requested analysis comparing sotatercept with PCA in intermediate–high- or high-risk populations, using published data discussed by clinical experts
ITC	• EAG's ITC approach should be used in decision making because of potential bias in the company's within-trial post-hoc analysis; suggested MAIC
Post hoc analysis using STELLAR data	• Further analysis such as propensity scoring accounting for differences in the sub-populations
Short-term transition probabilities for selexipag	Short-term transition probabilities for selexipag informed by WHO FC relative risks derived from the ITC with GRIPHON and TRACE
Long-term transition probabilities	• Long-term transition probabilities derived by applying half of relative risk reduction of disease progression observed for sotatercept versus selexipag at 24 weeks (based on the ITC with GRIPHON and TRACE) • Requested further analysis using alternative data sets to inform and validate the relative risk reduction
No clinical improvement after PGI2 initiation	Model structure should reflect improvements in risk status after starting PCA

FC: functional class; PGI2: prostaglandin I2; PCA: prostacyclin analogue; WHO: World Health Organization

Committee conclusions at ACM1

Issue	Committee consideration/conclusion at ACM1
Initiation of PGI2 analogues in sotatercept model arm	• Progression to intermediate-high risk state: initiation of PGI2 analogues in 39.9% of model arm • Progression to high risk: further scenario analyses requested including exploration of other data sources around sotatercept with PCA analogues
Proportion of PGI2 analogues	85% have PGI2 analogues following progression to intermediate-high risk or high-risk state on selexipag (or to high-risk state on sotatercept)
Weight-based doses applied to IV PCA preparations	• 23 ng/kg/minute for epoprostenol • 42.5 ng/kg/minute for treprostinil
Utility	• EQ-5D data from STELLAR should be used to provide insight into • overall improvement intravenous PCA is started • Removal of intravenous PCA administration disutility if no possibility of clinical improvement after PGI2 • Hospitalisation utility decrement of 0.071, applied for the duration of the cycle in which events occur
Hospitalisation QALY loss calculations	Adjusted to 12-week cycle length of the model
Severity	Further analysis needed – severity modifier to be reassessed following updated model structure and alignment with UK NAPH population

FC: functional class; PGI2: prostaglandin I2; PCA: prostacyclin analogue; WHO: World Health Organization; NAPH, National Audit of Pulmonary Hypertension

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

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.

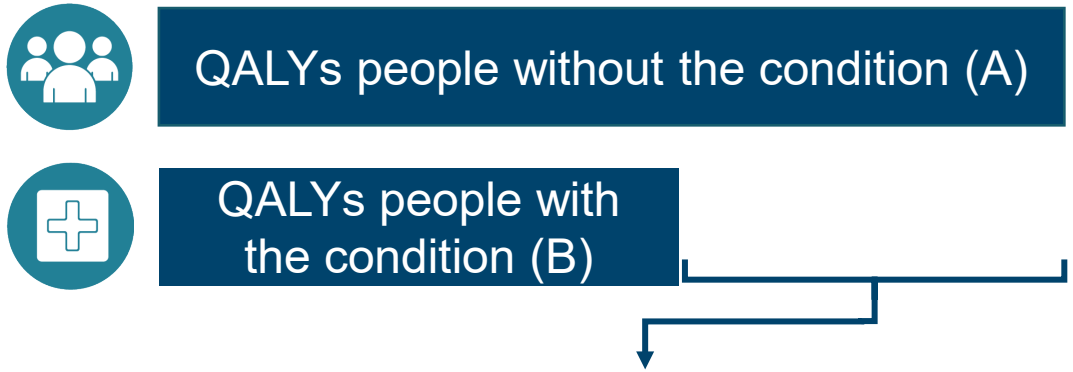
Source: ESC guidelines

- 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

QALY weightings for severity (1/2)

Severity modifier calculations and components:



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

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

Abbreviations: QALY, quality-adjusted life year

Comparability of UK National Audit of Pulmonary Hypertension compared with STELLAR

	STELLAR		UK NAPH	
	n	%	n	%
Participants in population	323	-	4812	-
Mean starting age	47.9 years	-	58 years	-
Males	-	20.7	-	32
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

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EAG mortality modelling scenarios

Model projections of proportion alive and free of progression to higher risk states – baseline characteristics from UK NAPH

Model projections of proportion alive and free of progression to higher risk states – based on dependent Gompertz model for 4 risk strata

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NAPH, National Audit of Pulmonary Hypertension; OS, overall survival

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EAG mortality modelling scenarios

Model projections of proportion alive and free of progression to higher risk states – based on UK NAPH baseline characteristics, dependent Gompertz model for 4 risk strata and recalibration of long-term transition probabilities

NICE

NAPH, National Audit of Pulmonary Hypertension; OS, overall survival

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Other changes to model with minor impact on ICER

Company wastage correction

- Company identified error in model for sotatercept wastage costs related to the number of 45 mg and 60 mg vials needed for patients in different weight bands
  - EAG agree with correction – included in updated model

EAG correction to healthcare resource use with PCA initiation

- EAG noted calculations for one-off and ongoing HRCU associated with PCA initiation appeared to:
  - recount the cost of initiating PCA in each health state in which patients would remain on it;
  - potentially overestimate ongoing PCA HCRU by applying quarterly costs as an approximation for 12 weekly cycle costs
- EAG explored approach applying PCA initiation costs as one off transition cost, weighted by the proportion of patients expected to initiate PCA in each relevant state
- Also adjusted ongoing costs per cycle length
- Changes affect both model arms, so impact on incremental cost and ICER is minimal

Should the EAG's approach to healthcare resource use associated with PCA initiation and ongoing use be used?

PCA, prostacyclin analogue; HCRU, healthcare resource use; ICER, incremental cost effectiveness ratio

Other considerations

In consultation response, company highlighted some of the benefits not captured in the modelling, previously in original company submission:

- Patient and caregiver productivity
- Increased capacity on transplant list
- Psychological benefit of an innovative treatment option
- The potential for stable disease to lead to more remote management of PAH
- Wider cardiovascular health benefits from improved exercise capacity
- Reduced use of anticoagulation medicines
- Insensitivity of utility measure to disease changes in PAH
- Survival benefit beyond time spent in improved health states
- Selexipag adverse event impact on quality of life

Are there any additional uncaptured benefits that should be considered in decision making?