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Dossier zur Nutzenbewertung gemäß § 35a SGB V

Letermovir (PREVYMIS®)

MSD Sharp & Dohme GmbH

Modul 4A

Anhang 4-G: Weitere Ergebnisse

Prophylaxe einer Cytomegalievirus (CMV)-Reaktivierung und -Erkrankung bei erwachsenen CMV-seropositiven Empfängern [R+] einer allogenen hämatopoetischen Stammzelltransplantation

Stand: 12.12.2023

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Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.2.6 bzw. Abschnitt 4.3.1.3.1.3.1 die Rücklaufquoten des EQ-5D-VAS und die Rücklaufquoten des FACT-BMT dargestellt.

Alle Ergebnisse beziehen sich auf den letztverfügbaren Analysezeitpunkt.

Anhang 4-G1.1: Rücklaufquoten der EQ-5D-VAS

Tabelle 4G-1: Gründe für das Fehlen von Werten im EQ-5D VAS

Study: MK8228 P001[a]		Letermovir	Placebo
Visit	EQ-5D VAS	N[b] = 325 n (%)	N[b] = 170 n (%)
Baseline	Expected to Complete Questionnaires	325 (100.00)	170 (100.00)
	Completed	243 (74.77)	135 (79.41)
	Compliance (% in those expected to complete questionnaires)[c]	243 (74.77)	135 (79.41)
	Not completed	82 (25.23)	35 (20.59)
	Participant lost to follow-up/unable to contact	0 (0.00)	1 (0.59)
	Other	82 (25.23)	34 (20.00)
	Missing by Design	0 (0.00)	0 (0.00)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to death	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by participant	0 (0.0)	0 (0.0)
	Discontinued due to participant lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Week 14 Post-transplant	Expected to Complete Questionnaires	325 (100.00)	170 (100.00)
	Completed	241 (74.15)	119 (70.00)
	Compliance (% in those expected to complete questionnaires)[c]	241 (74.15)	119 (70.00)
	Not completed	84 (25.85)	51 (30.00)
	Participant lost to follow-up/unable to contact	2 (0.62)	4 (2.35)
	Other	82 (25.23)	47 (27.65)
	Missing by Design	0 (0.00)	0 (0.00)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to death	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by participant	0 (0.0)	0 (0.0)
	Discontinued due to participant lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Week 24 Post-transplant	Expected to Complete Questionnaires	285 (87.69)	144 (84.71)
	Completed	183 (56.31)	84 (49.41)
	Compliance (% in those expected to complete questionnaires)[c]	183 (64.21)	84 (58.33)
	Not completed	102 (31.38)	60 (35.29)
	Participant lost to follow-up/unable to contact	3 (0.92)	1 (0.59)
	Other	99 (30.46)	59 (34.71)
	Missing by Design	40 (12.31)	26 (15.29)
	Discontinued due to adverse event	5 (1.54)	1 (0.59)
	Discontinued due to death	17 (5.23)	12 (7.06)
	Discontinued due to physician decision	2 (0.62)	3 (1.76)
	Discontinued due to withdrawal by participant	16 (4.92)	7 (4.12)
	Discontinued due to participant lost to follow-up/unable to contact	0 (0.00)	3 (1.76)
Week 48 Post-transplant	Expected to Complete Questionnaires	248 (76.31)	116 (68.24)
	Completed	174 (53.54)	86 (50.59)
	Compliance (% in those expected to complete questionnaires)[c]	174 (70.16)	86 (74.14)
	Not completed	74 (22.77)	30 (17.65)
	Participant lost to follow-up/unable to contact	4 (1.23)	0 (0.00)
	Other	70 (21.54)	30 (17.65)
	Missing by Design	77 (23.69)	54 (31.76)
	Discontinued due to adverse event	6 (1.85)	1 (0.59)
	Discontinued due to death	43 (13.23)	32 (18.82)
	Discontinued due to physician decision	5 (1.54)	4 (2.35)

Study: MK8228 P001[a]		Letermovir	Placebo
Visit	EQ-5D VAS	N[b] = 325 n (%)	N[b] = 170 n (%)
	Discontinued due to withdrawal by participant	21 (6.46)	13 (7.65)
	Discontinued due to participant lost to follow-up/unable to contact	2 (0.62)	4 (2.35)

a: Database Lock Date: 28JAN2017
b: Number of participants: Full Analysis Set Population
c: Compliance is the proportion of participants who completed the PRO questionnaire among these who are expected to complete at each time point, excluding those missing by design
EQ-5D VAS: EuroQoL Visual Analog Scale; PRO: Patient Reported Outcome

Anhang 4-G1.1: Rücklaufquoten des FACT-BMT

Tabelle 4G-2: Gründe für das Fehlen von Werten im FACT-BMT

Study: MK8228 P001[a]		Letermovir	Placebo
Visit	FACT-BMT	N[b] = 325 n (%)	N[b] = 170 n (%)
Baseline	Expected to Complete Questionnaires	325 (100.00)	170 (100.00)
	Completed	258 (79.38)	138 (81.18)
	Compliance (% in those expected to complete questionnaires)[c]	258 (79.38)	138 (81.18)
	Not completed	67 (20.62)	32 (18.82)
	Participant lost to follow-up/unable to contact	0 (0.00)	1 (0.59)
	Other	67 (20.62)	31 (18.24)
	Missing by Design	0 (0.00)	0 (0.00)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to death	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by participant	0 (0.0)	0 (0.0)
	Discontinued due to participant lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Week 14 Post-transplant	Expected to Complete Questionnaires	325 (100.00)	170 (100.00)
	Completed	250 (76.92)	121 (71.18)
	Compliance (% in those expected to complete questionnaires)[c]	250 (76.92)	121 (71.18)
	Not completed	75 (23.08)	49 (28.82)
	Participant lost to follow-up/unable to contact	2 (0.62)	4 (2.35)
	Other	73 (22.46)	45 (26.47)
	Missing by Design	0 (0.00)	0 (0.00)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to death	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by participant	0 (0.0)	0 (0.0)
	Discontinued due to participant lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Week 24 Post-transplant	Expected to Complete Questionnaires	285 (87.69)	144 (84.71)
	Completed	185 (56.92)	87 (51.18)
	Compliance (% in those expected to complete questionnaires)[c]	185 (64.91)	87 (60.42)
	Not completed	100 (30.77)	57 (33.53)
	Participant lost to follow-up/unable to contact	3 (0.92)	1 (0.59)
	Other	97 (29.85)	56 (32.94)
	Missing by Design	40 (12.31)	26 (15.29)
	Discontinued due to adverse event	5 (1.54)	1 (0.59)
	Discontinued due to death	17 (5.23)	12 (7.06)
	Discontinued due to physician decision	2 (0.62)	3 (1.76)
	Discontinued due to withdrawal by participant	16 (4.92)	7 (4.12)
	Discontinued due to participant lost to follow-up/unable to contact	0 (0.00)	3 (1.76)
Week 48 Post-transplant	Expected to Complete Questionnaires	248 (76.31)	116 (68.24)
	Completed	178 (54.77)	90 (52.94)
	Compliance (% in those expected to complete questionnaires)[c]	178 (71.77)	90 (77.59)
	Not completed	70 (21.54)	26 (15.29)
	Participant lost to follow-up/unable to contact	4 (1.23)	0 (0.00)
	Other	66 (20.31)	26 (15.29)

Study: MK8228 P001[a]		Letermovir	Placebo
Visit	FACT-BMT	N[b] = 325 n (%)	N[b] = 170 n (%)
	Missing by Design	77 (23.69)	54 (31.76)
	Discontinued due to adverse event	6 (1.85)	1 (0.59)
	Discontinued due to death	43 (13.23)	32 (18.82)
	Discontinued due to physician decision	5 (1.54)	4 (2.35)
	Discontinued due to withdrawal by participant	21 (6.46)	13 (7.65)
	Discontinued due to participant lost to follow-up/unable to contact	2 (0.62)	4 (2.35)

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Compliance is the proportion of participants who completed the PRO questionnaire among these who are expected to complete at each time point, excluding those missing by design

FACT-BMT: Functional Assessment of Cancer Therapy - Bone Marrow Transplant; PRO: Patient Reported Outcome

Anhang 4-G2: Kaplan-Meier-Kurven der Subgruppen mit signifikantem Interaktionstest (p < 0,05)

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.2.2 die Kaplan-Meier-Kurven der Subgruppenanalysen, für die ein signifikanter Interaktionstest (p < 0,05) vorliegt, dargestellt.

Alle Ergebnisse beziehen sich auf den letztverfügbaren Analysezeitpunkt.

Mortalität

Gesamtmortalität

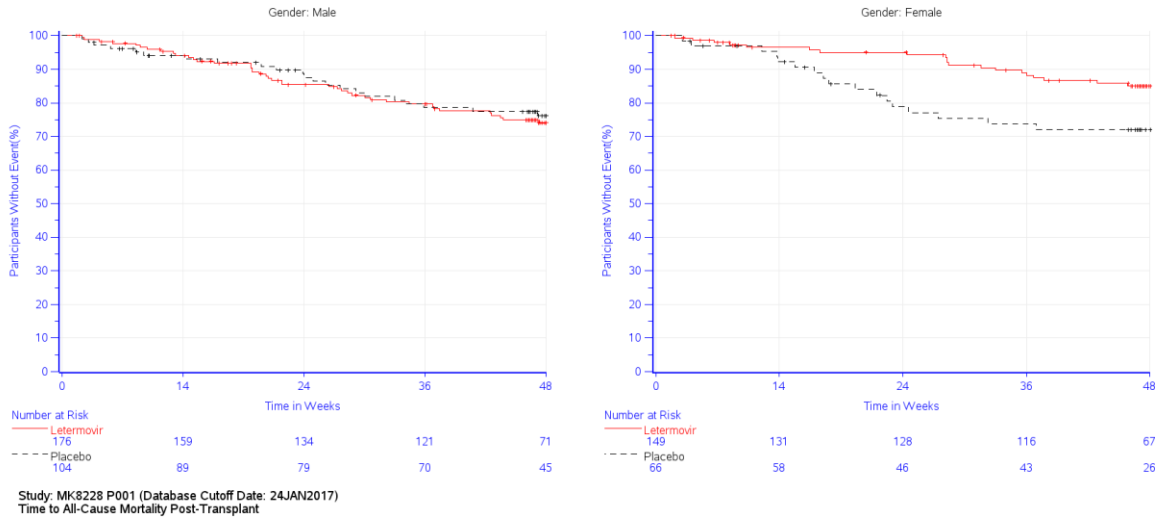


Abbildung 4G-1: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Geschlecht für den Endpunkt Gesamtmortalität

CMV-assoziierte Mortalität

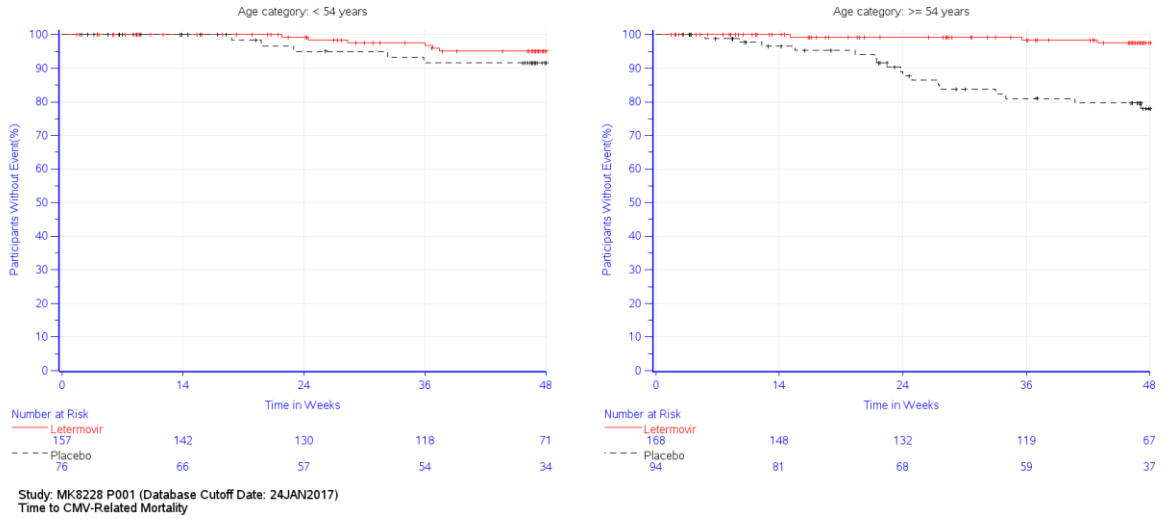


Abbildung 4G-2: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Alter für den Endpunkt CMV-assoziierte Mortalität

Nebenwirkungen

Unerwünschte Ereignisse Gesamtraten

Schwerwiegende unerwünschte Ereignisse

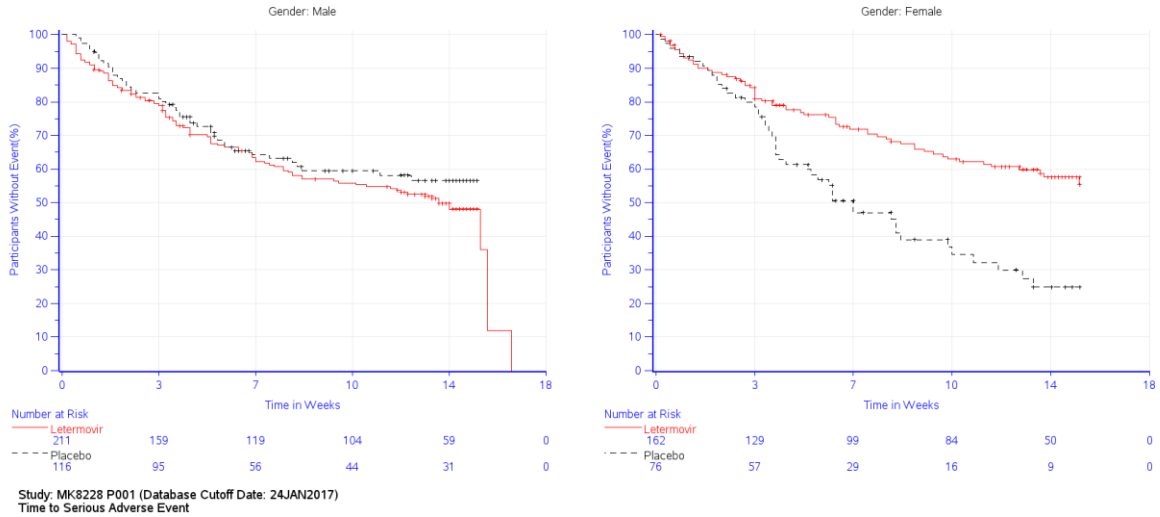


Abbildung 4G-3: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Geschlecht für den Endpunkt Schwerwiegende unerwünschte Ereignisse

Schwere unerwünschte Ereignisse

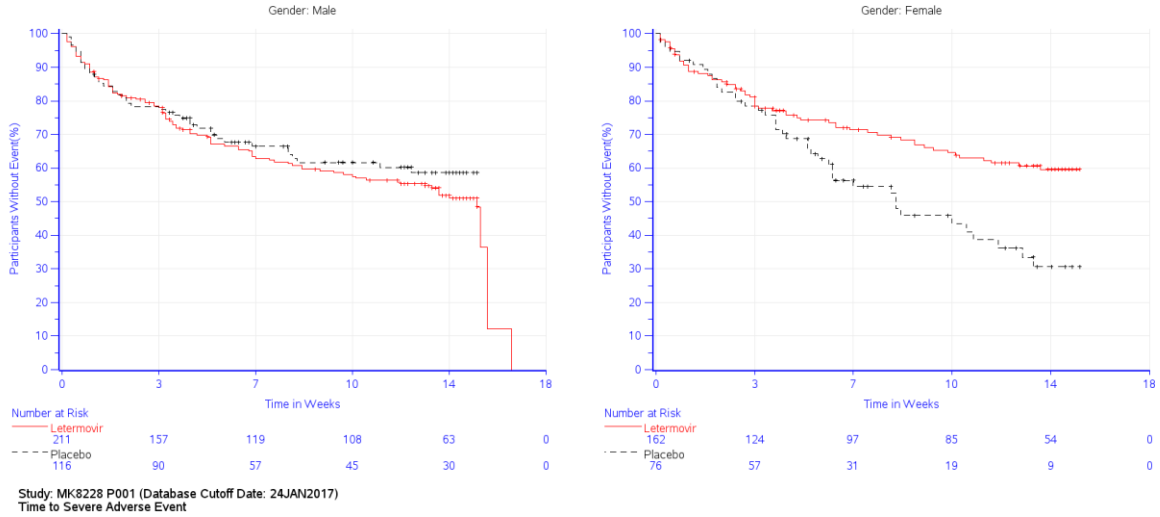


Abbildung 4G-4: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Geschlecht für den Endpunkt Schwere unerwünschte Ereignisse

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

PT Cytomegalievirus-Infection

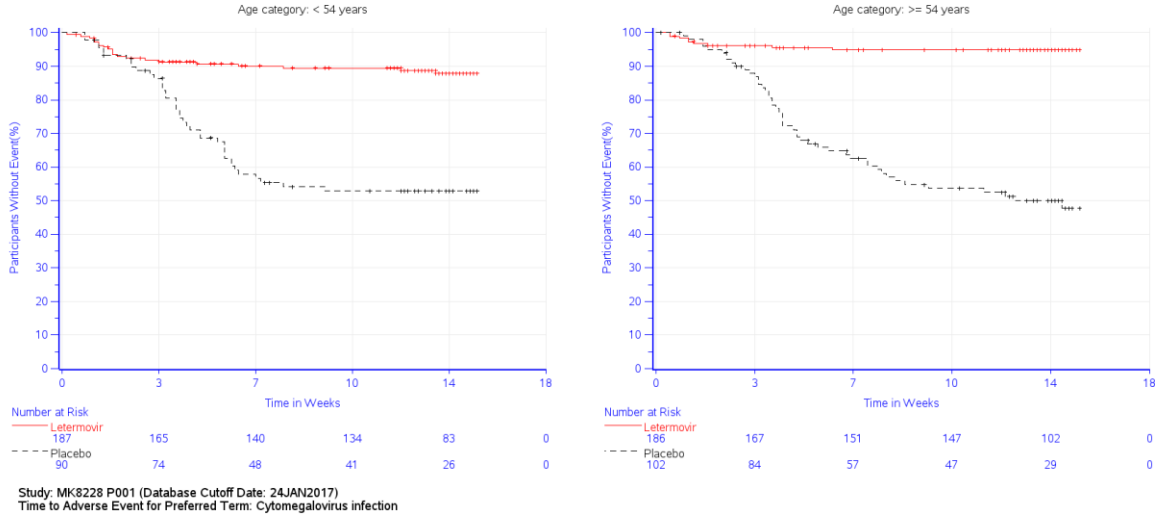


Abbildung 4G-5: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Alter für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT Cytomegalievirus-Infektion

PT Dyspnoe

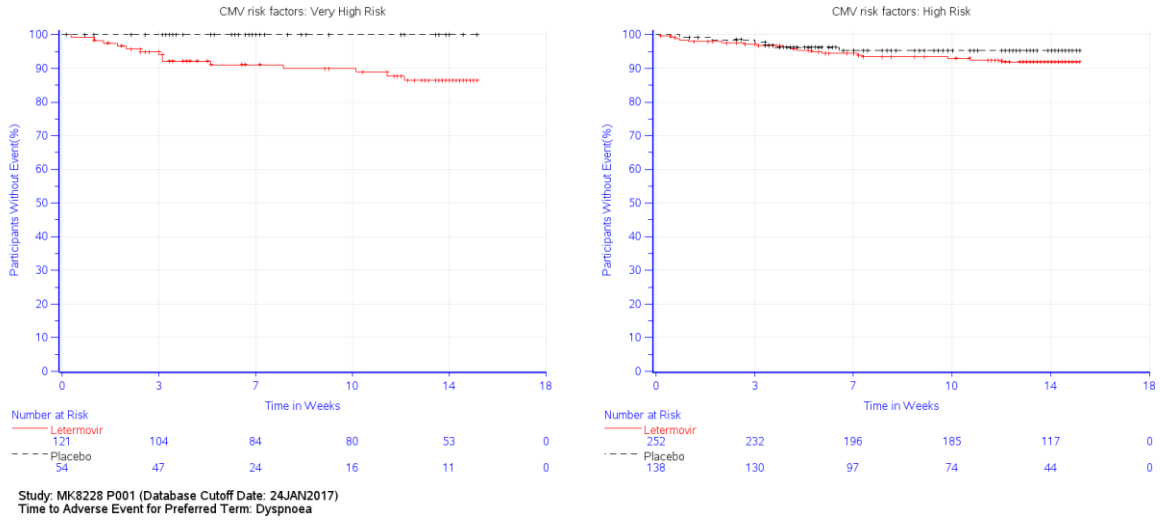


Abbildung 4G-6: Kaplan-Meier-Kurven für die Subgruppenanalyse nach CMV-Risikogruppe für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT Dyspnoe

Anhang 4-G3: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest ($p \geq 0,05$)

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

Alle Ergebnisse beziehen sich auf den letztverfügbaren Analysezeitpunkt.

Mortalität

Gesamtmortalität

Tabelle 4G-3: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Gesamtmortalität aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		
All-Cause Mortality	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age category									
< 54 years	157	26 (16.6)	Not reached [-; -]	76	15 (19.7)	Not reached [52.6; -]	0.79 [0.42; 1.50]	0.477	0.738
≥ 54 years	168	35 (20.8)	Not reached [-; -]	94	25 (26.6)	Not reached [-; -]	0.71 [0.42; 1.20]	0.200	
Country									
Germany	21	4 (19.0)	Not reached [-; -]	10	2 (20.0)	Not reached [24.9; -]	0.71 [0.10; 5.10]	0.738	0.786
Rest of world	304	57 (18.8)	Not reached [-; -]	160	38 (23.8)	Not reached [52.6; -]	0.72 [0.48; 1.09]	0.122	
CMV risk factors									
Very High Risk	102	25 (24.5)	Not reached [-; -]	45	14 (31.1)	Not reached [34.0; -]	0.68 [0.35; 1.30]	0.241	0.771
High Risk	223	36 (16.1)	Not reached [-; -]	125	26 (20.8)	Not reached [52.6; -]	0.76 [0.46; 1.27]	0.297	
Dose									
240 mg (+CsA)	162	20 (12.3)	Not reached [-; -]	90	20 (22.2)	Not reached [-; -]	0.50 [0.27; 0.92]	0.027	0.118
480 mg	163	41 (25.2)	Not reached [-; -]	80	20 (25.0)	52.6 [52.6; -]	0.99 [0.58; 1.69]	0.966	
Donor serostatus									
Positive	200	39 (19.5)	Not reached [-; -]	98	17 (17.3)	Not reached [52.6; -]	1.02 [0.57; 1.81]	0.947	0.082
Negative	122	21 (17.2)	Not reached [-; -]	72	23 (31.9)	Not reached [-; -]	0.50 [0.28; 0.91]	0.024	

a: Database Lock Date: 28JAN2017
b: Number of participants: Full Analysis Set Population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate stratified by CMV risk factor group (high vs very high)
e: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
CI: confidence interval; CMV: cytomegalovirus

CMV-assoziierte Mortalität

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

Study: MK8228 P001[a]	**Letermovir**			**Placebo**			**Letermovir vs. Placebo**		
CMV-Associated Mortality	**N**[b]	**Participants with Event n (%)**	**Median Time**[c] **in Weeks [95 %-CI]**	**N**[b]	**Participants with Event n (%)**	**Median Time**[c] **in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI]**[d]	**p-Value**[d,e]	**p-Value for Interaction Test**[f]
Gender									
Male	176	4 (2.3)	Not reached [-; -]	104	13 (12.5)	Not reached [-; -]	0.17 [0.06; 0.53]	0.002	0.961
Female	149	5 (3.4)	Not reached [-; -]	66	10 (15.2)	52.6 [52.6; -]	0.17 [0.06; 0.49]	0.001	
Country									
Germany	21	0 (0.0)	Not reached [-; -]	10	2 (20.0)	Not reached [24.9; -]	n.a. [n.a.; n.a.]	0.113	0.211
Rest of world	304	9 (3.0)	Not reached [-; -]	160	21 (13.1)	Not reached [52.6; -]	0.20 [0.09; 0.43]	< 0.001	
CMV risk factors									
Very High Risk	102	7 (6.9)	Not reached [-; -]	45	7 (15.6)	Not reached [-; -]	0.36 [0.13; 1.04]	0.058	0.053
High Risk	223	2 (0.9)	Not reached [-; -]	125	16 (12.8)	Not reached [52.6; -]	0.07 [0.02; 0.30]	< 0.001	
Dose									
240 mg (+CsA)	162	3 (1.9)	Not reached [-; -]	90	12 (13.3)	Not reached [-; -]	0.12 [0.03; 0.42]	< 0.001	0.377
480 mg	163	6 (3.7)	Not reached [-; -]	80	11 (13.8)	Not reached [52.6; -]	0.26 [0.09; 0.71]	0.008	
Donor serostatus									
Positive	200	6 (3.0)	Not reached [-; -]	98	9 (9.2)	Not reached [52.6; -]	0.30 [0.11; 0.86]	0.025	0.245
Negative	122	3 (2.5)	Not reached [-; -]	72	14 (19.4)	Not reached [-; -]	0.11 [0.03; 0.39]	< 0.001	

a: Database Lock Date: 28JAN2017
b: Number of participants: Full Analysis Set Population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate stratified by CMV risk factor group (high vs very high)
e: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
CI: confidence interval; CMV: cytomegalovirus; n.a.: not applicable (when estimation not possible)

Morbidität

Klinisch bedeutsame CMV-Infektion

Tabelle 4G-5: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Klinisch bedeutsame CMV-Infektion aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir**		**Placebo**		**Letermovir vs. Placebo**		
Clinically Significant CMV Infection	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**p-Value for Interaction[e] Test**
Age category							
< 54 years	157	56 (35.7)	76	45 (59.2)	0.60 [0.45; 0.79]	< 0.001	0.898
≥ 54 years	168	66 (39.3)	94	58 (61.7)	0.63 [0.49; 0.81]	< 0.001	
Country							
Germany	21	8 (38.1)	10	5 (50.0)	0.82 [0.36; 1.91]	0.651	0.548
Rest of world	304	114 (37.5)	160	98 (61.3)	0.61 [0.50; 0.73]	< 0.001	
CMV risk factors							
Very High Risk	102	43 (42.2)	45	33 (73.3)	0.57 [0.43; 0.77]	< 0.001	0.279
High Risk	223	79 (35.4)	125	70 (56.0)	0.63 [0.50; 0.80]	< 0.001	
Dose							
240 mg (+CsA)	162	58 (35.8)	90	60 (66.7)	0.53 [0.42; 0.69]	< 0.001	0.077
480 mg	163	64 (39.3)	80	43 (53.8)	0.72 [0.55; 0.96]	0.024	
Donor serostatus							
Positive	200	64 (32.0)	98	55 (56.1)	0.57 [0.43; 0.74]	< 0.001	0.661
Negative	122	57 (46.7)	72	48 (66.7)	0.70 [0.54; 0.89]	0.004	
Race[f]							
White	268	96 (35.8)	148	91 (61.5)	0.58 [0.47; 0.71]	< 0.001	0.208
Non-white	57	26 (45.6)	22	12 (54.5)	0.84 [0.52; 1.35]	0.476	
Ethnic							
Hispanic or Latino	24	12 (50.0)	10	5 (50.0)	1.00 [0.49; 2.04]	> 0.999	0.197
Not Hispanic or Latino	288	107 (37.2)	155	96 (61.9)	0.59 [0.49; 0.71]	< 0.001	

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively

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

e: Based on a generalized linear model stratified by risk factor group (very high vs high), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)

f: Non-white includes missing race group

CI: confidence interval; CMV: cytomegalovirus

Einleiten einer PET

Tabelle 4G-6: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Einleiten einer PET aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir**		**Placebo**		**Letermovir vs. Placebo**		
Initiation of PET for Documented CMV Viremia	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**p-Value for Interaction[e] Test**
Age category							
< 54 years	157	55 (35.0)	76	45 (59.2)	0.59 [0.45; 0.78]	< 0.001	0.764
≥ 54 years	168	64 (38.1)	94	56 (59.6)	0.63 [0.49; 0.82]	< 0.001	
Country							
Germany	21	8 (38.1)	10	5 (50.0)	0.82 [0.36; 1.91]	0.651	0.556
Rest of world	304	111 (36.5)	160	96 (60.0)	0.60 [0.50; 0.73]	< 0.001	
CMV risk factors							
Very High Risk	102	42 (41.2)	45	33 (73.3)	0.56 [0.42; 0.75]	< 0.001	0.219
High Risk	223	77 (34.5)	125	68 (54.4)	0.63 [0.50; 0.81]	< 0.001	
Dose							
240 mg (+CsA)	162	56 (34.6)	90	59 (65.6)	0.52 [0.41; 0.68]	< 0.001	0.065
480 mg	163	63 (38.7)	80	42 (52.5)	0.73 [0.55; 0.97]	0.031	
Donor serostatus							
Positive	200	64 (32.0)	98	55 (56.1)	0.57 [0.43; 0.74]	< 0.001	0.617
Negative	122	54 (44.3)	72	46 (63.9)	0.69 [0.53; 0.89]	0.005	
Race[f]							
White	268	93 (34.7)	148	89 (60.1)	0.57 [0.46; 0.70]	< 0.001	0.213
Non-white	57	26 (45.6)	22	12 (54.5)	0.84 [0.52; 1.35]	0.476	
Ethnic							
Hispanic or Latino	24	12 (50.0)	10	4 (40.0)	1.27 [0.55; 2.96]	0.575	0.067
Not Hispanic or Latino	288	104 (36.1)	155	95 (61.3)	0.58 [0.48; 0.70]	< 0.001	

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively

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

e: Based on a generalized linear model stratified by risk factor group (very high vs high), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)

f: Non-white includes missing race group

CI: confidence interval; CMV: cytomegalovirus

Auftreten einer CMV-Endorganerkrankung

Tabelle 4G-7: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt CMV Organerkrankung aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir**		**Placebo**		**Letermovir vs. Placebo**		
CMV End-Organ Disease	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**p-Value for Interaction[e] Test**
Age category							
< 54 years	157	51 (32.5)	76	27 (35.5)	0.91 [0.63; 1.33]	0.634	0.936
≥ 54 years	168	69 (41.1)	94	41 (43.6)	0.92 [0.69; 1.23]	0.570	
Gender							
Male	176	76 (43.2)	104	42 (40.4)	1.07 [0.80; 1.42]	0.662	0.165
Female	149	44 (29.5)	66	26 (39.4)	0.74 [0.50; 1.08]	0.118	
Country							
Germany	21	8 (38.1)	10	5 (50.0)	0.71 [0.29; 1.73]	0.445	0.637
Rest of world	304	112 (36.8)	160	63 (39.4)	0.93 [0.73; 1.18]	0.533	
CMV risk factors							
Very High Risk	102	43 (42.2)	45	22 (48.9)	0.86 [0.59; 1.26]	0.439	0.686
High Risk	223	77 (34.5)	125	46 (36.8)	0.94 [0.70; 1.26]	0.669	
Dose							
240 mg (+CsA)	162	60 (37.0)	90	35 (38.9)	0.95 [0.68; 1.31]	0.746	0.781
480 mg	163	60 (36.8)	80	33 (41.3)	0.88 [0.63; 1.22]	0.448	
Donor serostatus							
Positive	200	66 (33.0)	98	34 (34.7)	0.93 [0.66; 1.30]	0.662	0.780
Negative	122	52 (42.6)	72	34 (47.2)	0.90 [0.65; 1.24]	0.519	
Race[f]							
White	268	98 (36.6)	148	59 (39.9)	0.91 [0.71; 1.17]	0.463	0.938
Non-white	57	22 (38.6)	22	9 (40.9)	0.93 [0.51; 1.68]	0.807	
Ethnic							
Hispanic or Latino	24	7 (29.2)	10	4 (40.0)	0.82 [0.32; 2.07]	0.671	0.619
Not Hispanic or Latino	288	110 (38.2)	155	62 (40.0)	0.94 [0.74; 1.19]	0.607	

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively

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

e: Based on a generalized linear model stratified by risk factor group (very high vs high), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)

f: Non-white includes missing race group

CI: confidence interval; CMV: cytomegalovirus

Bakterielle und/oder fungale Infektionen

Tabelle 4G-8: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Bakterielle und/oder fungale Infektionen aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir**		**Placebo**		**Letermovir vs. Placebo**		
Bacterial and/or Fungal Opportunistic Infections	**N**[b]	**Participants with Event n (%)**	**N**[b]	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio**[c] **[95 %-CI]**	**p-Value**[d]	**p-Value for Interaction**[e] **Test**
Age category							
< 54 years	157	54 (34.4)	76	26 (34.2)	1.00 [0.69; 1.46]	0.986	0.694
≥ 54 years	168	58 (34.5)	94	29 (30.9)	1.07 [0.75; 1.54]	0.707	
Gender							
Male	176	60 (34.1)	104	28 (26.9)	1.24 [0.85; 1.80]	0.266	0.144
Female	149	52 (34.9)	66	27 (40.9)	0.84 [0.59; 1.20]	0.340	
Country							
Germany	21	8 (38.1)	10	4 (40.0)	0.74 [0.26; 2.12]	0.569	0.820
Rest of world	304	104 (34.2)	160	51 (31.9)	1.06 [0.81; 1.39]	0.690	
CMV risk factors							
Very High Risk	102	43 (42.2)	45	20 (44.4)	0.95 [0.64; 1.41]	0.795	0.591
High Risk	223	69 (30.9)	125	35 (28.0)	1.11 [0.78; 1.56]	0.568	
Dose							
240 mg (+CsA)	162	61 (37.7)	90	33 (36.7)	1.02 [0.73; 1.43]	0.897	0.730
480 mg	163	51 (31.3)	80	22 (27.5)	1.09 [0.71; 1.67]	0.696	
Donor serostatus							
Positive	200	68 (34.0)	98	37 (37.8)	0.88 [0.64; 1.22]	0.450	0.117
Negative	122	43 (35.2)	72	18 (25.0)	1.40 [0.89; 2.20]	0.151	

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively

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

e: Based on a generalized linear model stratified by risk factor group (very high vs high), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)

CI: confidence interval; CMV: cytomegalovirus

Akute und/oder chronische GvHD

Tabelle 4G-9: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Akute und/oder chronische GvHD aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir**		**Placebo**		**Letermovir vs. Placebo**		
Acute and/or Chronic GVHD	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**p-Value for Interaction[e] Test**
Age category							
< 54 years	157	95 (60.5)	76	47 (61.8)	0.98 [0.79; 1.21]	0.836	0.861
≥ 54 years	168	95 (56.5)	94	56 (59.6)	0.96 [0.78; 1.19]	0.740	
Country							
Germany	21	12 (57.1)	10	4 (40.0)	1.62 [0.70; 3.73]	0.260	0.298
Rest of world	304	178 (58.6)	160	99 (61.9)	0.95 [0.81; 1.11]	0.486	
CMV risk factors							
Very High Risk	102	61 (59.8)	45	25 (55.6)	1.08 [0.79; 1.46]	0.637	0.395
High Risk	223	129 (57.8)	125	78 (62.4)	0.93 [0.78; 1.11]	0.400	
Dose							
240 mg (+CsA)	162	92 (56.8)	90	53 (58.9)	0.96 [0.77; 1.20]	0.735	0.971
480 mg	163	98 (60.1)	80	50 (62.5)	0.97 [0.78; 1.20]	0.785	
Donor serostatus							
Positive	200	118 (59.0)	98	63 (64.3)	0.92 [0.76; 1.11]	0.397	0.400
Negative	122	71 (58.2)	72	40 (55.6)	1.05 [0.81; 1.35]	0.726	

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively

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

e: Based on a generalized linear model stratified by risk factor group (very high vs high), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)

CI: confidence interval; CMV: cytomegalovirus

Wiedereinweisung ins Krankenhaus wegen einer CMV-Reaktivierung bzw. CMV-Erkrankung

Tabelle 4G-10: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Wiedereinweisung ins Krankenhaus wegen einer CMV-Reaktivierung bzw. CMV-Erkrankung aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir**		**Placebo**		**Letermovir vs. Placebo**		
Re-Hospitalization After Transplant for CMV Infection/Disease	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**p-Value for Interaction[e] Test**
Age category							
< 54 years	157	5 (3.2)	76	9 (11.8)	0.27 [0.09; 0.78]	0.015	0.472
≥ 54 years	168	5 (3.0)	94	6 (6.4)	0.47 [0.14; 1.56]	0.216	
Gender							
Male	176	8 (4.5)	104	11 (10.6)	0.43 [0.18; 1.05]	0.065	0.512

Female	149	2 (1.3)	66	4 (6.1)	0.22 [0.04; 1.22]	0.083	
Country							
Germany	21	0 (0.0)	10	0 (0.0)	n.a. [n.a.; n.a.]	n.a.	> 0.999
Rest of world	304	10 (3.3)	160	15 (9.4)	0.31 [0.13; 0.72]	0.007	
CMV risk factors							
Very High Risk	102	4 (3.9)	45	2 (4.4)	0.88 [0.17; 4.64]	0.883	0.188
High Risk	223	6 (2.7)	125	13 (10.4)	0.26 [0.10; 0.66]	0.005	
Dose							
240 mg (+CsA)	162	4 (2.5)	90	8 (8.9)	0.28 [0.09; 0.90]	0.033	0.612
480 mg	163	6 (3.7)	80	7 (8.8)	0.41 [0.14; 1.23]	0.113	
Donor serostatus							
Positive	200	4 (2.0)	98	9 (9.2)	0.23 [0.07; 0.72]	0.012	0.221
Negative	122	6 (4.9)	72	6 (8.3)	0.59 [0.19; 1.77]	0.346	

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively

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

e: Based on a generalized linear model stratified by risk factor group (very high vs high), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)

CI: confidence interval; CMV: cytomegalovirus

Engraftment

Tabelle 4G-11: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Engraftment aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir**		**Placebo**		**Letermovir vs. Placebo**		
Engraftment		**Participants with Event**		**Participants with Event**	**Risk Ratio/ Peto-Odds Ratio[c]**		**p-Value for Interaction[e]**
	N[b]	**n (%)**	**N[b]**	**n (%)**	**[95 %-CI]**	**p-Value[d]**	**Test**
Age category							
< 54 years	187	181 (96.8)	90	84 (93.3)	1.04 [0.98; 1.11]	0.225	0.484
≥ 54 years	186	177 (95.2)	102	96 (94.1)	1.01 [0.95; 1.07]	0.751	
Gender							
Male	211	203 (96.2)	116	108 (93.1)	1.04 [0.98; 1.10]	0.235	0.604
Female	162	155 (95.7)	76	72 (94.7)	1.01 [0.95; 1.07]	0.756	
Country							
Germany	23	21 (91.3)	10	9 (90.0)	1.11 [0.90; 1.37]	0.318	0.790
Rest of world	350	337 (96.3)	182	171 (94.0)	1.02 [0.98; 1.07]	0.259	
CMV risk factors							
Very High Risk	121	116 (95.9)	54	49 (90.7)	1.06 [0.96; 1.16]	0.246	0.464
High Risk	252	242 (96.0)	138	131 (94.9)	1.01 [0.97; 1.06]	0.622	
Dose							
240 mg (+CsA)	193	185 (95.9)	100	93 (93.0)	1.03 [0.97; 1.10]	0.331	0.800
480 mg	180	173 (96.1)	92	87 (94.6)	1.02 [0.96; 1.08]	0.577	
Donor serostatus							
Positive	230	220 (95.7)	114	108 (94.7)	1.01 [0.96; 1.06]	0.683	0.464
Negative	138	133 (96.4)	78	72 (92.3)	1.04 [0.97; 1.12]	0.240	

a: Database Lock Date: 28JAN2017
b: Number of participants: All Participants as Treated Population
c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively
d: Two-sided p-Value based on Wald test
e: Based on a generalized linear model stratified by risk factor group (very high vs high), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)
CI: confidence interval; CMV: cytomegalovirus

Gesundheitszustand anhand der EQ-5D-VAS

Tabelle 4G-12: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesundheitszustand anhand der EQ-5D VAS aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir**		**Placebo**		**Letermovir vs. Placebo**		
EQ-5D VAS (15 points)	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**p-Value for Interaction[e] Test**
Age category							
< 54 years	157	80 (51.0)	76	31 (40.8)	1.29 [0.84; 1.98]	0.249	0.297
≥ 54 years	168	83 (49.4)	94	46 (48.9)	1.02 [0.72; 1.44]	0.903	
Gender							
Male	176	86 (48.9)	104	44 (42.3)	1.14 [0.77; 1.68]	0.512	0.582
Female	149	77 (51.7)	66	33 (50.0)	1.10 [0.78; 1.57]	0.580	
Country							
Germany	21	9 (42.9)	10	3 (30.0)	1.28 [0.36; 4.54]	0.703	0.618
Rest of world	304	154 (50.7)	160	74 (46.3)	1.13 [0.85; 1.49]	0.399	
CMV risk factors							
Very High Risk	102	51 (50.0)	45	19 (42.2)	1.33 [0.74; 2.41]	0.343	0.696
High Risk	223	112 (50.2)	125	58 (46.4)	1.07 [0.80; 1.43]	0.655	
Dose							
240 mg (+CsA)	162	87 (53.7)	90	38 (42.2)	1.33 [0.91; 1.95]	0.140	0.158
480 mg	163	76 (46.6)	80	39 (48.8)	0.94 [0.66; 1.34]	0.745	
Donor serostatus							
Positive	200	100 (50.0)	98	46 (46.9)	1.08 [0.77; 1.51]	0.644	0.564
Negative	122	63 (51.6)	72	31 (43.1)	1.23 [0.79; 1.92]	0.357	

a: Database Lock Date: 28JAN2017
b: Number of participants: Full Analysis Set Population
c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively
d: Two-sided p-Value based on Wald test
e: Based on a generalized linear model, with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)
Event is defined as an improvement compared to baseline in endpoint score of 15% or more of the endpoint scale range (minimal important difference), based on multiple imputation for missing data controlling for treatment, death, very high vs high risk stratum, and study timepoints assuming missing at random, data missing not at random after recorded death were not imputed
CI: Confidence Interval; CMV: Cytomegalovirus; EQ-5D VAS: European Quality of Life 5 Dimensions Visual Analogue Scale

Gesundheitsbezogene Lebensqualität

Gesundheitsbezogene Lebensqualität

Tabelle 4G-13: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den FACT-BMT Gesamtscore aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir**		**Placebo**		**Letermovir vs. Placebo**		
FACT-BMT Total Score (24 Points)	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**p-Value for Interaction[e] Test**
Age category							
< 54 years	157	119 (75.8)	76	45 (59.2)	1.33 [1.00; 1.77]	0.051	0.083
≥ 54 years	168	118 (70.2)	94	65 (69.1)	1.03 [0.82; 1.29]	0.818	
Gender							
Male	176	135 (76.7)	104	71 (68.3)	1.13 [0.92; 1.40]	0.253	0.827
Female	149	102 (68.5)	66	39 (59.1)	1.22 [0.89; 1.67]	0.210	
Country							
Germany	21	14 (66.7)	10	7 (70.0)	0.91 [0.46; 1.83]	0.795	0.523
Rest of world	304	223 (73.4)	160	103 (64.4)	1.17 [0.97; 1.41]	0.108	
CMV risk factors							
Very High Risk	102	75 (73.5)	45	27 (60.0)	1.35 [0.92; 1.98]	0.129	0.455
High Risk	223	162 (72.6)	125	83 (66.4)	1.09 [0.90; 1.32]	0.371	
Dose							
240 mg (+CsA)	162	115 (71.0)	90	59 (65.6)	1.12 [0.87; 1.44]	0.389	0.540
480 mg	163	122 (74.8)	80	51 (63.8)	1.18 [0.94; 1.49]	0.155	
Donor serostatus							
Positive	200	145 (72.5)	98	68 (69.4)	1.04 [0.85; 1.28]	0.694	0.116
Negative	122	92 (75.4)	72	42 (58.3)	1.34 [0.97; 1.86]	0.075	

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively

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

e: Based on a generalized linear model, with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)

Event is defined as an improvement compared to baseline in endpoint score of 15% or more of the endpoint scale range (minimal important difference), based on multiple imputation for missing data controlling for treatment, death, very high vs high risk stratum, and study timepoints assuming missing at random, data missing not at random after recorded death were not imputed

CI: Confidence Interval; CMV: Cytomegalovirus; FACT-BMT: Functional Assessment of Cancer Therapy (FACT) - Bone Marrow Transplantation (BMT)

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

Study: MK8228 P001[a]	**Letermovir**		**Placebo**		**Letermovir vs. Placebo**		
FACT-G (17 Points)	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**p-Value for Interaction[e] Test**
Age category							
< 54 years	157	45 (28.7)	76	17 (22.4)	1.37 [0.70; 2.68]	0.361	0.464

Study: MK8228 P001[a]	Letermovir		Placebo		Letermovir vs. Placebo		
FACT-G (17 Points)	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	p-Value for Interaction[e] Test
≥ 54 years	168	49 (29.2)	94	27 (28.7)	1.03 [0.61; 1.74]	0.902	
Gender							
Male	176	51 (29.0)	104	26 (25.0)	1.16 [0.65; 2.07]	0.609	0.773
Female	149	43 (28.9)	66	18 (27.3)	1.15 [0.62; 2.13]	0.649	
Country							
Germany	21	6 (28.6)	10	2 (20.0)	1.92 [0.30; 12.25]	0.488	0.718
Rest of world	304	88 (28.9)	160	42 (26.3)	1.12 [0.72; 1.74]	0.609	
CMV risk factors							
Very High Risk	102	29 (28.4)	45	9 (20.0)	1.76 [0.61; 5.08]	0.295	0.402
High Risk	223	65 (29.1)	125	35 (28.0)	1.03 [0.66; 1.61]	0.897	
Dose							
240 mg (+CsA)	162	43 (26.5)	90	20 (22.2)	1.25 [0.64; 2.44]	0.511	0.665
480 mg	163	51 (31.3)	80	24 (30.0)	1.08 [0.67; 1.76]	0.741	
Donor serostatus							
Positive	200	56 (28.0)	98	27 (27.6)	1.02 [0.60; 1.75]	0.933	0.413
Negative	122	38 (31.1)	72	17 (23.6)	1.41 [0.70; 2.84]	0.330	

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively

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

e: Based on a generalized linear model, with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)

Event is defined as an improvement compared to baseline in endpoint score of 15% or more of the endpoint scale range (minimal important difference), based on multiple imputation for missing data controlling for treatment, death, very high vs high risk stratum, and study timepoints assuming missing at random, data missing not at random after recorded death were not imputed

CI: Confidence Interval; CMV: Cytomegalovirus; FACT-G: Functional Assessment of Cancer Therapy (FACT) - General (G)

Tabelle 4G-15: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den FACT-BMT Körperliches Wohlbefinden aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir		Placebo		Letermovir vs. Placebo		
FACT-BMT Physical Well-Being (5 Points)	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	p-Value for Interaction[e] Test
Age category							
< 54 years	157	82 (52.2)	76	29 (38.2)	1.42 [0.93; 2.16]	0.104	0.202
≥ 54 years	168	76 (45.2)	94	41 (43.6)	1.03 [0.71; 1.50]	0.866	
Gender							
Male	176	87 (49.4)	104	43 (41.3)	1.18 [0.81; 1.72]	0.380	0.906
Female	149	71 (47.7)	66	27 (40.9)	1.24 [0.80; 1.94]	0.338	
Country							
Germany	21	10 (47.6)	10	5 (50.0)	0.81 [0.29; 2.23]	0.680	0.585
Rest of world	304	148 (48.7)	160	65 (40.6)	1.23 [0.91; 1.66]	0.174	
CMV risk factors							

Study: MK8228 P001[a]	Letermovir		Placebo		Letermovir vs. Placebo		
FACT-BMT Physical Well-Being (5 Points)	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	p-Value for Interaction[e] Test
Very High Risk	102	53 (52.0)	45	17 (37.8)	1.53 [0.87; 2.70]	0.139	0.378
High Risk	223	105 (47.1)	125	53 (42.4)	1.10 [0.81; 1.49]	0.544	
Dose							
240 mg (+CsA)	162	77 (47.5)	90	34 (37.8)	1.32 [0.85; 2.05]	0.211	0.545
480 mg	163	81 (49.7)	80	36 (45.0)	1.10 [0.77; 1.56]	0.604	
Donor serostatus							
Positive	200	91 (45.5)	98	42 (42.9)	1.07 [0.75; 1.51]	0.725	0.190
Negative	122	67 (54.9)	72	28 (38.9)	1.45 [0.91; 2.33]	0.117	

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively

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

e: Based on a generalized linear model, with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)

Event is defined as an improvement compared to baseline in endpoint score of 15% or more of the endpoint scale range (minimal important difference), based on multiple imputation for missing data controlling for treatment, death, very high vs high risk stratum, and study timepoints assuming missing at random, data missing not at random after recorded death were not imputed

CI: Confidence Interval; CMV: Cytomegalovirus; FACT-BMT: Functional Assessment of Cancer Therapy (FACT) - Bone Marrow Transplantation (BMT)

Tabelle 4G-16: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den FACT-BMT Soziales/Familiäres Wohlbefinden aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir		Placebo		Letermovir vs. Placebo		
FACT-BMT Social Well-Being (5 Points)	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	p-Value for Interaction[e] Test
Age category							
< 54 years	157	19 (12.1)	76	6 (7.9)	1.97 [0.44; 8.86]	0.375	0.121
≥ 54 years	168	15 (8.9)	94	13 (13.8)	0.60 [0.20; 1.78]	0.356	
Gender							
Male	176	20 (11.4)	104	11 (10.6)	1.15 [0.40; 3.30]	0.790	0.553
Female	149	14 (9.4)	66	8 (12.1)	0.85 [0.27; 2.72]	0.790	
Country							
Germany	21	2 (9.5)	10	2 (20.0)	0.62 [0.06; 6.71]	0.696	0.454
Rest of world	304	32 (10.5)	160	17 (10.6)	0.98 [0.45; 2.15]	0.961	
CMV risk factors							
Very High Risk	102	9 (8.8)	45	4 (8.9)	1.18 [0.17; 8.00]	0.868	0.926
High Risk	223	25 (11.2)	125	15 (12.0)	0.95 [0.42; 2.14]	0.902	
Dose							
240 mg (+CsA)	162	15 (9.3)	90	11 (12.2)	0.85 [0.28; 2.56]	0.776	0.428
480 mg	163	19 (11.7)	80	8 (10.0)	1.22 [0.38; 3.88]	0.734	
Donor serostatus							
Positive	200	21 (10.5)	98	10 (10.2)	1.13 [0.40; 3.19]	0.822	0.730

Study: MK8228 P001[a]	Letermovir		Placebo		Letermovir vs. Placebo		
FACT-BMT Social Well-Being (5 Points)	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	p-Value for Interaction[e] Test
Negative	122	13 (10.7)	72	9 (12.5)	0.87 [0.27; 2.79]	0.818	

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively

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

e: Based on a generalized linear model, with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)

Event is defined as an improvement compared to baseline in endpoint score of 15% or more of the endpoint scale range (minimal important difference), based on multiple imputation for missing data controlling for treatment, death, very high vs high risk stratum, and study timepoints assuming missing at random, data missing not at random after recorded death were not imputed

CI: Confidence Interval; CMV: Cytomegalovirus; FACT-BMT: Functional Assessment of Cancer Therapy (FACT) - Bone Marrow Transplantation (BMT)

Tabelle 4G-17: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den FACT-BMT Emotionales Wohlbefinden aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir		Placebo		Letermovir vs. Placebo		
FACT-BMT Emotional Well-Being (4 Points)	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	p-Value for Interaction[e] Test
Age category							
< 54 years	157	30 (19.1)	76	13 (17.1)	1.20 [0.53; 2.71]	0.658	0.823
≥ 54 years	168	31 (18.5)	94	17 (18.1)	1.01 [0.49; 2.06]	0.979	
Gender							
Male	176	34 (19.3)	104	19 (18.3)	1.06 [0.53; 2.11]	0.871	0.947
Female	149	27 (18.1)	66	11 (16.7)	1.19 [0.51; 2.75]	0.690	
Country							
Germany	21	2 (9.5)	10	1 (10.0)	0.70 [0.06; 8.66]	0.778	0.922
Rest of world	304	59 (19.4)	160	29 (18.1)	1.07 [0.60; 1.89]	0.819	
CMV risk factors							
Very High Risk	102	23 (22.5)	45	10 (22.2)	1.09 [0.46; 2.57]	0.852	0.908
High Risk	223	38 (17.0)	125	20 (16.0)	1.11 [0.58; 2.12]	0.761	
Dose							
240 mg (+CsA)	162	25 (15.4)	90	15 (16.7)	1.04 [0.46; 2.39]	0.922	0.554
480 mg	163	36 (22.1)	80	15 (18.8)	1.13 [0.58; 2.18]	0.717	
Donor serostatus							
Positive	200	38 (19.0)	98	18 (18.4)	1.03 [0.52; 2.02]	0.931	0.829
Negative	122	23 (18.9)	72	12 (16.7)	1.15 [0.49; 2.73]	0.749	

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively

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

e: Based on a generalized linear model, with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)

Event is defined as an improvement compared to baseline in endpoint score of 15% or more of the endpoint scale range (minimal important

Study: MK8228 P001[a]	Letermovir		Placebo		Letermovir vs. Placebo		
FACT-BMT Emotional Well-Being (4 Points)	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	p-Value for Interaction[e] Test
difference), based on multiple imputation for missing data controlling for treatment, death, very high vs high risk stratum, and study timepoints assuming missing at random, data missing not at random after recorded death were not imputed							
CI: Confidence Interval; CMV: Cytomegalovirus; FACT-BMT: Functional Assessment of Cancer Therapy (FACT) - Bone Marrow Transplantation (BMT)							

Tabelle 4G-18: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den FACT-BMT Funktionales Wohlbefinden aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir		Placebo		Letermovir vs. Placebo		
FACT-BMT Functional Well-Being (5 Points)	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	p-Value for Interaction[e] Test
Age category							
< 54 years	157	70 (44.6)	76	26 (34.2)	1.37 [0.85; 2.21]	0.199	0.448
≥ 54 years	168	74 (44.0)	94	38 (40.4)	1.09 [0.74; 1.62]	0.659	
Gender							
Male	176	82 (46.6)	104	38 (36.5)	1.28 [0.84; 1.95]	0.243	0.429
Female	149	62 (41.6)	66	26 (39.4)	1.11 [0.69; 1.77]	0.665	
Country							
Germany	21	7 (33.3)	10	4 (40.0)	0.83 [0.25; 2.74]	0.762	0.489
Rest of world	304	137 (45.1)	160	60 (37.5)	1.23 [0.89; 1.72]	0.210	
CMV risk factors							
Very High Risk	102	47 (46.1)	45	15 (33.3)	1.56 [0.81; 3.03]	0.185	0.410
High Risk	223	97 (43.5)	125	49 (39.2)	1.10 [0.78; 1.54]	0.585	
Dose							
240 mg (+CsA)	162	66 (40.7)	90	33 (36.7)	1.16 [0.72; 1.88]	0.533	0.651
480 mg	163	78 (47.9)	80	31 (38.8)	1.23 [0.84; 1.80]	0.289	
Donor serostatus							
Positive	200	87 (43.5)	98	40 (40.8)	1.06 [0.72; 1.56]	0.762	0.252
Negative	122	57 (46.7)	72	24 (33.3)	1.48 [0.86; 2.55]	0.157	

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively

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

e: Based on a generalized linear model, with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)

Event is defined as an improvement compared to baseline in endpoint score of 15% or more of the endpoint scale range (minimal important difference), based on multiple imputation for missing data controlling for treatment, death, very high vs high risk stratum, and study timepoints assuming missing at random, data missing not at random after recorded death were not imputed

CI: Confidence Interval; CMV: Cytomegalovirus; FACT-BMT: Functional Assessment of Cancer Therapy (FACT) - Bone Marrow Transplantation (BMT)

Tabelle 4G-19: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den FACT-BMTS: Spezifische Aspekte für Patienten einer Stammzelltransplantation aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir**		**Placebo**		**Letermovir vs. Placebo**		
BMTS (8 Points)	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**p-Value for Interaction[e] Test**
Age category							
< 54 years	157	31 (19.7)	76	16 (21.1)	1.02 [0.48; 2.15]	0.964	0.585
≥ 54 years	168	39 (23.2)	94	19 (20.2)	1.14 [0.62; 2.09]	0.668	
Gender							
Male	176	39 (22.2)	104	21 (20.2)	1.11 [0.60; 2.06]	0.731	0.764
Female	149	31 (20.8)	66	14 (21.2)	1.05 [0.52; 2.09]	0.898	
Country							
Germany	21	4 (19.0)	10	1 (10.0)	1.42 [0.18; 11.38]	0.743	0.531
Rest of world	304	66 (21.7)	160	34 (21.3)	1.04 [0.64; 1.72]	0.862	
CMV risk factors							
Very High Risk	102	22 (21.6)	45	7 (15.6)	1.77 [0.57; 5.42]	0.320	0.401
High Risk	223	48 (21.5)	125	28 (22.4)	0.94 [0.57; 1.56]	0.816	
Dose							
240 mg (+CsA)	162	36 (22.2)	90	18 (20.0)	1.20 [0.61; 2.36]	0.597	0.737
480 mg	163	34 (20.9)	80	17 (21.3)	0.97 [0.53; 1.76]	0.910	
Donor serostatus							
Positive	200	48 (24.0)	98	25 (25.5)	0.97 [0.57; 1.64]	0.907	0.428
Negative	122	22 (18.0)	72	10 (13.9)	1.36 [0.54; 3.45]	0.516	

a: Database Lock Date: 28JAN2017

b: Number of participants: Full Analysis Set Population

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by risk factor group (very high vs high) and each pre-specified subgroup where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively

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

e: Based on a generalized linear model, with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term)

Event is defined as an improvement compared to baseline in endpoint score of 15% or more of the endpoint scale range (minimal important difference), based on multiple imputation for missing data controlling for treatment, death, very high vs high risk stratum, and study timepoints assuming missing at random, data missing not at random after recorded death were not imputed

CI: Confidence Interval; CMV: Cytomegalovirus; FACT-BMT: Functional Assessment of Cancer Therapy (FACT) - Bone Marrow Transplantation (BMT)

Nebenwirkungen

Unerwünschte Ereignisse Gesamtraten

Unerwünschte Ereignisse gesamt

Tabelle 4G-20: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		
Adverse Event	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age category									
< 54 years	187	181 (96.8)	0.4 [0.4; 0.6]	90	90 (100.0)	0.6 [0.4; 0.7]	0.97 [0.75; 1.25]	0.807	0.295
≥ 54 years	186	184 (98.9)	0.4 [0.3; 0.6]	102	102 (100.0)	0.6 [0.4; 0.7]	1.17 [0.91; 1.49]	0.217	
Gender									
Male	211	206 (97.6)	0.4 [0.4; 0.6]	116	116 (100.0)	0.5 [0.4; 0.7]	1.03 [0.82; 1.29]	0.802	0.698
Female	162	159 (98.1)	0.4 [0.3; 0.6]	76	76 (100.0)	0.6 [0.4; 0.7]	1.09 [0.83; 1.44]	0.530	
Country									
Germany	23	23 (100.0)	0.3 [0.1; 0.4]	10	10 (100.0)	0.3 [0.1; 0.4]	0.87 [0.41; 1.85]	0.716	0.372
Rest of world	350	342 (97.7)	0.4 [-; -]	182	182 (100.0)	0.6 [0.4; 0.7]	1.06 [0.89; 1.27]	0.504	
CMV risk factors									
Very High Risk	121	118 (97.5)	0.3 [0.3; 0.4]	54	54 (100.0)	0.4 [0.3; 0.7]	1.05 [0.76; 1.46]	0.748	0.961
High Risk	252	247 (98.0)	0.4 [0.4; 0.6]	138	138 (100.0)	0.6 [0.4; 0.7]	1.05 [0.85; 1.30]	0.625	
Dose									
240 mg (+CsA)	193	188 (97.4)	0.4 [0.3; 0.6]	100	100 (100.0)	0.6 [0.4; 0.9]	1.04 [0.81; 1.32]	0.771	0.953
480 mg	180	177 (98.3)	0.4 [-; -]	92	92 (100.0)	0.5 [0.4; 0.7]	1.07 [0.83; 1.38]	0.582	
Donor serostatus									
Positive	230	225 (97.8)	0.4 [0.4; 0.6]	114	114 (100.0)	0.6 [0.4; 0.7]	1.01 [0.80; 1.26]	0.947	0.473
Negative	138	135 (97.8)	0.4 [0.3; 0.4]	78	78 (100.0)	0.6 [0.3; 0.9]	1.16 [0.88; 1.54]	0.299	

a: Database Lock Date: 28JAN2017
b: Number of participants: All Participants as Treated Population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
CI: confidence interval; CMV: cytomegalovirus

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-21: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		
Serious Adverse Event	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age category									
< 54 years	187	75 (40.1)	16.6 [13.6; -]	90	47 (52.2)	9.9 [6.0; -]	0.70 [0.48; 1.01]	0.053	0.190
≥ 54 years	186	91 (48.9)	14.0 [10.1; -]	102	45 (44.1)	12.9 [7.4; -]	0.94 [0.65; 1.35]	0.734	
Country									
Germany	23	9 (39.1)	Not reached [3.3; -]	10	4 (40.0)	Not reached [1.6; -]	1.08 [0.33; 3.50]	0.903	0.637
Rest of world	350	157 (44.9)	15.3 [12.7; 15.6]	182	88 (48.4)	9.9 [7.0; -]	0.80 [0.61; 1.04]	0.091	
CMV risk factors									
Very High Risk	121	61 (50.4)	11.6 [6.9; -]	54	25 (46.3)	10.9 [3.1; -]	0.83 [0.52; 1.33]	0.446	0.873
High Risk	252	105 (41.7)	15.3 [13.6; -]	138	67 (48.6)	11.1 [8.1; -]	0.77 [0.57; 1.06]	0.106	
Dose									
240 mg (+CsA)	193	87 (45.1)	15.3 [9.6; 15.6]	100	51 (51.0)	10.0 [6.1; 13.3]	0.77 [0.54; 1.09]	0.144	0.713
480 mg	180	79 (43.9)	15.1 [12.7; -]	92	41 (44.6)	Not reached [6.9; -]	0.87 [0.60; 1.27]	0.470	
Donor serostatus									
Positive	230	100 (43.5)	15.3 [12.7; -]	114	54 (47.4)	12.4 [7.0; -]	0.87 [0.63; 1.22]	0.424	0.488
Negative	138	63 (45.7)	15.6 [10.6; -]	78	38 (48.7)	8.3 [5.3; -]	0.72 [0.47; 1.08]	0.109	

a: Database Lock Date: 28JAN2017
b: Number of participants: All Participants as Treated Population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
CI: confidence interval; CMV: cytomegalovirus

Schwere unerwünschte Ereignisse

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		
Severe Adverse Event	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age category									

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		
Severe Adverse Event	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
< 54 years	187	77 (41.2)	16.6 [11.9; -]	90	43 (47.8)	10.9 [6.1; -]	0.79 [0.54; 1.15]	0.225	0.458
≥ 54 years	186	83 (44.6)	15.3 [13.0; -]	102	42 (41.2)	Not reached [8.3; -]	0.93 [0.64; 1.35]	0.689	
Country									
Germany	23	6 (26.1)	Not reached [6.9; -]	10	4 (40.0)	Not reached [1.6; -]	0.59 [0.17; 2.12]	0.423	0.597
Rest of world	350	154 (44.0)	15.3 [13.6; 15.6]	182	81 (44.5)	11.9 [8.1; -]	0.87 [0.66; 1.14]	0.321	
CMV risk factors									
Very High Risk	121	61 (50.4)	10.3 [6.3; -]	54	26 (48.1)	8.0 [2.4; -]	0.85 [0.53; 1.35]	0.482	0.942
High Risk	252	99 (39.3)	15.3 [15.1; -]	138	59 (42.8)	Not reached [8.4; -]	0.82 [0.60; 1.14]	0.244	
Dose									
240 mg (+CsA)	193	83 (43.0)	15.3 [11.6; -]	100	52 (52.0)	8.4 [6.1; 12.9]	0.72 [0.50; 1.02]	0.062	0.150
480 mg	180	77 (42.8)	15.6 [13.0; -]	92	33 (35.9)	Not reached [10.6; -]	1.08 [0.72; 1.63]	0.710	
Donor serostatus									
Positive	230	96 (41.7)	15.3 [13.6; -]	114	53 (46.5)	12.4 [8.1; -]	0.85 [0.61; 1.20]	0.357	0.975
Negative	138	61 (44.2)	15.6 [11.3; -]	78	32 (41.0)	Not reached [6.9; -]	0.86 [0.56; 1.33]	0.492	

a: Database Lock Date: 28JAN2017

b: Number of participants: All Participants as Treated Population

c: From product-limit (Kaplan-Meier) method for censored data

d: Based on Cox regression model with treatment as a covariate using Wald confidence interval

e: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)

CI: confidence interval; CMV: cytomegalovirus

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir**			**Placebo**			**Letermovir vs. Placebo**		
Adverse Event Leading to Treatment Discontinuation	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Age category									
< 54 years	187	42 (22.5)	Not reached [-; -]	90	43 (47.8)	Not reached [5.7; -]	0.42 [0.28; 0.65]	< 0.001	0.130
≥ 54 years	186	31 (16.7)	Not reached [-; -]	102	56 (54.9)	8.3 [5.6; -]	0.26 [0.16; 0.40]	< 0.001	
Gender									
Male	211	40 (19.0)	Not reached [-; -]	116	57 (49.1)	12.7 [6.0; -]	0.34 [0.23; 0.51]	< 0.001	0.807
Female	162	33 (20.4)	Not reached [-; -]	76	42 (55.3)	7.7 [5.7; -]	0.31 [0.20; 0.49]	< 0.001	
Country									
Germany	23	4 (17.4)	Not reached [-; -]	10	5 (50.0)	11.9 [2.3; -]	0.33 [0.09; 1.26]	0.105	0.895
Rest of world	350	69 (19.7)	Not reached [-; -]	182	94 (51.6)	10.9 [6.0; -]	0.33 [0.24; 0.45]	< 0.001	
CMV risk factors									
Very High Risk	121	29 (24.0)	Not reached [-; -]	54	36 (66.7)	4.3 [3.3; 6.0]	0.27 [0.17; 0.45]	< 0.001	0.401
High Risk	252	44 (17.5)	Not reached [-; -]	138	63 (45.7)	Not reached [7.9; -]	0.35 [0.23; 0.51]	< 0.001	
Dose									
240 mg (+CsA)	193	36 (18.7)	Not reached [-; -]	100	55 (55.0)	8.0 [6.0; -]	0.29 [0.19; 0.44]	< 0.001	0.503
480 mg	180	37 (20.6)	Not reached [-; -]	92	44 (47.8)	Not reached [5.7; -]	0.38 [0.24; 0.59]	< 0.001	
Donor serostatus									
Positive	230	46 (20.0)	Not reached [-; -]	114	55 (48.2)	Not reached [7.7; -]	0.38 [0.26; 0.56]	< 0.001	0.267
Negative	138	26 (18.8)	Not reached [-; -]	78	44 (56.4)	7.1 [4.1; -]	0.27 [0.16; 0.44]	< 0.001	

a: Database Lock Date: 28JAN2017
b: Number of participants: All Participants as Treated Population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
CI: confidence interval; CMV: cytomegalovirus

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-24: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		p-Value for Interaction Test[f]
Adverse Event by SOC and PT	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	
SOC: Infections and infestations - PT: Cytomegalovirus infection									
Gender									
Male	211	19 (9.0)	Not reached [-; -]	116	52 (44.8)	Not reached [7.1; -]	0.17 [0.10; 0.29]	< 0.001	0.411
Female	162	11 (6.8)	Not reached [-; -]	76	36 (47.4)	12.1 [6.7; -]	0.12 [0.06; 0.23]	< 0.001	
Country									
Germany	23	1 (4.3)	Not reached [-; -]	10	3 (30.0)	Not reached [2.3; -]	0.16 [0.02; 1.52]	0.111	0.989
Rest of world	350	29 (8.3)	Not reached [-; -]	182	85 (46.7)	14.4 [7.4; -]	0.15 [0.10; 0.22]	< 0.001	
CMV risk factors									
Very High Risk	121	14 (11.6)	Not reached [-; -]	54	31 (57.4)	5.1 [4.0; 14.4]	0.15 [0.08; 0.29]	< 0.001	0.887
High Risk	252	16 (6.3)	Not reached [-; -]	138	57 (41.3)	Not reached [9.3; -]	0.13 [0.08; 0.23]	< 0.001	
Dose									
240 mg (+CsA)	193	19 (9.8)	Not reached [-; -]	100	50 (50.0)	11.3 [6.0; -]	0.16 [0.10; 0.28]	< 0.001	0.504
480 mg	180	11 (6.1)	Not reached [-; -]	92	38 (41.3)	Not reached [7.4; -]	0.12 [0.06; 0.24]	< 0.001	
Donor serostatus									
Positive	230	17 (7.4)	Not reached [-; -]	114	50 (43.9)	Not reached [7.9; -]	0.15 [0.09; 0.26]	< 0.001	0.868
Negative	138	12 (8.7)	Not reached [-; -]	78	38 (48.7)	8.6 [5.1; -]	0.14 [0.07; 0.27]	< 0.001	
SOC: Respiratory, thoracic and mediastinal disorders - PT: Dyspnoea									
Age category									
< 54 years	187	11 (5.9)	Not reached [-; -]	90	2 (2.2)	Not reached [-; -]	2.48 [0.55; 11.19]	0.239	0.943
≥ 54 years	186	21 (11.3)	Not reached [-; -]	102	4 (3.9)	Not reached [-; -]	2.68 [0.92; 7.82]	0.071	
Gender									
Male	211	23 (10.9)	Not reached [-; -]	116	4 (3.4)	Not reached [-; -]	3.00 [1.03; 8.68]	0.043	0.645
Female	162	9 (5.6)	Not reached [-; -]	76	2 (2.6)	Not reached [-; -]	1.91 [0.41; 8.88]	0.408	
Country									
Germany	23	3 (13.0)	Not reached [-; -]	10	1 (10.0)	Not reached [3.0; -]	1.25 [0.13; 12.13]	0.846	0.571
Rest of world	350	29 (8.3)	Not reached [-; -]	182	5 (2.7)	Not reached [-; -]	2.79 [1.08; 7.23]	0.034	

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		p-Value for Interaction Test[f]
Adverse Event by SOC and PT	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	
Dose									
240 mg (+CsA)	193	18 (9.3)	Not reached [-; -]	100	3 (3.0)	Not reached [-; -]	3.08 [0.91; 10.46]	0.072	0.744
480 mg	180	14 (7.8)	Not reached [-; -]	92	3 (3.3)	Not reached [-; -]	2.09 [0.60; 7.29]	0.247	
Donor serostatus									
Positive	230	21 (9.1)	Not reached [-; -]	114	3 (2.6)	Not reached [-; -]	3.35 [1.00; 11.23]	0.051	0.502
Negative	138	11 (8.0)	Not reached [-; -]	78	3 (3.8)	Not reached [-; -]	1.81 [0.50; 6.51]	0.366	

a: Database Lock Date: 28JAN2017
b: Number of participants: All Participants as Treated Population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
A specific adverse event appears on this report only if its incidence is ≥10% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is < 0.05, and the interaction p-value is ≥ 0.05 or not calculated
CI: confidence interval; CMV: cytomegalovirus; PT: Preferred Term; SOC: System Organ Class

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		p-Value for Interaction Test[f]
Serious Adverse Event by SOC	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	
SOC: Nervous system disorders									
Age category									
< 54 years	187	5 (2.7)	n.c.	90	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥ 54 years	186	7 (3.8)	n.c.	102	0 (0.0)	n.c.	n.c.	n.c.	
Gender									
Male	211	8 (3.8)	n.c.	116	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Female	162	4 (2.5)	n.c.	76	0 (0.0)	n.c.	n.c.	n.c.	
Country									
Germany	23	0 (0.0)	Not reached [-; -]	10	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	0.997
Rest of world	350	12 (3.4)	Not reached [-; -]	182	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.020	
CMV risk factors									
Very High Risk	121	6	n.c.	54	0	n.c.	n.c.	n.c.	n.c.

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		p-Value for Interaction Test[f]
Serious Adverse Event by SOC	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	
		(5.0)			(0.0)				
High Risk	252	6 (2.4)	n.c.	138	0 (0.0)	n.c.	n.c.	n.c.	
Dose									
240 mg (+CsA)	193	6 (3.1)	n.c.	100	0 (0.0)	n.c.	n.c.	n.c.	n.c.
480 mg	180	6 (3.3)	n.c.	92	0 (0.0)	n.c.	n.c.	n.c.	
Donor serostatus									
Positive	230	6 (2.6)	n.c.	114	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Negative	138	6 (4.3)	n.c.	78	0 (0.0)	n.c.	n.c.	n.c.	
SOC: Renal and urinary disorders									
Age category									
< 54 years	187	5 (2.7)	Not reached [-; -]	90	6 (6.7)	Not reached [-; -]	0.36 [0.11; 1.19]	0.093	0.763
≥ 54 years	186	5 (2.7)	Not reached [-; -]	102	5 (4.9)	Not reached [-; -]	0.41 [0.12; 1.44]	0.163	
Gender									
Male	211	8 (3.8)	Not reached [-; -]	116	6 (5.2)	Not reached [-; -]	0.66 [0.23; 1.91]	0.444	0.140
Female	162	2 (1.2)	Not reached [-; -]	76	5 (6.6)	Not reached [-; -]	0.13 [0.03; 0.68]	0.016	
Country									
Germany	23	1 (4.3)	Not reached [-; -]	10	1 (10.0)	Not reached [3.4; -]	0.48 [0.03; 7.67]	0.603	0.963
Rest of world	350	9 (2.6)	Not reached [-; -]	182	10 (5.5)	Not reached [-; -]	0.38 [0.15; 0.94]	0.036	
CMV risk factors									
Very High Risk	121	5 (4.1)	Not reached [-; -]	54	4 (7.4)	Not reached [-; -]	0.51 [0.14; 1.90]	0.314	0.852
High Risk	252	5 (2.0)	Not reached [-; -]	138	7 (5.1)	Not reached [-; -]	0.31 [0.10; 0.99]	0.048	
Dose									
240 mg (+CsA)	193	6 (3.1)	Not reached [-; -]	100	5 (5.0)	Not reached [-; -]	0.52 [0.16; 1.71]	0.279	0.495
480 mg	180	4 (2.2)	Not reached [-; -]	92	6 (6.5)	Not reached [-; -]	0.29 [0.08; 1.03]	0.057	
Donor serostatus									
Positive	230	5 (2.2)	Not reached [-; -]	114	5 (4.4)	Not reached [-; -]	0.45 [0.13; 1.58]	0.214	0.801
Negative	138	5 (3.6)	Not reached [-; -]	78	6 (7.7)	Not reached [-; -]	0.33 [0.10; 1.10]	0.072	

a: Database Lock Date: 28JAN2017
b: Number of participants: All Participants as Treated Population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		p-Value for Interaction Test[f]
Serious Adverse Event by SOC	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	
A specific adverse event appears on this report only if its incidence is ≥5% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is < 0.05, and the interaction p-value is ≥ 0.05 or not calculated									
CI: confidence interval; CMV: cytomegalovirus; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 participants with events in one of the subgroups necessary); PT: Preferred Term; SOC: System Organ Class									

Tabelle 4G-26: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		p-Value for Interaction Test[f]
Serious Adverse Event by SOC and PT	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	
SOC: Infections and infestations - PT: Cytomegalovirus infection									
Age category									
< 54 years	187	7 (3.7)	Not reached [-; -]	90	9 (10.0)	Not reached [-; -]	0.34 [0.13; 0.91]	0.033	0.880
≥ 54 years	186	3 (1.6)	Not reached [-; -]	102	5 (4.9)	Not reached [-; -]	0.29 [0.07; 1.21]	0.090	
Gender									
Male	211	7 (3.3)	Not reached [-; -]	116	7 (6.0)	Not reached [-; -]	0.49 [0.17; 1.40]	0.185	0.225
Female	162	3 (1.9)	Not reached [-; -]	76	7 (9.2)	Not reached [-; -]	0.18 [0.05; 0.71]	0.014	
Country									
Germany	23	0 (0.0)	Not reached [-; -]	10	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	0.997
Rest of world	350	10 (2.9)	Not reached [-; -]	182	14 (7.7)	Not reached [-; -]	0.33 [0.15; 0.75]	0.008	
CMV risk factors									
Very High Risk	121	4 (3.3)	Not reached [-; -]	54	1 (1.9)	Not reached [-; -]	1.67 [0.19; 14.94]	0.648	0.101
High Risk	252	6 (2.4)	Not reached [-; -]	138	13 (9.4)	Not reached [-; -]	0.23 [0.09; 0.61]	0.003	
Dose									
240 mg (+CsA)	193	6 (3.1)	Not reached [-; -]	100	9 (9.0)	Not reached [-; -]	0.32 [0.11; 0.90]	0.031	0.863
480 mg	180	4 (2.2)	Not reached [-; -]	92	5 (5.4)	Not reached [-; -]	0.36 [0.10; 1.35]	0.130	
Donor serostatus									
Positive	230	6 (2.6)	Not reached [-; -]	114	9 (7.9)	Not reached [-; -]	0.31 [0.11; 0.88]	0.027	0.814
Negative	138	4 (2.9)	Not reached [-; -]	78	5 (6.4)	Not reached [-; -]	0.39 [0.10; 1.47]	0.163	
a: Database Lock Date: 28JAN2017									
b: Number of participants: All Participants as Treated Population									
c: From product-limit (Kaplan-Meier) method for censored data									
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval									
e: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)									
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for									

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		p-Value for Interaction Test[f]
Serious Adverse Event by SOC and PT	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	
interaction term)									
A specific adverse event appears on this report only if its incidence is ≥5% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is < 0.05, and the interaction p-value is ≥ 0.05 or not calculated									
CI: confidence interval; CMV: cytomegalovirus; n.a.: not applicable (when estimation not possible); PT: Preferred Term; SOC: System Organ Class									

Anhang 4-G4: Abbruchgründe für Patient:innen ohne Angaben zum Überlebensstatus

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.1.1 die Abbruchgründe ohne Angaben zum Überlebensstatus für die APaT- und für die FAS-Population dargestellt.

Alle Ergebnisse beziehen sich auf den letztverfügbaren Analysezeitpunkt.

Tabelle 4G-27: Abbruchgründe für Patient:innen ohne Angaben zum Überlebensstatus auf Basis der APaT-Population aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir (N^b = 14)**	**Placebo (N^b = 4)**
Reasons For Discontinuation		
Adverse Event	1 (7.1)	0 (0.0)
Lost to Follow-up	2 (14.3)	1 (25.0)
Physician Decision	5 (35.7)	1 (25.0)
Withdrawal by Participant	6 (42.9)	2 (50.0)
a: Database Lock Date: 28JAN2017 b: Number of participants: All Participants as Treated Population Without Post-Study Vital Status		

Tabelle 4G-28: Abbruchgründe für Patient:innen ohne Angaben zum Überlebensstatus auf Basis der FAS-Population aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir (N^b = 10)**	**Placebo (N^b = 4)**
Reasons For Discontinuation		
Adverse Event	1 (10.0)	0 (0.0)
Lost to Follow-up	1 (10.0)	1 (25.0)
Physician Decision	3 (30.0)	1 (25.0)
Withdrawal by Participant	5 (50.0)	2 (50.0)
a: Database Lock Date: 28JAN2017 b: Number of participants: Full Analysis Set Population Without Post-Study Vital Status		

Anhang 4-G5: Unerwünschte Ereignisse, die die Ereignisse CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen ausschließen

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.4 die Unerwünschten Ereignisse, die die CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen ausschließen, dargestellt.

Alle Ergebnisse beziehen sich auf den letztverfügbaren Analysezeitpunkt.

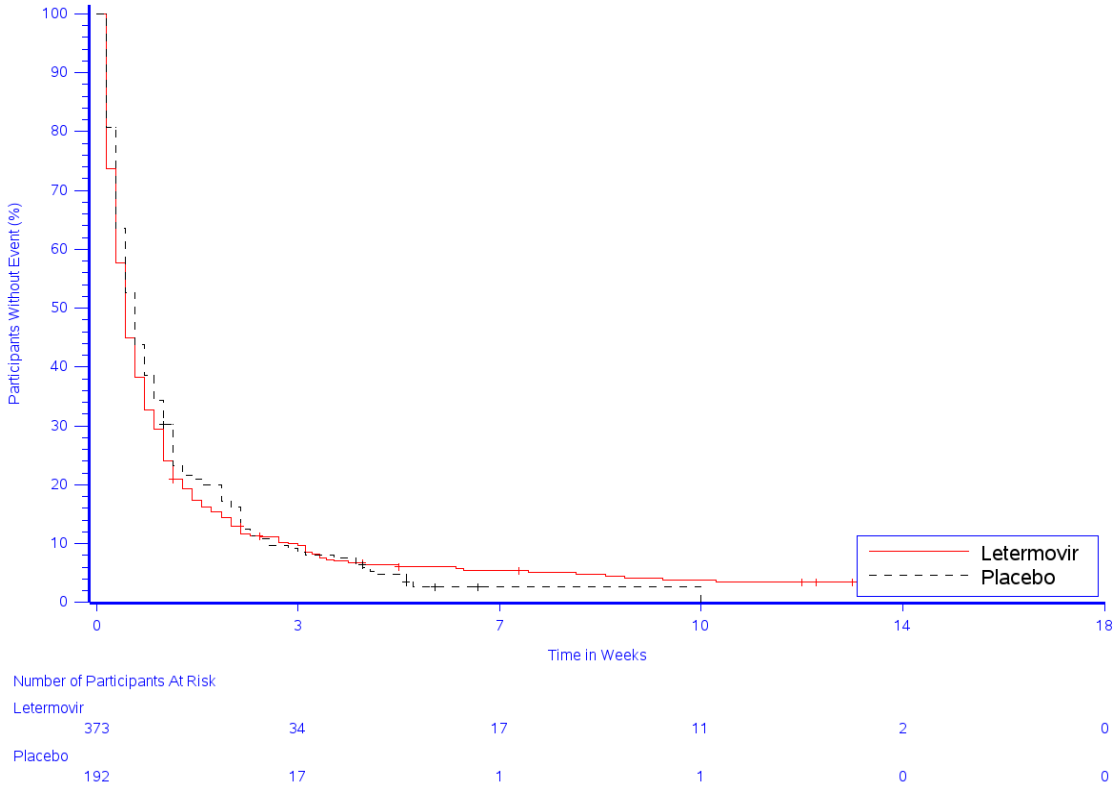
Anhang 4-G5.1 Unerwünschte Ereignisse Gesamtraten

Tabelle 4G-29: Ergebnisse für den Endpunkt Unerwünschte Ereignisse Gesamtraten (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir**			**Placebo**			**Letermovir vs. Placebo**	
Time to Adverse Event Related Endpoints	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**
Adverse Events	373	357 (95.7)	0.4 [0.4; 0.6]	192	185 (96.4)	0.6 [0.4; 0.7]	1.07 [0.90; 1.28]	0.456
Serious Adverse Events	373	145 (38.9)	15.3 [15.1; 15.6]	192	72 (37.5)	Not reached [11.1; -]	0.90 [0.67; 1.19]	0.450
Severe Adverse Events	373	145 (38.9)	15.3 [15.3; 15.6]	192	74 (38.5)	Not reached [11.1; -]	0.88 [0.67; 1.17]	0.386
Adverse Events Leading to Treatment Discontinuation	373	47 (12.6)	Not reached [-; -]	192	21 (10.9)	Not reached [-; -]	1.06 [0.63; 1.78]	0.818

a: Database Lock Date: 28JAN2017
b: Number of participants: All Participants as Treated Population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate
e: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
The following AE have been excluded: CMV Infection, CMV Viramea, GVHD, Bacterial and/or fungal opportunistic infection
CI: confidence interval; CMV: cytomegalovirus

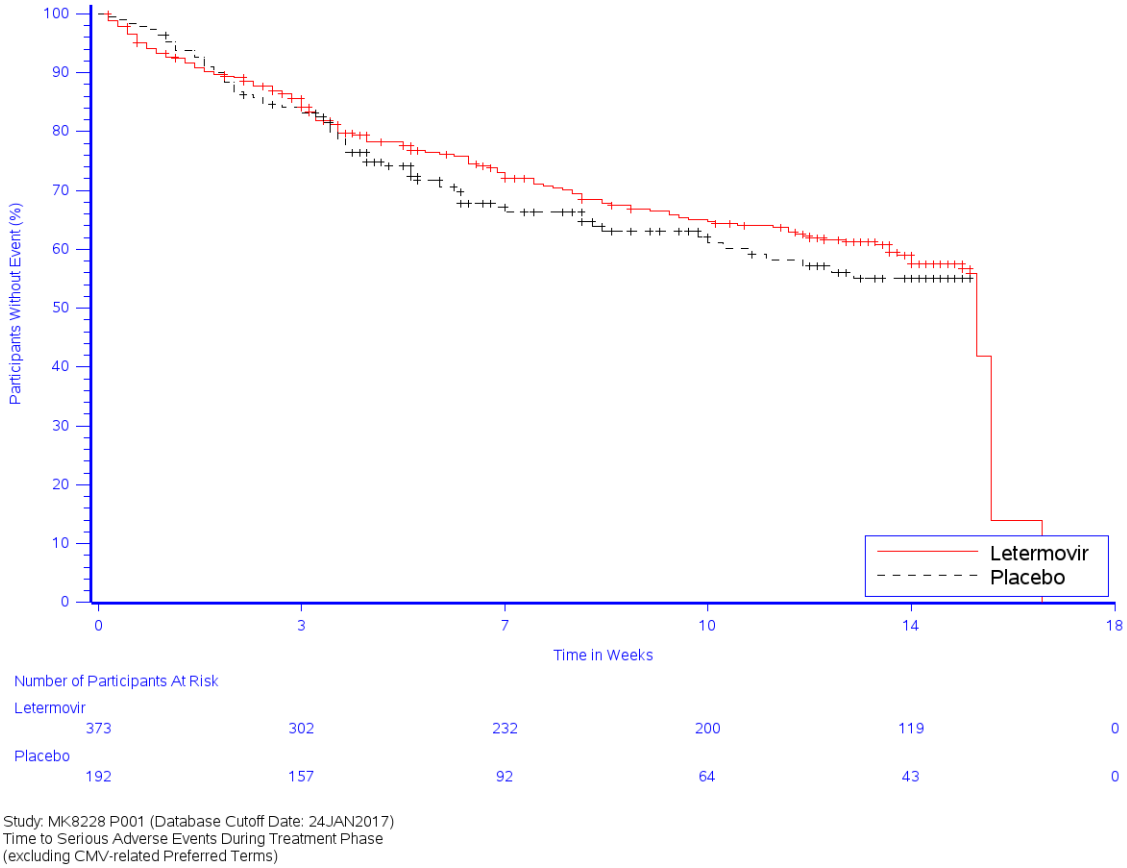
Unerwünschte Ereignisse gesamt



Study: MK8228 P001 (Database Cutoff Date: 24JAN2017)
Time to Adverse Events During Treatment Phase
(excluding CMV-related Preferred Terms)

Abbildung 4G-7: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Unerwünschte Ereignisse gesamt (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) der Studie MK-8228-001

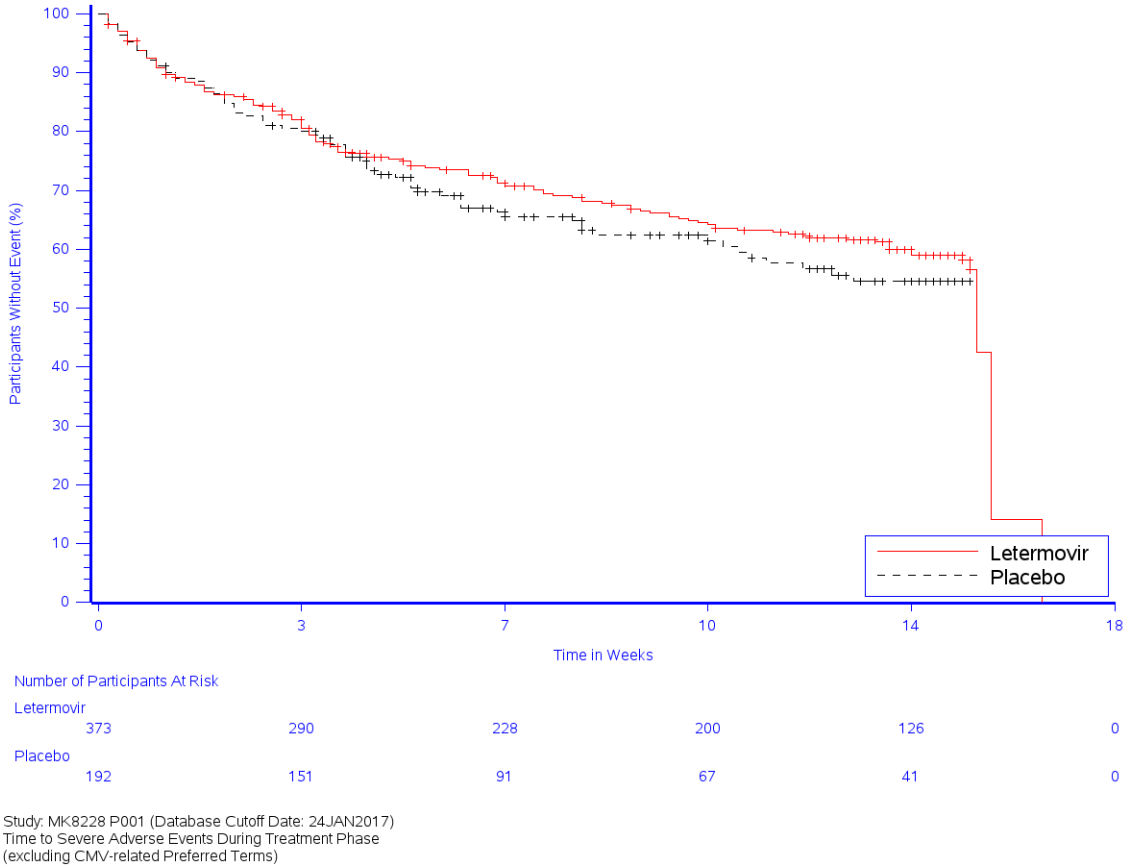
Schwerwiegende unerwünschte Ereignisse



Study: MK8228 P001 (Database Cutoff Date: 24JAN2017)
Time to Serious Adverse Events During Treatment Phase
(excluding CMV-related Preferred Terms)

Abbildung 4G-8: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwerwiegende unerwünschte Ereignisse (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) der Studie MK-8228-001

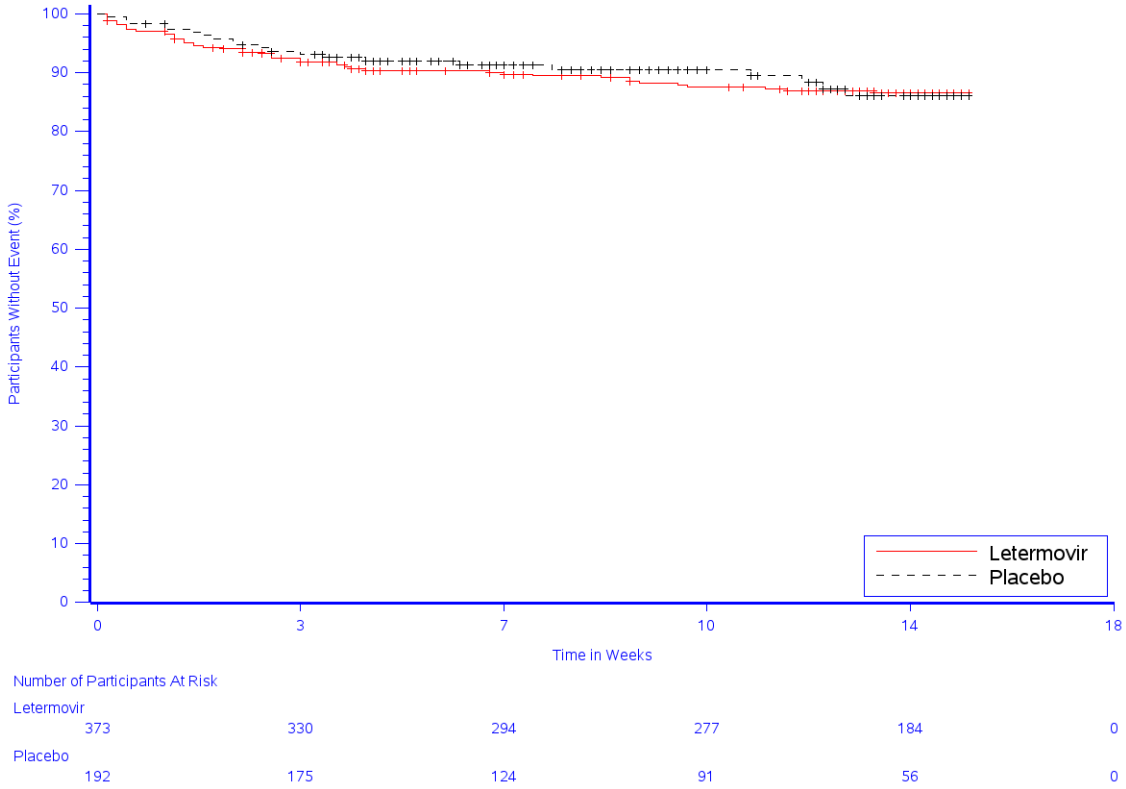
Schwere unerwünschte Ereignisse



Study: MK8228 P001 (Database Cutoff Date: 24JAN2017)
Time to Severe Adverse Events During Treatment Phase
(excluding CMV-related Preferred Terms)

Abbildung 4G-9: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwere unerwünschte Ereignisse (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) der Studie MK-8228-001

Therapieabbruch wegen unerwünschter Ereignisse



Study: MK8228 P001 (Database Cutoff Date: 24JAN2017)
Time to Adverse Events Leading to Treatment Discontinuation During Treatment Phase
(excluding CMV-related Preferred Terms)

Abbildung 4G-10: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) der Studie MK-8228-001

Anhang 4-GG5.2 Unerwünschte Ereignisse (gegliedert nach SOC und PT) – RCT

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-30: Ergebnisse für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir (N[b]=373)		Placebo (N[b]=192)		Letermovir vs. Placebo		
Adverse Events by SOC and PT[c]	Participants with Event n (%)	Median Time[d] in Days [95 %-CI]	Participants with Event n (%)	Median Time[d] in Days [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	Adjusted p-Value[g]
Blood and lymphatic system disorders	101 (27.08)	Not reached [-; -]	52 (27.08)	Not reached [-; -]	0.92 [0.66; 1.29]	0.634	0.976
Cardiac disorders	49 (13.14)	Not reached [-; -]	13 (6.77)	Not reached [-; -]	1.79 [0.97; 3.31]	0.062	0.639
Ear and labyrinth disorders	17 (4.56)	Not reached [-; -]	3 (1.56)	Not reached [-; -]	2.64 [0.77; 9.03]	0.122	0.639
Eye disorders	65 (17.43)	Not reached [-; -]	33 (17.19)	Not reached [-; -]	0.97 [0.64; 1.47]	0.881	0.976
Gastrointestinal disorders	268 (71.85)	17.00 [12.00; 24.00]	132 (68.75)	16.00 [12.00; 25.00]	1.01 [0.82; 1.25]	0.895	0.976
General disorders and administration site conditions	216 (57.91)	44.00 [32.00; 58.00]	102 (53.13)	42.00 [26.00; 92.00]	1.04 [0.82; 1.32]	0.752	0.976
Hepatobiliary disorders	22 (5.90)	Not reached [-; -]	15 (7.81)	Not reached [-; -]	0.71 [0.37; 1.38]	0.315	0.968
Immune system disorders	16 (4.29)	Not reached [-; -]	10 (5.21)	107.00 [-; -]	0.83 [0.36; 1.88]	0.651	0.976
Infections and infestations	222 (59.52)	48.00 [38.00; 63.00]	91 (47.40)	76.00 [46.00; -]	1.24 [0.97; 1.58]	0.090	0.639
Injury, poisoning and procedural complications	41 (10.99)	Not reached [-; -]	28 (14.58)	Not reached [-; -]	0.68 [0.42; 1.10]	0.117	0.639
Investigations	138 (37.00)	117.00 [-; -]	62 (32.29)	Not reached [-; -]	1.12 [0.83; 1.51]	0.461	0.968
Metabolism and nutrition disorders	136 (36.46)	Not reached [-; -]	66 (34.38)	Not reached [-; -]	0.99 [0.74; 1.33]	0.947	0.976
Musculoskeletal and connective tissue disorders	127 (34.05)	Not reached [-; -]	60 (31.25)	Not reached [-; -]	0.99 [0.73; 1.34]	0.931	0.976
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	39 (10.46)	107.00 [-; -]	18 (9.38)	112.00 [-; -]	0.95 [0.54; 1.69]	0.872	0.976
Nervous system disorders	139 (37.27)	Not reached [-; -]	66 (34.38)	Not reached [102.00; -]	1.03 [0.77; 1.39]	0.830	0.976
Psychiatric disorders	76 (20.38)	Not reached [-; -]	31 (16.15)	Not reached [-; -]	1.20 [0.79; 1.82]	0.403	0.968
Renal and urinary disorders	85 (22.79)	Not reached [-; -]	48 (25.00)	112.00 [-; -]	0.87 [0.61; 1.24]	0.443	0.968
Reproductive system and breast disorders	31 (8.31)	Not reached [-; -]	11 (5.73)	Not reached [-; -]	1.32 [0.66; 2.64]	0.428	0.968
Respiratory, thoracic and mediastinal disorders	151 (40.48)	Not reached [93.00; -]	74 (38.54)	Not reached [96.00; -]	1.00 [0.76; 1.33]	0.976	0.976
Skin and subcutaneous tissue disorders	189 (50.67)	67.00 [45.00; 97.00]	85 (44.27)	71.00 [43.00; -]	1.09 [0.84; 1.40]	0.523	0.976

Study: MK8228 P001[a]	Letermovir (N[b]=373)		Placebo (N[b]=192)		Letermovir vs. Placebo		
Adverse Events by SOC and PT[c]	Participants with Event n (%)	Median Time[d] in Days [95 %-CI]	Participants with Event n (%)	Median Time[d] in Days [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	Adjusted p-Value[g]
Vascular disorders	72 (19.30)	Not reached [-; -]	43 (22.40)	Not reached [-; -]	0.78 [0.53; 1.14]	0.197	0.829

a: Database Lock Date: 28JAN2017

b: Number of participants: All Participants as Treated Population

c: A system organ class or specific adverse event appears on this report only if its incidence ≥10% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate

f: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

The following AE have been excluded: CMV Infection, CMV Viramea, GVHD, Bacterial and/or fungal opportunistic infection

g: Adjusted p-values for treatment comparisons of adverse events at the SOC level were computed using the FDR procedure, and they were computed using the double FDR procedure for comparisons of adverse events at the PT level. Not significant (i.e., 'n.s.') is reported for PTs in a SOC when the SOC did not meet the threshold p-Value criteria in the first step of the double FDR procedure. Adjusted p-Values should be used for evaluating the results in order to reduce the number of false discoveries (i.e., statistical findings) when numerous statistical tests are performed

CI: confidence interval; CMV: cytomegalovirus; FDR: False Discovery Rate; n.s.: Not Significant; PT: Preferred Term; SOC: System Organ Class

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-31: Ergebnisse für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir (N[b]=373)		Placebo (N[b]=192)		Letermovir vs. Placebo		
Serious Adverse Events by SOC and PT[c]	Participants with Event n (%)	Median Time[d] in Days [95 %-CI]	Participants with Event n (%)	Median Time[d] in Days [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	Adjusted p-Value[g]
Blood and lymphatic system disorders	16 (4.29)	Not reached [-; -]	4 (2.08)	Not reached [-; -]	1.70 [0.57; 5.11]	0.344	0.803
Gastrointestinal disorders	12 (3.22)	Not reached [-; -]	7 (3.65)	Not reached [-; -]	0.78 [0.31; 1.99]	0.607	0.849
General disorders and administration site conditions	13 (3.49)	Not reached [-; -]	7 (3.65)	112.00 [-; -]	1.02 [0.39; 2.69]	0.971	0.971
Infections and infestations	69 (18.50)	109.00 [109.00; -]	25 (13.02)	Not reached [-; -]	1.19 [0.75; 1.89]	0.466	0.816
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	30 (8.04)	107.00 [-; -]	14 (7.29)	112.00 [-; -]	0.97 [0.51; 1.87]	0.936	0.971
Nervous system disorders	12 (3.22)	Not reached [-; -]	0 (0.00)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.020	0.113
Renal and urinary disorders	10 (2.68)	Not reached [-; -]	11 (5.73)	Not reached [-; -]	0.39 [0.16; 0.92]	0.032	0.113

a: Database Lock Date: 28JAN2017

b: Number of participants: All Participants as Treated Population

c: A system organ class or specific adverse event appears on this report only if its incidence ≥5% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate

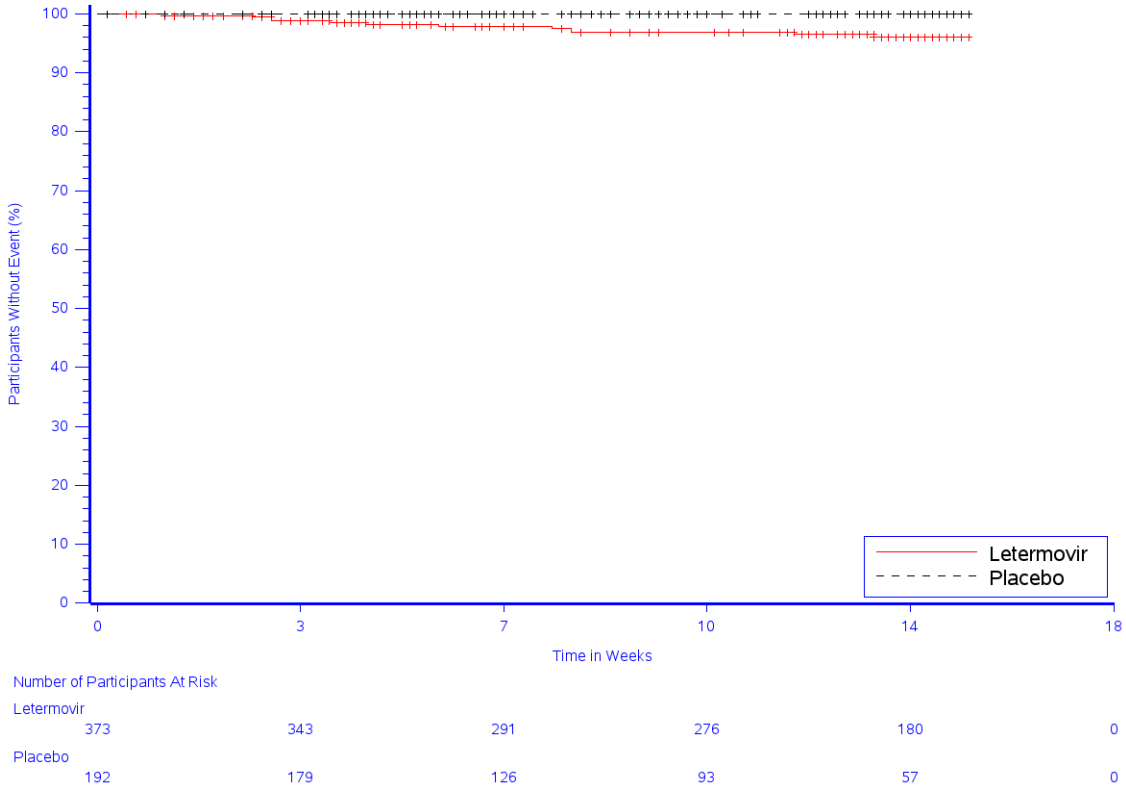
Study: MK8228 P001[a]	Letermovir (N[b]=373)		Placebo (N[b]=192)		Letermovir vs. Placebo		
Serious Adverse Events by SOC and PT[c]	Participants with Event n (%)	Median Time[d] in Days [95 %-CI]	Participants with Event n (%)	Median Time[d] in Days [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	Adjusted p-Value[g]

f: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

g: Adjusted p-values for treatment comparisons of adverse events at the SOC level were computed using the FDR procedure, and they were computed using the double FDR procedure for comparisons of adverse events at the PT level. Not significant (i.e., 'n.s.') is reported for PTs in a SOC when the SOC did not meet the threshold p-Value criteria in the first step of the double FDR procedure. Adjusted p-Values should be used for evaluating the results in order to reduce the number of false discoveries (i.e., statistical findings) when numerous statistical tests are performed

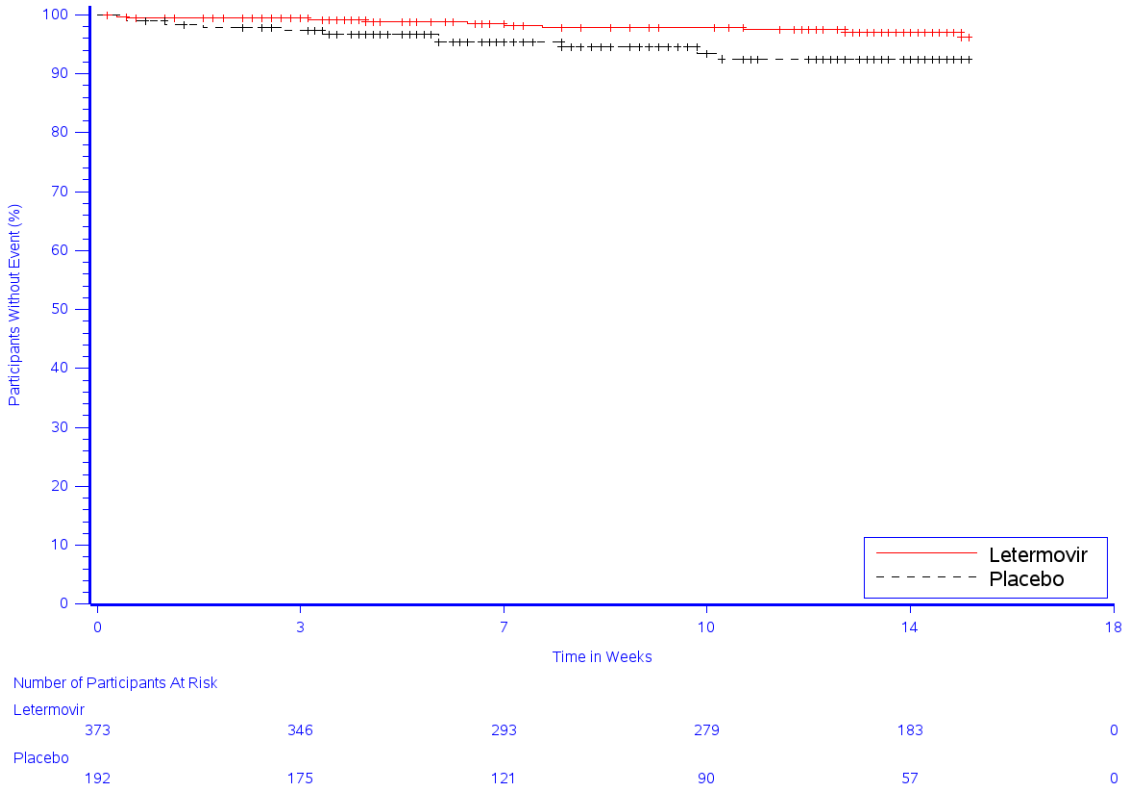
The following AE have been excluded: CMV Infection, CMV Viramea, GVHD, Bacterial and/or fungal opportunistic infection

CI: confidence interval; CMV: cytomegalovirus; FDR: False Discovery Rate; n.a.: not applicable (when estimation not possible); n.s.: Not Significant; PT: Preferred Term; SOC: System Organ Class



Study: MK8228 P001 (Database Cutoff Date: 24JAN2017)
Time to Serious Adverse Event System Organ Class: Nervous system disorders
(excluding CMV-related Preferred Terms)

Abbildung 4G-11: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwere unerwünschte Ereignisse (SOC: Erkrankungen des Nervensystems) (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) der Studie MK-8228-001



Study: MK8228 P001 (Database Cutoff Date: 24JAN2017)
Time to Serious Adverse Event System Organ Class: Renal and urinary disorders
(excluding CMV-related Preferred Terms)

Abbildung 4G-12: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwere unerwünschte Ereignisse (SOC: Erkrankungen der Nieren und Harnwege) (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) der Studie MK-8228-001

Schwere unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-32: Ergebnisse für den Endpunkt Schwere unerwünschte Ereignisse (SOC und PT) (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	**Letermovir (Nb=373)**		**Placebo (Nb=192)**		**Letermovir vs. Placebo**		
Severe Adverse Events by SOC and PT[c]	**Participants with Event n (%)**	**Median Time[d] in Days [95 %-CI]**	**Participants with Event n (%)**	**Median Time[d] in Days [95 %-CI]**	**Hazard Ratio[e] [95 %-CI]**	**p-Value[e,f]**	**Adjusted p-Value[g]**
Blood and lymphatic system disorders	25 (6.70)	107.00 [-; -]	14 (7.29)	Not reached [-; -]	0.75 [0.39; 1.46]	0.403	0.921
Gastrointestinal disorders	12 (3.22)	Not reached [-; -]	5 (2.60)	Not reached [-; -]	1.05 [0.37; 3.00]	0.921	0.921
General disorders and administration site conditions	22 (5.90)	Not reached [-; -]	7 (3.65)	112.00 [-; -]	1.77 [0.72; 4.37]	0.216	0.863
Infections and infestations	62 (16.62)	109.00 [109.00; -]	25 (13.02)	Not reached [-; -]	1.05 [0.66; 1.69]	0.828	0.921
Investigations	11	Not reached	5	Not reached	1.11	0.853	0.921

Study: MK8228 P001[a]	Letermovir (Nb=373)		Placebo (Nb=192)		Letermovir vs. Placebo		
Severe Adverse Events by SOC and PT[c]	Participants with Event n (%)	Median Time[d] in Days [95 %-CI]	Participants with Event n (%)	Median Time[d] in Days [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	Adjusted p-Value[g]
	(2.95)	[-; -]	(2.60)	[-; -]	[0.38; 3.18]		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	24 (6.43)	107.00 [-; -]	13 (6.77)	112.00 [-; -]	0.84 [0.42; 1.68]	0.616	0.921
Nervous system disorders	13 (3.49)	Not reached [-; -]	1 (0.52)	Not reached [-; -]	6.11 [0.80; 46.78]	0.082	0.652
Respiratory, thoracic and mediastinal disorders	13 (3.49)	Not reached [-; -]	8 (4.17)	Not reached [-; -]	0.80 [0.33; 1.93]	0.616	0.921

a: Database Lock Date: 28JAN2017

b: Number of participants: All Participants as Treated Population

c: A system organ class or specific adverse event appears on this report only if its incidence ≥5% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate

f: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

g: Adjusted p-values for treatment comparisons of adverse events at the SOC level were computed using the FDR procedure, and they were computed using the double FDR procedure for comparisons of adverse events at the PT level. Not significant (i.e., 'n.s.') is reported for PTs in a SOC when the SOC did not meet the threshold p-Value criteria in the first step of the double FDR procedure. Adjusted p-Values should be used for evaluating the results in order to reduce the number of false discoveries (i.e., statistical findings) when numerous statistical tests are performed

The following AE have been excluded: CMV Infection, CMV Viramea, GVHD, Bacterial and/or fungal opportunistic infection

CI: confidence interval; CMV: cytomegalovirus; FDR: False Discovery Rate; n.s.: Not Significant; PT: Preferred Term; SOC: System Organ Class

Therapieabbruch wegen unerwünschter Ereignisse (SOC und PT)

Tabelle 4G-33: Ergebnisse für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse (SOC und PT) (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Participants with Event n (%)	
	Letermovir (N^b = 373)	Placebo (N^b = 192)
Participants in population with one or more adverse events leading to treatment discontinuation	47 (12.6)	21 (10.9)
Blood and lymphatic system disorders	6 (1.6)	1 (0.5)
Anaemia	1 (0.3)	0 (0.0)
Leukopenia	1 (0.3)	0 (0.0)
Neutropenia	1 (0.3)	1 (0.5)
Pancytopenia	1 (0.3)	0 (0.0)
Thrombocytopenia	2 (0.5)	0 (0.0)
Cardiac disorders	1 (0.3)	0 (0.0)
Cardiac failure	1 (0.3)	0 (0.0)
Gastrointestinal disorders	11 (2.9)	4 (2.1)
Abdominal pain	2 (0.5)	0 (0.0)
Diarrhoea	1 (0.3)	1 (0.5)
Mouth ulceration	0 (0.0)	1 (0.5)
Nausea	6 (1.6)	2 (1.0)
Vomiting	3 (0.8)	0 (0.0)
Hepatobiliary disorders	3 (0.8)	2 (1.0)
Acute hepatic failure	1 (0.3)	0 (0.0)

Study: MK8228 P001[a]	Participants with Event n (%)	
	Letermovir (N[b] = 373)	Placebo (N[b] = 192)
Venoocclusive liver disease	2 (0.5)	2 (1.0)
Immune system disorders	1 (0.3)	0 (0.0)
Hypersensitivity	1 (0.3)	0 (0.0)
Infections and infestations	9 (2.4)	6 (3.1)
Bacterial sepsis	0 (0.0)	1 (0.5)
Bronchopulmonary aspergillosis	2 (0.5)	1 (0.5)
Herpes zoster	1 (0.3)	0 (0.0)
Meningoencephalitis herpetic	1 (0.3)	0 (0.0)
Oral herpes	0 (0.0)	1 (0.5)
Pneumocystis jirovecii pneumonia	0 (0.0)	1 (0.5)
Pneumonia	2 (0.5)	0 (0.0)
Sepsis	1 (0.3)	0 (0.0)
Septic shock	1 (0.3)	2 (1.0)
Viraemia	1 (0.3)	0 (0.0)
Injury, poisoning and procedural complications	1 (0.3)	1 (0.5)
Delayed engraftment	1 (0.3)	0 (0.0)
Subdural haematoma	0 (0.0)	1 (0.5)
Investigations	3 (0.8)	2 (1.0)
Alanine aminotransferase increased	0 (0.0)	1 (0.5)
Blood creatinine increased	2 (0.5)	1 (0.5)
Hepatic enzyme increased	1 (0.3)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.3)	3 (1.6)
Acute myeloid leukaemia recurrent	4 (1.1)	1 (0.5)
Bowen's disease	0 (0.0)	1 (0.5)
Myelodysplastic syndrome	1 (0.3)	1 (0.5)
Nervous system disorders	3 (0.8)	0 (0.0)
Cerebral haemorrhage	1 (0.3)	0 (0.0)
Encephalopathy	1 (0.3)	0 (0.0)
Headache	1 (0.3)	0 (0.0)
Psychiatric disorders	1 (0.3)	1 (0.5)
Confusional state	1 (0.3)	0 (0.0)
Mental status changes	0 (0.0)	1 (0.5)
Renal and urinary disorders	0 (0.0)	1 (0.5)
Acute kidney injury	0 (0.0)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	0 (0.0)
Respiratory failure	1 (0.3)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (0.3)	0 (0.0)
Rash	1 (0.3)	0 (0.0)
Vascular disorders	1 (0.3)	0 (0.0)
Venoocclusive disease	1 (0.3)	0 (0.0)

a: Database Lock Date: 28JAN2017

b: Number of participants: All Participants as Treated Population

Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a system organ class is counted a single time for that system organ class

A system organ class or specific adverse event appears on this report only if its incidence is > 0% in one or more treatment groups,

The following AE have been excluded: CMV Infection, CMV Viramea, GVHD, Bacterial and/or fungal opportunistic infection

Anhang 4-G5.3 Subgruppenanalysen mit signifikantem Interaktionstest (p < 0,05) der unerwünschten Ereignisse, die die Ereignisse CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen ausschließen – RCT

Unerwünschte Ereignisse Gesamtraten

Tabelle 4G-34: Überblick der Ergebnisse der Interaktionstests aus Subgruppenanalysen der Studie MK-8228-001 für den Endpunkt Unerwünschte Ereignisse Gesamtraten (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen)

Study: MK8228 P001[a]	**P-Values of Treatment by Subgroup Interaction Test[b]**					
	Age category (< 54 years vs. ≥ 54 years)	**Gender (Male vs. Female)**	**Country (Germany vs. Rest of world)**	**CMV risk factors (Very High Risk vs. High Risk)**	**Dose (240 mg (+CsA) vs. 480 mg)**	**Donor serostatus (Positive vs. Negative)**
Adverse Events						
Adverse Events	0.482	0.943	0.388	0.727	0.943	0.176
Serious Adverse Events	0.311	**0.002[c]**	0.910	0.986	0.590	0.758
Severe Adverse Events	0.924	**0.004[c]**	0.373	0.891	0.421	0.877
Adverse Events Leading to Treatment Discontinuation	0.974	0.625	0.597	0.534	0.720	0.539

a: Database Lock Date: 28JAN2017
b: Based on Cox regression model with treatment as a covariate, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
The following AE have been excluded: CMV Infection, CMV Viramea, GVHD, Bacterial and/or fungal opportunistic infection
c: p-value for interaction test smaller than 0.05

Tabelle G-35: Subgruppenanalysen mit positivem Interaktionstest (p < 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse Gesamtraten (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		
Time to Serious Adverse Event	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Male	211	92 (43.6)	15.3 [13.3; 15.6]	116	35 (30.2)	Not reached [-; -]	1.33 [0.90; 1.97]	0.152	0.002
Female	162	53 (32.7)	Not reached [15.1; -]	76	37 (48.7)	10.0 [6.1; -]	0.52 [0.34; 0.79]	0.002	

a: Database Lock Date: 28JAN2017
b: Number of participants: All Participants as Treated Population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
The following AE have been excluded: CMV Infection, CMV Viramea, GVHD, Bacterial and/or fungal opportunistic infection
CI: confidence interval; CMV: cytomegalovirus

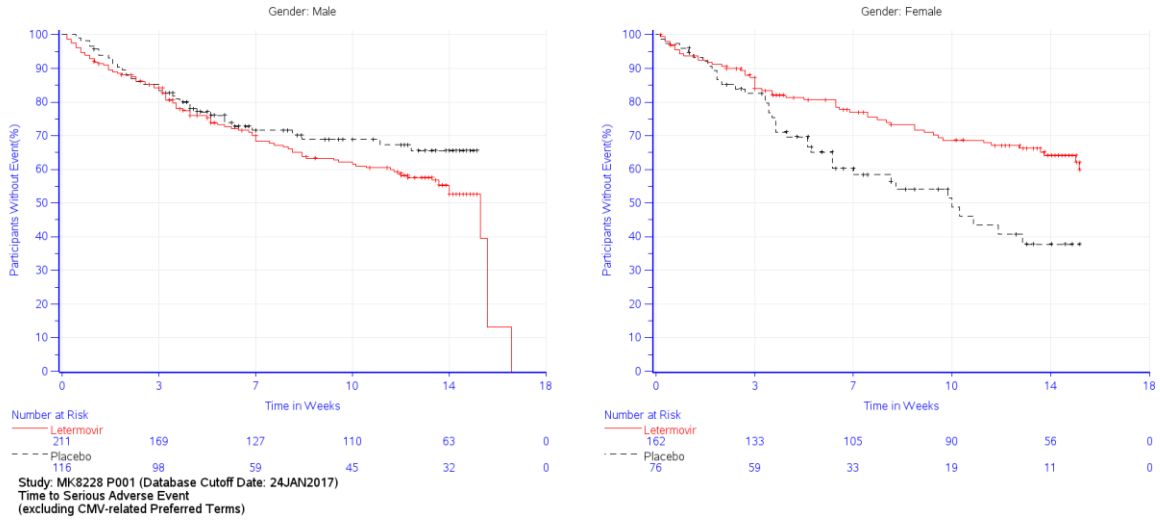


Abbildung 4G-13: Kaplan-Meier-Kurven mit positivem Interaktionstest (p < 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse Gesamtraten nach Geschlecht (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) aus RCT mit dem zu bewertenden Arzneimittel

Tabelle G-36: Subgruppenanalysen mit positivem Interaktionstest (p < 0,05) für den Endpunkt Schwere unerwünschte Ereignisse Gesamtraten (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK8228 P001[a]	Letermovir			Placebo			Letermovir vs. Placebo		
Time to Severe Adverse Event	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Male	211	94 (44.5)	15.3 [13.3; 15.6]	116	37 (31.9)	Not reached [-; -]	1.26 [0.86; 1.85]	0.231	0.004
Female	162	51 (31.5)	Not reached [-; -]	76	37 (48.7)	10.3 [6.1; -]	0.53 [0.35; 0.81]	0.004	

a: Database Lock Date: 28JAN2017
b: Number of participants: All Participants as Treated Population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
The following AE have been excluded: CMV Infection, CMV Viramea, GVHD, Bacterial and/or fungal opportunistic infection
CI: confidence interval; CMV: cytomegalovirus

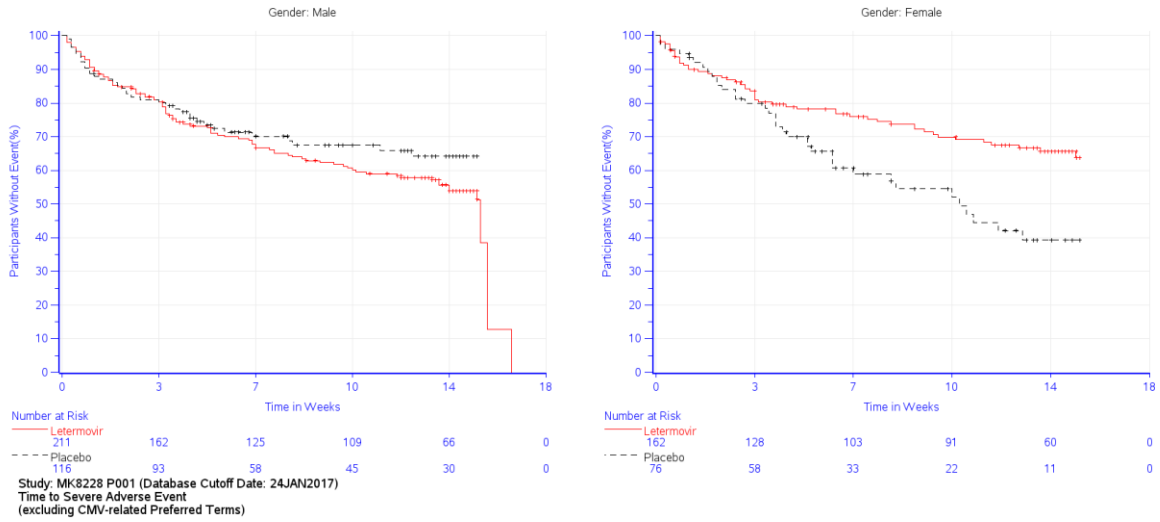


Abbildung 4G-14: Kaplan-Meier-Kurven mit positivem Interaktionstest (p < 0,05) für den Endpunkt Schwere unerwünschte Ereignisse Gesamtraten nach Geschlecht (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen) aus RCT mit dem zu bewertenden Arzneimittel

Schwerwiegende unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle G-37: Überblick der Ergebnisse der Interaktionstests aus Subgruppenanalysen der Studie MK-8228-001 für den Endpunkt Schwerwiegende unerwünschte Ereignisse gesamt (SOC und PT) (exkl. CMV-Infektion, CMV-Virämie, GvHD und bakterielle und/oder fungale Infektionen)

Study: MK8228 P001[a]	**P-Values of Treatment by Subgroup Interaction Test[b]**					
	Age category (< 54 years vs. ≥ 54 years)	**Gender (Male vs. Female)**	**Country (Germany vs. Rest of world)**	**CMV risk factors (Very High Risk vs. High Risk)**	**Dose (240 mg (+CsA) vs. 480 mg)**	**Donor serostatus (Positive vs. Negative)**
Serious Adverse Events						
Nervous system disorders	n.c.	n.c.	0.997	n.c.	n.c.	n.c.
Renal and urinary disorders	0.763	0.140	0.963	0.852	0.495	0.801

a: Database Lock Date: 28JAN2017
b: Based on Cox regression model with treatment as a covariate, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
The following AE have been excluded: CMV Infection, CMV Viramea, GVHD, Bacterial and/or fungal opportunistic infection
n.c.: not calculated (at least 10 participants per subgroup category and at least 10 participants with events in one of the subgroup categories necessary)