Dokumentvorlage, Version vom 26.12.2021

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Sotatercept (WINREVAIR®)

MSD Sharp & Dohme GmbH

Modul 4A

Anhang 4-G

Pulmonale Arterielle Hypertonie

Medizinischer Nutzen und
medizinischer Zusatznutzen,
Patientengruppen mit therapeutisch
bedeutsamem Zusatznutzen

Stand: 13.09.2024

Inhaltsverzeichnis

Seite

Abbildungsverzeichnis

Seite

Tabellenverzeichnis

Seite

Anhang 4-G1: Rücklaufquoten des Dyspnoe-Score gemäß Borg CR10 Skala pre 6MWD-Test, PAH-SYMPACT und EQ-5D VAS

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.2.2 die Rücklaufquoten des Dyspnoe-Scores gemäß Borg CR10 Skala pre 6MWD-Test, die Rücklaufquoten des PAH-SYMPACT und die Rücklaufquoten des EQ-5D VAS dargestellt.

Alle Ergebnisse beziehen sich auf den finalen Datenschnitt (06.12.2022).

Anhang 4-G1.1: Rücklaufquoten der 6MWD, Dyspnoe-Score gemäß Borg CR10 Skala pre 6MWD-Test und der EQ-5D VAS

Tabelle 4G-1: Rücklaufquoten des 6MWD Dyspnoe-Score gemäß Borg CR10 Skala pre 6MWD-Test

Studie: STELLAR (MK-7962-003)[a]	**Sotatercept (N^b = 163)**	**Placebo (N^b = 160)**
Pre-6MWD Dyspnoe Rücklaufquoten, n (%)[c]		
Baseline	160 (98,2)	160 (100,0)
Woche 3	156 (95,7)	154 (96,3)
Woche 12	153 (93,9)	151 (94,4)
Woche 24	157 (96,3)	146 (91,3)
Baseline und Woche 24	155 (95,1)	146 (91,3)
Woche 36	146 (89,6)	122 (76,3)
Woche 48	83 (50,9)	53 (33,1)
Woche 60	41 (25,2)	24 (15,0)
Woche 72	13 (8,0)	7 (4,4)
Woche 84	2 (1,2)	1 (0,6)

a: Datenschnitt: 06. Dezember 2022
b: Anzahl der Patient:innen: Full-Analysis-Set
c: Patient:innen mit nicht-fehlender Erhebung zum entsprechenden Zeitpunkt der Visite
6MWD: 6-Minuten Gehstrecke; CR10: 10 Punkte Category Ratio scale

Anhang 4-G1.2: Rücklaufquoten des PAH-SYMPACT

Tabelle 4G-2: Rücklaufquoten des PAH-SYMPACT

Studie: STELLAR (MK-7962-003)[a]	**Sotatercept (N^b = 163)**	**Placebo (N^b = 160)**
PAH-SYMPACT Rücklaufquoten, n (%)[c]		
Kardiopulmonale Symptome Score	141 (86,5)	137 (85,6)
Baseline	115 (70,6)	117 (73,1)
Woche 24	122 (74,8)	113 (70,6)
Baseline und Woche 24	96 (58,9)	93 (58,1)
Kardiovaskuläre Symptome Score	141 (86,5)	137 (85,6)
Baseline	115 (70,6)	117 (73,1)
Woche 24	122 (74,8)	113 (70,6)
Baseline und Woche 24	96 (58,9)	93 (58,1)
Score für die Domäne zu Kognitiven/Emotionalen Auswirkungen	146 (89,6)	141 (88,1)
Baseline	117 (71,8)	123 (76,9)
Woche 24	115 (70,6)	110 (68,8)
Baseline und Woche 24	86 (52,8)	92 (57,5)
Score für die Domäne Körperliche Auswirkungen	146 (89,6)	141 (88,1)
Baseline	117 (71,8)	123 (76,9)
Woche 24	115 (70,6)	110 (68,8)
Baseline und Woche 24	86 (52,8)	92 (57,5)

Studie: STELLAR (MK-7962-003)[a]	**Sotatercept (N^b = 163)**	**Placebo (N^b = 160)**
PAH-SYMPACT Rücklaufquoten, n (%)[c]		
a: Datenschnitt: 06. Dezember 2022 b: Anzahl der Patient:innen: Full-Analysis-Set c: Patient:innen mit nicht-fehlender Erhebung zu dem entsprechenden Parameter/Zeitpunkt der Visite. Jede(r) Patient:in wird einmal gezählt für jede entsprechende Reihe und Spalte. Während der Studie könnte ein(e) Patient:in Erhebungen zu den Visiten verpasst haben, jedoch mindestens eine Erhebung zu einer Visite aufweisen. Dadurch ist der Unterschied zwischen der Anzahl an Parametern und den Anzahl an Visiten zu erklären PAH-SYMPACT: pulmonal arterielle Hypertonie-Symptome und Auswirkungen		

Anhang 4-G1.3: Rücklaufquoten des EQ-5D VAS

Tabelle 4G-3: Rücklaufquoten des EQ-5D VAS

Studie: STELLAR (MK-7962-003)[a]	**Sotatercept (N^b = 163)**	**Placebo (N^b = 160)**
EQ-5D VAS Rücklaufquoten, n (%)[c]		
Baseline	125 (76,7)	126 (78,8)
Woche 24	109 (66,9)	104 (65,0)
Baseline und Woche 24	90 (55,2)	89 (55,6)
a: Datenschnitt: 06. Dezember 2022 b: Anzahl der Patient:innen: Full-Analysis-Set c: Patient:innen mit nicht-fehlender Erhebung zum entsprechenden Zeitpunkt der Visite EQ-5D: European Quality of Life 5 Dimensions; VAS: Visuelle Analogskala		

Anhang 4-G2: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest (p ≥ 0,05)

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.2.2 die Ergebnisse der Subgruppenanalysen, für die ein nicht signifikanter Interaktionstest (p ≥ 0,05) vorliegt, dargestellt.

Alle Ergebnisse beziehen sich auf den finalen Datenschnitt (06.12.2022).

Mortalität

Mortalität zu Woche 24

Tabelle 4G-4: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	Sotatercept		Placebo		Sotatercept vs. Placebo			
Overall Survival up to Week 24	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Adjusted Difference[e] [95 %-CI]	p-Value for Interaction[f] Test
Sex								
Male	34	0 (0.0)	33	4 (12.1)	n.c.	n.c.	n.c.	n.c.
Female	129	0 (0.0)	127	2 (1.6)	n.c.	n.c.	n.c.	
Age (Years)								
< 65 years	138	0 (0.0)	131	2 (1.5)	n.c.	n.c.	n.c.	n.c.
≥ 65 years	25	0 (0.0)	29	4 (13.8)	n.c.	n.c.	n.c.	
Severity of Disease								
WHO FC II	79	0 (0.0)	78	1 (1.3)	n.c.	n.c.	n.c.	n.c.
WHO FC III	84	0 (0.0)	82	5 (6.1)	n.c.	n.c.	n.c.	
Region[g]								
WHO Stratum A	135	0 (0.0)	127	4 (3.1)	n.c.	n.c.	n.c.	n.c.
Rest of the World	28	0 (0.0)	33	2 (6.1)	n.c.	n.c.	n.c.	
Background PAH Therapy								
Mono/Double	65	0 (0.0)	60	2 (3.3)	n.c.	n.c.	n.c.	n.c.
Triple	98	0 (0.0)	100	4 (4.0)	n.c.	n.c.	n.c.	
a: Database Cutoff Date: 06DEC2022								

Study: STELLAR (MK-7962-003)[a]	Sotatercept		Placebo		Sotatercept vs. Placebo			p-Value for Interaction[f]
Overall Survival up to Week 24	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Risk Ratio/Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**Adjusted Difference[e] [95 %-CI]**	**Test**

b: Number of participants: full analysis set population. Participants with missing assessment at week 24 not due to COVID-19 are considered a non-responder. Participants who missed assessment at week 24 due to COVID-19 are taken out of the population

c: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

d: Two-sided p-value based on Wald test

e: Miettinen and Nurminen method stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

f: Based on generalized linear model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

g: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States

CI: Confidence Interval; COVID-19: Coronavirus Disease of 2019; FC: Functional Class; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; WHO: World Health Organization

Morbidität

Verbesserung der 6MWD - Responderanalysen

Tabelle 4G-5: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Verbesserung der 6MWD - Responderanalysen aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	Sotatercept		Placebo		Sotatercept vs. Placebo			p-Value for Interaction[g]
Improvement in 6-Minute Walk Distance[b]	N[c]	Participants with Event n (%)	N[c]	Participants with Event n (%)	Risk Ratio/Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]	Test
Sex								
Male	34	16 (47.1)	33	7 (21.2)	2.19 [1.02; 4.68]	0.045	25.53 [2.12; 46.44]	0.880
Female	129	56 (43.4)	126	22 (17.5)	2.47 [1.61; 3.78]	< 0.001	25.70 [14.66; 36.28]	
Age (Years)								
< 65 years	138	65 (47.1)	130	23 (17.7)	2.65 [1.75; 4.00]	< 0.001	29.23 [18.29; 39.54]	0.149
≥ 65 years	25	7 (28.0)	29	6 (20.7)	1.41 [0.55; 3.61]	0.469	8.64 [-15.28; 32.24]	
Severity of Disease								
WHO FC II	79	33 (41.8)	78	17 (21.8)	1.91 [1.17; 3.12]	0.010	19.86 [5.44; 33.70]	0.204
WHO FC III	84	39 (46.4)	81	12 (14.8)	3.08 [1.75; 5.42]	< 0.001	31.47 [17.79; 44.16]	
Region[h]								
WHO Stratum A	135	59 (43.7)	127	23 (18.1)	2.35 [1.56; 3.56]	< 0.001	24.98 [13.91; 35.54]	0.918
Rest of the World	28	13 (46.4)	32	6 (18.8)	2.85 [1.21; 6.72]	0.017	31.37 [7.20; 52.13]	
Background PAH Therapy								
Mono/Double	65	31 (47.7)	59	15 (25.4)	1.89 [1.14; 3.12]	0.013	22.52 [5.48; 38.25]	0.339
Triple	98	41 (41.8)	100	14 (14.0)	2.98 [1.74; 5.13]	< 0.001	27.87 [15.67; 39.53]	

a: Database Cutoff Date: 06DEC2022

b: Fulfilled if the difference in participant's 6-minute walk distance at week 24 relative to 6-minute walk distance at baseline ≥ 40m

c: Number of participants: full analysis set population. Participants with missing assessment at week 24 not due to COVID-19 are considered a non-responder. Participants who missed assessment at week 24 due to COVID-19 are taken out of the population

d: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

e:Two-sided p-value based on Wald test

f: Miettinen and Nurminen method stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

g: Based on generalized linear model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

Study: STELLAR (MK-7962-003)[a]	Sotatercept		Placebo		Sotatercept vs. Placebo			p-Value for Interaction[g]
Improvement in 6-Minute Walk Distance[b]	N[c]	Participants with Event n (%)	N[c]	Participants with Event n (%)	Risk Ratio/Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]	Test
h: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States CI: Confidence Interval; COVID-19: Coronavirus Disease of 2019; FC: Functional Class; WHO: World Health Organization								

Verbesserung der 6MWD – Veränderung gegenüber Baseline

Tabelle 4G-6: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Verbesserung der 6MWD – Veränderung gegenüber Baseline aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	**Sotatercept N[b]=163**	**Placebo N[b]=160**	**Sotatercept vs. Placebo**	
Change from Baseline in 6-Minute Walk Distance (meters) at Week 24[c]	**Participants n (%)**	**Participants n (%)**	**Hodges-Lehmann Location Shift (ASE) [95 %-CI][d]**	**p-Value for Interaction Test[e]**
Sex				
Male	34 (20.9)	33 (20.6)	58.3 (19.48) [20.16; 96.51]	0.303
Female	129 (79.1)	127 (79.4)	36.8 (7.42) [22.31; 51.38]	
Age (Years)				
< 65	138 (84.7)	131 (81.9)	45.6 (7.00) [31.87; 59.32]	0.088
≥ 65	25 (15.3)	29 (18.1)	10.2 (19.49) [-28.00; 48.42]	
Region[f]				
WHO Stratum A	135 (82.8)	127 (79.4)	39.8 (7.12) [25.84; 53.74]	0.661
RoW	28 (17.2)	33 (20.6)	49.6 (21.08) [8.24; 90.88]	
Background PAH Therapy				
Mono/Double	65 (39.9)	60 (37.5)	36.2 (11.03) [14.59; 57.85]	0.614
Triple	98 (60.1)	100 (62.5)	43.3 (8.65) [26.33; 60.23]	
PAH Etiological Subgroups				
iPAH [Idiopathic PAH]	83 (50.9)	106 (66.3)	50.7 (9.77) [31.50; 69.80]	0.103
hPAH [Heritable PAH]	35 (21.5)	24 (15.0)	25.2 (13.51) [-1.31; 51.66]	
Drug/Toxin-induced PAH	7 (4.3)	4 (2.5)	18.4 (16.78) [-14.51; 51.25]	
Connective Tissue Disease	29 (17.8)	19 (11.9)	8.0 (17.26) [-25.88; 41.79]	
Congenital Heart Disease with s/p Shunt Repair	9 (5.5)	7 (4.4)	97.9 (57.47) [-14.75; 210.55]	
Prostacyclin Infusion Therapy at Baseline				
Yes	65 (39.9)	65 (40.6)	42.3 (10.39) [21.95; 62.69]	0.776
No	98 (60.1)	95 (59.4)	38.4 (8.81) [21.18; 55.72]	
Baseline PVR				
≤ 800 (dynes*sec/cm^5)	108 (66.3)	108 (67.5)	30.9 (7.72) [15.73; 45.99]	0.052
> 800 (dynes*sec/cm^5)	55 (33.7)	52 (32.5)	60.8 (13.33) [34.65; 86.89]	

a: Database Cutoff Date: 06DEC2022

b: Number of participants: full analysis set population

c: Participants who had missing 6MWD at week 24 for reasons other than death or a clinical worsening event, a standard multiple imputation method was used to impute missing data used in computing change from baseline. Change from baseline in 6MWD at week 24 for participants who died was assigned a value of -2000 meters to receive the worst rank. Change from baseline in 6MWD at week 24 for participants who have missing data due to a non-fatal clinical worsening event was imputed to -1000 meters to receive the next worst-rank

Study: STELLAR (MK-7962-003)[a]	Sotatercept N[b]=163	Placebo N[b]=160	Sotatercept vs. Placebo	
Change from Baseline in 6-Minute Walk Distance (meters) at Week 24[c]	Participants n (%)	Participants n (%)	Hodges-Lehmann Location Shift (ASE) [95 %-CI][d]	p-Value for Interaction Test[e]

d: Hodges-Lehmann Location Shift from the placebo estimate, median of all paired differences between the two treatment arms

e: Cochran's Q (chi-squared) two-sided p-value for heterogeneity test among subgroup categories Hodges-Lehmann Location Shift estimates

f: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States

6MWD: 6-Minute Walk Distance; ASE: Asymptotic Standard Error; CI: Confidence Interval; PAH: Pulmonary Arterial Hypertension; PVR: Pulmonary Vascular Resistance; RoW: Rest of the World; s/p: systemic-to-pulmonary; WHO: World Health Organisation

Zeit bis zur klinischen Verschlechterung oder Tod

Tabelle 4G-7: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Zeit bis zur klinischen Verschlechterung oder Tod aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	Sotatercept			Placebo			Sotatercept vs. Placebo		
Time to First Clinical Worsening or Death[b]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Sex									
Male	34	2 (5.9)	Not reached [58.14; -]	33	13 (39.4)	Not reached [28.57; -]	0.13 [0.03; 0.58]	0.0075	0.356
Female	129	9 (7.0)	Not reached [-; -]	127	29 (22.8)	78.00 [-; -]	0.28 [0.13; 0.59]	0.0008	
Age (Years)									
< 65 years	138	6 (4.3)	Not reached [-; -]	131	33 (25.2)	78.00 [-; -]	0.16 [0.07; 0.37]	< 0.0001	0.082
≥ 65 years	25	5 (20.0)	Not reached [-; -]	29	9 (31.0)	Not reached [48.57; -]	0.58 [0.19; 1.76]	0.3382	
Severity of Disease									
WHO FC II	79	4 (5.1)	Not reached [-; -]	78	14 (17.9)	78.00 [-; -]	0.27 [0.09; 0.84]	0.0230	0.700
WHO FC III	84	7 (8.3)	Not reached [-; -]	82	28 (34.1)	Not reached [48.14; -]	0.21 [0.09; 0.47]	0.0002	
Region[h]									
WHO Stratum A	135	9 (6.7)	Not reached [-; -]	127	32 (25.2)	78.00 [-; -]	0.24 [0.11; 0.50]	0.0001	0.756
Rest of the World	28	2 (7.1)	Not reached [-; -]	33	10 (30.3)	Not reached [33.43; -]	0.15 [0.03; 0.72]	0.0174	
Background PAH Therapy									
Mono/Double	65	6 (9.2)	Not reached [-; -]	60	14 (23.3)	Not reached [48.57; -]	0.35 [0.13; 0.91]	0.0310	0.258
Triple	98	5 (5.1)	Not reached [-; -]	100	28 (28.0)	78.00 [-; -]	0.16 [0.06; 0.42]	0.0002	

a: Database Cutoff Date: 06DEC2022

b: Clinical Worsening includes endpoints of death, worsening related listing for lung and/or heart transplant, need to initiate rescue therapy with an approved PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more, need for atrial septostomy, hospitalization for worsening of PAH (≥ 24 hours) and deterioration of PAH based on WHO FC and 6MWD

Study: STELLAR (MK-7962-003)[a]	Sotatercept			Placebo			Sotatercept vs. Placebo		p-Value for Interaction Test[g]
Time to First Clinical Worsening or Death[b]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	
c: Number of participants: full analysis set population									
d: From product-limit (Kaplan-Meier) method for censored data									
e: Based on Cox regression model with treatment as a covariate stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)									
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)									
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)									
h: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States									
CI: Confidence Interval; FC: Functional Class; PAH: Pulmonary Arterial Hypertension; WHO: World Health Organisation									

Verbesserung der Dyspnoe gemäß Borg CR10-Skala pre 6MWD-Test

Tabelle 4G-8: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Verbesserung der Dyspnoe gemäß Borg CR10-Skala pre 6MWD-Test aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	**Sotatercept**		**Placebo**		**Sotatercept vs. Placebo**			
Improvement in Pre-6MWD Dyspnea Score (Borg CR10 Scale)[b]	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]**	**p-Value[e]**	**Adjusted Difference[f] [95 %-CI]**	**p-Value for Interaction[g] Test**
Sex								
Male	34	10 (29.4)	33	10 (30.3)	0.96 [0.46; 2.00]	0.908	-1.27 [-23.57; 20.96]	0.885
Female	126	28 (22.2)	126	27 (21.4)	1.03 [0.65; 1.65]	0.889	0.75 [-9.60; 10.98]	
Age (Years)								
< 65	135	32 (23.7)	130	31 (23.8)	0.99 [0.65; 1.52]	0.971	-0.20 [-10.57; 10.07]	0.781
≥ 65	25	6 (24.0)	29	6 (20.7)	1.30 [0.47; 3.62]	0.615	5.23 [-17.51; 26.75]	
Severity of Disease								
WHO FC II	77	19 (24.7)	78	18 (23.1)	1.07 [0.61; 1.86]	0.823	1.52 [-11.99; 14.80]	0.821
WHO FC III	83	19 (22.9)	81	19 (23.5)	0.98 [0.56; 1.71]	0.941	-0.49 [-13.61; 12.57]	
Region[h]								
WHO Stratum A	132	35 (26.5)	127	32 (25.2)	1.03 [0.69; 1.56]	0.876	0.83 [-9.98; 11.53]	0.541
RoW	28	3 (10.7)	32	5 (15.6)	0.90 [0.22; 3.77]	0.891	-1.59 [-20.47; 17.59]	
Background PAH Therapy								
Mono/Double	64	15 (23.4)	59	19 (32.2)	0.74 [0.42; 1.31]	0.303	-8.32 [-24.17; 7.50]	0.135
Triple	96	23 (24.0)	100	18 (18.0)	1.34 [0.77; 2.31]	0.303	6.01 [-5.48; 17.52]	

a: Database Cutoff Date: 06DEC2022

b: Fulfilled if a participant achieves improvement from baseline in Pre-6MWD Dyspnea Score assessed by Borg CR10 Scale (decrease ≥ 15%) at week 24

c: Number of participants: full analysis set population. Participants with missing assessment at week 24 not due to COVID-19 are considered a non-responder. Participants who missed assessment at week 24 due to COVID-19 are taken out of the population

d: Peto-Odds Ratio instead of Relative Risk if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

e: Two-sided p-value based on Wald test

f: Miettinen and Nurminen method stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

g: Based on generalized linear model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

h: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom

Study: STELLAR (MK-7962-003)[a]	Sotatercept	Placebo	Sotatercept vs. Placebo		p-Value for Interaction[g]
Improvement in Pre-6MWD Dyspnea Score (Borg CR10 Scale)[b]	Participants with Event	Participants with Event	Risk Ratio/ Peto-Odds Ratio[d]	Adjusted Difference[f]	
and United States					

6MWD: Six-Minute Walk Distance; CI: Confidence Interval; COVID-19: Coronavirus Disease of 2019; CR10: 10 Point Category Ratio scale; FC: Functional Class; PAH: Pulmonary Arterial Hypertension; RoW: Rest of World; WHO: World Health Organization

Krankheitssymptomatik und Gesundheitszustand

PAH-SYMPACT: Kardiopulmonale Symptome

Tabelle 4G-9: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0{,}05$) für die Domäne Kardiopulmonale Symptome des PAH-SYMPACT aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	Sotatercept		Placebo		Sotatercept vs. Placebo			p-Value for Interaction[g]
Improvement in PAH-SYMPACT: Cardiopulmonary Symptoms Domain Score[b]	N[c]	Participants with Event n (%)	N[c]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]	Test
Sex								
Male	22	11 (50.0)	22	6 (27.3)	1.63 [0.79; 3.33]	0.184	19.13 [-7.40; 45.42]	0.381
Female	93	36 (38.7)	95	29 (30.5)	1.28 [0.86; 1.90]	0.229	8.32 [-5.34; 21.71]	
Age (Years)								
< 65	95	43 (45.3)	97	30 (30.9)	1.45 [1.00; 2.10]	0.052	13.93 [0.12; 27.30]	0.270
≥ 65	20	4 (20.0)	20	5 (25.0)	0.89 [0.29; 2.68]	0.833	-3.78 [-30.78; 25.00]	
Severity of Disease								
WHO FC II	60	26 (43.3)	64	23 (35.9)	1.20 [0.77; 1.87]	0.426	7.05 [-10.15; 24.01]	0.439
WHO FC III	55	21 (38.2)	53	12 (22.6)	1.63 [0.90; 2.93]	0.105	14.50 [-2.82; 31.21]	
Region[h]								
WHO Stratum A	98	36 (36.7)	94	25 (26.6)	1.36 [0.89; 2.09]	0.154	9.76 [-3.52; 22.76]	0.585
RoW	17	11 (64.7)	23	10 (43.5)	1.47 [0.77; 2.78]	0.240	17.71 [-15.28; 46.41]	
Background PAH Therapy								
Mono/Double	42	16 (38.1)	42	16 (38.1)	0.98 [0.56; 1.72]	0.948	-0.68 [-21.23; 20.09]	0.175
Triple	73	31 (42.5)	75	19 (25.3)	1.66 [1.05; 2.64]	0.031	16.88 [1.83; 31.40]	

Study: STELLAR (MK-7962-003)[a]	Sotatercept		Placebo		Sotatercept vs. Placebo			p-Value for Interaction[g] Test
Improvement in PAH-SYMPACT: Cardiopulmonary Symptoms Domain Score[b]	N[c]	Participants with Event n (%)	N[c]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]	

a: Database Cutoff Date: 06DEC2022

b: Fulfilled if a participant achieves improvement from baseline in Cardiopulmonary Symptoms Domain Score of PAH-SYMPACT (decrease ≥ 15%) at week 24

c: Number of participants: full analysis set population, participants without missing assessment at both baseline and week 24 or missing at week 24 not due to COVID-19. Participants with missing assessment at week 24 not due to COVID-19 are considered a non-responder. Participants who missed assessment at week 24 due to COVID-19 are taken out of the population

d: Peto-Odds Ratio instead of Relative Risk if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

e: Two-sided p-value based on Wald test

f: Miettinen and Nurminen method stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

g: Based on generalized linear model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

h: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States

CI: Confidence Interval; COVID-19: Coronavirus Disease of 2019; FC: Functional Class; PAH-SYMPACT: Pulmonary Arterial Hypertension - Symptoms and Impact; PAH: Pulmonary Arterial Hypertension; RoW: Rest of World; WHO: World Health Organization

PAH-SYMPACT: Kardiovaskuläre Symptome

Tabelle 4G-10: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Domäne Kardiovaskuläre Symptome des PAH-SYMPACT aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	Sotatercept		Placebo		Sotatercept vs. Placebo			p-Value for Interaction[g] Test
Improvement in PAH-SYMPACT: Cardiovascular Symptoms Domain Score[b]	N[c]	Participants with Event n (%)	N[c]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]	
Sex								
Male	22	12 (54.5)	22	6 (27.3)	2.10 [0.89; 4.92]	0.088	27.65 [-2.36; 52.50]	0.318
Female	93	37 (39.8)	95	28 (29.5)	1.35 [0.91; 2.01]	0.139	10.32 [-3.34; 23.68]	
Age (Years)								
< 65	95	46 (48.4)	97	31 (32.0)	1.49 [1.04; 2.14]	0.028	15.87 [2.01; 29.22]	0.461
≥ 65	20	3 (15.0)	20	3 (15.0)	1.15 [0.23; 5.90]	0.864	0.90 [-23.72; 27.53]	
Severity of Disease								

Study: STELLAR (MK-7962-003)[a]	Sotatercept		Placebo		Sotatercept vs. Placebo			
Improvement in PAH-SYMPACT: Cardiovascular Symptoms Domain Score[b]	N[c]	Participants with Event n (%)	N[c]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]	p-Value for Interaction[g] Test
WHO FC II	60	27 (45.0)	64	18 (28.1)	1.64 [1.02; 2.63]	0.042	17.65 [0.85; 33.61]	0.584
WHO FC III	55	22 (40.0)	53	16 (30.2)	1.32 [0.77; 2.25]	0.317	9.52 [-8.64; 27.12]	
Region[h]								
WHO Stratum A	98	39 (39.8)	94	23 (24.5)	1.61 [1.03; 2.52]	0.038	14.87 [1.59; 27.72]	0.708
RoW	17	10 (58.8)	23	11 (47.8)	1.37 [0.72; 2.58]	0.336	17.55 [-16.41; 44.65]	
Background PAH Therapy								
Mono/Double	42	23 (54.8)	42	14 (33.3)	1.69 [1.01; 2.83]	0.047	22.44 [0.93; 41.81]	0.418
Triple	73	26 (35.6)	75	20 (26.7)	1.34 [0.82; 2.18]	0.243	9.00 [-6.03; 23.70]	

a: Database Cutoff Date: 06DEC2022

b: Fulfilled if a participant achieves improvement from baseline in Cardiovascular Symptoms Domain Score of PAH-SYMPACT (decrease ≥ 15%) at week 24

c: Number of participants: full analysis set population, participants without missing assessment at both baseline and week 24 or missing at week 24 not due to COVID-19. Participants with missing assessment at week 24 not due to COVID-19 are considered a non-responder. Participants who missed assessment at week 24 due to COVID-19 are taken out of the population

d: Peto-Odds Ratio instead of Relative Risk if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

e: Two-sided p-value based on Wald test

f: Miettinen and Nurminen method stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

g: Based on generalized linear model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

h: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States

CI: Confidence Interval; COVID-19: Coronavirus Disease of 2019; FC: Functional Class; PAH-SYMPACT: Pulmonary Arterial Hypertension - Symptoms and Impact; PAH: Pulmonary Arterial Hypertension; RoW: Rest of World; WHO: World Health Organization

EQ-5D VAS

Tabelle 4G-11: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0{,}05$) für die VAS des EQ-5D aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	**Sotatercept**		**Placebo**		**Sotatercept vs. Placebo**			
Improvement in EQ-5D VAS[b]	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]**	**p-Value[e]**	**Adjusted Difference[f] [95 %-CI]**	**p-Value for Interaction[g] Test**
Sex								
Male	24	5 (20.8)	24	4 (16.7)	1.30 [0.38; 4.40]	0.675	4.73 [-18.72; 28.18]	0.758
Female	100	24 (24.0)	102	16 (15.7)	1.52 [0.86; 2.68]	0.149	8.28 [-2.82; 19.31]	
Age (Years)								
< 65	104	22 (21.2)	103	14 (13.6)	1.55 [0.85; 2.84]	0.151	7.59 [-2.95; 18.13]	0.884
≥ 65	20	7 (35.0)	23	6 (26.1)	1.17 [0.44; 3.16]	0.750	4.95 [-22.00; 32.88]	
Region[h]								
WHO Stratum A	104	22 (21.2)	104	18 (17.3)	1.24 [0.71; 2.17]	0.443	4.15 [-6.75; 15.02]	0.109
RoW	20	7 (35.0)	22	2 (9.1)	4.85 [0.86; 27.32]	0.074	26.87 [0.90; 51.01]	

a: Database Cutoff Date: 06DEC2022

b: Fulfilled if a participant achieves improvement from baseline in EQ-5D VAS (increase ≥ 15%) at week 24

c: Number of participants: full analysis set population, participants without missing assessment at both baseline and week 24 or missing at week 24 not due to COVID-19. Participants with missing assessment at week 24 not due to COVID-19 are considered a non-responder. Participants who missed assessment at week 24 due to COVID-19 are taken out of the population

d: Peto-Odds Ratio instead of Relative Risk if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

e: Two-sided p-value based on Wald test

f: Miettinen and Nurminen method stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

g: Based on generalized linear model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

h: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States

CI: Confidence Interval; COVID-19: Coronavirus Disease of 2019; EQ-5D: European Quality of Life 5 Dimensions; PAH: Pulmonary Arterial Hypertension; RoW: Rest of World; VAS: Visual Analog Scale; WHO: World Health Organization

Gesundheitsbezogene Lebensqualität

PAH-SYMPACT: Körperliche Auswirkungen

Tabelle 4G-12: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Domäne Körperliche Auswirkungen des PAH-SYMPACT aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	**Sotatercept**		**Placebo**		**Sotatercept vs. Placebo**			
Improvement in PAH-SYMPACT: Physical Impacts Domain Score[b]	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]**	**p-Value[e]**	**Adjusted Difference[f] [95 %-CI]**	**p-Value for Interaction[g] Test**
Sex								
Male	24	6 (25.0)	25	7 (28.0)	0.88 [0.34; 2.29]	0.793	-3.49 [-28.95; 21.39]	0.345
Female	93	33 (35.5)	98	24 (24.5)	1.42 [0.91; 2.21]	0.124	10.26 [-2.82; 23.19]	
Age (Years)								
< 65	95	37 (38.9)	100	29 (29.0)	1.30 [0.87; 1.94]	0.200	8.80 [-4.57; 22.04]	0.716
≥ 65	22	2 (9.1)	23	2 (8.7)	0.97 [0.18; 5.25]	0.968	-0.68 [-21.63; 21.96]	
Severity of Disease								
WHO FC II	55	16 (29.1)	64	18 (28.1)	1.03 [0.58; 1.83]	0.907	0.95 [-15.27; 17.52]	0.231
WHO FC III	62	23 (37.1)	59	13 (22.0)	1.65 [0.92; 2.94]	0.091	14.40 [-1.98; 30.20]	
Region[h]								
WHO Stratum A	98	30 (30.6)	101	24 (23.8)	1.26 [0.79; 2.01]	0.322	6.36 [-6.13; 18.82]	0.668
RoW	19	9 (47.4)	22	7 (31.8)	1.36 [0.57; 3.24]	0.485	9.26 [-20.02; 40.31]	
Background PAH Therapy								
Mono/Double	42	16 (38.1)	43	12 (27.9)	1.33 [0.70; 2.53]	0.379	9.19 [-10.99; 28.97]	0.848
Triple	75	23 (30.7)	80	19 (23.8)	1.29 [0.77; 2.17]	0.334	6.93 [-7.17; 20.96]	

a: Database Cutoff Date: 06DEC2022

b: Fulfilled if a participant achieves improvement from baseline in Physical Impacts Domain Score of PAH-SYMPACT (decrease ≥ 15%) at week 24

c: Number of participants: full analysis set population, participants without missing assessment at both baseline and week 24 or missing at week 24 not due to COVID-19. Participants with missing assessment at week 24 not due to COVID-19 are considered a non-responder. Participants who missed assessment at week 24 due to COVID-19 are taken out of the population

d: Peto-Odds Ratio instead of Relative Risk if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

e: Two-sided p-value based on Wald test

f: Miettinen and Nurminen method stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

g: Based on generalized linear model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

Study: STELLAR (MK-7962-003)[a]	Sotatercept		Placebo		Sotatercept vs. Placebo			p-Value for Interaction[g] Test
Improvement in PAH-SYMPACT: Physical Impacts Domain Score[b]	N[c]	Participants with Event n (%)	N[c]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]	
h: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States								
CI: Confidence Interval; COVID-19: Coronavirus Disease of 2019; FC: Functional Class; PAH-SYMPACT: Pulmonary Arterial Hypertension - Symptoms and Impact; PAH: Pulmonary Arterial Hypertension; RoW: Rest of World; WHO: World Health Organization								

PAH-SYMPACT: Kognitive/Emotionale Auswirkungen

Tabelle 4G-13: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Domäne Kognitive/Emotionale Auswirkungen des PAH-SYMPACT aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	Sotatercept		Placebo		Sotatercept vs. Placebo			p-Value for Interaction[g] Test
Improvement in PAH-SYMPACT: Cognitive/Emotional Impacts Domain Score[b]	N[c]	Participants with Event n (%)	N[c]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]	
Sex								
Male	24	5 (20.8)	25	6 (24.0)	0.84 [0.28; 2.56]	0.760	-3.95 [-28.30; 19.11]	0.686
Female	93	25 (26.9)	98	24 (24.5)	1.07 [0.67; 1.71]	0.780	1.67 [-10.76; 14.12]	
Age (Years)								
< 65	95	24 (25.3)	100	27 (27.0)	0.89 [0.56; 1.40]	0.608	-3.29 [-15.53; 8.94]	0.226
≥ 65	22	6 (27.3)	23	3 (13.0)	1.68 [0.50; 5.63]	0.398	10.00 [-15.08; 36.15]	
Severity of Disease								
WHO FC II	55	15 (27.3)	64	19 (29.7)	0.92 [0.51; 1.64]	0.772	-2.48 [-18.58; 14.11]	0.456
WHO FC III	62	15 (24.2)	59	11 (18.6)	1.22 [0.63; 2.36]	0.563	4.18 [-10.59; 18.71]	
Region[h]								
WHO Stratum A	98	23 (23.5)	101	23 (22.8)	1.00 [0.61; 1.65]	0.994	-0.03 [-11.79; 11.77]	0.804
RoW	19	7 (36.8)	22	7 (31.8)	0.99 [0.40; 2.50]	0.988	-0.78 [-29.10; 29.33]	
Background PAH Therapy								
Mono/Double	42	12 (28.6)	43	15 (34.9)	0.79 [0.42; 1.51]	0.480	-7.27 [-26.73; 12.94]	0.321
Triple	75	18 (24.0)	80	15 (18.8)	1.29 [0.71; 2.34]	0.411	5.35 [-7.58; 18.34]	

Study: STELLAR (MK-7962-003)[a]	Sotatercept		Placebo		Sotatercept vs. Placebo			p-Value for Interaction[g] Test
Improvement in PAH-SYMPACT: Cognitive/Emotional Impacts Domain Score[b]	N[c]	Participants with Event n (%)	N[c]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]	

a: Database Cutoff Date: 06DEC2022

b: Fulfilled if a participant achieves improvement from baseline in Cognitive/Emotional Impacts Domain Score of PAH-SYMPACT (decrease ≥ 15%) at week 24

c: Number of participants: full analysis set population, participants without missing assessment at both baseline and week 24 or missing at week 24 not due to COVID-19. Participants with missing assessment at week 24 not due to COVID-19 are considered a non-responder. Participants who missed assessment at week 24 due to COVID-19 are taken out of the population

d: Peto-Odds Ratio instead of Relative Risk if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

e: Two-sided p-value based on Wald test

f: Miettinen and Nurminen method stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

g: Based on generalized linear model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy)

h: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States

CI: Confidence Interval; COVID-19: Coronavirus Disease of 2019; FC: Functional Class; PAH-SYMPACT: Pulmonary Arterial Hypertension - Symptoms and Impact; PAH: Pulmonary Arterial Hypertension; RoW: Rest of World; WHO: World Health Organization

Nebenwirkungen

Unerwünschte Ereignisse

Unerwünschte Ereignisse gesamt

Tabelle 4G-14: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	**Sotatercept**		**Placebo**		**Sotatercept vs. Placebo**		
Adverse Events	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
Sex							
Male	34	28 (82.35)	33	30 (90.91)	0.91 [0.75; 1.09]	0.308	0.243
Female	129	123 (95.35)	127	119 (93.70)	1.02 [0.96; 1.08]	0.563	
Age (Years)							
< 65	138	129 (93.48)	131	122 (93.13)	1.00 [0.94; 1.07]	0.909	0.532
≥ 65	25	22 (88.00)	29	27 (93.10)	0.95 [0.79; 1.13]	0.523	
Severity of Disease							
WHO FC II	79	73 (92.41)	78	74 (94.87)	0.97 [0.90; 1.06]	0.528	0.486
WHO FC III	84	78 (92.86)	82	75 (91.46)	1.02 [0.93; 1.11]	0.739	
Region[f]							
WHO Stratum A	135	130 (96.30)	127	122 (96.06)	1.00 [0.96; 1.05]	0.922	0.602
RoW	28	21 (75.00)	33	27 (81.82)	0.92 [0.70; 1.20]	0.520	
Background PAH Therapy							
Mono/Double	65	59 (90.77)	60	58 (96.67)	0.94 [0.86; 1.03]	0.180	0.124
Triple	98	92 (93.88)	100	91 (91.00)	1.03 [0.95; 1.12]	0.445	

a: Database Cutoff Date: 06DEC2022

b: Number of participants: safety set population

c: Based on 2x2 contingency table, using Wald confidence interval. In case no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test. In case no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'

f: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States

CI: Confidence Interval; FC: Functional Class; n.a.: not applicable (when estimation not possible); PAH: Pulmonary Arterial Hypertension; RoW: Rest of the World; WHO: World Health Organisation

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-15: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	**Sotatercept**		**Placebo**		**Sotatercept vs. Placebo**		
Serious Adverse Events	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
Sex							
Male	34	7 (20.59)	33	11 (33.33)	0.62 [0.27; 1.40]	0.243	0.411
Female	129	33 (25.58)	127	36 (28.35)	0.90 [0.60; 1.35]	0.619	
Age (Years)							
< 65	138	28 (20.29)	131	32 (24.43)	0.83 [0.53; 1.30]	0.416	0.885
≥ 65	25	12 (48.00)	29	15 (51.72)	0.93 [0.54; 1.59]	0.787	
Severity of Disease							
WHO FC II	79	16 (20.25)	78	17 (21.79)	0.93 [0.51; 1.70]	0.813	0.595
WHO FC III	84	24 (28.57)	82	30 (36.59)	0.78 [0.50; 1.22]	0.272	
Region[f]							
WHO Stratum A	135	36 (26.67)	127	41 (32.28)	0.83 [0.57; 1.20]	0.319	0.982
RoW	28	4 (14.29)	33	6 (18.18)	0.79 [0.25; 2.51]	0.685	
Background PAH Therapy							
Mono/Double	65	16 (24.62)	60	18 (30.00)	0.82 [0.46; 1.46]	0.501	0.936
Triple	98	24 (24.49)	100	29 (29.00)	0.84 [0.53; 1.34]	0.475	

a: Database Cutoff Date: 06DEC2022

b: Number of participants: safety set population

c: Based on 2x2 contingency table, using Wald confidence interval. In case no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test. In case no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'

f: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States

CI: Confidence Interval; FC: Functional Class; n.a.: not applicable (when estimation not possible); PAH: Pulmonary Arterial Hypertension; RoW: Rest of the World; WHO: World Health Organisation

Schwere unerwünschte Ereignisse

Tabelle 4G-16: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	**Sotatercept**		**Placebo**		**Sotatercept vs. Placebo**		
Severe Adverse Events	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
Sex							
Male	34	5 (14.71)	33	8 (24.24)	0.61 [0.22; 1.66]	0.327	0.707
Female	129	19 (14.73)	127	25 (19.69)	0.75 [0.43; 1.29]	0.294	
Age (Years)							
< 65	138	16 (11.59)	131	21 (16.03)	0.72 [0.40; 1.32]	0.292	0.964
≥ 65	25	8 (32.00)	29	12 (41.38)	0.77 [0.38; 1.58]	0.481	
Severity of Disease							
WHO FC II	79	8 (10.13)	78	14 (17.95)	0.56 [0.25; 1.27]	0.159	0.495
WHO FC III	84	16 (19.05)	82	19 (23.17)	0.82 [0.46; 1.48]	0.516	
Region[f]							
WHO Stratum A	135	24 (17.78)	127	31 (24.41)	0.73 [0.45; 1.17]	0.189	0.281
RoW	28	0	33	2 (6.06)	n.a. [n.a.; n.a.]	n.a.	
Background PAH Therapy							
Mono/Double	65	10 (15.38)	60	16 (26.67)	0.58 [0.28; 1.17]	0.122	0.415
Triple	98	14 (14.29)	100	17 (17.00)	0.84 [0.44; 1.61]	0.600	

a: Database Cutoff Date: 06DEC2022

b: Number of participants: safety set population

c: Based on 2x2 contingency table, using Wald confidence interval. In case no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test. In case no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'

f: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States

CI: Confidence Interval; FC: Functional Class; n.a.: not applicable (when estimation not possible); PAH: Pulmonary Arterial Hypertension; RoW: Rest of the World; WHO: World Health Organisation

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-17: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: STELLAR (MK-7962-003)[a]	**Sotatercept**		**Placebo**		**Sotatercept vs. Placebo**		
Adverse Events Leading to Treatment Discontinuation	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
Sex							
Male	34	2 (5.88)	33	3 (9.09)	0.65 [0.12; 3.63]	0.620	0.810
Female	129	4 (3.10)	127	8 (6.30)	0.49 [0.15; 1.59]	0.227	
Age (Years)							
< 65	138	5 (3.62)	131	6 (4.58)	0.79 [0.25; 2.53]	0.693	0.275
≥ 65	25	1 (4.00)	29	5 (17.24)	0.23 [0.03; 1.86]	0.126	
Severity of Disease							
WHO FC II	79	4 (5.06)	78	6 (7.69)	0.66 [0.19; 2.24]	0.501	0.621
WHO FC III	84	2 (2.38)	82	5 (6.10)	0.39 [0.08; 1.96]	0.235	
Region[f]							
WHO Stratum A	135	6 (4.44)	127	9 (7.09)	0.63 [0.23; 1.71]	0.358	0.312
RoW	28	0	33	2 (6.06)	n.a. [n.a.; n.a.]	n.a.	
Background PAH Therapy							
Mono/Double	65	4 (6.15)	60	3 (5.00)	1.23 [0.29; 5.27]	0.780	0.131
Triple	98	2 (2.04)	100	8 (8.00)	0.26 [0.06; 1.17]	0.056	

a: Database Cutoff Date: 06DEC2022

b: Number of participants: safety set population

c: Based on 2x2 contingency table, using Wald confidence interval. In case no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test. In case no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'

f: Countries included in the WHO Stratum A category are Andorra, Australia, Austria, Belgium, Brunei Darussalam, Canada, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States

CI: Confidence Interval; FC: Functional Class; n.a.: not applicable (when estimation not possible); PAH: Pulmonary Arterial Hypertension; RoW: Rest of the World; WHO: World Health Organisation

Anhang 4-G3: Auswertungen über den Studienverlauf

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1 die Auswertungen über den Studienverlauf der 6MWD, der Dyspnoe gemäß Borg CR10-Skala pre 6MWD-Test, EQ-5D VAS sowie des PAH-SYMPACTS dargestellt.

6MWD

Tabelle 4G-18: Auswertungen über den Studienverlauf des Endpunkts 6MWD aus RCT mit dem zu bewertenden Arzneimittel

Deskriptive Zusammenfassung der 6MWD (in Metern)	**Studie: STELLAR (MK-7962-003)[a]**	
	Sotatercept	**Placebo**
	N[b]= 163	N[b]= 160
Baseline		
N[c]	163	160
Mittelwert (SD)	397,6 (84,3)	404,7 (80,6)
Median (Q1; Q3)	417,0 (348,0; 464,5)	427,1 (365,0; 465,0)
Min, Max	160,5; 497,5	151,5; 514,5
Woche 3		
N[c]	157	154
Mittelwert (SD)	412,4 (85,0)	415,0 (85,9)
Median (Q1; Q3)	424,0 (367,8; 475,5)	433,0 (362,0; 474,0)
Min, Max	151,3; 635,0	140,0; 598,0
Woche 12		
N[c]	154	151
Mittelwert (SD)	429,1 (87,2)	408,4 (97,4)
Median (Q1; Q3)	440,5 (390,0; 486,0)	425,0 (351,0; 482,0)
Min, Max	160,0; 633,0	120,0; 646,0
Woche 24		
N[c]	158	147
Mittelwert (SD)	439,9 (97,2)	409,2 (100,5)
Median (Q1; Q3)	454,0 (392,0; 504,0)	425,0 (344,3; 471,5)
Min, Max	42,0; 691,0	63,0; 647,0
Woche 36		
N[c]	147	122
Mittelwert (SD)	443,8 (95,1)	411,9 (102,7)
Median (Q1; Q3)	459,0 (399,0; 510,0)	423,0 (342,0; 492,0)
Min, Max	120,0; 616,0	144,9; 656,0
Woche 48		
N[c]	83	53
Mittelwert (SD)	452,8 (98,1)	422,5 (90,0)
Median (Q1; Q3)	465,0 (415,0; 512,0)	444,0 (352,3; 473,0)
Min, Max	85,0; 645,0	188,0; 645,0
Woche 60		
N[c]	41	24
Mittelwert (SD)	454,5 (88,2)	398,9 (105,1)
Median (Q1; Q3)	459,0 (399,9; 506,0)	435,0 (317,0; 472,5)
Min, Max	250,0; 637,0	196,0; 570,0
Woche 72		
N[c]	13	7
Mittelwert (SD)	427,8 (141,1)	381,4 (111,1)
Median (Q1; Q3)	457,0 (329,0; 558,0)	447,1 (270,0; 474,0)

Deskriptive Zusammenfassung der 6MWD (in Metern)	Studie: STELLAR (MK-7962-003)[a]	
	Sotatercept N[b]= 163	**Placebo** N[b]= 160
Min, Max	195,0; 595,0	208,0; 488,0
Woche 84		
N[c]	2	1
Mittelwert (SD)	367,3 (34,4)	328,0 (-)
Median (Q1; Q3)	367,3 (342,9; 391,6)	328,0 (328,0; 328,0)
Min, Max	342,9; 391,6	328,0; 328,0

a: Datenschnitt: 06. Dezember 2022
b: Anzahl der Patient:innen: Full-Analysis-Set
c: Anzahl der Patient:innen ohne fehlende Erhebung zur jeweiligen Visite
Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

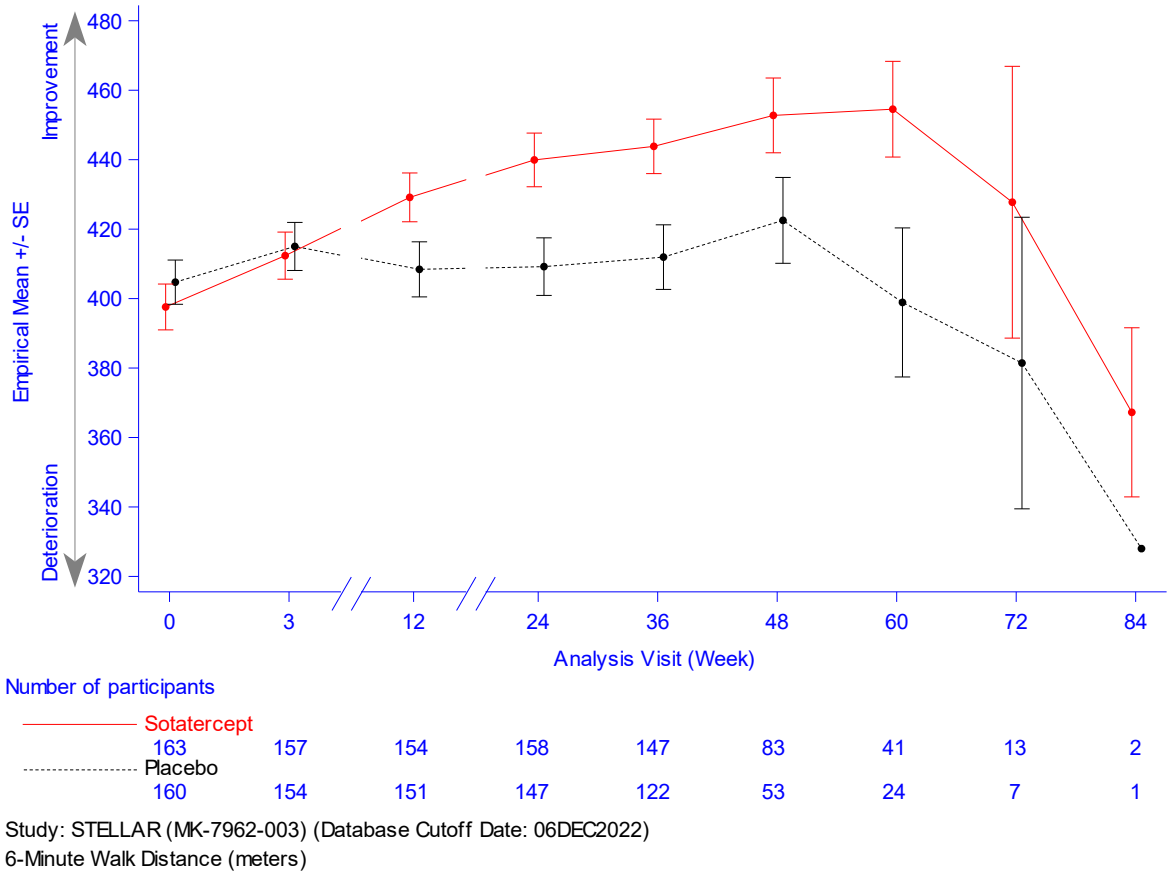

Abbildung 4G-1: Darstellung über den Studienverlauf: Mittelwert +/- Standardfehler zu den verschiedenen Erhebungszeitpunkten des Endpunkts 6MWD aus RCT mit dem zu bewertenden Arzneimittel

Dyspnoe gemäß Borg CR10-Skala pre 6MWD-Test

Tabelle 4G-19: Auswertungen über den Studienverlauf des Endpunkts Dyspnoe gemäß Borg CR10-Skala aus RCT mit dem zu bewertenden Arzneimittel

Pre-6MWD Dyspnea Score (Borg CR10 Scale)	Study: STELLAR (MK-7962-003)[a]	
	Sotatercept N[b]=163	Placebo N[b]=160
Baseline		
N[c]	160	160
Mean (SD)	2.6 (2.4)	2.8 (2.7)
Median (Q1; Q3)	1.0 (1.0; 3.0)	1.0 (1.0; 4.0)
Min; Max	1.0; 9.5	1.0; 12.0
Week 3		
N[c]	156	154
Mean (SD)	2.3 (2.3)	2.9 (2.9)
Median (Q1; Q3)	1.0 (1.0; 3.0)	1.0 (1.0; 5.0)
Min; Max	1.0; 10.0	1.0; 11.0
Week 12		
N[c]	153	151
Mean (SD)	2.2 (2.4)	3.1 (3.1)
Median (Q1; Q3)	1.0 (1.0; 2.0)	1.0 (1.0; 5.0)
Min; Max	1.0; 10.0	1.0; 15.0
Week 24		
N[c]	157	146
Mean (SD)	2.8 (2.9)	3.2 (3.3)
Median (Q1; Q3)	1.0 (1.0; 5.0)	1.0 (1.0; 5.0)
Min; Max	1.0; 13.0	1.0; 13.5
Week 36		
N[c]	146	122
Mean (SD)	2.3 (2.7)	3.4 (3.2)
Median (Q1; Q3)	1.0 (1.0; 2.0)	1.0 (1.0; 5.0)
Min; Max	1.0; 16.0	1.0; 14.0
Week 48		
N[c]	83	53
Mean (SD)	2.4 (2.5)	3.2 (2.9)
Median (Q1; Q3)	1.0 (1.0; 3.0)	1.0 (1.0; 5.0)
Min; Max	1.0; 11.0	1.0; 9.0
Week 60		
N[c]	41	24
Mean (SD)	2.7 (2.7)	3.3 (3.2)
Median (Q1; Q3)	1.0 (1.0; 5.0)	1.0 (1.0; 6.5)
Min; Max	1.0; 9.0	1.0; 10.0
Week 72		
N[c]	13	7
Mean (SD)	1.7 (2.0)	4.6 (2.3)
Median (Q1; Q3)	1.0 (1.0; 1.0)	5.0 (2.0; 7.0)
Min; Max	1.0; 8.0	1.0; 7.0
Week 84		
N[c]	2	1
Mean (SD)	2.0 (1.4)	7.0 (-)
Median (Q1; Q3)	2.0 (1.0; 3.0)	7.0 (7.0; 7.0)
Min; Max	1.0; 3.0	7.0; 7.0

Pre-6MWD Dyspnea Score (Borg CR10 Scale)	Study: STELLAR (MK-7962-003)[a]	
	Sotatercept	Placebo
	N[b]=163	N[b]=160

a: Database Cutoff Date: 06DEC2022
b: Number of participants: full analysis set population
c: Number of participants with non-missing assessment at the given visit
6MWD: Six-Minute Walk Distance; CR10: 10 Point Category Ratio scale; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

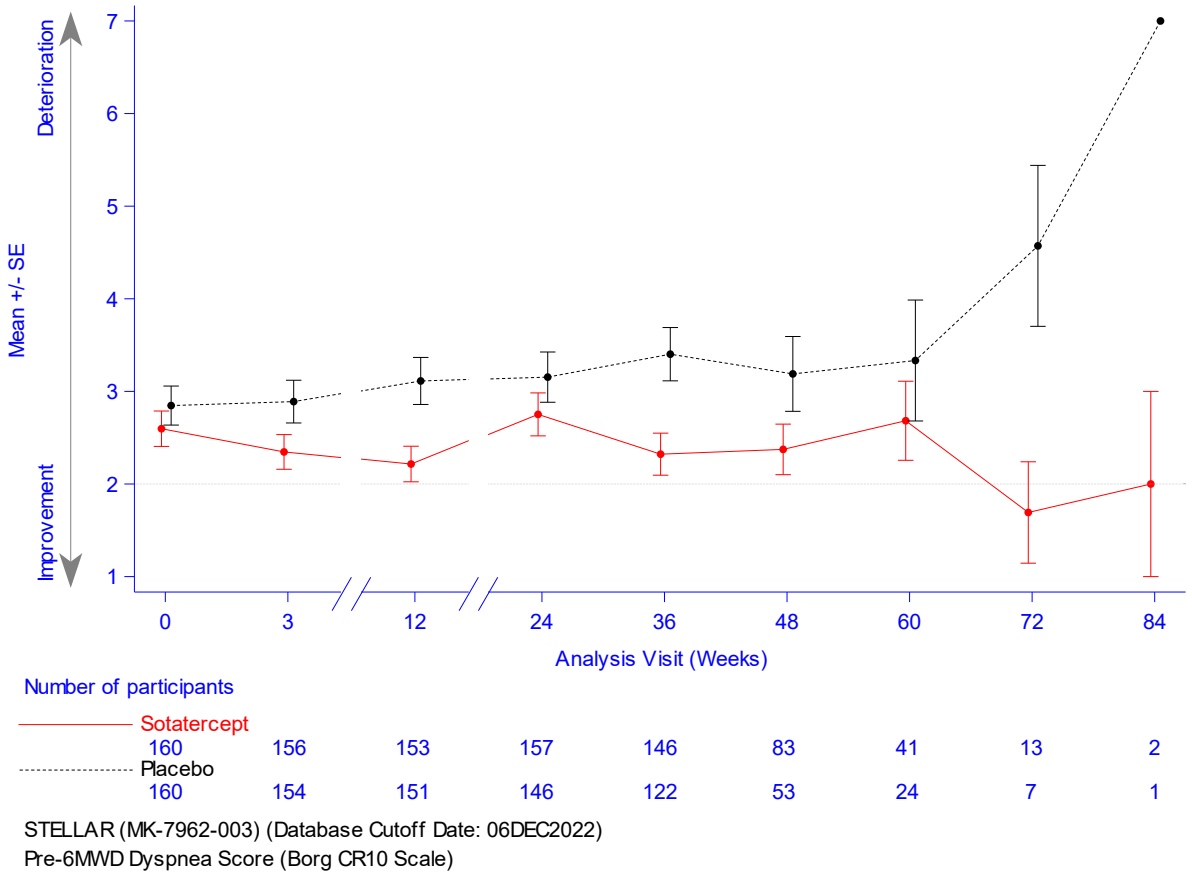

Abbildung 4G-2: Darstellung über den Studienverlauf: Mittelwert +/- Standardfehler zu den verschiedenen Erhebungszeitpunkten des Endpunkts Dyspnoe gemäß Borg CR10-Skala pre 6MWD-Test aus RCT mit dem zu bewertenden Arzneimittel

EQ-5D VAS

Tabelle 4G-20: Auswertungen über den Studienverlauf der VAS des EQ-5D aus RCT mit dem zu bewertenden Arzneimittel

EQ-5D VAS	Study: STELLAR (MK-7962-003)[a]	
	Sotatercept N[b]=163	**Placebo** N[b]=160
Baseline		
N[c]	125	126
Mean (SD)	68.5 (17.8)	68.9 (19.0)
Median (Q1; Q3)	70.0 (55.0; 80.0)	70.5 (59.0; 83.0)
Min; Max	23.0; 100.0	9.0; 100.0
Week 24		
N[c]	109	104
Mean (SD)	72.9 (18.1)	67.2 (20.1)
Median (Q1; Q3)	76.0 (61.0; 88.0)	70.0 (50.0; 85.0)
Min; Max	25.0; 100.0	5.0; 100.0

a: Database Cutoff Date: 06DEC2022
b: Number of participants: full analysis set population
c: Number of participants with non-missing assessment at the given visit
EQ-5D: European Quality of Life 5 Dimensions; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation; VAS: Visual Analog Scale

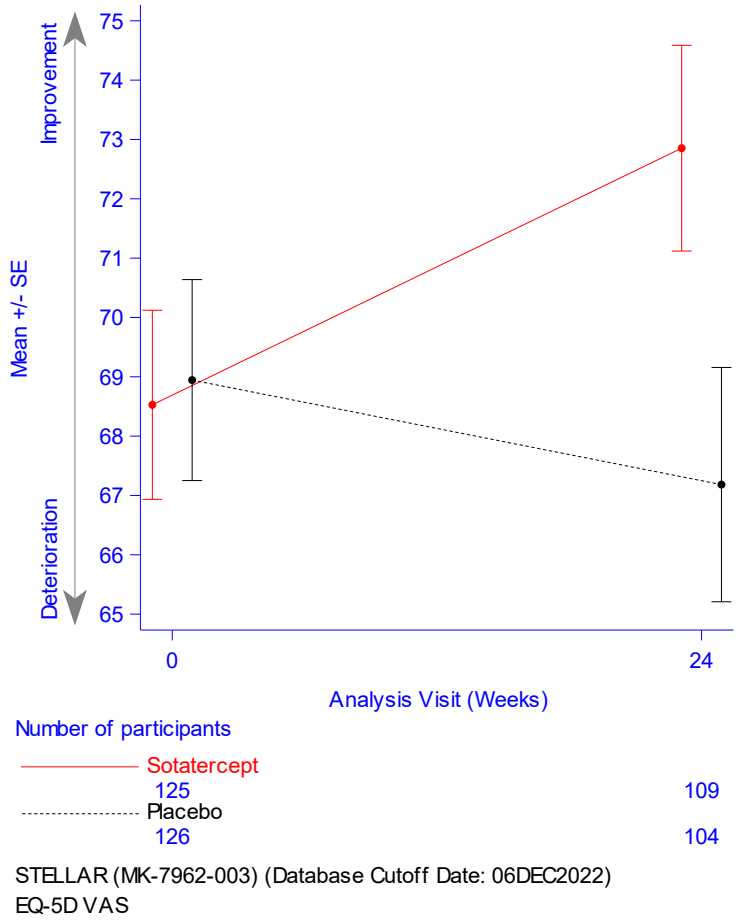

Abbildung 4G-3: Darstellung über den Studienverlauf: Mittelwert +/- Standardfehler zu den beiden Erhebungszeitpunkten der VAS des EQ-5D aus RCT mit dem zu bewertenden Arzneimittel

PAH-SYMPACT

Kardiopulmonale Symptome

Tabelle 4G-21: Auswertungen über den Studienverlauf des PAH-SYMPACT Kardiopulmonale Symptome aus RCT mit dem zu bewertenden Arzneimittel

PAH-SYMPACT: Cardiopulmonary Symptoms Domain Score	**Study: STELLAR (MK-7962-003)[a]**	
	Sotatercept N[b]=163	**Placebo** N[b]=160
Baseline		
N[c]	115	117
Mean (SD)	0.9 (0.6)	0.8 (0.5)
Median (Q1; Q3)	0.9 (0.5; 1.4)	0.8 (0.4; 1.3)
Min; Max	0.0; 2.3	0.0; 2.4
Week 24		
N[c]	122	113

PAH-SYMPACT: Cardiopulmonary Symptoms Domain Score	Study: STELLAR (MK-7962-003)[a]	
	Sotatercept N[b]=163	Placebo N[b]=160
Mean (SD)	0.8 (0.5)	0.8 (0.6)
Median (Q1; Q3)	0.7 (0.4; 1.2)	0.7 (0.4; 1.2)
Min; Max	0.0; 2.3	0.0; 2.8

a: Database Cutoff Date: 06DEC2022
b: Number of participants: full analysis set population
c: Number of participants with non-missing assessment at the given visit
Max: Maximum; Min: Minimum; PAH-SYMPACT: Pulmonary Arterial Hypertension-Symptoms and Impact; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

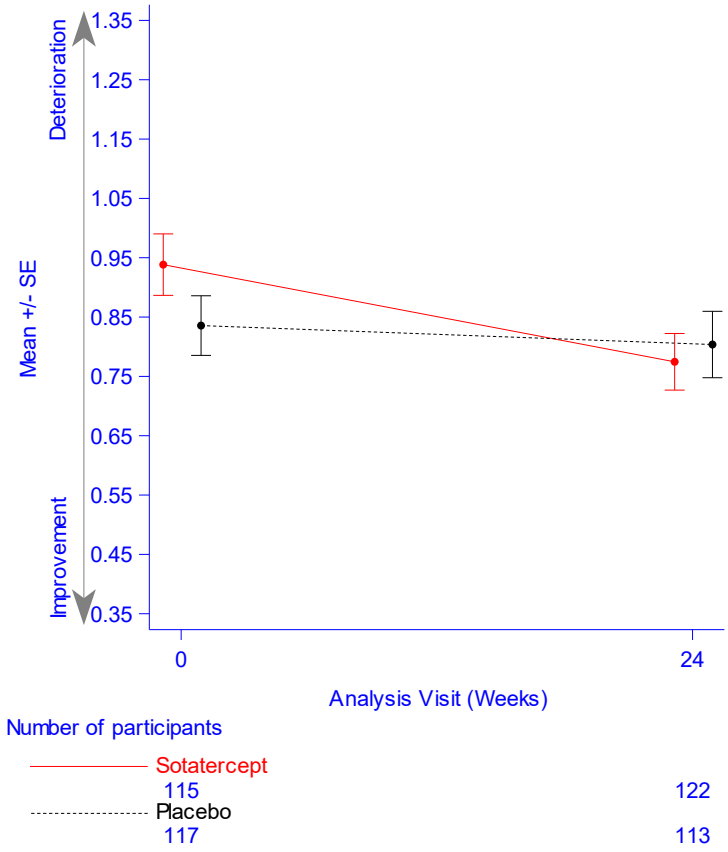

Abbildung 4G-4: Darstellung über den Studienverlauf: Mittelwert +/- Standardfehler zu den beiden Erhebungszeitpunkten des PAH-SYMPACTS Kardiopulmonale Symptome aus RCT mit dem zu bewertenden Arzneimittel

Kardivaskuläre Symptome

Tabelle 4G-22: Auswertungen über den Studienverlauf des PAH-SYMPACT Kardiovaskuläre Symptome aus RCT mit dem zu bewertenden Arzneimittel

PAH-SYMPACT: Cardiovascular Symptoms Domain Score	**Study: STELLAR (MK-7962-003)[a]**	
	Sotatercept	**Placebo**
	N[b]=163	N[b]=160
Baseline		
N[c]	115	117
Mean (SD)	0.6 (0.5)	0.5 (0.5)
Median (Q1; Q3)	0.5 (0.1; 0.8)	0.3 (0.1; 0.7)
Min; Max	0.0; 2.2	0.0; 2.1
Week 24		
N[c]	122	113
Mean (SD)	0.4 (0.4)	0.4 (0.5)
Median (Q1; Q3)	0.2 (0.1; 0.6)	0.3 (0.1; 0.5)
Min; Max	0.0; 2.2	0.0; 2.3

a: Database Cutoff Date: 06DEC2022
b: Number of participants: full analysis set population
c: Number of participants with non-missing assessment at the given visit
Max: Maximum; Min: Minimum; PAH-SYMPACT: Pulmonary Arterial Hypertension-Symptoms and Impact; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

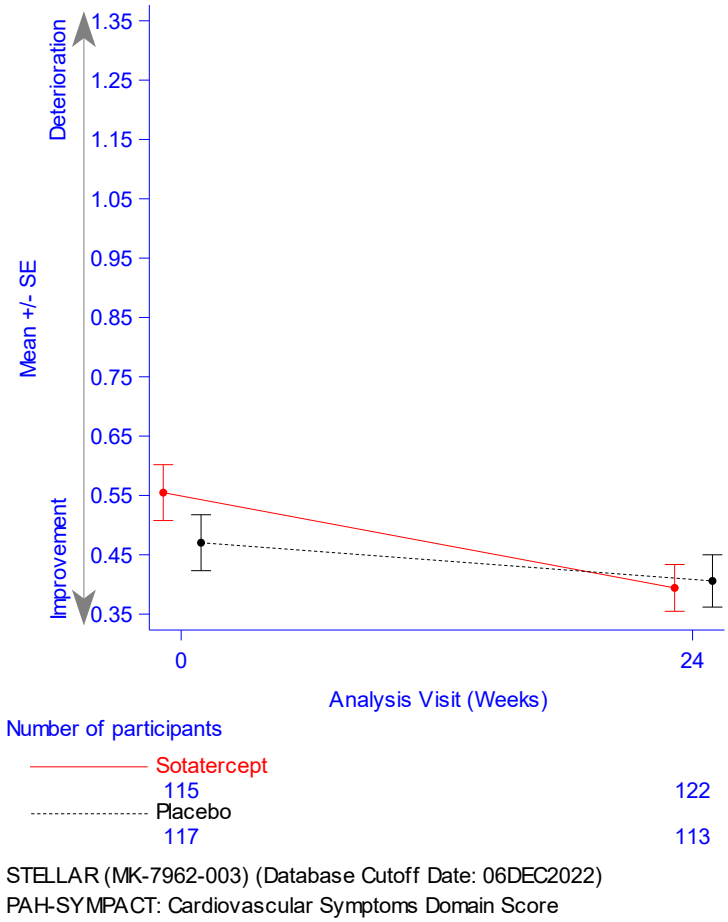

Abbildung 4G-5: Darstellung über den Studienverlauf: Mittelwert +/- Standardfehler zu den beiden Erhebungszeitpunkten des PAH-SYMPACTS Kardiovaskuläre Symptome aus RCT mit dem zu bewertenden Arzneimittel

Körperliche Auswirkungen

Tabelle 4G-23: Auswertungen über den Studienverlauf des PAH-SYMPACT Körperliche Funktion aus RCT mit dem zu bewertenden Arzneimittel

PAH-SYMPACT: Physical Impacts Domain Score	Study: STELLAR (MK-7962-003)[a]	
	Sotatercept N[b]=163	Placebo N[b]=160
Baseline		
N[c]	117	123
Mean (SD)	1.2 (0.9)	1.2 (0.8)
Median (Q1; Q3)	1.1 (0.6; 1.9)	1.1 (0.6; 1.6)
Min; Max	0.0; 3.6	0.0; 3.6
Week 24		
N[c]	115	110
Mean (SD)	0.9 (0.7)	1.1 (0.8)
Median (Q1; Q3)	0.9 (0.4; 1.4)	0.9 (0.4; 1.6)

PAH-SYMPACT: Physical Impacts Domain Score	Study: STELLAR (MK-7962-003)[a]	
	Sotatercept N[b]=163	Placebo N[b]=160
Min; Max	0.0; 3.4	0.0; 3.7

a: Database Cutoff Date: 06DEC2022
b: Number of participants: full analysis set population
c: Number of participants with non-missing assessment at the given visit
Max: Maximum; Min: Minimum; PAH-SYMPACT: Pulmonary Arterial Hypertension-Symptoms and Impact; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

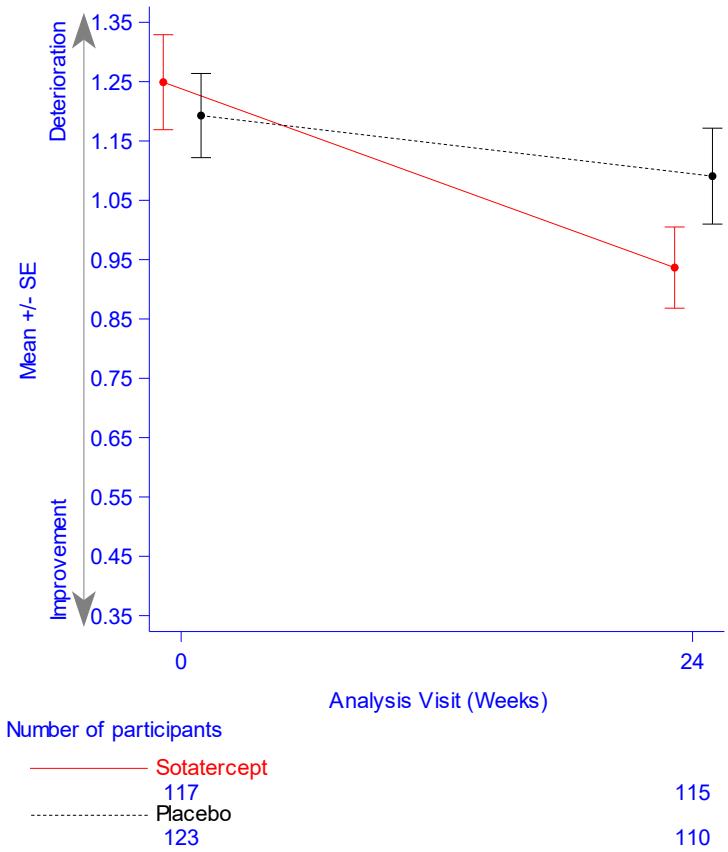

Abbildung 4G-6: Darstellung über den Studienverlauf: Mittelwert +/- Standardfehler zu den beiden Erhebungszeitpunkten des PAH-SYMPACTS Körperliche Funktion aus RCT mit dem zu bewertenden Arzneimittel

Kognitive/Emotionale Funktion

Tabelle 4G-24: Auswertungen über den Studienverlauf des PAH-SYMPACT Kognitive/Emotionale Auswirkungen aus RCT mit dem zu bewertenden Arzneimittel

PAH-SYMPACT: Cognitive/Emotional Impacts Domain Score	**Study: STELLAR (MK-7962-003)[a]**	
	Sotatercept	**Placebo**
	N[b]=163	N[b]=160
Baseline		
N[c]	117	123
Mean (SD)	0.9 (0.8)	0.9 (0.8)
Median (Q1; Q3)	0.8 (0.3; 1.3)	0.8 (0.3; 1.5)
Min; Max	0.0; 2.8	0.0; 3.5
Week 24		
N[c]	115	110
Mean (SD)	0.7 (0.7)	0.9 (0.8)
Median (Q1; Q3)	0.5 (0.3; 1.3)	0.8 (0.3; 1.5)
Min; Max	0.0; 2.5	0.0; 3.3

a: Database Cutoff Date: 06DEC2022
b: Number of participants: full analysis set population
c: Number of participants with non-missing assessment at the given visit
Max: Maximum; Min: Minimum; PAH-SYMPACT: Pulmonary Arterial Hypertension-Symptoms and Impact; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

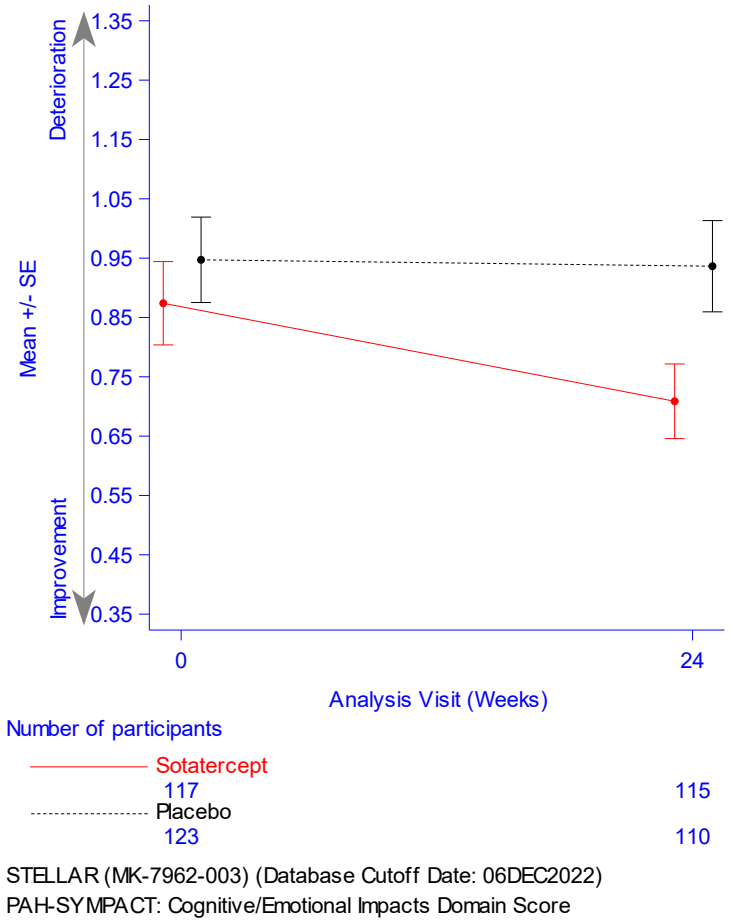

Abbildung 4G-7: Darstellung über den Studienverlauf: Mittelwert +/- Standardfehler zu den beiden Erhebungszeitpunkten des PAH-SYMPACTS Kognitive/Emotionale Auswirkungen aus RCT mit dem zu bewertenden Arzneimittel