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Dossier zur Nutzenbewertung gemäß § 35a SGB V

Letermovir (PREVYMIS®)

MSD Sharp & Dohme GmbH

Modul 4 A

Anhang 4-G: Weitere Ergebnisse

Prophylaxe einer CMV-Erkrankung bei CMV-seronegativen Erwachsenen angewendet, die eine Nierentransplantation von einem CMV-seropositiven Spender erhalten haben [D+/R-]

Medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen

Stand: 12.12.2023

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Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.2.7 bzw. Abschnitt 4.3.1.3.1.3.1 die Rücklaufquoten der EQ-5D VAS und die Rücklaufquoten des SF-36v2 dargestellt.

Alle Ergebnisse beziehen sich auf den finalen Analysezeitpunkt.

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

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

Study: MK-8228-002[a]		Letermovir	Valganciclovir
Visit	EQ-5D VAS Questionnaires[c]	N[b] = 289 n (%)	N[b] = 297 n (%)
Baseline	Expected to Complete Questionnaires[d]	289 (100.00)	297 (100.00)
	Completed[e]	274 (94.81)	276 (92.93)
	Compliance (% in those expected to complete questionnaires)[f]	274 (94.81)	276 (92.93)
	Not completed	15 (5.19)	21 (7.07)
	With visit, no record	15 (5.19)	21 (7.07)
	Missing by Design[g]	0 (0.00)	0 (0.00)
Week 12	Expected to Complete Questionnaires[d]	269 (93.08)	283 (95.29)
	Completed[e]	220 (76.12)	234 (78.79)
	Compliance (% in those expected to complete questionnaires)[f]	220 (81.78)	234 (82.69)
	Not completed	49 (16.96)	49 (16.50)
	With visit, no record	49 (16.96)	49 (16.50)
	Missing by Design[g]	20 (6.92)	14 (4.71)
	Discontinued due to physician decision	2 (0.69)	0 (0.00)
	Discontinued due to withdrawal by participant	17 (5.88)	12 (4.04)
	Discontinued due to other reasons	1 (0.35)	2 (0.67)
Week 28	Expected to Complete Questionnaires[d]	260 (89.97)	276 (92.93)
	Completed[e]	226 (78.20)	242 (81.48)
	Compliance (% in those expected to complete questionnaires)[f]	226 (86.92)	242 (87.68)
	Not completed	34 (11.76)	34 (11.45)
	With visit, no record	34 (11.76)	34 (11.45)
	Missing by Design[g]	29 (10.03)	21 (7.07)
	Discontinued due to death	2 (0.69)	2 (0.67)
	Discontinued due to physician decision	3 (1.04)	1 (0.34)
	Discontinued due to withdrawal by participant	23 (7.96)	16 (5.39)
	Discontinued due to other reasons	1 (0.35)	2 (0.67)
Week 52	Expected to Complete Questionnaires[d]	255 (88.24)	268 (90.24)
	Completed[e]	208 (71.97)	217 (73.06)
	Compliance (% in those expected to complete questionnaires)[f]	208 (81.57)	217 (80.97)
	Not completed	47 (16.26)	51 (17.17)
	With visit, no record	47 (16.26)	51 (17.17)
	Missing by Design[g]	34 (11.76)	29 (9.76)
	Discontinued due to death	3 (1.04)	2 (0.67)
	Discontinued due to lost to follow-up	1 (0.35)	2 (0.67)
	Discontinued due to physician decision	3 (1.04)	3 (1.01)
	Discontinued due to withdrawal by participant	26 (9.00)	20 (6.73)
	Discontinued due to other reasons	1 (0.35)	2 (0.67)

a: Database Lock Date: 27JUL2022
b: Number of participants: full-analysis-set population
c: Assessments of Quality of Life completed prior to study procedures at this visit.
d: Expected to complete questionnaire includes all participants who do not have missing data due to a missing by design reason
e: Completion is the proportion of participants who completed the PRO questionnaire among the analysis population.
f: Compliance is the proportion of participants who completed the PRO questionnaire among those who were expected to complete the questionnaire at this time point, excluding those in Missing by design category, all the other categories are defined as the proportion of participants in the analysis population (N)
g: The missing by design includes adverse event, death, discontinuation, translations not available, and no visit scheduled
EQ-5D VAS: European Quality of Life 5 Dimensions Visual Analogue Scale; PRO: Patient Reported Outcome

Anhang 4-G1.2: Rücklaufquoten des SF-36v2

Tabelle 4G-2: Gründe für das Fehlen von Werten im SF-36v2

Study: MK-8228-002[a]		Letermovir	Valganciclovir
Visit	SF-36v2 Questionnaires[c]	N[b] = 289 n (%)	N[b] = 297 n (%)
Baseline	Expected to Complete Questionnaires[d]	289 (100.0)	297 (100.0)
	Completed[e]	270 (93.4)	273 (91.9)
	Compliance (% in those expected to complete questionnaires)[f]	270 (93.4)	273 (91.9)
	Not completed	19 (6.6)	24 (8.1)
	With visit, no record	19 (6.6)	24 (8.1)
	Missing by Design[g]	0 (0.0)	0 (0.0)
Week 12	Expected to Complete Questionnaires[d]	269 (93.1)	283 (95.3)
	Completed[e]	204 (70.6)	223 (75.1)
	Compliance (% in those expected to complete questionnaires)[f]	204 (75.8)	223 (78.8)
	Not completed	65 (22.5)	60 (20.2)
	With visit, no record	65 (22.5)	60 (20.2)
	Missing by Design[g]	20 (6.9)	14 (4.7)
	Discontinued due to physician decision	2 (0.7)	0 (0.0)
	Discontinued due to withdrawal by participant	17 (5.9)	12 (4.0)
	Discontinued due to other reasons	1 (0.3)	2 (0.7)
Week 28	Expected to Complete Questionnaires[d]	260 (90.0)	276 (92.9)
	Completed[e]	223 (77.2)	240 (80.8)
	Compliance (% in those expected to complete questionnaires)[f]	223 (85.8)	240 (87.0)
	Not completed	37 (12.8)	36 (12.1)
	With visit, no record	37 (12.8)	36 (12.1)
	Missing by Design[g]	29 (10.0)	21 (7.1)
	Discontinued due to death	2 (0.7)	2 (0.7)
	Discontinued due to physician decision	3 (1.0)	1 (0.3)
	Discontinued due to withdrawal by participant	23 (8.0)	16 (5.4)
	Discontinued due to other reasons	1 (0.3)	2 (0.7)
Week 52	Expected to Complete Questionnaires[d]	255 (88.2)	268 (90.2)
	Completed[e]	204 (70.6)	216 (72.7)
	Compliance (% in those expected to complete questionnaires)[f]	204 (80.0)	216 (80.6)
	Not completed	51 (17.6)	52 (17.5)
	With visit, no record	51 (17.6)	52 (17.5)
	Missing by Design[g]	34 (11.8)	29 (9.8)
	Discontinued due to death	3 (1.0)	2 (0.7)
	Discontinued due to lost to follow-up	1 (0.3)	2 (0.7)
	Discontinued due to physician decision	3 (1.0)	3 (1.0)
	Discontinued due to withdrawal by participant	26 (9.0)	20 (6.7)
	Discontinued due to other reasons	1 (0.3)	2 (0.7)

a: Database Lock Date: 27JUL2022

b: Number of participants: full-analysis-set population

c: Assessments of Quality of Life completed prior to study procedures at this visit.

d: Expected to complete questionnaire includes all participants who do not have missing data due to a missing by design reason

e: Completion is the proportion of participants who completed the PRO questionnaire among the analysis population.

f: Compliance is the proportion of participants who completed the PRO questionnaire among those who were expected to complete the questionnaire at this time point, excluding those in Missing by design category, all the other categories are defined as the proportion of participants in the analysis population (N)

g: The missing by design includes adverse event, death, discontinuation, translations not available, and no visit scheduled

SF-36v2: 36-Items Short Form Health Survey version 2.0; PRO: Patient Reported Outcome

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

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

Alle Ergebnisse beziehen sich auf den finalen Analysezeitpunkt.

Anhang 4-G2.1: Mortalität

Gesamtmortalität

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

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction[e]
All-Cause Mortality	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Test
Sex							
Male	210	4 (1.9)	209	3 (1.4)	n.c.	n.c.	n.c.
Female	79	0 (0.0)	88	0 (0.0)	n.c.	n.c.	
Age Group (Years)							
< 65	242	4 (1.7)	242	2 (0.8)	n.c.	n.c.	n.c.
≥ 65	47	0 (0.0)	55	1 (1.8)	n.c.	n.c.	
Induction Therapy							
Use	131	4 (3.1)	138	3 (2.2)	n.c.	n.c.	n.c.
Non-use	158	0 (0.0)	159	0 (0.0)	n.c.	n.c.	
Region							
Germany	21	0 (0.0)	23	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	268	4 (1.5)	274	3 (1.1)	n.c.	n.c.	

a: Database Lock Date: 27JUL2022

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 use of induction therapy (use vs. non-use), where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively. Approach to handling missing values is the Observed Failure (OF) approach, where participants who discontinue prematurely from the study for any reason are not considered failures.

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

e: Based on a generalized linear model stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Analysis is performed through 52 weeks

CI: Confidence Interval; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary

Anhang 4-G2.2: Morbidität

CMV-Erkrankung

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

Study: MK-8228-002[a]	Letermovir	Valganciclovir	Letermovir vs. Valganciclovir	
	Participants	Participants	Risk Ratio/	p-Value for

Adjudicated CMV Disease	N[b]	with Event n (%)	N[b]	with Event n (%)	Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Interaction[e] Test
Sex							
Male	210	25 (11.9)	209	24 (11.5)	1.04 [0.62; 1.76]	0.873	0.208
Female	79	5 (6.3)	88	11 (12.5)	0.50 [0.18; 1.38]	0.180	
Age Group (Years)							
< 65	242	26 (10.7)	242	23 (9.5)	1.13 [0.66; 1.92]	0.657	0.061
≥ 65	47	4 (8.5)	55	12 (21.8)	0.43 [0.15; 1.18]	0.100	
Induction Therapy							
Use	131	18 (13.7)	138	17 (12.3)	1.12 [0.60; 2.07]	0.729	0.287
Non-use	158	12 (7.6)	159	18 (11.3)	0.67 [0.33; 1.35]	0.261	
Region							
Germany	21	2 (9.5)	23	4 (17.4)	0.52 [0.11; 2.56]	0.425	0.524
Rest of the World	268	28 (10.4)	274	31 (11.3)	0.93 [0.57; 1.50]	0.759	
Race Group							
White	250	28 (11.2)	243	29 (11.9)	0.94 [0.58; 1.53]	0.809	0.371
non-White	39	2 (5.1)	54	6 (11.1)	0.46 [0.09; 2.28]	0.341	

a: Database Lock Date: 27JUL2022

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 use of induction therapy (use vs. non-use), where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively. Approach to handling missing values is the Observed Failure (OF) approach, where participants who discontinue prematurely from the study for any reason are not considered failures.

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

e: Based on a generalized linear model stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

For the subgroup Race, non-white includes missing race group

Analysis is performed through 52 weeks

CI: Confidence Interval; CMV: cytomegalovirus

Tabelle 4G-5: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt CMV-Syndrom aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
CMV Syndrome	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
Sex							
Male	210	20 (9.5)	209	23 (11.0)	0.87 [0.49; 1.53]	0.629	0.217
Female	79	4 (5.1)	88	11 (12.5)	0.40 [0.13; 1.21]	0.105	
Age Group (Years)							
< 65	242	20 (8.3)	242	23 (9.5)	0.87 [0.49; 1.54]	0.628	0.220
≥ 65	47	4 (8.5)	55	11 (20.0)	0.46 [0.16; 1.29]	0.139	
Induction Therapy							
Use	131	14 (10.7)	138	16 (11.6)	0.92 [0.47; 1.81]	0.813	0.334
Non-use	158	10 (6.3)	159	18 (11.3)	0.56 [0.27; 1.17]	0.124	
Region							
Germany	21	2 (9.5)	23	4 (17.4)	0.52 [0.11; 2.56]	0.425	0.696
Rest of the World	268	22 (8.2)	274	30 (10.9)	0.75 [0.45; 1.27]	0.287	
Race Group							

White	250	22 (8.8)	243	28 (11.5)	0.77 [0.45; 1.30]	0.323	0.537
non-White	39	2 (5.1)	54	6 (11.1)	0.46 [0.09; 2.28]	0.341	

a: Database Lock Date: 27JUL2022

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 use of induction therapy (use vs. non-use), where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively. Approach to handling missing values is the Observed Failure (OF) approach, where participants who discontinue prematurely from the study for any reason are not considered failures.

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

e: Based on a generalized linear model stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

For the subgroup Race, non-white includes missing race group

Analysis is performed through 52 weeks

CI: Confidence Interval; CMV: cytomegalovirus

Tabelle 4G-6: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt CMV-Endorganerkrankung aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	**Letermovir**		**Valganciclovir**		**Letermovir vs. Valganciclovir**		
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**
Sex							
Male	210	5 (2.4)	209	1 (0.5)	n.c.	n.c.	n.c.
Female	79	1 (1.3)	88	0 (0.0)	n.c.	n.c.	
Age Group (Years)							
< 65	242	6 (2.5)	242	0 (0.0)	n.c.	n.c.	n.c.
≥ 65	47	0 (0.0)	55	1 (1.8)	n.c.	n.c.	
Induction Therapy							
Use	131	4 (3.1)	138	1 (0.7)	n.c.	n.c.	n.c.
Non-use	158	2 (1.3)	159	0 (0.0)	n.c.	n.c.	
Region							
Germany	21	0 (0.0)	23	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	268	6 (2.2)	274	1 (0.4)	n.c.	n.c.	
Race Group							
White	250	6 (2.4)	243	1 (0.4)	n.c.	n.c.	n.c.
non-White	39	0 (0.0)	54	0 (0.0)	n.c.	n.c.	

a: Database Lock Date: 27JUL2022

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 use of induction therapy (use vs. non-use), where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively. Approach to handling missing values is the Observed Failure (OF) approach, where participants who discontinue prematurely from the study for any reason are not considered failures.

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

e: Based on a generalized linear model stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

For the subgroup Race, non-white includes missing race group

Analysis is performed through 52 weeks

CI: Confidence Interval; CMV: cytomegalovirus; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary

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

Study: MK-8228-002[a]	**Letermovir**			**Valganciclovir**			**Letermovir vs. Valganciclovir**		
Time to Onset of Adjudicated CMV Disease	**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]**
Sex									
Male	210	25 (11.9)	Not reached [-; -]	209	24 (11.5)	Not reached [-; -]	1.07 [0.61; 1.87]	0.8213	0.216
Female	79	5 (6.3)	Not reached [-; -]	88	11 (12.5)	Not reached [-; -]	0.51 [0.18; 1.48]	0.2173	
Age Group (Years)									
< 65	242	26 (10.7)	Not reached [-; -]	242	23 (9.5)	Not reached [-; -]	1.17 [0.67; 2.05]	0.5886	0.075
≥ 65	47	4 (8.5)	Not reached [-; -]	55	12 (21.8)	Not reached [-; -]	0.42 [0.13; 1.31]	0.1353	
Region									
Germany	21	2 (9.5)	Not reached [-; -]	23	4 (17.4)	Not reached [-; -]	0.48 [0.09; 2.62]	0.3957	0.516
Rest of the World	268	28 (10.4)	Not reached [-; -]	274	31 (11.3)	Not reached [-; -]	0.95 [0.57; 1.59]	0.8529	
Induction Therapy									
Use	131	18 (13.7)	Not reached [-; -]	138	17 (12.3)	Not reached [-; -]	1.17 [0.60; 2.26]	0.6509	0.267
Non-use	158	12 (7.6)	Not reached [-; -]	159	18 (11.3)	Not reached [-; -]	0.67 [0.32; 1.39]	0.2811	

a: Database Lock Date: 27JUL2022

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 using Wald confidence interval stratified by use of induction therapy (use vs. non-use)

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

f: Based on stratified Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Analysis is performed through 52 weeks

CI: Confidence Interval; CMV: cytomegalovirus

Dysfunktion und/oder Abstoßung des Transplantats

Tabelle 4G-8: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Dysfunktion und/oder Abstoßung des Transplantats aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction[e]
Allograft Dysfunction and/or Rejection	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Test
Sex							
Male	210	139 (66.2)	209	141 (67.5)	0.98 [0.85; 1.12]	0.734	0.595
Female	79	53 (67.1)	88	64 (72.7)	0.92 [0.76; 1.13]	0.445	
Age Group (Years)							
< 65	242	156 (64.5)	242	165 (68.2)	0.95 [0.83; 1.07]	0.396	0.454
≥ 65	47	36 (76.6)	55	40 (72.7)	1.04 [0.83; 1.31]	0.729	
Induction Therapy							
Use	131	76 (58.0)	138	92 (66.7)	0.87 [0.72; 1.05]	0.146	0.171
Non-use	158	116 (73.4)	159	113 (71.1)	1.03 [0.90; 1.18]	0.641	
Region							
Germany	21	14 (66.7)	23	18 (78.3)	0.81 [0.57; 1.17]	0.266	0.475
Rest of the World	268	178 (66.4)	274	187 (68.2)	0.97 [0.86; 1.09]	0.631	

a: Database Lock Date: 27JUL2022

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 use of induction therapy (use vs. non-use), where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively. Approach to handling missing values is the Observed Failure (OF) approach, where participants who discontinue prematurely from the study for any reason are not considered failures.

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

e: Based on a generalized linear model stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Analysis is performed through 52 weeks

CI: Confidence Interval

Tabelle 4G-9: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt ≥ 20 % Rückgang der post-Transplant eGFR von Woche 4 bis Woche 28 nach Transplantation aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction[e]
≥20% Decline in Post-transplant eGFR From 4 weeks Post-Transplant	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Test
Sex							
Male	210	44 (21.0)	209	47 (22.5)	0.92 [0.64; 1.33]	0.659	0.631
Female	79	18 (22.8)	88	25 (28.4)	0.81 [0.48; 1.36]	0.429	
Age Group (Years)							
< 65	242	54 (22.3)	242	62 (25.6)	0.87 [0.64; 1.20]	0.404	0.857
≥ 65	47	8 (17.0)	55	10 (18.2)	0.87 [0.35; 2.15]	0.763	
Induction Therapy							
Use	131	17 (13.0)	138	31 (22.5)	0.58 [0.34; 0.99]	0.047	0.052

Non-use	158	45 (28.5)	159	41 (25.8)	1.10 [0.77; 1.59]	0.590	
Region							
Germany	21	5 (23.8)	23	4 (17.4)	1.31 [0.41; 4.22]	0.652	0.443
Rest of the World	268	57 (21.3)	274	68 (24.8)	0.85 [0.63; 1.16]	0.310	

a: Database Lock Date: 27JUL2022

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 use of induction therapy (use vs. non-use), where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively. Approach to handling missing values is the Observed Failure (OF) approach, where participants who discontinue prematurely from the study for any reason are not considered failures.

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

e: Based on a generalized linear model stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Analysis is performed through 28 weeks

CI: Confidence Interval

Tabelle 4G-10: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Akute Nierentransplantatabstoßung aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	**Letermovir**		**Valganciclovir**		**Letermovir vs. Valganciclovir**		**p-Value for Interaction[e]**
Biopsy-Proven Acute Renal Graft Rejection	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**Test**
Sex							
Male	210	18 (8.6)	209	12 (5.7)	1.47 [0.73; 2.95]	0.284	0.239
Female	79	5 (6.3)	88	8 (9.1)	0.71 [0.24; 2.06]	0.526	
Induction Therapy							
Use	131	6 (4.6)	138	7 (5.1)	0.90 [0.31; 2.62]	0.851	0.551
Non-use	158	17 (10.8)	159	13 (8.2)	1.32 [0.66; 2.62]	0.434	
Region							
Germany	21	3 (14.3)	23	3 (13.0)	1.05 [0.24; 4.62]	0.951	0.922
Rest of the World	268	20 (7.5)	274	17 (6.2)	1.20 [0.64; 2.23]	0.575	

a: Database Lock Date: 27JUL2022

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 use of induction therapy (use vs. non-use), where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively. Approach to handling missing values is the Observed Failure (OF) approach, where participants who discontinue prematurely from the study for any reason are not considered failures.

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

e: Based on a generalized linear model stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Analysis is performed through 52 weeks

CI: Confidence Interval

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

Study: MK-8228-002[a]	**Letermovir**		**Valganciclovir**		**Letermovir vs. Valganciclovir**		**p-Value for Interaction[e]**
Graft Loss	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**Test**

Sex							
Male	210	2 (1.0)	209	4 (1.9)	n.c.	n.c.	n.c.
Female	79	0 (0.0)	88	2 (2.3)	n.c.	n.c.	
Age Group (Years)							
< 65	242	2 (0.8)	242	5 (2.1)	n.c.	n.c.	n.c.
≥ 65	47	0 (0.0)	55	1 (1.8)	n.c.	n.c.	
Induction Therapy							
Use	131	1 (0.8)	138	3 (2.2)	n.c.	n.c.	n.c.
Non-use	158	1 (0.6)	159	3 (1.9)	n.c.	n.c.	
Region							
Germany	21	0 (0.0)	23	1 (4.3)	n.c.	n.c.	n.c.
Rest of the World	268	2 (0.7)	274	5 (1.8)	n.c.	n.c.	

a: Database Lock Date: 27JUL2022

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 use of induction therapy (use vs. non-use), where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively. Approach to handling missing values is the Observed Failure (OF) approach, where participants who discontinue prematurely from the study for any reason are not considered failures.

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

e: Based on a generalized linear model stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Analysis is performed through 52 weeks

CI: Confidence Interval; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary

Tabelle 4G-12: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt eGFR < 60ml/min/1.73m^2 bis Woche 28 nach Transplantation aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	**Letermovir**		**Valganciclovir**		**Letermovir vs. Valganciclovir**		
eGFR <60 mL/min/1.73m^2	**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**
Sex							
Male	210	120 (57.1)	209	127 (60.8)	0.94 [0.80; 1.10]	0.425	0.953
Female	79	48 (60.8)	88	57 (64.8)	0.94 [0.74; 1.19]	0.606	
Age Group (Years)							
< 65	242	135 (55.8)	242	145 (59.9)	0.93 [0.80; 1.08]	0.364	0.774
≥ 65	47	33 (70.2)	55	39 (70.9)	0.99 [0.77; 1.27]	0.924	
Induction Therapy							
Use	131	70 (53.4)	138	81 (58.7)	0.91 [0.74; 1.13]	0.386	0.779
Non-use	158	98 (62.0)	159	103 (64.8)	0.96 [0.81; 1.13]	0.611	
Region							
Germany	21	13 (61.9)	23	17 (73.9)	0.80 [0.53; 1.20]	0.283	0.527
Rest of the World	268	155 (57.8)	274	167 (60.9)	0.95 [0.82; 1.09]	0.451	

a: Database Lock Date: 27JUL2022

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 use of induction therapy (use vs. non-use), where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively. Approach to handling missing values is the Observed Failure (OF) approach, where participants who discontinue prematurely from the study for any reason are not considered failures.

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

e: Based on a generalized linear model stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and

treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Analysis is performed through 28 weeks

CI: Confidence Interval

Neu aufgetretener Diabetes mellitus nach Transplantation (NODAT)

Tabelle 4G-13: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Neu aufgetretener Diabetes mellitus nach Transplantation (NODAT) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
New Onset Diabetes Mellitus	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
Sex							
Male	210	14 (6.7)	209	16 (7.7)	0.85 [0.43; 1.68]	0.643	0.749
Female	79	4 (5.1)	88	4 (4.5)	1.12 [0.28; 4.54]	0.870	
Region							
Germany	21	0 (0.0)	23	2 (8.7)	0.14 [0.01; 2.23]	0.162	0.105
Rest of the World	268	18 (6.7)	274	18 (6.6)	1.01 [0.51; 2.00]	0.969	

a: Database Lock Date: 27JUL2022

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 use of induction therapy (use vs. non-use), where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively. Approach to handling missing values is the Observed Failure (OF) approach, where participants who discontinue prematurely from the study for any reason are not considered failures.

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

e: Based on a generalized linear model stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Analysis is performed through 52 weeks

CI: Confidence Interval

Wiedereinweisung ins Krankenhaus

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

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
All Cause Re-Hospitalization	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
Sex							
Male	210	91 (43.3)	209	106 (50.7)	0.86 [0.70; 1.05]	0.141	0.841
Female	79	36 (45.6)	88	45 (51.1)	0.89 [0.65; 1.23]	0.488	
Age Group (Years)							
< 65	242	103 (42.6)	242	113 (46.7)	0.91 [0.75; 1.11]	0.355	0.186
≥ 65	47	24 (51.1)	55	38 (69.1)	0.73 [0.52; 1.02]	0.067	
Induction Therapy							
Use	131	60 (45.8)	138	73 (52.9)	0.87 [0.68; 1.10]	0.247	0.962
Non-use	158	67 (42.4)	159	78 (49.1)	0.86 [0.68; 1.10]	0.236	
Region							
Germany	21	12 (57.1)	23	12 (52.2)	1.14 [0.65; 2.00]	0.639	0.414
Rest of the World	268	115 (42.9)	274	139 (50.7)	0.85 [0.71; 1.01]	0.071	

a: Database Lock Date: 27JUL2022

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 use of induction therapy (use vs. non-use), where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively. Approach to handling missing values is the Observed Failure (OF) approach, where participants who discontinue prematurely from the study for any reason are not considered failures.

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

e: Based on a generalized linear model stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Analysis is performed through 52 weeks

CI: Confidence Interval

Wiedereinweisung ins Krankenhaus wegen einer CMV-Erkrankung

Tabelle 4G-15: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Wiedereinweisung ins Krankenhaus wegen einer CMV-Erkrankung aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
Re-Hospitalization for CMV 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
Sex							
Male	210	27 (12.9)	209	29 (13.9)	0.93 [0.57; 1.52]	0.776	0.273
Female	79	8 (10.1)	88	5 (5.7)	1.77 [0.61; 5.18]	0.294	
Age Group (Years)							
< 65	242	31 (12.8)	242	24 (9.9)	1.29 [0.78; 2.13]	0.321	0.083
≥ 65	47	4 (8.5)	55	10 (18.2)	0.46 [0.15; 1.41]	0.174	
Induction Therapy							
Use	131	16 (12.2)	138	19 (13.8)	0.89 [0.48; 1.65]	0.705	0.426

Non-use	158	19 (12.0)	159	15 (9.4)	1.27 [0.67; 2.42]	0.457	
Region							
Germany	21	2 (9.5)	23	2 (8.7)	1.05 [0.16; 6.77]	0.961	0.971
Rest of the World	268	33 (12.3)	274	32 (11.7)	1.06 [0.67; 1.67]	0.814	

a: Database Lock Date: 27JUL2022

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 use of induction therapy (use vs. non-use), where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively. Approach to handling missing values is the Observed Failure (OF) approach, where participants who discontinue prematurely from the study for any reason are not considered failures.

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

e: Based on a generalized linear model stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Analysis is performed through 52 weeks

CI: Confidence Interval; CMV: cytomegalovirus

Gabe von G-CSF

Tabelle 4G-16: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gabe von G-CSF aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction[e]
Use of G-CSF	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Test
Sex							
Male	210	11 (5.2)	209	38 (18.2)	0.29 [0.16; 0.56]	< 0.001	0.144
Female	79	10 (12.7)	88	18 (20.5)	0.61 [0.30; 1.25]	0.176	
Age Group (Years)							
< 65	242	18 (7.4)	242	47 (19.4)	0.38 [0.23; 0.64]	< 0.001	0.954
≥ 65	47	3 (6.4)	55	9 (16.4)	0.45 [0.14; 1.45]	0.181	
Induction Therapy							
Use	131	14 (10.7)	138	32 (23.2)	0.46 [0.26; 0.82]	0.009	0.455
Non-use	158	7 (4.4)	159	24 (15.1)	0.29 [0.13; 0.66]	0.003	
Region							
Germany	21	0 (0.0)	23	0 (0.0)	n.a. [n.a.; n.a.]	n.a.	> 0.999
Rest of the World	268	21 (7.8)	274	56 (20.4)	0.36 [0.22; 0.58]	< 0.001	

a: Database Lock Date: 27JUL2022

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 use of induction therapy (use vs. non-use), where the common Odds Ratio and common Risk Ratio across strata are calculated using the Peto method and the Mantel-Haenszel method, respectively. Approach to handling missing values is the Observed Failure (OF) approach, where participants who discontinue prematurely from the study for any reason are not considered failures.

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

e: Based on a generalized linear model stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Analysis is performed during whole study

CI: Confidence Interval; G-CSF: Granulocyte Colony-Stimulating Factor; n.a.: not applicable (when estimation not possible)

Gesundheitszustand anhand der EQ-5D VAS

Tabelle 4G-17: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction[e]
EQ-5D VAS	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Test
Sex							
Male	208	73 (35.1)	207	73 (35.3)	0.99 [0.76; 1.29]	0.960	0.418
Female	76	27 (35.5)	87	25 (28.7)	1.24 [0.79; 1.95]	0.341	
Age Group (Years)							
< 65	238	88 (37.0)	241	90 (37.3)	0.99 [0.79; 1.25]	0.939	0.193
≥ 65	46	12 (26.1)	53	8 (15.1)	1.66 [0.76; 3.64]	0.204	
Induction Therapy							
Use	130	44 (33.8)	137	43 (31.4)	1.08 [0.76; 1.52]	0.668	0.878
Non-use	154	56 (36.4)	157	55 (35.0)	1.04 [0.77; 1.40]	0.806	
Region							
Germany	21	8 (38.1)	23	9 (39.1)	0.93 [0.44; 1.95]	0.851	0.830
Rest of the World	263	92 (35.0)	271	89 (32.8)	1.06 [0.84; 1.35]	0.604	

a: Database Lock Date: 27JUL2022

b: Number of participants: PRO full-analysis-set population with at least one assessment for the considered PRO instrument

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by use of induction therapy (use vs. non-use) 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 use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Responder is defined as participant who experience an improvement at week 52 in endpoint score of at least 1 MID (≥ 15% of the scale range) compared to baseline. An improvement corresponds to a positive change (> 0) from Baseline

CI: Confidence Interval; EQ-5D VAS: European Quality of Life 5 Dimensions Visual Analogue Scale; MID: Minimal Important Difference

Anhang 4-G2.3: Gesundheitsbezogene Lebensqualität

SF-36v2: Subskala Körperliche Funktionsfähigkeit

Tabelle 4G-18: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Subskala Körperliche Funktionsfähigkeit des SF-36v2 aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
SF-36 Physical Functioning	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
Sex							
Male	208	96 (46.2)	207	98 (47.3)	0.97 [0.79; 1.19]	0.775	0.728
Female	76	40 (52.6)	85	43 (50.6)	1.05 [0.78; 1.41]	0.762	
Age Group (Years)							
< 65	238	117 (49.2)	241	125 (51.9)	0.95 [0.80; 1.13]	0.566	0.242
≥ 65	46	19 (41.3)	51	16 (31.4)	1.29 [0.76; 2.21]	0.347	
Induction Therapy							
Use	130	54 (41.5)	136	62 (45.6)	0.91 [0.69; 1.20]	0.506	0.423
Non-use	154	82 (53.2)	156	79 (50.6)	1.05 [0.85; 1.30]	0.646	
Region							
Germany	21	12 (57.1)	22	12 (54.5)	1.00 [0.59; 1.69]	> 0.999	0.838
Rest of the World	263	124 (47.1)	270	129 (47.8)	0.99 [0.82; 1.18]	0.876	

a: Database Lock Date: 27JUL2022

b: Number of participants: PRO full-analysis-set population with at least one assessment for the considered PRO instrument

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by use of induction therapy (use vs. non-use) 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 use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Responder is defined as participant who experience an improvement at week 52 in endpoint score of at least 1 MID (≥ 15% of the scale range) compared to baseline. An improvement corresponds to a positive change (> 0) from Baseline

CI: Confidence Interval; MID: Minimal Important Difference; SF-36: 36-items Short Form Health Survey

SF-36v2: Subskala Körperliche Rollenfunktion

Tabelle 4G-19: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Subskala Körperliche Rollenfunktion des SF-36v2 aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction[e]
SF-36 Role Physical	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Test
Sex							
Male	208	87 (41.8)	207	83 (40.1)	1.04 [0.83; 1.31]	0.739	0.447
Female	76	38 (50.0)	85	35 (41.2)	1.21 [0.87; 1.71]	0.261	
Age Group (Years)							
< 65	238	109 (45.8)	241	104 (43.2)	1.06 [0.87; 1.30]	0.549	0.621
≥ 65	46	16 (34.8)	51	14 (27.5)	1.32 [0.71; 2.44]	0.378	
Induction Therapy							
Use	130	53 (40.8)	136	54 (39.7)	1.03 [0.77; 1.38]	0.860	0.578
Non-use	154	72 (46.8)	156	64 (41.0)	1.14 [0.89; 1.47]	0.311	
Region							
Germany	21	7 (33.3)	22	6 (27.3)	1.17 [0.47; 2.89]	0.739	0.828
Rest of the World	263	118 (44.9)	270	112 (41.5)	1.08 [0.89; 1.31]	0.434	

a: Database Lock Date: 27JUL2022

b: Number of participants: PRO full-analysis-set population with at least one assessment for the considered PRO instrument

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by use of induction therapy (use vs. non-use) 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 use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Responder is defined as participant who experience an improvement at week 52 in endpoint score of at least 1 MID (≥ 15% of the scale range) compared to baseline. An improvement corresponds to a positive change (> 0) from Baseline

CI: Confidence Interval; MID: Minimal Important Difference; SF-36: 36-items Short Form Health Survey

SF-36v2: Subskala Körperliche Schmerzen

Tabelle 4G-20: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Subskala Körperliche Schmerzen des SF-36v2 aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
SF-36 Bodily Pain	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
Sex							
Male	208	89 (42.8)	207	78 (37.7)	1.13 [0.90; 1.43]	0.298	0.854
Female	76	30 (39.5)	85	28 (32.9)	1.21 [0.80; 1.83]	0.373	
Age Group (Years)							
< 65	238	104 (43.7)	241	93 (38.6)	1.13 [0.91; 1.41]	0.251	0.780
≥ 65	46	15 (32.6)	51	13 (25.5)	1.31 [0.69; 2.46]	0.407	
Induction Therapy							
Use	130	55 (42.3)	136	43 (31.6)	1.34 [0.97; 1.84]	0.073	0.231
Non-use	154	64 (41.6)	156	63 (40.4)	1.03 [0.79; 1.34]	0.834	
Region							
Germany	21	4 (19.0)	22	8 (36.4)	0.50 [0.18; 1.41]	0.190	0.094
Rest of the World	263	115 (43.7)	270	98 (36.3)	1.20 [0.98; 1.48]	0.082	

a: Database Lock Date: 27JUL2022

b: Number of participants: PRO full-analysis-set population with at least one assessment for the considered PRO instrument

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by use of induction therapy (use vs. non-use) 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 use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Responder is defined as participant who experience an improvement at week 52 in endpoint score of at least 1 MID (≥ 15% of the scale range) compared to baseline. An improvement corresponds to a positive change (> 0) from Baseline

CI: Confidence Interval; MID: Minimal Important Difference; SF-36: 36-items Short Form Health Survey

SF-36v2: Subskala Allgemeine Gesundheitswahrnehmung

Tabelle 4G-21: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Subskala Allgemeine Gesundheitswahrnehmung des SF-36v2 aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
SF-36 General Health	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
Sex							
Male	208	64 (30.8)	207	52 (25.1)	1.22 [0.89; 1.66]	0.210	0.995
Female	76	24 (31.6)	85	22 (25.9)	1.21 [0.74; 1.98]	0.437	
Age Group (Years)							
< 65	238	76 (31.9)	241	66 (27.4)	1.17 [0.89; 1.54]	0.273	0.439
≥ 65	46	12 (26.1)	51	8 (15.7)	1.67 [0.76; 3.67]	0.201	
Induction Therapy							
Use	130	41 (31.5)	136	31 (22.8)	1.38 [0.93; 2.06]	0.111	0.420
Non-use	154	47 (30.5)	156	43 (27.6)	1.11 [0.78; 1.57]	0.567	
Region							
Germany	21	5 (23.8)	22	6 (27.3)	0.83 [0.30; 2.31]	0.726	0.494
Rest of the World	263	83 (31.6)	270	68 (25.2)	1.25 [0.95; 1.64]	0.105	

a: Database Lock Date: 27JUL2022

b: Number of participants: PRO full-analysis-set population with at least one assessment for the considered PRO instrument

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by use of induction therapy (use vs. non-use) 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 use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Responder is defined as participant who experience an improvement at week 52 in endpoint score of at least 1 MID (≥ 15% of the scale range) compared to baseline. An improvement corresponds to a positive change (> 0) from Baseline

CI: Confidence Interval; MID: Minimal Important Difference; SF-36: 36-items Short Form Health Survey

SF-36v2: Subskala Vitalität

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Subskala Vitalität des SF-36v2 aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction[e]
SF-36 Vitality	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Test
Sex							
Male	208	85 (40.9)	207	69 (33.3)	1.22 [0.95; 1.57]	0.122	0.707
Female	76	30 (39.5)	85	30 (35.3)	1.11 [0.75; 1.66]	0.598	
Age Group (Years)							
< 65	238	101 (42.4)	241	86 (35.7)	1.19 [0.95; 1.49]	0.128	0.938
≥ 65	46	14 (30.4)	51	13 (25.5)	1.19 [0.62; 2.27]	0.599	
Induction Therapy							
Use	130	47 (36.2)	136	46 (33.8)	1.07 [0.77; 1.48]	0.690	0.347
Non-use	154	68 (44.2)	156	53 (34.0)	1.30 [0.98; 1.72]	0.068	
Region							
Germany	21	5 (23.8)	22	7 (31.8)	0.71 [0.27; 1.89]	0.499	0.300
Rest of the World	263	110 (41.8)	270	92 (34.1)	1.23 [0.99; 1.53]	0.067	

a: Database Lock Date: 27JUL2022

b: Number of participants: PRO full-analysis-set population with at least one assessment for the considered PRO instrument

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by use of induction therapy (use vs. non-use) 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 use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Responder is defined as participant who experience an improvement at week 52 in endpoint score of at least 1 MID (≥ 15% of the scale range) compared to baseline. An improvement corresponds to a positive change (> 0) from Baseline

CI: Confidence Interval; MID: Minimal Important Difference; SF-36: 36-items Short Form Health Survey

SF-36v2: Subskala Soziale Funktionsfähigkeit

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Subskala Soziale Funktionsfähigkeit des SF-36v2 aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
SF-36 Social Functioning	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
Sex							
Male	208	66 (31.7)	207	63 (30.4)	1.04 [0.78; 1.38]	0.799	0.598
Female	76	22 (28.9)	85	20 (23.5)	1.23 [0.73; 2.07]	0.432	
Age Group (Years)							
< 65	238	76 (31.9)	241	76 (31.5)	1.01 [0.78; 1.32]	0.914	0.161
≥ 65	46	12 (26.1)	51	7 (13.7)	1.99 [0.82; 4.82]	0.125	
Induction Therapy							
Use	130	36 (27.7)	136	37 (27.2)	1.02 [0.69; 1.50]	0.929	0.637
Non-use	154	52 (33.8)	156	46 (29.5)	1.15 [0.82; 1.59]	0.419	
Region							
Germany	21	4 (19.0)	22	8 (36.4)	0.50 [0.18; 1.41]	0.190	0.131
Rest of the World	263	84 (31.9)	270	75 (27.8)	1.15 [0.88; 1.49]	0.297	

a: Database Lock Date: 27JUL2022

b: Number of participants: PRO full-analysis-set population with at least one assessment for the considered PRO instrument

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by use of induction therapy (use vs. non-use) 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 use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Responder is defined as participant who experience an improvement at week 52 in endpoint score of at least 1 MID (≥ 15% of the scale range) compared to baseline. An improvement corresponds to a positive change (> 0) from Baseline

CI: Confidence Interval; MID: Minimal Important Difference; SF-36: 36-items Short Form Health Survey

SF-36v2: Subskala Emotionale Rollenfunktion

Tabelle 4G-24: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Subskala Emotionale Rollenfunktion des SF-36v2 aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction[e]
SF-36 Role Emotional	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Test
Sex							
Male	208	46 (22.1)	207	43 (20.8)	1.06 [0.73; 1.53]	0.752	0.762
Female	76	18 (23.7)	85	17 (20.0)	1.19 [0.66; 2.13]	0.558	
Age Group (Years)							
< 65	238	57 (23.9)	241	51 (21.2)	1.13 [0.81; 1.58]	0.457	0.569
≥ 65	46	7 (15.2)	51	9 (17.6)	0.89 [0.34; 2.28]	0.803	
Induction Therapy							
Use	130	25 (19.2)	136	28 (20.6)	0.93 [0.58; 1.51]	0.782	0.382
Non-use	154	39 (25.3)	156	32 (20.5)	1.23 [0.82; 1.86]	0.315	
Region							
Germany	21	3 (14.3)	22	6 (27.3)	0.50 [0.14; 1.74]	0.276	0.209
Rest of the World	263	61 (23.2)	270	54 (20.0)	1.16 [0.84; 1.60]	0.374	

a: Database Lock Date: 27JUL2022

b: Number of participants: PRO full-analysis-set population with at least one assessment for the considered PRO instrument

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by use of induction therapy (use vs. non-use) 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 use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Responder is defined as participant who experience an improvement at week 52 in endpoint score of at least 1 MID (≥ 15% of the scale range) compared to baseline. An improvement corresponds to a positive change (> 0) from Baseline

CI: Confidence Interval; MID: Minimal Important Difference; SF-36: 36-items Short Form Health Survey

SF-36v2: Subskala Psychisches Wohlbefinden

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Subskala Psychisches Wohlbefinden des SF-36v2 aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
SF-36 Mental Health	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
Sex							
Male	208	50 (24.0)	207	49 (23.7)	1.01 [0.72; 1.42]	0.966	0.657
Female	76	19 (25.0)	85	18 (21.2)	1.18 [0.67; 2.07]	0.571	
Age Group (Years)							
< 65	238	63 (26.5)	241	57 (23.7)	1.12 [0.82; 1.53]	0.465	0.284
≥ 65	46	6 (13.0)	51	10 (19.6)	0.69 [0.27; 1.73]	0.425	
Induction Therapy							
Use	130	29 (22.3)	136	27 (19.9)	1.12 [0.71; 1.79]	0.624	0.743
Non-use	154	40 (26.0)	156	40 (25.6)	1.01 [0.69; 1.48]	0.947	
Region							
Germany	21	3 (14.3)	22	7 (31.8)	0.43 [0.13; 1.44]	0.170	0.125
Rest of the World	263	66 (25.1)	270	60 (22.2)	1.13 [0.83; 1.53]	0.439	

a: Database Lock Date: 27JUL2022

b: Number of participants: PRO full-analysis-set population with at least one assessment for the considered PRO instrument

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by use of induction therapy (use vs. non-use) 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 use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Responder is defined as participant who experience an improvement at week 52 in endpoint score of at least 1 MID (≥ 15% of the scale range) compared to baseline. An improvement corresponds to a positive change (> 0) from Baseline

CI: Confidence Interval; MID: Minimal Important Difference; SF-36: 36-items Short Form Health Survey

SF-36v2: Körperlicher Summenscore

Tabelle 4G-26: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Körperlichen Summenscore des SF-36v2 aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
SF-36 Physical Component Summary	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
Sex							
Male	208	85 (40.9)	207	73 (35.3)	1.15 [0.90; 1.47]	0.260	0.411
Female	76	35 (46.1)	85	28 (32.9)	1.41 [0.96; 2.08]	0.081	
Age Group (Years)							
< 65	238	105 (44.1)	241	92 (38.2)	1.16 [0.94; 1.43]	0.176	0.268
≥ 65	46	15 (32.6)	51	9 (17.6)	1.85 [0.90; 3.81]	0.096	
Induction Therapy							
Use	130	47 (36.2)	136	42 (30.9)	1.17 [0.83; 1.64]	0.363	0.653
Non-use	154	73 (47.4)	156	59 (37.8)	1.25 [0.97; 1.63]	0.090	
Region							
Germany	21	9 (42.9)	22	10 (45.5)	0.90 [0.46; 1.75]	0.757	0.465
Rest of the World	263	111 (42.2)	270	91 (33.7)	1.25 [1.01; 1.56]	0.045	

a: Database Lock Date: 27JUL2022

b: Number of participants: PRO full-analysis-set population with at least one assessment for the considered PRO instrument

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by use of induction therapy (use vs. non-use) 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 use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Responder is defined as participant who experience an improvement at week 52 in endpoint score of at least 1 MID (≥ 15% of the scale range) compared to baseline. An improvement corresponds to a positive change (> 0) from Baseline

CI: Confidence Interval; MID: Minimal Important Difference; SF-36: 36-items Short Form Health Survey

SF-36v2: Psychischer Summenscore

Tabelle 4G-27: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Psychischen Summenscore des SF-36v2 aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction[e]
SF-36 Mental Component Summary	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Test
Sex							
Male	208	23 (11.1)	207	33 (15.9)	0.69 [0.42; 1.14]	0.148	0.425
Female	76	10 (13.2)	85	11 (12.9)	1.00 [0.45; 2.22]	0.992	
Induction Therapy							
Use	130	16 (12.3)	136	21 (15.4)	0.80 [0.44; 1.46]	0.462	0.890
Non-use	154	17 (11.0)	156	23 (14.7)	0.75 [0.42; 1.35]	0.333	
Region							
Germany	21	1 (4.8)	22	3 (13.6)	0.33 [0.04; 2.95]	0.323	0.443
Rest of the World	263	32 (12.2)	270	41 (15.2)	0.80 [0.52; 1.23]	0.313	

a: Database Lock Date: 27JUL2022

b: Number of participants: PRO full-analysis-set population with at least one assessment for the considered PRO instrument

c: Peto-Odds Ratio instead of Risk Ratio if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by use of induction therapy (use vs. non-use) 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 use of induction therapy (use vs. non-use), with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction test for interaction term). For the subgroup induction therapy which is the stratification factor, an unstratified model is used.

Responder is defined as participant who experience an improvement at week 52 in endpoint score of at least 1 MID (≥ 15% of the scale range) compared to baseline. An improvement corresponds to a positive change (> 0) from Baseline

CI: Confidence Interval; MID: Minimal Important Difference; SF-36: 36-items Short Form Health Survey

Anhang 4-G2.4: Nebenwirkungen

Unerwünschte Ereignisse Gesamtraten

Unerwünschte Ereignisse gesamt

Tabelle 4G-28: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction Test[e]
	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	p-Value[d]	
Adverse Events							
Sex							
Male	213	198 (92.96)	209	194 (92.82)	1.00 [0.95; 1.06]	0.957	0.991
Female	79	72 (91.14)	88	80 (90.91)	1.00 [0.91; 1.10]	0.959	
Age Group (Years)							
< 65	244	224 (91.80)	242	224 (92.56)	0.99 [0.94; 1.04]	0.756	0.301
≥ 65	48	46 (95.83)	55	50 (90.91)	1.05 [0.95; 1.17]	0.324	
Induction Therapy							
Use	134	127 (94.78)	138	128 (92.75)	1.02 [0.96; 1.09]	0.492	0.425
Non-use	158	143 (90.51)	159	146 (91.82)	0.99 [0.92; 1.06]	0.680	
Region							
Germany	21	19 (90.48)	23	22 (95.65)	0.95 [0.80; 1.11]	0.501	0.465
Rest of the World	271	251 (92.62)	274	252 (91.97)	1.01 [0.96; 1.06]	0.777	

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

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

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

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

CI: Confidence Interval; n.a.: not applicable (when estimation not possible)

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-29: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction Test[e]
	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	p-Value[d]	
Serious Adverse Events							
Sex							
Male	213	71 (33.33)	209	71 (33.97)	0.98 [0.75; 1.28]	0.890	0.933
Female	79	27 (34.18)	88	30 (34.09)	1.00 [0.66; 1.53]	0.991	
Age Group (Years)							
< 65	244	81 (33.20)	242	78 (32.23)	1.03 [0.80; 1.33]	0.821	0.485

≥ 65	48	17 (35.42)	55	23 (41.82)	0.85 [0.52; 1.39]	0.508	
Induction Therapy							
Use	134	51 (38.06)	138	53 (38.41)	0.99 [0.73; 1.34]	0.953	0.985
Non-use	158	47 (29.75)	159	48 (30.19)	0.99 [0.70; 1.38]	0.932	
Region							
Germany	21	9 (42.86)	23	5 (21.74)	1.97 [0.79; 4.94]	0.138	0.111
Rest of the World	271	89 (32.84)	274	96 (35.04)	0.94 [0.74; 1.19]	0.589	

a: Database Lock Date: 27JUL2022
b: Number of participants: all-participants-as-treated population
c: Based on 2x2 contingency table, using Wald confidence interval. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'
d: Based on Cochran-Mantel-Haenszel test. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'
e: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'
CI: Confidence Interval; n.a.: not applicable (when estimation not possible)

Schwere unerwünschte Ereignisse

Tabelle 4G-30: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	**Letermovir**		**Valganciclovir**		**Letermovir vs. Valganciclovir**		**p-Value for Interaction Test[e]**
	N[b]	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	
Severe Adverse Events[f]							
Sex							
Male	213	60 (28.17)	209	70 (33.49)	0.84 [0.63; 1.12]	0.237	0.370
Female	79	26 (32.91)	88	27 (30.68)	1.07 [0.69; 1.67]	0.758	
Age Group (Years)							
< 65	244	66 (27.05)	242	72 (29.75)	0.91 [0.69; 1.21]	0.509	0.962
≥ 65	48	20 (41.67)	55	25 (45.45)	0.92 [0.59; 1.43]	0.700	
Induction Therapy							
Use	134	45 (33.58)	138	53 (38.41)	0.87 [0.64; 1.20]	0.408	0.734
Non-use	158	41 (25.95)	159	44 (27.67)	0.94 [0.65; 1.35]	0.729	
Region							
Germany	21	6 (28.57)	23	7 (30.43)	0.94 [0.38; 2.35]	0.894	0.924
Rest of the World	271	80 (29.52)	274	90 (32.85)	0.90 [0.70; 1.15]	0.402	

a: Database Lock Date: 27JUL2022
b: Number of participants: all-participants-as-treated population
c: Based on 2x2 contingency table, using Wald confidence interval. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'
d: Based on Cochran-Mantel-Haenszel test. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'
e: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'
f: Severe adverse events are defined as per investigator assessment (severe)
CI: Confidence Interval; n.a.: not applicable (when estimation not possible)

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-31: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction Test[e]
	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	p-Value[d]	
Adverse Events Leading to Treatment Discontinuation							
Age Group (Years)							
< 65	244	7 (2.87)	242	25 (10.33)	0.28 [0.12; 0.63]	0.001	0.410
≥ 65	48	5 (10.42)	55	11 (20.00)	0.52 [0.19; 1.39]	0.183	
Induction Therapy							
Use	134	6 (4.48)	138	21 (15.22)	0.29 [0.12; 0.71]	0.003	0.589
Non-use	158	6 (3.80)	159	15 (9.43)	0.40 [0.16; 1.01]	0.044	
Region							
Germany	21	1 (4.76)	23	3 (13.04)	0.37 [0.04; 3.24]	0.345	0.952
Rest of the World	271	11 (4.06)	274	33 (12.04)	0.34 [0.17; 0.65]	0.001	

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

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

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

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

CI: Confidence Interval; n.a.: not applicable (when estimation not possible)

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-32: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction Test[e]
Adverse Events	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	p-Value[d]	
SOC[f]: Blood and lymphatic system disorders							
Sex							
Male	213	47 (22.07)	209	99 (47.37)	0.47 [0.35; 0.62]	<0.001	0.173
Female	79	29 (36.71)	88	46 (52.27)	0.70 [0.49; 1.00]	0.044	
Age Group (Years)							
< 65	244	59 (24.18)	242	115 (47.52)	0.51 [0.39; 0.66]	<0.001	0.563
≥ 65	48	17 (35.42)	55	30 (54.55)	0.65 [0.41; 1.02]	0.053	
Induction Therapy							
Use	134	37 (27.61)	138	75 (54.35)	0.51 [0.37; 0.70]	<0.001	0.459
Non-use	158	39 (24.68)	159	70 (44.03)	0.56 [0.41; 0.78]	<0.001	
Region							

Germany	21	8 (38.10)	23	13 (56.52)	0.67 [0.35; 1.29]	0.227	0.671
Rest of the World	271	68 (25.09)	274	132 (48.18)	0.52 [0.41; 0.66]	<0.001	
SOC[f]: Nervous system disorders							
Sex							
Male	213	67 (31.46)	209	52 (24.88)	1.26 [0.93; 1.72]	0.134	0.506
Female	79	37 (46.84)	88	29 (32.95)	1.42 [0.97; 2.08]	0.068	
Age Group (Years)							
< 65	244	78 (31.97)	242	62 (25.62)	1.25 [0.94; 1.65]	0.123	0.273
≥ 65	48	26 (54.17)	55	19 (34.55)	1.57 [1.00; 2.45]	0.046	
Induction Therapy							
Use	134	52 (38.81)	138	40 (28.99)	1.34 [0.96; 1.87]	0.088	0.789
Non-use	158	52 (32.91)	159	41 (25.79)	1.28 [0.90; 1.80]	0.164	
Region							
Germany	21	8 (38.10)	23	4 (17.39)	2.19 [0.77; 6.22]	0.128	0.314
Rest of the World	271	96 (35.42)	274	77 (28.10)	1.26 [0.98; 1.62]	0.067	

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

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

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

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

f: A system organ class appears on this report only if its incidence ≥10% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05, and the interaction p-value is greater than or equal to 0.05 or rule of 10 is not met

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); PT: Preferred Term; SOC: System Organ Class

Tabelle 4G-33: 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: MK-8228-002[a]	**Letermovir**		**Valganciclovir**		**Letermovir vs. Valganciclovir**		
Adverse Events	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
SOC: Blood and lymphatic system disorders PT[f]: Leukocytosis							
Sex							
Male	213	9 (4.23)	209	4 (1.91)	2.21 [0.69; 7.06]	0.170	0.178
Female	79	4 (5.06)	88	0	n.a. [n.a.; n.a.]	n.a.	
Age Group (Years)							
< 65	244	11 (4.51)	242	4 (1.65)	2.73 [0.88; 8.45]	0.069	0.371
≥ 65	48	2 (4.17)	55	0	n.a. [n.a.; n.a.]	n.a.	
Induction Therapy							
Use	134	8 (5.97)	138	2 (1.45)	4.12 [0.89; 19.05]	0.048	0.653
Non-use	158	5 (3.16)	159	2 (1.26)	2.52 [0.50; 12.78]	0.249	
Region							
Germany	21	3 (14.29)	23	0	n.a. [n.a.; n.a.]	n.a.	0.252
Rest of the World	271	10 (3.69)	274	4 (1.46)	2.53 [0.80; 7.96]	0.100	
SOC: Blood and lymphatic system disorders PT[f]: Leukopenia							
Sex							

Male	213	22 (10.33)	209	77 (36.84)	0.28 [0.18; 0.43]	<0.001	0.511
Female	79	11 (13.92)	88	33 (37.50)	0.37 [0.20; 0.68]	0.001	
Age Group (Years)							
< 65	244	28 (11.48)	242	90 (37.19)	0.31 [0.21; 0.45]	<0.001	0.903
≥ 65	48	5 (10.42)	55	20 (36.36)	0.29 [0.12; 0.70]	0.002	
Induction Therapy							
Use	134	18 (13.43)	138	56 (40.58)	0.33 [0.21; 0.53]	<0.001	0.807
Non-use	158	15 (9.49)	159	54 (33.96)	0.28 [0.16; 0.47]	<0.001	
Region							
Germany	21	3 (14.29)	23	13 (56.52)	0.25 [0.08; 0.76]	0.004	0.465
Rest of the World	271	30 (11.07)	274	97 (35.40)	0.31 [0.22; 0.45]	<0.001	
SOC: Blood and lymphatic system disorders PT[f]: Neutropenia							
Sex							
Male	213	5 (2.35)	209	34 (16.27)	0.14 [0.06; 0.36]	<0.001	0.589
Female	79	3 (3.80)	88	15 (17.05)	0.22 [0.07; 0.74]	0.006	
Age Group (Years)							
< 65	244	5 (2.05)	242	41 (16.94)	0.12 [0.05; 0.30]	<0.001	0.105
≥ 65	48	3 (6.25)	55	8 (14.55)	0.43 [0.12; 1.53]	0.176	
Induction Therapy							
Use	134	3 (2.24)	138	24 (17.39)	0.13 [0.04; 0.42]	<0.001	0.551
Non-use	158	5 (3.16)	159	25 (15.72)	0.20 [0.08; 0.51]	<0.001	
Region							
Germany	21	0	23	1 (4.35)	n.a. [n.a.; n.a.]	n.a.	0.712
Rest of the World	271	8 (2.95)	274	48 (17.52)	0.17 [0.08; 0.35]	<0.001	
SOC: Investigations PT[f]: Immunosuppressant drug level increased							
Sex							
Male	213	7 (3.29)	209	2 (0.96)	n.c. [n.c.; n.c.]	n.c.	n.c.
Female	79	3 (3.80)	88	1 (1.14)	n.c. [n.c.; n.c.]	n.c.	
Age Group (Years)							
< 65	244	8 (3.28)	242	3 (1.24)	2.64 [0.71; 9.85]	0.131	0.366
≥ 65	48	2 (4.17)	55	0	n.a. [n.a.; n.a.]	n.a.	
Induction Therapy							
Use	134	8 (5.97)	138	3 (2.17)	2.75 [0.74; 10.13]	0.113	0.411
Non-use	158	2 (1.27)	159	0	n.a. [n.a.; n.a.]	n.a.	
Region							
Germany	21	0	23	0	n.a. [n.a.; n.a.]	n.a.	n.a.
Rest of the World	271	10 (3.69)	274	3 (1.09)	3.37 [0.94; 12.11]	0.047	
SOC: Investigations PT[f]: White blood cell count decreased							
Sex							
Male	213	2 (0.94)	209	12 (5.74)	0.16 [0.04; 0.72]	0.006	0.686
Female	79	1 (1.27)	88	4 (4.55)	0.28 [0.03; 2.44]	0.216	
Age Group (Years)							
< 65	244	3 (1.23)	242	10 (4.13)	0.30 [0.08; 1.07]	0.048	0.215
≥ 65	48	0	55	6 (10.91)	n.a. [n.a.; n.a.]	n.a.	
Induction Therapy							
Use	134	2 (1.49)	138	12 (8.70)	0.17 [0.04; 0.75]	0.007	0.747
Non-use	158	1 (0.63)	159	4 (2.52)	0.25 [0.03; 2.23]	0.179	

Region							
Germany	21	0	23	0	n.a. [n.a.; n.a.]	n.a.	n.a.
Rest of the World	271	3 (1.11)	274	16 (5.84)	0.19 [0.06; 0.64]	0.003	
SOC: Respiratory, thoracic and mediastinal disorders PT[f]: Dyspnoea							
Sex							
Male	213	4 (1.88)	209	16 (7.66)	0.25 [0.08; 0.72]	0.005	0.948
Female	79	1 (1.27)	88	5 (5.68)	0.22 [0.03; 1.87]	0.127	
Age Group (Years)							
< 65	244	3 (1.23)	242	16 (6.61)	0.19 [0.05; 0.63]	0.002	0.390
≥ 65	48	2 (4.17)	55	5 (9.09)	0.46 [0.09; 2.26]	0.324	
Induction Therapy							
Use	134	3 (2.24)	138	13 (9.42)	0.24 [0.07; 0.82]	0.012	0.927
Non-use	158	2 (1.27)	159	8 (5.03)	0.25 [0.05; 1.17]	0.056	

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

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

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

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

f: A system organ class appears on this report only if its incidence ≥10% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05, and the interaction p-value is greater than or equal to 0.05 or rule of 10 is not met

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term; SOC: System Organ Class

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-34: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	**Letermovir**		**Valganciclovir**		**Letermovir vs. Valganciclovir**		
Serious Adverse Events	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
SOC[f]: General disorders and administration site conditions							
Sex							
Male	213	7 (3.29)	209	2 (0.96)	n.c. [n.c.; n.c.]	n.c.	n.c.
Female	79	6 (7.59)	88	2 (2.27)	n.c. [n.c.; n.c.]	n.c.	
Age Group (Years)							
< 65	244	10 (4.10)	242	3 (1.24)	3.31 [0.92; 11.87]	0.051	0.967
≥ 65	48	3 (6.25)	55	1 (1.82)	3.44 [0.37; 31.96]	0.248	
Induction Therapy							
Use	134	7 (5.22)	138	2 (1.45)	n.c. [n.c.; n.c.]	n.c.	n.c.
Non-use	158	6 (3.80)	159	2 (1.26)	n.c. [n.c.; n.c.]	n.c.	
Region							
Germany	21	0	23	1 (4.35)	n.a. [n.a.; n.a.]	n.a.	0.070
Rest of the World	271	13 (4.80)	274	3 (1.09)	4.38 [1.26; 15.20]	0.011	

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

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

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

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

f: A system organ class appears on this report only if its incidence ≥5% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05, and the interaction p-value is greater than or equal to 0.05 or rule of 10 is not met

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term; SOC: System Organ Class

Schwere unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-35: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (SOC) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
Severe Adverse Events	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	p-Value[d]	p-Value for Interaction Test[e]
SOC[f]: Blood and lymphatic system disorders							
Sex							
Male	213	4 (1.88)	209	18 (8.61)	0.22 [0.08; 0.63]	0.002	0.247
Female	79	4 (5.06)	88	8 (9.09)	0.56 [0.17; 1.78]	0.316	
Age Group (Years)							
< 65	244	7 (2.87)	242	16 (6.61)	0.43 [0.18; 1.04]	0.052	0.183
≥ 65	48	1 (2.08)	55	10 (18.18)	0.11 [0.02; 0.86]	0.009	
Induction Therapy							
Use	134	6 (4.48)	138	16 (11.59)	0.39 [0.16; 0.96]	0.032	0.495
Non-use	158	2 (1.27)	159	10 (6.29)	0.20 [0.04; 0.90]	0.019	
Region							
Germany	21	1 (4.76)	23	1 (4.35)	1.10 [0.07; 16.43]	0.948	0.316
Rest of the World	271	7 (2.58)	274	25 (9.12)	0.28 [0.12; 0.64]	0.001	
SOC[f]: Injury, poisoning and procedural complications							
Sex							
Male	213	4 (1.88)	209	12 (5.74)	0.33 [0.11; 1.00]	0.038	0.600
Female	79	2 (2.53)	88	4 (4.55)	0.56 [0.10; 2.96]	0.486	
Age Group (Years)							
< 65	244	4 (1.64)	242	14 (5.79)	0.28 [0.09; 0.85]	0.016	0.198
≥ 65	48	2 (4.17)	55	2 (3.64)	1.15 [0.17; 7.83]	0.890	
Induction Therapy							
Use	134	2 (1.49)	138	9 (6.52)	0.23 [0.05; 1.04]	0.036	0.341
Non-use	158	4 (2.53)	159	7 (4.40)	0.58 [0.17; 1.93]	0.364	
Region							
Germany	21	1 (4.76)	23	4 (17.39)	0.27 [0.03; 2.26]	0.192	0.668
Rest of the World	271	5 (1.85)	274	12 (4.38)	0.42 [0.15; 1.18]	0.089	

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

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

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

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

f: A system organ class appears on this report only if its incidence ≥5% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05, and the interaction p-value is greater than or equal to 0.05 or rule of 10 is not met

Severe adverse events are defined as per investigator assessment (severe)

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); PT: Preferred Term; SOC: System Organ Class

Tabelle 4G-36: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (SOC und PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction Test[e]
Severe Adverse Events	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	p-Value[d]	
SOC: Blood and lymphatic system disorders PT[f]: Leukopenia							
Sex							
Male	213	1 (0.47)	209	10 (4.78)	0.10 [0.01; 0.76]	0.005	0.303
Female	79	2 (2.53)	88	6 (6.82)	0.37 [0.08; 1.79]	0.197	
Age Group (Years)							
< 65	244	3 (1.23)	242	9 (3.72)	0.33 [0.09; 1.21]	0.077	0.160
≥ 65	48	0	55	7 (12.73)	n.a. [n.a.; n.a.]	n.a.	
Induction Therapy							
Use	134	2 (1.49)	138	9 (6.52)	0.23 [0.05; 1.04]	0.036	0.734
Non-use	158	1 (0.63)	159	7 (4.40)	0.14 [0.02; 1.15]	0.033	
Region							
Germany	21	0	23	1 (4.35)	n.a. [n.a.; n.a.]	n.a.	0.669
Rest of the World	271	3 (1.11)	274	15 (5.47)	0.20 [0.06; 0.69]	0.004	

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

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

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

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

f: A system organ class appears on this report only if its incidence ≥5% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05, and the interaction p-value is greater than or equal to 0.05 or rule of 10 is not met

Severe adverse events are defined as per investigator assessment (severe)

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); PT: Preferred Term; SOC: System Organ Class

Unerwünschte Ereignisse von besonderem Interesse

Leukopenien und/oder Neutropenien gesamt (PT)

Tabelle 4G-37: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Leukopenien und/oder Neutropenien (PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
AEOSI	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
Leukopenia (Preferred Term)							
Sex							
Male	213	22 (10.33)	209	77 (36.84)	0.28 [0.18; 0.43]	<0.001	0.511
Female	79	11 (13.92)	88	33 (37.50)	0.37 [0.20; 0.68]	0.001	
Age Group (Years)							
< 65	244	28 (11.48)	242	90 (37.19)	0.31 [0.21; 0.45]	<0.001	0.903
≥ 65	48	5 (10.42)	55	20 (36.36)	0.29 [0.12; 0.70]	0.002	
Induction Therapy							
Use	134	18 (13.43)	138	56 (40.58)	0.33 [0.21; 0.53]	<0.001	0.807
Non-use	158	15 (9.49)	159	54 (33.96)	0.28 [0.16; 0.47]	<0.001	
Region							
Germany	21	3 (14.29)	23	13 (56.52)	0.25 [0.08; 0.76]	0.004	0.465
Rest of the World	271	30 (11.07)	274	97 (35.40)	0.31 [0.22; 0.45]	<0.001	
Neutropenia (Preferred Term)							
Sex							
Male	213	5 (2.35)	209	34 (16.27)	0.14 [0.06; 0.36]	<0.001	0.589
Female	79	3 (3.80)	88	15 (17.05)	0.22 [0.07; 0.74]	0.006	
Age Group (Years)							
< 65	244	5 (2.05)	242	41 (16.94)	0.12 [0.05; 0.30]	<0.001	0.105
≥ 65	48	3 (6.25)	55	8 (14.55)	0.43 [0.12; 1.53]	0.176	
Induction Therapy							
Use	134	3 (2.24)	138	24 (17.39)	0.13 [0.04; 0.42]	<0.001	0.551
Non-use	158	5 (3.16)	159	25 (15.72)	0.20 [0.08; 0.51]	<0.001	
Region							
Germany	21	0	23	1 (4.35)	n.a. [n.a.; n.a.]	n.a.	0.712
Rest of the World	271	8 (2.95)	274	48 (17.52)	0.17 [0.08; 0.35]	<0.001	

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

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

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

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

AEOSI: Adverse Events of Special Interest; CI: Confidence Interval; n.a.: not applicable (when estimation not possible)

Schwerwiegende Leukopenien und/oder Neutropenien (PT)

Tabelle 4G-38: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende Leukopenien und/oder Neutropenien (PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
Serious AEOSI	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
Serious Leukopenia (Preferred Term)							
Sex							
Male	213	1 (0.47)	209	7 (3.35)	n.c. [n.c.; n.c.]	n.c.	n.c.
Female	79	1 (1.27)	88	2 (2.27)	n.c. [n.c.; n.c.]	n.c.	
Age Group (Years)							
< 65	244	2 (0.82)	242	8 (3.31)	0.25 [0.05; 1.16]	0.054	0.646
≥ 65	48	0	55	1 (1.82)	n.a. [n.a.; n.a.]	n.a.	
Induction Therapy							
Use	134	1 (0.75)	138	5 (3.62)	n.c. [n.c.; n.c.]	n.c.	n.c.
Non-use	158	1 (0.63)	159	4 (2.52)	n.c. [n.c.; n.c.]	n.c.	
Region							
Germany	21	0	23	0	n.a. [n.a.; n.a.]	n.a.	n.a.
Rest of the World	271	2 (0.74)	274	9 (3.28)	0.22 [0.05; 1.03]	0.035	
Serious Neutropenia (Preferred Term)							
Sex							
Male	213	1 (0.47)	209	2 (0.96)	n.c. [n.c.; n.c.]	n.c.	n.c.
Female	79	1 (1.27)	88	1 (1.14)	n.c. [n.c.; n.c.]	n.c.	
Age Group (Years)							
< 65	244	2 (0.82)	242	2 (0.83)	n.c. [n.c.; n.c.]	n.c.	n.c.
≥ 65	48	0	55	1 (1.82)	n.c. [n.c.; n.c.]	n.c.	
Induction Therapy							
Use	134	1 (0.75)	138	1 (0.72)	n.c. [n.c.; n.c.]	n.c.	n.c.
Non-use	158	1 (0.63)	159	2 (1.26)	n.c. [n.c.; n.c.]	n.c.	
Region							
Germany	21	0	23	0	n.c. [n.c.; n.c.]	n.c.	n.c.
Rest of the World	271	2 (0.74)	274	3 (1.09)	n.c. [n.c.; n.c.]	n.c.	

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

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

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

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

AEOSI: Adverse Events of Special Interest; CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary)

Schwere Leukopenien und/oder Neutropenien (PT)

Tabelle 4G-39: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere Leukopenien und/oder Neutropenien (PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		
Severe AEOSI	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
Severe Leukopenia (Preferred Term)							
Sex							
Male	213	1 (0.47)	209	10 (4.78)	0.10 [0.01; 0.76]	0.005	0.303
Female	79	2 (2.53)	88	6 (6.82)	0.37 [0.08; 1.79]	0.197	
Age Group (Years)							
< 65	244	3 (1.23)	242	9 (3.72)	0.33 [0.09; 1.21]	0.077	0.160
≥ 65	48	0	55	7 (12.73)	n.a. [n.a.; n.a.]	n.a.	
Induction Therapy							
Use	134	2 (1.49)	138	9 (6.52)	0.23 [0.05; 1.04]	0.036	0.734
Non-use	158	1 (0.63)	159	7 (4.40)	0.14 [0.02; 1.15]	0.033	
Region							
Germany	21	0	23	1 (4.35)	n.a. [n.a.; n.a.]	n.a.	0.669
Rest of the World	271	3 (1.11)	274	15 (5.47)	0.20 [0.06; 0.69]	0.004	
Severe Neutropenia (Preferred Term)							
Sex							
Male	213	1 (0.47)	209	5 (2.39)	n.c. [n.c.; n.c.]	n.c.	n.c.
Female	79	2 (2.53)	88	1 (1.14)	n.c. [n.c.; n.c.]	n.c.	
Age Group (Years)							
< 65	244	3 (1.23)	242	3 (1.24)	n.c. [n.c.; n.c.]	n.c.	n.c.
≥ 65	48	0	55	3 (5.45)	n.c. [n.c.; n.c.]	n.c.	
Induction Therapy							
Use	134	2 (1.49)	138	4 (2.90)	n.c. [n.c.; n.c.]	n.c.	n.c.
Non-use	158	1 (0.63)	159	2 (1.26)	n.c. [n.c.; n.c.]	n.c.	
Region							
Germany	21	0	23	0	n.c. [n.c.; n.c.]	n.c.	n.c.
Rest of the World	271	3 (1.11)	274	6 (2.19)	n.c. [n.c.; n.c.]	n.c.	

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

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

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

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

AEOSI: Adverse Events of Special Interest; CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary)

Leukopenien und/oder Neutropenien nach CTCAE-Schweregrad

Tabelle 4G-40: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Leukopenien und/oder Neutropenien nach CTCAE-Schweregrad aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Letermovir		Valganciclovir		Letermovir vs. Valganciclovir		p-Value for Interaction Test[e]
Leukopenia by CTCAE Grade	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	
Grade 1							
Sex							
Male	213	43 (20.19)	209	94 (44.98)	0.45 [0.33; 0.61]	<0.001	0.941
Female	79	16 (20.25)	88	39 (44.32)	0.46 [0.28; 0.75]	0.001	
Age Group (Years)							
< 65	244	48 (19.67)	242	109 (45.04)	0.44 [0.33; 0.58]	<0.001	0.604
≥ 65	48	11 (22.92)	55	24 (43.64)	0.53 [0.29; 0.96]	0.028	
Induction Therapy							
Use	134	29 (21.64)	138	68 (49.28)	0.44 [0.31; 0.63]	<0.001	0.639
Non-use	158	30 (18.99)	159	65 (40.88)	0.46 [0.32; 0.67]	<0.001	
Region							
Germany	21	5 (23.81)	23	8 (34.78)	0.68 [0.27; 1.77]	0.431	0.329
Rest of the World	271	54 (19.93)	274	125 (45.62)	0.44 [0.33; 0.57]	<0.001	
Grade 2							
Sex							
Male	213	27 (12.68)	209	93 (44.50)	0.28 [0.19; 0.42]	<0.001	0.484
Female	79	13 (16.46)	88	39 (44.32)	0.37 [0.21; 0.64]	<0.001	
Age Group (Years)							
< 65	244	31 (12.70)	242	111 (45.87)	0.28 [0.19; 0.40]	<0.001	0.130
≥ 65	48	9 (18.75)	55	21 (38.18)	0.49 [0.25; 0.97]	0.031	
Induction Therapy							
Use	134	20 (14.93)	138	74 (53.62)	0.28 [0.18; 0.43]	<0.001	0.220
Non-use	158	20 (12.66)	159	58 (36.48)	0.35 [0.22; 0.55]	<0.001	
Region							
Germany	21	4 (19.05)	23	9 (39.13)	0.49 [0.18; 1.35]	0.149	0.361
Rest of the World	271	36 (13.28)	274	123 (44.89)	0.30 [0.21; 0.41]	<0.001	
Grade 3							
Age Group (Years)							
< 65	244	14 (5.74)	242	57 (23.55)	0.24 [0.14; 0.43]	<0.001	0.467
≥ 65	48	4 (8.33)	55	12 (21.82)	0.38 [0.13; 1.11]	0.061	
Induction Therapy							
Use	134	11 (8.21)	138	40 (28.99)	0.28 [0.15; 0.53]	<0.001	0.926
Non-use	158	7 (4.43)	159	29 (18.24)	0.24 [0.11; 0.54]	<0.001	
Region							
Germany	21	0	23	5 (21.74)	n.a. [n.a.; n.a.]	n.a.	0.253
Rest of the World	271	18 (6.64)	274	64 (23.36)	0.28 [0.17; 0.47]	<0.001	
Grade 4							
Sex							
Male	213	1 (0.47)	209	10 (4.78)	0.10 [0.01; 0.76]	0.005	0.107

Female	79	3 (3.80)	88	5 (5.68)	0.67 [0.17; 2.71]	0.570	
Age Group (Years)							
< 65	244	4 (1.64)	242	12 (4.96)	0.33 [0.11; 1.01]	0.041	0.358
≥ 65	48	0	55	3 (5.45)	n.a. [n.a.; n.a.]	n.a.	
Induction Therapy							
Use	134	3 (2.24)	138	10 (7.25)	0.31 [0.09; 1.10]	0.053	0.754
Non-use	158	1 (0.63)	159	5 (3.14)	0.20 [0.02; 1.70]	0.101	
Region							
Germany	21	0	23	0	n.a. [n.a.; n.a.]	n.a.	n.a.
Rest of the World	271	4 (1.48)	274	15 (5.47)	0.27 [0.09; 0.80]	0.011	

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

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

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

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

CTCAE grades for leukopenia, WBC (cells/µl), are defined according to NIH NCI Common Terminology Criteria for AEs v5.0 as Grade 1: < LLN and ≥3000, Grade 2: <3000 and ≥2000, Grade 3: <2000 and ≥1000, Grade 4: <1000, Grade 5 is not applicable.

CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; LLN: Lower Limit of Normal; n.a.: not applicable (when estimation not possible)

Neutropenien nach CTCAE-Schweregrad

Tabelle 4G-41: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Neutropenien nach CTCAE-Schweregrad aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	**Letermovir**		**Valganciclovir**		**Letermovir vs. Valganciclovir**		
Neutropenia by CTCAE Grade	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
Grade 1							
Sex							
Male	213	16 (7.51)	209	51 (24.40)	0.31 [0.18; 0.52]	<0.001	0.075
Female	79	11 (13.92)	88	18 (20.45)	0.68 [0.34; 1.35]	0.267	
Age Group (Years)							
< 65	244	21 (8.61)	242	60 (24.79)	0.35 [0.22; 0.55]	<0.001	0.131
≥ 65	48	6 (12.50)	55	9 (16.36)	0.76 [0.29; 1.99]	0.581	
Induction Therapy							
Use	134	11 (8.21)	138	39 (28.26)	0.29 [0.16; 0.54]	<0.001	0.124
Non-use	158	16 (10.13)	159	30 (18.87)	0.54 [0.30; 0.94]	0.027	
Region							
Germany	21	3 (14.29)	23	3 (13.04)	1.10 [0.25; 4.84]	0.906	0.144
Rest of the World	271	24 (8.86)	274	66 (24.09)	0.37 [0.24; 0.57]	<0.001	
Grade 2							
Sex							
Male	213	20 (9.39)	209	54 (25.84)	0.36 [0.23; 0.59]	<0.001	0.720
Female	79	7 (8.86)	88	25 (28.41)	0.31 [0.14; 0.68]	0.001	
Age Group (Years)							

< 65	244	22 (9.02)	242	67 (27.69)	0.33 [0.21; 0.51]	<0.001	0.450
≥ 65	48	5 (10.42)	55	12 (21.82)	0.48 [0.18; 1.26]	0.122	
Induction Therapy							
Use	134	12 (8.96)	138	36 (26.09)	0.34 [0.19; 0.63]	<0.001	0.975
Non-use	158	15 (9.49)	159	43 (27.04)	0.35 [0.20; 0.61]	<0.001	
Region							
Germany	21	2 (9.52)	23	6 (26.09)	0.37 [0.08; 1.61]	0.160	0.945
Rest of the World	271	25 (9.23)	274	73 (26.64)	0.35 [0.23; 0.53]	<0.001	
Grade 3							
Sex							
Male	213	9 (4.23)	209	33 (15.79)	0.27 [0.13; 0.55]	<0.001	0.875
Female	79	3 (3.80)	88	14 (15.91)	0.24 [0.07; 0.80]	0.010	
Age Group (Years)							
< 65	244	9 (3.69)	242	40 (16.53)	0.22 [0.11; 0.45]	<0.001	0.284
≥ 65	48	3 (6.25)	55	7 (12.73)	0.49 [0.13; 1.79]	0.270	
Induction Therapy							
Use	134	3 (2.24)	138	17 (12.32)	0.18 [0.05; 0.61]	0.001	0.534
Non-use	158	9 (5.70)	159	30 (18.87)	0.30 [0.15; 0.62]	<0.001	
Region							
Germany	21	2 (9.52)	23	6 (26.09)	0.37 [0.08; 1.61]	0.160	0.741
Rest of the World	271	10 (3.69)	274	41 (14.96)	0.25 [0.13; 0.48]	<0.001	
Grade 4							
Sex							
Male	213	3 (1.41)	209	26 (12.44)	0.11 [0.03; 0.37]	<0.001	0.068
Female	79	4 (5.06)	88	9 (10.23)	0.50 [0.16; 1.54]	0.215	
Age Group (Years)							
< 65	244	5 (2.05)	242	30 (12.40)	0.17 [0.07; 0.42]	<0.001	0.264
≥ 65	48	2 (4.17)	55	5 (9.09)	0.46 [0.09; 2.26]	0.324	
Induction Therapy							
Use	134	3 (2.24)	138	12 (8.70)	0.26 [0.07; 0.89]	0.020	0.601
Non-use	158	4 (2.53)	159	23 (14.47)	0.18 [0.06; 0.49]	<0.001	
Region							
Germany	21	1 (4.76)	23	1 (4.35)	1.10 [0.07; 16.43]	0.948	0.155
Rest of the World	271	6 (2.21)	274	34 (12.41)	0.18 [0.08; 0.42]	<0.001	

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

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

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

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

CTCAE grades for neutropenia, Neutrophil count(cells/µl), are defined according to NIH NCI Common Terminology Criteria for AEs v5.0 as Grade 1: < LLN and ≥1500, Grade 2: <1500 and ≥1000, Grade 3: <1000 and ≥500, Grade 4: <500, Grade 5 is not applicable.

CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; LLN: Lower Limit of Normal; n.a.: not applicable (when estimation not possible)

Anhang 4-G3: Unerwünschte Ereignisse, inklusive krankheitsbezogener Ereignisse und/oder Morbiditätsendpunkte

Tabelle 4G-42: Liste der krankheitsbezogenen Ereignisse und/oder Morbiditätsendpunkte, die von den Hauptanalysen der Unerwünschten Ereignisse ausgeschlossen wurden aus RCT mit dem zu bewertenden Arzneimittel

MedDRA System organ class term	MedDRA Preferred Term
Blood and lymphatic system disorders	Thrombocytopenia
General disorders and administration site conditions	Fatigue
	Malaise
Immune system disorders	Kidney transplant rejection
	Transplant rejection
Infections and infestations	BK virus infection
	Candida infection
	Cytomegalovirus colitis
	Cytomegalovirus gastritis
	Cytomegalovirus gastrointestinal infection
	Cytomegalovirus hepatitis
	Cytomegalovirus infection
	Cytomegalovirus syndrome
	Cytomegalovirus viraemia
	Genital candidiasis
	Herpes simplex
	Herpes zoster
	Human polyomavirus infection
	Lymph node tuberculosis
	Oesophageal candidiasis
	Oral candidiasis
	Oral herpes
	Pneumonia cytomegaloviral
	Polyomavirus viraemia
	Skin candida
	Upper respiratory fungal infection
Injury, poisoning and procedural complications	Renal transplant failure
	Transplant dysfunction
	Transplant failure
Investigations	Alanine aminotransferase increased
	BK polyomavirus test positive
	Cytomegalovirus test positive
	Fungal test positive
	Lymphocyte morphology abnormal
	Polyomavirus test positive
Metabolism and nutrition disorders	New onset diabetes after transplantation

Tabelle 4G-43: Ergebnisse für den Endpunkt Unerwünschte Ereignisse Gesamtraten inklusive krankheitsbezogener Ereignisse und/oder Morbiditätsendpunkte

Study: MK-8228-002[a]	Participants with Event n (%)		Letermovir vs. Valganciclovir	
	Letermovir (N[b]=292)	Valganciclovir (N[b]=297)	Relative Risk [95 %-CI][c]	p-Value[d]

Adverse Events	271 (92.81)	276 (92.93)	1.00 [0.95; 1.04]	0.955
Serious Adverse Events	106 (36.30)	113 (38.05)	0.95 [0.77; 1.18]	0.661
Severe Adverse Events[e]	93 (31.85)	103 (34.68)	0.92 [0.73; 1.15]	0.466
Adverse Events Leading to Treatment Discontinuation	12 (4.11)	40 (13.47)	0.31 [0.16; 0.57]	<0.001
Drug Related AE	58 (19.86)	104 (35.02)	0.57 [0.43; 0.75]	<0.001
Drug Related SAE Through 30 Weeks Post-Transplant	4 (1.37)	15 (5.05)	0.27 [0.09; 0.81]	0.012
Drug Related SAE Through 52 Weeks Post-Transplant	5 (1.71)	16 (5.39)	0.32 [0.12; 0.86]	0.016

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald confidence interval. In case no participant with event in one treatment group, a correction factor (+0.5) is applied to all cells [of the 2x2 contingency table] and Wald modified confidence interval is presented. In case no participant or all participants with event in both treatment groups, report 'n.a.'

d: Based on Mantel-Haenszel Chi-Squared test. In case no participant or all participants with event in both treatment groups, report 'n.a.'

Unless stated otherwise, events are reported through 30 weeks post-transplant.

CI: Confidence Interval; n.a.: not applicable (when estimation not possible)

Tabelle 4G-44: Ergebnisse für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) inklusive krankheitsbezogener Ereignisse und/oder Morbiditätsendpunkte aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	**Participants with Event n (%)**		**Letermovir vs. Valganciclovir**		
Adverse Events by SOC and PT[b]	**Letermovir (N[c]=292)**	**Valganciclovir (N[c]=297)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	**Adjusted p-Value[f]**
Blood and lymphatic system disorders	78 (26.71)	146 (49.16)	0.54 [0.44; 0.68]	<0.001	<0.001
Anaemia	18 (6.16)	29 (9.76)	0.63 [0.36; 1.11]	0.107	0.134
Leukocytosis	13 (4.45)	4 (1.35)	3.31 [1.09; 10.02]	0.025	0.041
Leukopenia	33 (11.30)	110 (37.04)	0.31 [0.21; 0.43]	<0.001	<0.001
Neutropenia	8 (2.74)	49 (16.50)	0.17 [0.08; 0.34]	<0.001	<0.001
Thrombocytopenia	3 (1.03)	12 (4.04)	0.25 [0.07; 0.89]	0.020	0.041
Cardiac disorders	33 (11.30)	47 (15.82)	0.71 [0.47; 1.08]	0.109	0.693
Tachycardia	11 (3.77)	12 (4.04)	0.93 [0.42; 2.08]	0.864	n.s.
Eye disorders	9 (3.08)	11 (3.70)	0.83 [0.35; 1.98]	0.677	0.919
Gastrointestinal disorders	153 (52.40)	144 (48.48)	1.08 [0.92; 1.27]	0.343	0.814
Abdominal pain	20 (6.85)	15 (5.05)	1.36 [0.71; 2.60]	0.356	n.s.
Constipation	18 (6.16)	24 (8.08)	0.76 [0.42; 1.38]	0.367	n.s.
Diarrhoea	92 (31.51)	85 (28.62)	1.10 [0.86; 1.41]	0.445	n.s.
Dyspepsia	18 (6.16)	13 (4.38)	1.41 [0.70; 2.82]	0.332	n.s.
Nausea	25 (8.56)	33 (11.11)	0.77 [0.47; 1.26]	0.300	n.s.
Vomiting	18 (6.16)	27 (9.09)	0.68 [0.38; 1.20]	0.182	n.s.
General disorders and administration site conditions	96 (32.88)	97 (32.66)	1.01 [0.80; 1.27]	0.955	0.983
Fatigue	18 (6.16)	32 (10.77)	0.57 [0.33; 1.00]	0.045	n.s.
Oedema peripheral	39 (13.36)	38 (12.79)	1.04 [0.69; 1.58]	0.840	n.s.
Pyrexia	21 (7.19)	15 (5.05)	1.42 [0.75; 2.71]	0.278	n.s.
Immune system disorders	23 (7.88)	22 (7.41)	1.06 [0.61; 1.86]	0.830	0.939
Kidney transplant rejection	12 (4.11)	8 (2.69)	1.53 [0.63; 3.68]	0.343	n.s.
Transplant rejection	8 (2.74)	12 (4.04)	0.68 [0.28; 1.63]	0.384	n.s.
Infections and infestations	131 (44.86)	146 (49.16)	0.91 [0.77; 1.08]	0.297	0.814
BK virus infection	14 (4.79)	10 (3.37)	1.42 [0.64; 3.15]	0.381	n.s.
Nasopharyngitis	5 (1.71)	10 (3.37)	0.51 [0.18; 1.47]	0.203	n.s.
Oral candidiasis	2 (0.68)	13 (4.38)	0.16 [0.04; 0.69]	0.004	n.s.
Polyomavirus viraemia	11 (3.77)	14 (4.71)	0.80 [0.37; 1.73]	0.569	n.s.
Upper respiratory tract infection	12 (4.11)	9 (3.03)	1.36 [0.58; 3.17]	0.480	n.s.
Urinary tract infection	41 (14.04)	42 (14.14)	0.99 [0.67; 1.48]	0.972	n.s.
Injury, poisoning and procedural complications	66 (22.60)	73 (24.58)	0.92 [0.69; 1.23]	0.573	0.906
Investigations	102 (34.93)	104 (35.02)	1.00 [0.80; 1.24]	0.983	0.983
Blood creatinine increased	30 (10.27)	41 (13.80)	0.74 [0.48; 1.16]	0.189	0.210

Immunosuppressant drug level increased	10 (3.42)	3 (1.01)	3.39 [0.94; 12.19]	0.046	0.066
White blood cell count decreased	3 (1.03)	16 (5.39)	0.19 [0.06; 0.65]	0.003	0.007
Metabolism and nutrition disorders	137 (46.92)	142 (47.81)	0.98 [0.83; 1.16]	0.828	0.939
Hyperglycaemia	10 (3.42)	17 (5.72)	0.60 [0.28; 1.28]	0.183	n.s.
Hyperkalaemia	27 (9.25)	32 (10.77)	0.86 [0.53; 1.40]	0.537	n.s.
Hypervolaemia	4 (1.37)	10 (3.37)	0.41 [0.13; 1.28]	0.112	n.s.
Hypocalcaemia	11 (3.77)	9 (3.03)	1.24 [0.52; 2.96]	0.622	n.s.
Hypokalaemia	17 (5.82)	10 (3.37)	1.73 [0.81; 3.71]	0.155	n.s.
Hypomagnesaemia	37 (12.67)	39 (13.13)	0.96 [0.63; 1.47]	0.868	n.s.
Hypophosphataemia	30 (10.27)	35 (11.78)	0.87 [0.55; 1.38]	0.559	n.s.
Metabolic acidosis	14 (4.79)	12 (4.04)	1.19 [0.56; 2.52]	0.656	n.s.
New onset diabetes after transplantation	10 (3.42)	15 (5.05)	0.68 [0.31; 1.48]	0.328	n.s.
Musculoskeletal and connective tissue disorders	57 (19.52)	64 (21.55)	0.91 [0.66; 1.25]	0.543	0.906
Arthralgia	12 (4.11)	10 (3.37)	1.22 [0.54; 2.78]	0.635	n.s.
Back pain	12 (4.11)	15 (5.05)	0.81 [0.39; 1.71]	0.585	n.s.
Muscle spasms	8 (2.74)	15 (5.05)	0.54 [0.23; 1.26]	0.148	n.s.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (3.42)	8 (2.69)	1.27 [0.51; 3.18]	0.607	0.906
Nervous system disorders	104 (35.62)	81 (27.27)	1.31 [1.03; 1.66]	0.029	0.278
Dizziness	15 (5.14)	9 (3.03)	1.70 [0.75; 3.81]	0.196	n.s.
Headache	20 (6.85)	19 (6.40)	1.07 [0.58; 1.96]	0.826	n.s.
Tremor	53 (18.15)	52 (17.51)	1.04 [0.73; 1.47]	0.839	n.s.
Psychiatric disorders	28 (9.59)	25 (8.42)	1.14 [0.68; 1.91]	0.620	0.906
Insomnia	10 (3.42)	12 (4.04)	0.85 [0.37; 1.93]	0.694	n.s.
Renal and urinary disorders	97 (33.22)	87 (29.29)	1.13 [0.89; 1.44]	0.304	0.814
Acute kidney injury	20 (6.85)	17 (5.72)	1.20 [0.64; 2.24]	0.574	n.s.
Dysuria	15 (5.14)	13 (4.38)	1.17 [0.57; 2.42]	0.665	n.s.
Haematuria	14 (4.79)	8 (2.69)	1.78 [0.76; 4.18]	0.179	n.s.
Proteinuria	11 (3.77)	9 (3.03)	1.24 [0.52; 2.96]	0.622	n.s.
Renal impairment	10 (3.42)	9 (3.03)	1.13 [0.47; 2.74]	0.787	n.s.
Reproductive system and breast disorders	13 (4.45)	19 (6.40)	0.70 [0.35; 1.38]	0.298	0.814
Respiratory, thoracic and mediastinal disorders	44 (15.07)	58 (19.53)	0.77 [0.54; 1.10]	0.153	0.727
Cough	14 (4.79)	20 (6.73)	0.71 [0.37; 1.38]	0.313	0.313
Dyspnoea	5 (1.71)	21 (7.07)	0.24 [0.09; 0.63]	0.002	0.005
Skin and subcutaneous tissue disorders	47 (16.10)	46 (15.49)	1.04 [0.72; 1.51]	0.840	0.939
Alopecia	10 (3.42)	7 (2.36)	1.45 [0.56; 3.77]	0.439	n.s.
Pruritus	12 (4.11)	12 (4.04)	1.02 [0.46; 2.23]	0.966	n.s.
Vascular disorders	83 (28.42)	75 (25.25)	1.13 [0.86; 1.47]	0.385	0.814
Hypertension	33 (11.30)	36 (12.12)	0.93 [0.60; 1.45]	0.757	n.s.
Hypotension	19 (6.51)	13 (4.38)	1.49 [0.75; 2.95]	0.255	n.s.
Lymphocele	13 (4.45)	11 (3.70)	1.20 [0.55; 2.64]	0.646	n.s.

a: Database Lock Date: 27JUL2022

b: 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

c: Number of participants: all-participants-as-treated population

d: Based on 2x2 contingency table, using Wald confidence interval. In case no participant with event in one treatment group, a correction factor (+0.5) is applied to all cells [of the 2x2 contingency table] and Wald modified confidence interval is presented. In case no participant or all participants with event in both treatment groups, report 'n.a.'

e: Based on Mantel-Haenszel Chi-Squared test. In case no participant or all participants with event in both treatment groups, report 'n.a.'

f: 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 (dFDR) 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 dFDR 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; FDR: False Discovery Rate; n.a.: not applicable (when estimation not possible); n.s.: Non-Significant (adjusted p-value ≥ 0.05); PT: Preferred Term; SOC: System Organ Class

Tabelle 4G-45: Ergebnisse für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) inklusive krankheitsbezogener Ereignisse und/oder Morbiditätsendpunkte aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Participants with Event n (%)		Letermovir vs. Valganciclovir		
Serious Adverse Events by SOC and PT[b]	Letermovir (N[c]=292)	Valganciclovir (N[c]=297)	Relative Risk [95 %-CI][d]	p-Value[e]	Adjusted p-Value[f]
Blood and lymphatic system disorders	8 (2.74)	16 (5.39)	0.51 [0.22; 1.17]	0.104	0.235
Gastrointestinal disorders	9 (3.08)	18 (6.06)	0.51 [0.23; 1.11]	0.084	0.235
General disorders and administration site conditions	13 (4.45)	4 (1.35)	3.31 [1.09; 10.02]	0.025	0.221
Immune system disorders	10 (3.42)	11 (3.70)	0.92 [0.40; 2.14]	0.855	0.939
Infections and infestations	36 (12.33)	36 (12.12)	1.02 [0.66; 1.57]	0.939	0.939
Injury, poisoning and procedural complications	12 (4.11)	23 (7.74)	0.53 [0.27; 1.05]	0.062	0.235
Metabolism and nutrition disorders	13 (4.45)	12 (4.04)	1.10 [0.51; 2.37]	0.804	0.939
Renal and urinary disorders	22 (7.53)	20 (6.73)	1.12 [0.62; 2.01]	0.706	0.939
Vascular disorders	19 (6.51)	15 (5.05)	1.29 [0.67; 2.49]	0.449	0.808

a: Database Lock Date: 27JUL2022

b: 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

c: Number of participants: all-participants-as-treated population

d: Based on 2x2 contingency table, using Wald confidence interval. In case no participant with event in one treatment group, a correction factor (+0.5) is applied to all cells [of the 2x2 contingency table] and Wald modified confidence interval is presented. In case no participant or all participants with event in both treatment groups, report 'n.a.'

e: Based on Mantel-Haenszel Chi-Squared test. In case no participant or all participants with event in both treatment groups, report 'n.a.'

f: 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 (dFDR) 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 dFDR 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; FDR: False Discovery Rate; n.a.: not applicable (when estimation not possible); n.s.: Non-Significant (adjusted p-value ≥ 0.05); PT: Preferred Term; SOC: System Organ Class

Tabelle 4G-46: Ergebnisse für den Endpunkt Schwere unerwünschte Ereignisse (SOC und PT) inklusive krankheitsbezogener Ereignisse und/oder Morbiditätsendpunkte aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Participants with Event n (%)		Letermovir vs. Valganciclovir		
Severe Adverse Events by SOC and PT[b]	Letermovir (N[c]=292)	Valganciclovir (N[c]=297)	Relative Risk [95 %-CI][d]	p-Value[e]	Adjusted p-Value[f]
Blood and lymphatic system disorders	8 (2.74)	26 (8.75)	0.31 [0.14; 0.68]	0.002	0.014
Leukopenia	3 (1.03)	16 (5.39)	0.19 [0.06; 0.65]	0.003	0.003
Gastrointestinal disorders	10 (3.42)	15 (5.05)	0.68 [0.31; 1.48]	0.328	0.588
General disorders and administration site conditions	12 (4.11)	5 (1.68)	2.44 [0.87; 6.84]	0.079	0.211
Infections and infestations	28 (9.59)	29 (9.76)	0.98 [0.60; 1.61]	0.943	0.943
Injury, poisoning and procedural complications	8 (2.74)	18 (6.06)	0.45 [0.20; 1.02]	0.050	0.200
Metabolism and nutrition disorders	11 (3.77)	13 (4.38)	0.86 [0.39; 1.89]	0.708	0.914
Renal and urinary disorders	21 (7.19)	16 (5.39)	1.33 [0.71; 2.51]	0.367	0.588
Vascular disorders	12 (4.11)	11 (3.70)	1.11 [0.50; 2.47]	0.799	0.914

a: Database Lock Date: 27JUL2022

b: 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

c: Number of participants: all-participants-as-treated population

d: Based on 2x2 contingency table, using Wald confidence interval. In case no participant with event in one treatment group, a correction factor (+0.5) is applied to all cells [of the 2x2 contingency table] and Wald modified confidence interval is presented. In case no participant or all participants with event in both treatment groups, report 'n.a.'

e: Based on Mantel-Haenszel Chi-Squared test. In case no participant or all participants with event in both treatment groups, report 'n.a.'

f: 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 (dFDR) 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 dFDR 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; FDR: False Discovery Rate; n.a.: not applicable (when estimation not possible); n.s.: Non-Significant (adjusted p-value ≥ 0.05); PT: Preferred Term; SOC: System Organ Class

Tabelle 4G-47: Ergebnisse für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse (SOC und PT) inklusive krankheitsbezogener Ereignisse und/oder Morbiditätsendpunkte aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	**Participants with Event n (%)**	
Adverse Events Leading to Treatment Discontinuation by SOC and PT[b]	**Letermovir (N[c]=292)**	**Valganciclovir (N[c]=297)**
Participants with one or more adverse events	12 (4.1)	40 (13.5)
Blood and lymphatic system disorders	8 (2.7)	21 (7.1)
Leukopenia	3 (1.0)	16 (5.4)
Neutropenia	4 (1.4)	5 (1.7)
Pancytopenia	2 (0.7)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	3 (1.0)
Diarrhoea	0 (0.0)	1 (0.3)
Dysphagia	0 (0.0)	1 (0.3)
Nausea	0 (0.0)	1 (0.3)
Immune system disorders	0 (0.0)	2 (0.7)
Kidney transplant rejection	0 (0.0)	1 (0.3)
Transplant rejection	0 (0.0)	1 (0.3)
Infections and infestations	3 (1.0)	3 (1.0)
Cytomegalovirus infection	0 (0.0)	2 (0.7)
Adenovirus infection	1 (0.3)	0 (0.0)
COVID-19 pneumonia	1 (0.3)	0 (0.0)
Endocarditis	1 (0.3)	0 (0.0)
Urosepsis	0 (0.0)	1 (0.3)
Investigations	0 (0.0)	5 (1.7)
White blood cell count decreased	0 (0.0)	4 (1.3)
Neutrophil count decreased	0 (0.0)	1 (0.3)
Metabolism and nutrition disorders	0 (0.0)	2 (0.7)
Hyperkalaemia	0 (0.0)	1 (0.3)
Hypoalbuminaemia	0 (0.0)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	1 (0.3)
Ocular lymphoma	0 (0.0)	1 (0.3)
Nervous system disorders	1 (0.3)	0 (0.0)
Nervous system disorder	1 (0.3)	0 (0.0)
Psychiatric disorders	0 (0.0)	1 (0.3)
Hallucination, visual	0 (0.0)	1 (0.3)
Renal and urinary disorders	0 (0.0)	2 (0.7)
Acute kidney injury	0 (0.0)	1 (0.3)
Renal failure	0 (0.0)	1 (0.3)

a: Database Lock Date: 27JUL2022

b: A SOC or specific adverse event appears on this report only if its incidence is > 0% in one or more treatment groups

c: Number of participants: all-participants-as-treated population

PT: Preferred Term; SOC: System Organ Class

Anhang 4-G4: Zusätzliche Analysen zu Leukopenie und/oder Neutropenie

Tabelle 4G-48: Ergebnisse für den Endpunkt Leukopenie und/oder Neutropenie als Laborereignis aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Participants with Event n (%)		Letermovir vs. Valganciclovir	
AEOSI	Letermovir (N[b]=292)	Valganciclovir (N[b]=297)	Relative Risk [95 %-CI][c]	p-Value[d]
Leukopenia (WBC <3,500 cells/uL)	64 (21.92)	178 (59.93)	0.37 [0.29; 0.46]	<0.001
Neutropenia (ANC <1000 cells/uL)	15 (5.14)	67 (22.56)	0.23 [0.13; 0.39]	<0.001

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald confidence interval. In case no participant with event in one treatment group, a correction factor (+0.5) is applied to all cells [of the 2x2 contingency table] and Wald modified confidence interval is presented. In case no participant or all participants with event in both treatment groups, report 'n.a.'

d: Based on Mantel-Haenszel Chi-Squared test. In case no participant or all participants with event in both treatment groups, report 'n.a.'

AEOSI: Adverse Events of Special Interest; CI: Confidence Interval; n.a.: not applicable (when estimation not possible)

Tabelle 4G-49: Ergebnisse für den Endpunkt Leukopenie und/oder Neutropenie als kombiniertes Ereignis aus RCT mit dem zu bewertenden Arzneimittel

Study: MK-8228-002[a]	Participants with Event n (%)		Letermovir vs. Valganciclovir	
AEOSI	Letermovir (N[b]=292)	Valganciclovir (N[b]=297)	Relative Risk [95 %-CI][c]	p-Value[d]
Leukopenia (Preferred Term or WBC <3,500 cells/uL)	72 (24.66)	185 (62.29)	0.40 [0.32; 0.49]	<0.001
Neutropenia (Preferred Term or ANC <1000 cells/uL)	18 (6.16)	88 (29.63)	0.21 [0.13; 0.34]	<0.001

a: Database Lock Date: 27JUL2022

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald confidence interval. In case no participant with event in one treatment group, a correction factor (+0.5) is applied to all cells [of the 2x2 contingency table] and Wald modified confidence interval is presented. In case no participant or all participants with event in both treatment groups, report 'n.a.'

d: Based on Mantel-Haenszel Chi-Squared test. In case no participant or all participants with event in both treatment groups, report 'n.a.'

AEOSI: Adverse Events of Special Interest; CI: Confidence Interval; n.a.: not applicable (when estimation not possible)