TITLE: Long-term mortality and morbidity impact on patients with pulmonary arterial hypertension (PAH) if access to sotatercept is delayed: a simulation model

RUNNING TITLE: What is the long-term mortality and morbidity impact on patients with pulmonary arterial hypertension (PAH) if access to sotatercept is delayed?

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Scoring for the COMPERA 2.0 4-stratum risk assessment method

Endpoint	Points assigned			
	1	2	3	4
WHO FC	I or II	N/A	III	IV
6MWD, meters	>440	440–320	319–165	<165
BNP, ng/L	<50	50–199	200–800	>800
NT-proBNP, ng/L	<300	300–649	650–1100	>1100

The points for the endpoints per participant are averaged and scores assigned to the risk categories: <1.5 for the low risk, 1.5–2.49 for the intermediate-low risk, 2.5–3.49 for the intermediate-high risk, and ≥3.5 for the high risk.
Sources: Boucly et al. (2022)(17); 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) treatment guideline(20)
6MWD: 6-minute walking distance; BNP: brain natriuretic peptide; N/A: not applicable; ng/L: Nanograms per liter; NT-proBNP: N-terminal pro–B-type natriuretic peptide; WHO FC: World Health Organization functional class.

Supplementary Table 2. Baseline patient characteristics of STELLAR and COMPERA

Parameter	STELLAR (Merck & Co., Inc., Rahway, NJ, USA data on file 2023) (N=323)	COMPERA (Rosenkranz et al. 2023)(19),* (N=208)	French registry (Boucly et al. 2022)(17) (N=2879)
Age, years			
Mean	47.9	NR	61.0
Median	48.0	51.0	NR
Proportion female	79.3%	67.8%	60.0%
BMI, kg/m^2			
Mean	26.4	NR	27.2
Median	25.5	24	NR
WHO FC, n (%)			
I	0	3 (1.5%)	925 (32.0%)
II	157 (48.6%)	41 (19.9%)	
III	166 (51.4%)	135 (65.5%)	1541 (54.0%)
IV	0	27 (13.1%)	413 (4.0%)
6MWD, meters			

Parameter	STELLAR (Merck & Co., Inc., Rahway, NJ, USA data on file 2023) (N=323)	COMPERA (Rosenkranz et al. 2023)(19),* (N=208)	French registry (Boucly et al. 2022)[17] (N=2879)
Mean	401.1	NR	NR
Median	424.0	373	300
Time from diagnosis to randomization, years			
Mean	8.8	0	NR
Median	7.3	0	NR
NT-proBNP, pg/mL			
Mean	1115.2 (SD=2582.8)	NR	NR
Median	424.0 (IQR: 158.0 to 1074.0)	1162 (IQR: 354 to 2236)	995 (IQR: 281 to 2726)
Mean pulmonary arterial pressure, mmHg			
Mean	52.6 (SD=13.8)	NR	45 (SD=12)
Median	51.0 (IQR: 43.0 to 61.0)	45 (IQR: 37 to 54)	NR
Background therapy composition, n (%)			
None	0 (0%)	NR	440 (15%)
Monotherapy	13 (4.0%)	NR	1397 (48%)
Double therapy	112 (34.7%)	NR	793 (48%)
Triple therapy	198 (61.3%)	NR	79 (3%)

* Among all the reported subgroups in Rosenkranz et al. (2023)(19), data for the no-comorbidity cohort were utilized, seeing as the patient characteristics in this cohort were the most comparable to those of the STELLAR trial ITT population, especially in terms of baseline age. This approach was validated via consultation with clinical experts.

6MWD: 6-minute walking distance; BMI: body mass index; IQR: interquartile range; kg: kilogram; mmHg: millimeter of mercury; ng/L: Nanograms per liter; NR: not reported; NT-proBNP: N-terminal pro–B-type natriuretic peptide; SD: standard deviation; WHO FC: World Health Organization functional class.

Supplementary Table 3. Analysis of the Proportion of Risk Status Improvement or Maintenance Relative to STELLAR Baseline. Participants who Enrolled to SOTERIA from STELLAR Sotatercept Arm and Continued Receiving Sotatercept

Endpoint	Sotatercept (N[a] = 153) n/N[b]	%	(95% CI)[c]
Risk Status Improvement or Maintenance Relative to STELLAR Baseline			
Week 3	129/134	96.3	(91.5, 98.8)
Week 12	128/131	97.7	(93.5, 99.5)
Week 24	137/140	97.9	(93.9, 99.6)
Week 36	136/140	97.1	(92.8, 99.2)
Week 52 (Year 1)	74/75	98.7	(92.8, 100.0)

n = Number of participants with improvement or maintenance of the endpoint assessment at a given timepoint relative to baseline.
a: Participants who enrolled to SOTERIA from STELLAR sotatercept arm and continued receiving sotatercept. 154 participants from STELLAR sotatercept arm enrolled to SOTERIA, but one participant discontinued before receiving study dose in SOTERIA.
b: Participants with non-missing endpoint assessment at both given timepoint and STELLAR baseline. Row percentages are based on this number.
c: Derived based on the Clopper-Pearson method (exact binomial distribution).
Risk status assessment is based on COMPERA version 2.0.
Database Cutoff Date: STELLAR (MK-7962-003) - 06DEC2022 / SOTERIA (MK-7962-004) - 08NOV2023

Supplementary Table 4. Analysis of Overall Survival

Overall Survival	STELLAR (MK-7962-003)[a] N[b]	STELLAR (MK-7962-003)[a] Participants with Event n (%)	SOTERIA (MK-7962-004)[a] N[c]	SOTERIA (MK-7962-004)[a] Participants with Event n (%)
Sotatercept in both STELLAR and SOTERIA	163	2 (1.2)	153	1 (0.65)
Placebo in STELLAR and Sotatercept in SOTERIA	160	7 (4.4)	143	4 (2.8)

a: Database Cutoff Date: STELLAR (MK-7962-003) - 06DEC2022/SOTERIA (MK-7962-004) - 08NOV2023
b: Number of participants: STELLAR full analysis set population.
c: Number of participants: SOTERIA full analysis set population, participants enrolled from STELLAR and received Sotatercept in SOTERIA

Supplementary Table 5. Model results for a 10-year time horizon

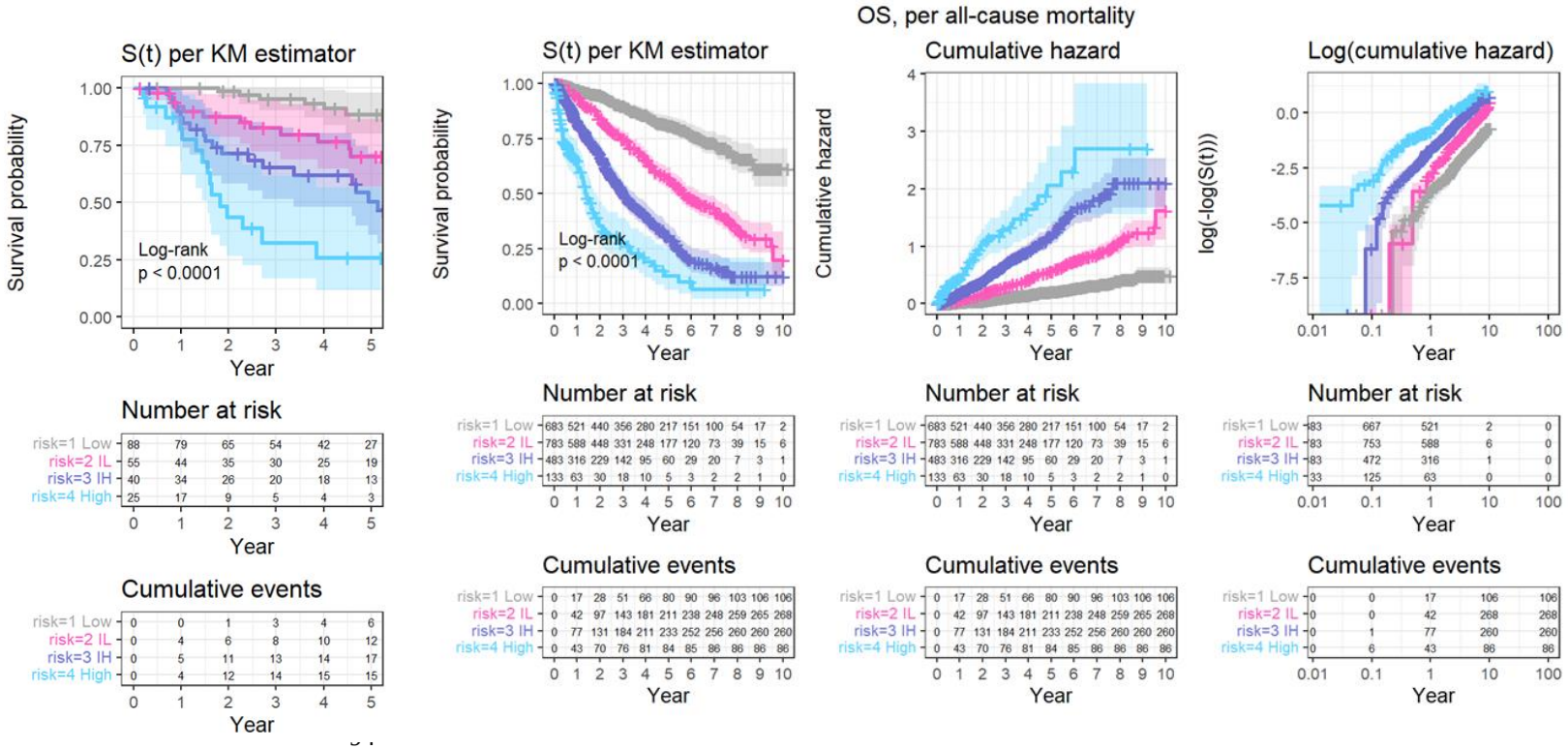
	Immediate treatment with sotatercept plus BGT	Delayed treatment with sotatercept plus BGT	BGT only	Immediate treatment with sotatercept vs. Delayed treatment with sotatercept	Immediate treatment with sotatercept vs. BGT only	Interpretation
Deterministic outcome						
Total LYs, per patient						
Accumulated by health state	**8.17**	**6.79**	**4.75**	**1.38**	**3.41**	Both comparisons favor immediate treatment with sotatercept plus BGT and the additional life expectancy for patients treated earlier with sotatercept was primarily driven by these patients transitioning earlier and remaining longer in the low-risk health state.
Low risk	6.41	3.67	1.38	2.73	5.03	
Intermediate-low risk	1.46	1.28	1.11	0.18	0.36	
Intermediate-high risk	0.26	0.52	0.80	-0.26	-0.53	
High risk	0.03	1.30	1.45	-1.26	-1.42	
Lung/heart-lung transplant	0.00	0.02	0.02	-0.02	-0.02	
By infused prostacyclin use	**8.17**	**6.79**	**4.75**	**1.38**	**3.41**	Both comparisons favor immediate treatment with
Infused prostacyclin-use	1.06	1.78	1.88	-0.72	-0.82	

	Immediate treatment with sotatercept plus BGT	Delayed treatment with sotatercept plus BGT	BGT only	Immediate treatment with sotatercept vs. Delayed treatment with sotatercept	Immediate treatment with sotatercept vs. BGT only	Interpretation
Infused prostacyclin-free	7.11	5.01	2.87	2.10	4.24	sotatercept plus BGT
Landmark survival (discounted)						
1 year	96.4%	91.9%	91.9%	4.5%	4.5%	Both comparisons favor immediate treatment with sotatercept plus BGT.
3 years	89.1%	75.2%	67.2%	13.9%	21.9%	
5 years	83.0%	67.6%	45.9%	15.4%	37.2%	
7 years	76.5%	59.9%	27.1%	16.6%	49.3%	
10 years	67.5%	50.0%	11.0%	17.5%	56.5%	
Clinical events, per 1000 patients						
PAH hospitalization	60	284	755	-224**	-695**	Both comparisons favor immediate treatment with sotatercept plus BGT.
All-cause death over a lifetime (30-year)	99	337	863	-238**	-764**	Both comparisons favor immediate treatment with sotatercept plus BGT.
Lung/heart-lung transplant	1	5	6	-4	-5	Both comparisons favor immediate treatment with

	Immediate treatment with sotatercept plus BGT	Delayed treatment with sotatercept plus BGT	BGT only	Immediate treatment with sotatercept vs. Delayed treatment with sotatercept	Immediate treatment with sotatercept vs. BGT only	Interpretation
						sotatercept plus BGT.
NNT						
Per an averted PAH hospitalization event				4.5	1.4	Both comparisons favor immediate treatment with sotatercept plus BGT.
Per an averted all-cause death event				4.2	1.3	Both comparisons favor immediate treatment with sotatercept plus BGT.
Per an averted Lung/heart-lung transplant				239	201	Both comparisons favor immediate treatment with sotatercept plus BGT.

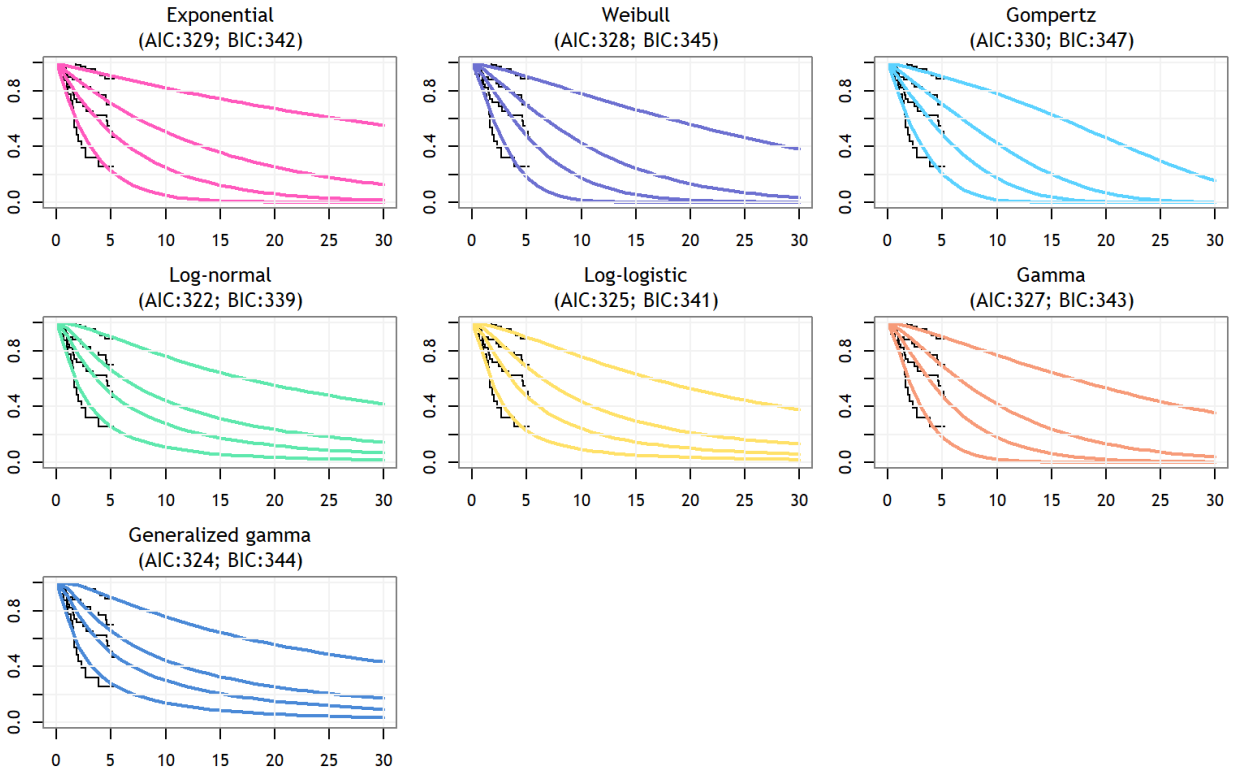
* All outcomes were discounted at 3% annually, as commonly adopted in population health models.
** The numbers were rounded down to the nearest integer to be conservative. Also, half-cycle correction was applied.
Crl, credible interval; LY, life-year; NNT, number needed to treat; PAH: pulmonary arterial hypertension.

Supplementary Figure 1. Kaplan-Meier curves for overall survival from Rosenkranz et al. (Left, Base case) and Boucly et al (Right, Sensitivity analyses)



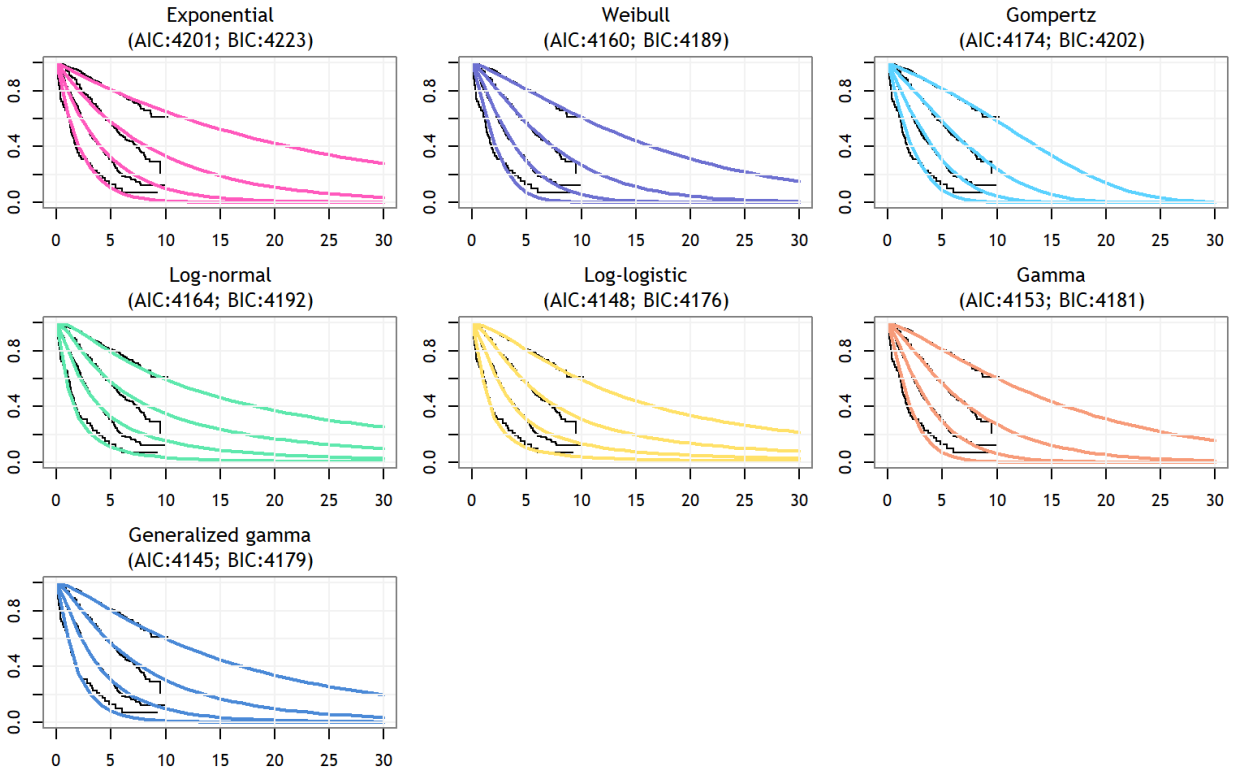
Sources: Boucly et al. (2022),(17) Rosenkranz et al. (2023)(19)
IH: intermediate-high; IL: low-intermediate

Supplementary Figure 2. Fitted parametric regression models for risk stratum–specific survival from Rosenkranz et al. (2023) for the base case analysis



Notes: Risk strata were included as covariates in each of the parametric models above. The x-axis refers to time in year since enrollment into COMPERA, whereas the y-axis refers to the cumulative proportion of patients alive. The transition probabilities from each risk stratum health state to death at time point *t* was estimated as: survival function at time *t-1* minus survival function at time *t*, divided by survival function at time *t-1*.
AIC: Akaike information criterion; BIC: Bayesian information criterion.

Supplementary Figure 3. Fitted parametric regression models for risk stratum-specific survival from Boucly et al. (2022) for a scenario analysis



Notes: Risk strata were included as covariates in each of the parametric models above. The x-axis refers to time in year since enrollment into COMPERA, whereas the y-axis refers to the cumulative proportion of patients alive. The transition probabilities from each risk stratum health state to death at time point *t* was estimated as: survival function at time *t-1* minus survival function at time *t*, divided by survival function at time *t-1*.
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