Letermovir (prophylaxis of CMV disease after kidney transplant)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
APaT	all participants as treated
AST	aspartate aminotransferase
CMV	cytomegalovirus
CrCl	creatinine clearance
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	full analysis set
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
G-CSF	granulocyte colony stimulating factor
HSV	herpes simplex virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NODAT	new-onset diabetes mellitus after transplantation
OF	observed failure
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SF-36v2	Short Form 36-version 2 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
ULN	upper limit of normal
VAS	visual analogue scale
VZV	varicella zoster virus
WHO	World Health Organization

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug letermovir. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 14 December 2023.

Research question

The aim of this report is to assess the added benefit of letermovir compared with ganciclovir or valganciclovir as appropriate comparator therapy (ACT) used for prophylaxis of cytomegalovirus (CMV) disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of letermovir

Therapeutic indication	**ACT**[a, b]
Prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor	Ganciclovir or **valganciclovir**
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. A prophylactic rather than a pre-emptive approach is assumed to be used in the present therapeutic indication. ACT: appropriate comparator therapy; CMV: cytomegalovirus; G-BA: Federal Joint Committee	

The company followed the G-BA's specification and chose valganciclovir from the specified options.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive added benefit.

Study pool and study design

The MK-8228-002 study is used for the benefit assessment. The MK-8228-002 study is a completed double-blind RCT comparing letermovir with valganciclovir. It included adult CMV-seronegative recipients of kidney transplants from CMV-seropositive donors. Patients with previous solid organ transplant (with the exception of previous kidney transplant) or previous haematopoietic stem cell transplant were excluded from the MK-8228-002 study. Adults with

severely impaired post-transplant renal function (creatinine clearance [CrCl] ≤ 10) as well as patients with a history of confirmed or suspected CMV disease within 6 months prior to randomization were also excluded from the study.

A total of 601 patients were enrolled and randomized in a 1:1 ratio to treatment with letermovir (N = 301) or valganciclovir (N = 300). Randomization was no later than 7 days after kidney transplantation.

Treatment with letermovir could be started on the day of the transplant up to Day 7 post-transplant, and was continued up to 28 weeks post-transplant (treatment could be discontinued prematurely due to a CMV infection, for example). Treatment was without relevant deviation from the recommendations of the Summary of Product Characteristics (SPC). In addition, aciclovir (400 mg orally twice daily) was administered in the intervention arm over the entire treatment period for prophylaxis of herpes simplex virus (HSV) and varicella zoster virus (VZV) infections. The uncertainty regarding the transferability of the results of the MK-8228-002 study to the German health care context resulting from this mandatory concomitant treatment with aciclovir in the intervention arm is addressed in the section on limitations below.

Treatment with valganciclovir could also be started on the day of the transplant up to Day 7 post-transplant, and was continued up to 28 weeks post-transplant (treatment could be discontinued prematurely due to a CMV infection, for example). Treatment was in compliance with the recommendations of the SPC.

The outcomes in the category of mortality, morbidity and health-related quality of life were to be observed up to 52 weeks post-transplant. Side effects were recorded only for the period of treatment with the study medication (plus 2 weeks).

The primary outcome of the study is the composite outcome of CMV disease, consisting of the components of CMV end-organ disease and CMV syndrome. Furthermore, patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Limitations of the MK-8228-002 study

The certainty of conclusions of the study results is limited due to the mandatory concomitant treatment with aciclovir in the intervention arm described above. The company justified the administration of aciclovir by stating that corresponding prophylaxis in the comparator arm was already covered by the administration of valganciclovir. However, it cannot be inferred from the SPC for letermovir that concomitant treatment with aciclovir should be carried per se. The guideline also provides no explicit recommendation for routine prophylaxis of HSV or VZV infection in this therapeutic indication. However, in accordance with the assessment of

the European Medicines Agency (EMA), it can be assumed that the administered dose of aciclovir has no anti-CMV activity. The uncertainty regarding the transferability of the study results to the German health care context is addressed in the certainty of the conclusions (see below).

Risk of bias

The risk of bias across outcomes was rated as low for the MK-8228-002 study. The risk of bias of the results for the outcome of all-cause mortality and for the adverse event (AE) outcomes was also rated as low. The risk of bias for the outcomes of morbidity, health status, and health-related quality of life was rated as high. The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias.

Summary assessment of the certainty of conclusions

Irrespective of the aspects described for the risk of bias, the certainty of conclusions of the study results is limited. Since all patients in the intervention arm, in addition to letermovir, received treatment with aciclovir for prophylaxis of HSV and VZV infection over the entire treatment period of 28 weeks, it is unclear to what extent the results of the MK-8228-002 study are fully transferable to the German health care context. Overall, at most hints, e.g. of an added benefit, can be therefore determined for all outcomes presented.

Results

Mortality

All-cause mortality

No statistically significant difference between treatment groups was shown for the outcome of all-cause mortality. There is no hint of an added benefit of letermovir in comparison with valganciclovir for the outcome of all-cause mortality; an added benefit is therefore not proven.

Morbidity

Graft loss

No statistically significant difference between treatment groups was shown for the outcome of graft loss. There is no hint of an added benefit of letermovir in comparison with valganciclovir for the outcome of graft loss; an added benefit is therefore not proven.

Severe CMV disease

No statistically significant difference between treatment groups was shown for the outcome of severe CMV disease. There is no hint of an added benefit of letermovir in comparison with valganciclovir for the outcome of severe CMV disease; an added benefit is therefore not proven.

New-onset diabetes mellitus after transplantation (NODAT)

No statistically significant difference between treatment groups was shown for the outcome of NODAT. However, there is an effect modification by the characteristic of age (< 65 versus ≥ 65 years). For patients ≥ 65 years of age, there is a hint of an added benefit of letermovir compared with valganciclovir. For patients < 65 years of age, there is no hint of an added benefit of letermovir compared with valganciclovir; an added benefit is therefore not proven for this patient group.

Health status (EQ-5D visual analogue scale [VAS])

No statistically significant difference between treatment groups was shown for the outcome of health status. There is no hint of an added benefit of letermovir in comparison with valganciclovir; an added benefit is therefore not proven.

Health-related quality of life

SF-36v2 – Physical and Mental Component Summary

Health-related quality of life outcomes were recorded using the Short Form 36-version 2 Health Survey (SF-36v2).

Statistically significant differences between treatment groups were shown neither for the Physical nor for the Mental Component Summary. There is no hint of an added benefit of letermovir in comparison with valganciclovir; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

No statistically significant difference between treatment groups was shown for the outcome of SAEs. There is no hint of greater or lesser harm from letermovir in comparison with valganciclovir; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference between treatment groups in favour of letermovir was shown for the outcome of discontinuation due to AEs. However, there is an effect modification by the characteristic of sex (male versus female). For men, there is a hint of lesser harm from letermovir in comparison with valganciclovir. For women, there is no hint of greater or lesser harm from letermovir in comparison with valganciclovir; greater or lesser harm is therefore not proven for women (see Section I 4.4).

Specific AEs

General disorders and administration site conditions

A statistically significant difference to the disadvantage of letermovir was shown for the outcome of general disorders and administration site conditions (System Organ Class [SOC], SAEs). There is a hint of greater harm from letermovir in comparison with valganciclovir.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug letermovir in comparison with the ACT are assessed as follows:

Overall, both positive and negative effects were shown, each with the probability of hint, but of different extents, and on the positive-side only in subgroups.

On the side of positive effects, there is a hint of considerable added benefit in the outcome category of serious/severe late complications for the outcome of NODAT, but only for adults ≥ 65 years. In men, there is an additional hint of lesser harm of considerable extent in the outcome category of non-serious/non-severe side effects for the outcome of discontinuation due to AEs. On the other hand, there is a hint of greater harm of minor extent in the outcome category of serious/severe side effects for the SAE of general disorders and administration site conditions. Overall, there is no added benefit of letermovir in comparison with the ACT.

In summary, there is no hint of an added benefit of letermovir in comparison with the ACT for prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor.

Table 3 shows a summary of probability and extent of the added benefit of letermovir.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Letermovir – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor	Ganciclovir or **valganciclovir**	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

ACT: appropriate comparator therapy; CMV: cytomegalovirus; G-BA: Federal Joint Committee

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of letermovir compared with ganciclovir or valganciclovir as ACT for prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of letermovir

Therapeutic indication	**ACT**[a, b]
Prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor	Ganciclovir or **valganciclovir**
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. A prophylactic rather than a pre-emptive approach is assumed to be used in the present therapeutic indication. ACT: appropriate comparator therapy; CMV: cytomegalovirus; G-BA: Federal Joint Committee	

The company followed the G-BA's specification and chose valganciclovir from the specified options.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on letermovir (status: 20 October 2023)
- bibliographical literature search on letermovir (last search on 4 October 2023)
- search in trial registries/trial results databases for studies on letermovir (last search on 5 October 2023)
- search on the G-BA website for letermovir (last search on 5 October 2023)

To check the completeness of the study pool:

- search in trial registries for studies on letermovir (last search on 19 December 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: letermovir vs. valganciclovir

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
MK-8228-002	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The MK-8228-002 study is used for the benefit assessment. The study pool is consistent with that selected by the company.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: letermovir vs. valganciclovir

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MK-8228-002	RCT, double-blind, parallel	Adult CMV-seronegative recipients of kidney transplants from CMV-seropositive donors[b]	Letermovir (N = 301) Valganciclovir (N = 300)[c, d]	▪ Screening: ≤ 14 days before transplantation ▪ Treatment: within 7 days post-transplant until Week 28 post-transplant, or until the occurrence of CMV disease, or until the occurrence of unacceptable toxicity, treatment discontinuation upon investigator or patient decision ▪ Observation: 52 weeks after transplantation	94 centres in Australia, Argentina, Austria, Belgium, Canada, Colombia, France, Germany, Hungary, Italy, Mexico, New Zealand, Poland, Spain, United Kingdom, United States 5/2018 – 4/2022 Data cut-off: ▪ 27 July 2022 (final analysis)	Primary: CMV disease until Week 52 post-transplant Secondary: mortality, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Randomization between Day 0 (day of transplantation) up to and including Day 7 post-transplant.
c. To analyse the efficacy outcomes, the company used the FAS population, defined as all randomized patients who received at least one dose of the study medication, who were assigned to the category of seronegative recipients, and who had no detectable CMV deoxyribonucleic acid on Day 1 of treatment.
d. To analyse the side effects, the company used the APaT population, defined as all randomized patients who received at least one dose of the study medication. In the analyses, patients are assigned to the treatment they actually received initially.

AE: adverse event; APaT: all participants as treated; CMV: cytomegalovirus; FAS: full analysis set; n: subpopulation analysed by the company; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: letermovir vs. valganciclovir

Study	Intervention	Comparison
MK-8228-002	▪ Letermovir 480 mg, orally, once daily[a] or letermovir, 240 mg, orally, once daily, with concomitant administration of ciclosporin[a] + ▪ aciclovir 400 mg, orally, twice daily, at 12-hour intervals[a, b] + ▪ placebo for valganciclovir	▪ Valganciclovir 900 mg, orally, once daily[a] + ▪ Placebo for aciclovir[a, b] + ▪ placebo for letermovira
	Dose adjustment: ▪ letermovir: not permitted ▪ treatment interruption possiblec ▪ aciclovir: dose reduction permitted for patients with reduced renal function[d]	Dose adjustment: ▪ dose reduction permitted for patients with reduced renal function[e] ▪ treatment interruption possible[c]
	Concomitant treatment ▪ ciclosporin ▪ aciclovir (only at a dose ≤ 3200 mg orally per day or < 25 mg/kg body weight IV per day) ▪ valaciclovir (not for prophylaxis of HSC/VZV infection and only at a dose ≤ 3000 mg or > 500 mg orally per day) ▪ famciclovir (not for prophylaxis of HSC/VZV infection and only at a dose ≤ 1500 mg or > 1000 mg orally per day) **Disallowed prior and concomitant treatment** ▪ simvastatin or pitavastatin (only applies to the intervention arm) ▪ atorvastatin (only applies to letermovir in combination with ciclosporin) ▪ foscarnet (≤ 7 days before randomization) ▪ cidofovir (≤ 30 days before randomization) ▪ CMV hyperimmunoglobulins (< 30 days before randomization)	

a. Patients who were unable to swallow and/or developed a condition that could interfere with the absorption of the oral formulation at or after randomization could start study treatment with the IV formulation or be switched to this formulation. Since, according to the clinical study report of study MK-8228-002, this only applied to 3 patients in the intervention arm and 2 patients in the control arm, the IV administration is not presented.
b. In the intervention arm, aciclovir was additionally administered over the entire treatment period for prophylaxis of HSV and VZV infections. A corresponding placebo was administered in the control arm because, according to the company, prophylaxis of HSV and VZV infection was covered by the administration of valganciclovir.
c. In patients with suspected CMV disease who therefore received CMV treatment, the study treatment had to be interrupted. If the suspected CMV disease was not confirmed within 7 days of CMV treatment and/or another medical condition unrelated to CMV was identified and CMV treatment was therefore discontinued, study treatment could be resumed.
d. Dose reduction of aciclovir was based on the CrCl in mL/min: CrCl > 10 and < 30: 400 mg orally once daily.
e. Dose reduction of valganciclovir was based on the CrCl (mL/min): CrCl 40–59: 450 mg orally once daily; CrCl 25–39: 40 mg orally every 2 days; CrCl 10–24: 450 mg twice weekly.

CMV: cytomegalovirus; CrCl: creatinine clearance; HSV: herpes simplex virus; IV: intravenous; RCT: randomized controlled trial; VZV: varicella zoster virus

The MK-8228-002 study is a completed double-blind RCT comparing letermovir with valganciclovir. It included adult CMV-seronegative recipients of kidney transplants from CMV-seropositive donors. Patients with previous solid organ transplant (with the exception of previous kidney transplant) or previous haematopoietic stem cell transplant were excluded from the MK-8228-002 study. Adults with severely impaired post-transplant renal function (CrCl ≤ 10) as well as patients with a history of confirmed or suspected CMV disease within 6 months prior to randomization were also excluded from the study.

A total of 601 patients were enrolled and randomly allocated in a 1:1 ratio to treatment with letermovir (N = 301) or valganciclovir (N = 300). Randomization was no later than 7 days after kidney transplantation and was stratified according to induction therapy (use versus non-use of highly cytolytic anti-lymphocyte immunotherapy during induction).

In Module 4 A of its dossier, the company presented analyses of 2 analysis populations. Outcomes in the categories of mortality, morbidity and health-related quality of life were based on the full analysis set (FAS) population, defined by the company, according to the study protocol, as all randomized patients who received at least one dose of the study medication, who were seronegative for previous CMV infection after retesting at study start, and who had no detectable CMV deoxyribonucleic acid (DNA) on Day 1 of treatment (letermovir N = 289; valganciclovir N = 297). In the present therapeutic indication, according to the guideline, all transplant recipients and their donors should be serologically tested for CMV antibodies shortly before transplantation. Monitoring the CMV DNA concentration under prophylaxis is not necessary, however, and should only be carried out if there is clinical suspicion of CMV replication [7]. It is therefore not assumed that, in everyday practice, patients are regularly tested for CMV DNA when starting prophylaxis treatment with letermovir or valganciclovir. Since only 2 patients were excluded from the FAS population due to CMV DNA detection on Day 1 of treatment, the company's approach has no consequences for the present benefit assessment.

Outcomes in the side effects category are based on the all-participants-as-treated (APaT) population, which comprises all randomized patients who received at least one dose of the study medication (letermovir N = 292; valganciclovir N = 297). This approach is appropriate.

Treatment with letermovir could be started on the day of the transplant up to Day 7 post-transplant, and was continued up to 28 weeks post-transplant (treatment could be discontinued prematurely due to a CMV infection, for example). Treatment was without relevant deviation from the recommendations of the SPC [8]. In addition, aciclovir (400 mg orally twice daily) was administered in the intervention arm over the entire treatment period for prophylaxis of HSV and VZV infections. The uncertainty regarding the transferability of the results of the MK-8228-002 study to the German health care context resulting from this mandatory concomitant treatment with aciclovir in the intervention arm is addressed in more detail in the section on limitations below.

Treatment with valganciclovir could also be started on the day of the transplant up to Day 7 post-transplant, and was continued up to 28 weeks post-transplant (treatment could be discontinued prematurely due to a CMV infection, for example). Treatment was in compliance with the recommendations of the SPC [9].

The outcomes in the category of mortality, morbidity and health-related quality of life were to be observed up to 52 weeks post-transplant. Side effects were recorded only for the period of treatment with the study medication (plus 2 weeks). The planned observation period corresponds to the actual median observation period stated by the company in Module 4 A.

The primary outcome of the study is the composite outcome of CMV disease, consisting of the components of CMV end-organ disease and CMV syndrome. Furthermore, patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Limitations of the MK-8228-002 study

The certainty of conclusions of the study results is limited due to the mandatory concomitant treatment with aciclovir in the intervention arm described above. The company justified the administration of aciclovir by stating that corresponding prophylaxis in the comparator arm was already covered by the administration of valganciclovir. This statement is correct according to the information in the SPC for valganciclovir [9]. However, it cannot be inferred from the SPC for letermovir [8] that concomitant treatment with aciclovir should be carried per se. The guideline [7] also provides no explicit recommendation for routine prophylaxis of HSV or VZV infection in this therapeutic indication. Only patients with a history of herpes zoster should be given prophylaxis against VZV in the first 3 to 6 months after transplantation. According to the clinical study report (CSR), only 2% of patients had herpes zoster infection. In addition, dosing regimen and treatment duration of aciclovir do not correspond to the recommendations in the SPC for aciclovir [10]. However, in accordance with the assessment of the EMA, it can be assumed that the administered dose of aciclovir has no anti-CMV activity [10,11]. The uncertainty regarding the transferability of the study results to the German health care context is addressed in the certainty of the conclusions (see Section I 4.2).

Characteristics of the study population

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: letermovir vs. valganciclovir (multipage table)

Study **Characteristic** **Category**	**Letermovir** **N[a] = 289**	**Valganciclovir** **N[a] = 297**
MK-8228-002		
Age [years], mean (SD)	50 (15)	50 (15)
Sex [F/M], %	27/73	30/70
Family origin, n (%)		
Native North American or Alaska Native	3 (1)	4 (1)
Asian	4 (1)	10 (3)
Black or African American	21 (7)	33 (11)
White	250 (87)	243 (82)
Multiple	9 (3)	6 (2)
Missing	2 (< 1)	1 (< 1)
Highly cytolytic, anti-lymphocyte immunotherapy, n (%)[b]		
Use	131 (45)	138 (47)
Non-use	158 (55)	159 (54)
Main reason for transplant, n (%)		
Alport syndrome	4 (1)	6 (2)
Chronic kidney disease/end-stage kidney disease	19 (7)	20 (7)
Congenital cystic kidney disease	52 (18)	50 (17)
Diabetes/diabetic nephropathy	37 (13)	46 (16)
Glomerulonephritis	37 (13)	30 (10)
Hypertension	42 (15)	53 (18)
IgA nephropathy	35 (12)	26 (9)
Lupus	2 (1)	5 (2)
Mesangioproliferative glomerulonephritis	2 (1)	1 (< 1)
Renal atrophy	5 (2)	3 (1)
Tubulointerstitial nephritis	3 (1)	7 (2)
Urinary obstruction	8 (3)	4 (1)
Other	43 (15)	46 (16)
Donor type, n (%)		
Living, related	55 (19)	64 (22)
Living, not related	65 (23)	51 (17)
Deceased	169 (59)	182 (61)
Days from transplantation to the start of treatment		
Mean (SD)	4.4 (1.9)	4.5 (1.9)
Treatment discontinuation, n (%)[c]	46 (15)	73 (24)
Study discontinuation, n (%)[d]	36 (12)	31 (10)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: letermovir vs. valganciclovir (multipage table)

Study Characteristic Category	Letermovir N[a] = 289	Valganciclovir N[a] = 297
a. Full analysis set population of the company, defined as all randomized patients who received at least one dose of the study medication, who were assigned to the category of seronegative recipients, and who had no detectable CMV deoxyribonucleic acid on Day 1 of treatment. b. Use of highly cytolytic, anti-lymphocyte immunotherapy comprised the use of one or several of the following agents: horse-derived or rabbit-derived antithymocyte globulin, alemtuzumab, or muromonab CD3 (OKT3). The stratum is based on the confirmation of high-cytolytic anti-lymphocyte immunotherapy received at the time of transplant. c. Common reasons for treatment discontinuation in the intervention vs. the control arm were: adverse event (4.3 vs. 13.3%), discontinuation at the patient's request (6.0% vs. 4.7%), decision by the investigator (2.0% vs. 2.3%). d. Common reasons for study discontinuation in the intervention vs. the control arm were: discontinuation at the patient's request (9.3% vs. 7.0%), death (1.0% vs. 1.0%), decision by the investigator (1.0% vs. 1.0%). CMV: cytomegalovirus; F: female; M: male; MD: mean difference; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation		

The patient characteristics are largely balanced between the study arms. The mean age of the patients was about 50 years, and the proportion of female patients (about 30%) was lower than the proportion of male patients in both arms. Slightly less than half of the patients received a highly cytolytic, anti-lymphocyte immunotherapy during induction therapy. Treatment discontinuations occurred more frequently in the control arm (24%) than in the intervention arm (15%). The number of study discontinuations is comparable between the arms (12% versus 10%).

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: letermovir vs. valganciclovir

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
MK-8228-002	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the MK-8228-002 study.

Transferability of the study results to the German health care context

From the company's point of view, the results of the MK-8228-002 study can be transferred to the German health care context due to the characteristics of the investigated patient population, the study design and the approval-compliant use of letermovir.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also Section I 4.2.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - graft loss
  - severe CMV disease
  - CMV end-organ disease
  - NODAT
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - measured using the SF-36v2
- Side effects
  - SAEs
  - discontinuation due to AEs
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 10 shows the outcomes for which data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: letermovir vs. valganciclovir

Study	Outcomes									
	All-cause mortality	Graft loss	Severe CMV disease[a]	CMV end-organ disease	NODAT[b]	Health status (EQ-5D VAS)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	General disorders and administration site conditions (SOC, SAEs)
MK-8228-002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Operationalized as rehospitalization for CMV disease.
b. Defined as the first occurrence of diabetes after kidney transplantation, according to WHO (World Health Organization) and ADA (American Diabetes Association) guidelines.

AE: adverse event; CMV: cytomegalovirus; NODAT: new-onset diabetes mellitus after transplantation; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36-version 2 Health Survey; SOC: System Organ Class; VAS: visual analogue scale

Notes on the outcomes

All-cause mortality

The company presented analyses based on the relative risk for the outcome of all-cause mortality. Even with the same observation periods, time-to-event analyses would generally be desirable for all-cause mortality in the present therapeutic indication, in which there is a relevant risk of death for the patients. However, due to the low number of events for this outcome in both treatment groups, it cannot be assumed in the present data situation that using the hazard ratio would produce a relevant difference in results. The analyses based on the relative risk are therefore used for the present benefit assessment.

Severe CMV disease

Severe CMV disease is defined as all hospitalizations due to CMV infection/CMV disease that occurred after the first post-transplant discharge. No further information is available on the conditions under which hospitalization due to CMV infection/CMV disease occurred. Furthermore, it remains unclear whether this was associated with a minimum time criterion. Hospitalization is assumed to have occurred upon the treating physician's discretion. Since the company stated in Module 4 A that these were inpatient stays, the events are assumed not to be short-term hospital stays. For the present benefit assessment, hospitalization due to CMV infection/CMV disease is used to represent severe CMV disease.

CMV end-organ disease

The outcome of CMV end-organ disease is used for the benefit assessment. This deviates from the approach of the company, which used the composite outcome of CMV disease in the benefit assessment. This is justified below.

The composite outcome of CMV disease used by the company comprises the following 2 components:

- CMV end-organ disease (involvement of ≥ 1 organ system with clinical manifestation in addition to detection of CMV)
- CMV syndrome operationalized by the following individual components, of which at least 2 criteria had to be met in addition to detection of CMV
  - fever ≥ 38°C for at least 2 days
  - new or increased malaise (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 2 or higher) or fatigue (CTCAE grade ≥ 3)
  - leukopenia or neutropenia on 2 separate measurements at least 24 hours apart
  - ≥ 5% atypical lymphocytes
  - thrombocytopenia
  - elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to ≥ 2 times upper limit of normal (ULN)

The operationalizations correspond to the definition according to Ljungman 2016 [12]. All events had to be confirmed by an independent blinded Clinical Adjudication Committee.

For a composite outcome to be eligible for inclusion in a benefit assessment, the individual components of the outcome must be patient relevant and of similar severity. This is not the case for the component CMV syndrome. Four of the 6 included events are based on laboratory parameters. For these laboratory parameters, it cannot be assumed per se that a change will result in symptoms noticeable for the patient. The threshold values predefined for leukopenia, neutropenia and thrombocytopenia correspond to CTCAE grades 1 or 2 and are therefore not directly patient relevant. Overall, it is unclear how many of the events qualifying for the composite outcome were directly patient relevant, which is why the individual component CMV syndrome in the present operationalization is not used for the benefit assessment. Regardless of the limitations described, there was no statistically significant difference between treatment groups for CMV syndrome at Week 52.

Various events involving an organ system were recorded in the component of CMV end-organ disease. The events “gastrointestinal disorders” and “pneumonia” occurred in study

MK-8228-002. According to the definition in the study protocol, these events were associated with symptoms and therefore directly patient relevant. The component of CMV end-organ disease is therefore used for the benefit assessment.

Graft loss

The outcome of graft loss is used for the benefit assessment. This differs from the company's approach, which used the composite outcome of graft dysfunction and/or rejection. This is justified below.

The composite outcome of graft dysfunction and/or rejection used by the company is defined as the occurrence of at least one of the following events:

- ≥ 20% decline in post-transplant estimated glomerular filtration rate (eGFR) from Week 4 to Week 28 and Week 52 post-transplant
- biopsy-proven acute kidney transplant rejection
- graft loss
- eGFR < 60 mL/min/1.73m^2 until Week 28 post-transplant

The operationalization chosen by the company in Module 4 A deviates from the operationalization planned in the study protocol, which does not include the component of eGFR < 60 mL/min/1.73m^2 until Week 28 post-transplant. This approach is not appropriate and was not explained by the company.

Irrespective of the operationalization deviating from the original planning, it is necessary, as already described above, that the individual components of a composite outcome are patient relevant. In this case, this only applies to the component of graft loss. This is further explained below:

Post-transplant eGFR

An eGFR < 60 mL/min/1.73 m^2 is not necessarily patient relevant. In view of the mean baseline eGFR of approx. 50 mL/min/1.73 m², a decline in post-transplant eGFR by ≥ 20% is also not assumed to represent a noticeable deterioration in renal function for the majority of affected patients.

Acute kidney transplant rejection

If acute rejection is detected, the patient is usually given appropriate treatment with the aim of preserving the transplant. The avoidance of this subsequent therapy is not considered a patient-relevant outcome per se. In the MK-8228-002 study, acute kidney transplant rejection had to be proven by biopsy. No further information is available for this outcome. It is therefore unclear whether the performance of a biopsy was necessarily associated with patient-

noticeable symptoms before the biopsy. If the treatment of acute rejection is unsuccessful and the graft is lost, this is already recorded with the patient-relevant outcome of graft loss. Any side effects that may be associated with the treatment of acute rejection are shown in the data on patient-relevant side effects (see I Appendix B of the full dossier assessment). Irrespective of this, there was no statistically significant difference between the treatment arms for the outcome of acute kidney transplant rejection.

Therefore, the benefit assessment only includes the component of graft loss, for which a separate analysis was planned study design. Similar to all-cause mortality, time-to-event analyses would also be desirable for the outcome of graft loss. However, due to the low number of events in both treatment groups, it cannot be assumed that using a time-to-event analysis would produce a relevant difference in results, so that the results based on the relative risk presented by the company are used for the benefit assessment.

Health status and health-related quality of life

For the health status outcomes (surveyed via EQ-5D VAS) and health-related quality of life (surveyed via SF-36v2), the company submitted responder analyses, using the following response criteria:

- EQ-5D VAS: improvement by ≥ 15 points, each at Week 28 and at Week 52 (scale range of EQ-5D VAS: 0 to 100 points)
- SF-36v2: improvement by 9.4 (Physical Component Summary) and 9.6 points (Mental Component Summary). (Although the company did not specify a scale range, it is assumed on the basis of the available data that the standardized scale with a minimum of approx. 7 or 6 and a maximum of approx. 70 was used.)

This corresponds to a 15% improvement of the respective scale range of the 2 outcomes. As explained in the IQWiG *General Methods* [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified (and exactly 15% of the scale range in post-hoc analyses). Accordingly, the results for the improvement by ≥ 15 points (in each case exactly 15% of the scale range) are used for the derivation of the added benefit for the outcomes of EQ-5D VAS and SF-36v2. The company presented analyses for both outcomes at Week 28 (end of treatment) and Week 52 (end of study) and, in addition to the responder analyses, presented the mean values with standard error over the course of the study. Since the results were constant over the course of the study and, no deviating results were shown at the end of treatment (Week 28) in particular, the responder analyses for the longest observation period (Week 52) are used in the present benefit assessment.

Proportion of missing values and imputation strategy chosen by the company

For the outcome of CMV end-organ disease, the proportion of missing values was given as approx. 18% per treatment group. For the other outcomes (graft loss, severe CMV disease and NODAT), no data on missing values are available, but a similar proportion of missing values in both treatment groups is assumed. Slightly more than half of the missing values per treatment group can be explained by study discontinuation before Week 52. The company provided no further information for the remaining approx. 8% of missing values at Week 52. The company imputed the missing values in its analyses using the prespecified observed failure (OF) approach, i.e. patients with premature study discontinuation or with missing value at Week 52 were assumed to have no event for the corresponding outcome at Week 52.

The company's assumption that no event in the outcomes described above occurred in patients without value at Week 52 cannot be verified. Due to the high proportion of missing values compared with the events actually observed, sensitivity analyses based on imputation methods for these outcomes are subject to high uncertainty. The high proportion of missing values is particularly problematic for outcomes that fell just short of statistical significance (see Table 12, e.g. outcome of CMV end-organ disease).

For the 2 patient-reported outcomes (EQ-5D VAS and SF-36v2), the proportion of missing values at Week 52 (as no questionnaire was available at this time) was just under 30% in both treatment groups. The information on the response rates provided in Module 4 A shows that even at baseline, about 5% to 8% of patients had not completed a questionnaire. The company restricted its analyses to patients for whom at least one recording (regardless of the time point) of the patient-reported outcome was available (intervention arm N = 284; control arm N = 292). The company did not state that it had used an imputation strategy for the missing values for these outcomes. However, the fact that the company excluded notably fewer than the 30% of patients with missing value at Week 52 from the analyses means that patients without value at baseline and/or Week 52 were also assumed to have no event at Week 52. The company did not present any sensitivity analyses (with alternative imputation strategies) for these outcomes.

In principle, the reasons for missing values are potentially informative. The influence of the missing values on the results of the outcomes described is unclear. The resulting uncertainty is addressed in the assessment of the outcome-specific risk of bias.

Side effects

SAEs and discontinuation due to AEs

In Module 4 A, the company presented analyses on side effects that exclude disease-related events and/or events that were already included in the morbidity outcomes analysed by the company. In Appendix 4 G to Module 4 A, the company listed the total of 36 Preferred Terms

(PTs) it had excluded from the analyses. The approach of the company is not appropriate. On the one hand, the approach is not consistent. For example, the events of neutropenia, leukopenia and fever were not excluded, although they are included in the outcome of CMV syndrome analysed by the company. On the other hand, it is not possible in this therapeutic indication to clearly differentiate between treatment-related side effects and events resulting from the kidney transplant. In the present situation, it would be appropriate to only exclude events that can be clearly attributed to a CMV infection (e.g. the PTs cytomegalovirus infection, cytomegalovirus hepatitis, etc.). In Appendix 4 G to Module 4 A, the company additionally presented analyses of the side effect outcomes with all events that occurred. The present benefit assessment uses these analyses of AEs, SAEs and discontinuations due to AEs, as the disease-related events (i.e. those attributable to the CMV infection) only account for a negligible proportion of all events that occurred.

Further outcomes used by the company for the benefit assessment

Opportunistic infections

This outcome is defined as the occurrence of one of the following events after transplantation:

- Pneumocystis jirovecii pneumonia
- BK virus infection
- human polyomavirus (non-BK virus) infection
- HSV infection (including superficial, e.g. oral HSV infection and systemic HSV infection)
- VZV infection (including primary VZV infection and herpes zoster)
- oral candidiasis
- candidiasis (i.e. non-oral Candida infection)
- Mycobacterium tuberculosis infection

The company presented analyses up to Week 28 and Week 52 for this outcome, without information on the individual events included. From the information in the company's dossier, it remains unclear how opportunistic infections were recorded during the study, i.e. whether there was systematic screening for the pathogens mentioned or whether testing was only carried out in case of suspected infection or symptoms. It can be inferred from the information provided in the CSR that most of the opportunistic infections occurred at Week 28 were due to a BK virus infection (in 28 out of 30 patients with infection in the intervention arm, and 28 out of 36 patients in the control arm). Corresponding information on Week 52 is missing. According to the guideline [7], regular testing for the BK virus should be carried out after a kidney transplant. Only if a certain viral load is exceeded and a renal function disorder is also present, should a biopsy be performed. An intervention should only take place in the case of histologically confirmed polyomavirus-associated nephropathy. Detection of a virus alone is

therefore not necessarily a patient-relevant event. The outcome of opportunistic infections without further information on the occurrence or severity of the observed opportunistic infections is therefore not used for the benefit assessment. Regardless of the limitations described, there was no statistically significant difference between treatment groups for opportunistic infections at Week 52.

Use of granulocyte colony stimulating factor (G-CSF)

The use or avoidance of the use of G-CSF is not patient relevant per se. The possible disadvantages of G-CSF use described by the company, such as side effects, are represented in the AE recordings. The analyses of G-CSF use presented by the company are therefore disregarded for the benefit assessment.

AEs of special interest

In Module 4 A, under the outcome of AEs of special interest, the company presented analyses on the outcomes of leukopenia and neutropenia, differentiating between 2 approaches:

- analyses based on the PTs (leukopenia and neutropenia) in the operationalizations of AEs, SAEs and severe AEs, recorded as part of the survey of side effects
- analyses according to CTCAE severity. For this purpose, the company transferred the laboratory values for the leukocyte count and the absolute neutrophil count systematically recorded in the study to the CTCAE threshold values for leukopenia and neutropenia.

For the analyses of the outcomes of leukopenia and neutropenia, the company used the analysis time point at Week 30 post-transplant in each case.

The analyses on leukopenia or neutropenia presented by the company on the basis of the retrospective severity classification according to CTCAE and the severity classification according to the investigator are not used for the benefit assessment. Leukopenia and neutropenia are taken into account in the analyses of SAEs, but are not presented separately. This is explained below.

Leukopenia or neutropenia as part of the side effects

As leukopenia and neutropenia are only recorded via laboratory values, it cannot be assumed per se that they are associated with any noticeable symptoms for the patient. Severe or serious leukopenia and/or neutropenia, on the other hand, is generally patient relevant. However, the analyses on severe leukopenia or neutropenia presented by the company are generally not suitable for the benefit assessment, as they are based exclusively on a severity classification into mild, moderate or severe according to the investigator's assessment. Serious leukopenia and neutropenia (SAEs) are taken into account, however. However, they

were very rare in the MK-8228-002 study and did not meet the criteria specified in the dossier template and applied by the company itself (< 10 patients per treatment group) for the presentation of analyses of SOCs and PTs. According to the methods used in benefit assessments, these events are therefore not used separately to derive the added benefit, but are included in the overall rates of SAEs.

Leukopenia and neutropenia based on subsequent CTCAE severity classification

The subsequent calculation of (individual) laboratory values into CTCAE severity grades does not provide a complete picture of the side effects that occurred during the course of the study. On the one hand, the laboratory parameters were only recorded during certain study visits and not continuously such as side effects; on the other hand, side effects that are not based on systematically recorded laboratory or vital parameters are not represented in such a post hoc analysis. Since this is therefore a selective consideration of events, this approach is not appropriate.

Irrespective of this selective and therefore inappropriate consideration, only events until Week 30 are presented, although a recording of these laboratory parameters was planned until Week 52. Furthermore, the discrepancy between the lower number of neutropenia and leukopenia events based on the analyses of side effects and the relatively high number of events based on CTCAE severity is not comprehensible. There were up to 3 times as many events based on the subsequent CTCAE severity classification. This discrepancy was not explained by the company.

I 4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: letermovir vs. valganciclovir

Study	Study level	Outcomes									
		All-cause mortality	Graft loss	Severe CMV disease[a]	CMV end-organ disease	NODAT[b]	Health status (EQ-5D VAS)	Health-related quality of life (SF 36v2)	SAEs	Discontinuation due to AEs	General disorders and administration site conditions (SOC, SAEs)
MK-8228-002	L	L	H[c]	H[c]	H[c]	H[c]	H[c]	H[c]	L[d]	L[e]	L[d]

a. Operationalized as rehospitalization for CMV disease.
b. Defined as the first occurrence of diabetes after kidney transplantation, according to WHO (World Health Organization) and ADA (American Diabetes Association) guidelines.
c. High proportion of missing or imputed values (see body of text below and Section I 4.1)
d. Limited observation period.
e. Despite a low risk of bias, the certainty of results for the outcome of discontinuation due to AEs is assumed to be limited (see body of text below).

AE: adverse event; CMV: cytomegalovirus; H: high; L: low; NODAT: new-onset diabetes mellitus after transplantation; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36-version 2 Health Survey; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results for the outcome of all-cause mortality was rated as low. The risk of bias for the outcomes of morbidity, health status, and health-related quality of life was rated as high. This is due to the high proportion of missing or imputed values at the relevant analysis date after 52 weeks (for the morbidity outcomes approx. 18% without relevant differences between treatment groups, and for health status and health-related quality of life just under 30% each without relevant differences between treatment groups).

The risk of bias for the AE outcomes was rated as low. However, the observation period is limited here (2 weeks after the last dose of study medication). The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias. Premature treatment discontinuation for reasons other than AEs represents a competing event for the outcome to be recorded, discontinuation due to AEs. This means that while AEs that would have led to treatment discontinuation might occur after discontinuation for other reasons, it is no longer possible to survey the criterion of “discontinuation” for them. It is impossible to estimate how many AEs are affected by this issue.

Summary assessment of the certainty of conclusions

Regardless of the aspects described for the risk of bias, the certainty of conclusions of the study results is limited due to the uncertainties described in Section I 3.2. Since all patients in the intervention arm, in addition to letermovir, received treatment with aciclovir for prophylaxis of HSV and VZV infection over the entire treatment period of 28 weeks, it is unclear to what extent the results of the MK-8228-002 study are fully transferable to the German health care context. Overall, at most hints, e.g. of an added benefit, can be therefore determined for all outcomes presented.

I 4.3 Results

Table 12 summarizes the results of the comparison of letermovir with valganciclovir for prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The results on common AEs, SAEs and discontinuation due to AEs are each presented in I Appendix B of the full dossier assessment. The results on overall hospitalization are presented as supplementary information in I Appendix C of the full dossier assessment.

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: letermovir vs. valganciclovir (multipage table)

Study Outcome category Outcome	Letermovir		Valganciclovir		Letermovir vs. valganciclovir
	N[a, b]	Patients with event n (%)	N[a, b]	Patients with event n (%)	RR [95% CI]; p-value[c]
MK-8228-002					
Mortality (until Week 52)					
All-cause mortality	289	4 (1.4)	297	3 (1.0)	1.41 [0.32; 6.33]; 0.651
Morbidity (until Week 52)					
Graft loss	289	2 (0.7)	297	6 (2.0)	0.37[d] [0.09; 1.51]; 0.167
Severe CMV disease	289	35 (12.1)	297	34 (11.4)	1.06 [0.68; 1.65]; 0.796
CMV end-organ disease[e]	289	6 (2.1)	297	1 (0.3)	4.42[d] [0.99; 19.61]; 0.051
NODAT[f]	289	18 (6.2)	297	20 (6.7)	0.92 [0.50; 1.69]; 0.782
Health status (EQ-5D VAS, improvement at Week 52)[g]	284	100 (35.2)	294	98 (33.3)	1.06 [0.84; 1.32]; 0.639
Health-related quality of life (improvement at Week 52)					
SF-36v2					
Physical Component Summary (PCS)[h]	284	120 (42.3)	292	101 (34.6)	1.22 [0.99; 1.50]; 0.061
Mental Component Summary (MCS)[i]	284	33 (11.6)	292	44 (15.1)	0.77 [0.51; 1.18]; 0.227
Physical functioning	284	136 (47.9)	292	141 (48.3)	0.99 [0.84; 1.17]
Physical role functioning	284	125 (44.0)	292	118 (40.4)	1.09 [0.90; 1.32]
Physical pain	284	119 (41.9)	292	106 (36.3)	1.15 [0.94; 1.41]
General health perception	284	88 (31.0)	292	74 (25.3)	1.22 [0.94; 1.59]
Vitality	284	115 (40.5)	292	99 (33.9)	1.19 [0.96; 1.48]
Social functioning	284	88 (31.0)	292	83 (28.4)	1.09 [0.85; 1.40]
Emotional role functioning	284	64 (22.5)	292	60 (20.5)	1.10 [0.80; 1.50]
Mental well-being	284	69 (24.3)	292	67 (22.9)	1.06 [0.79; 1.42]
Side effects (until Week 30)					
AEs (supplementary information)	292	271 (92.8)	297	276 (92.9)	–
SAEs	292	106 (36.3)	297	113 (38.1)	0.95 [0.77; 1.18]; 0.661
Discontinuation due to AEs	292	12 (4.1)	297	40 (13.5)	0.31 [0.16; 0.57]; < 0.001

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: letermovir vs. valganciclovir (multipage table)

Study Outcome category Outcome	Letermovir		Valganciclovir		Letermovir vs. valganciclovir
	N[a, b]	Patients with event n (%)	N[a, b]	Patients with event n (%)	RR [95% CI]; p-value[c]
General disorders and administration site conditions (SOC, SAEs)	292	13 (4.5)	297	4 (1.4)	3.31 [1.09; 10.02]; 0.025

a. Full analysis set population of the company, defined as all randomized patients who received at least one dose of the study medication, who were assigned to the category of seronegative recipients, and who had no detectable CMV deoxyribonucleic acid (DNA) on Day 1 of treatment.
b. Outcomes in the morbidity categories (except health status): Missing values were imputed using the "observed failure" approach. In this approach, for patients who discontinued the study prematurely or for whom no data were available at Week 52, it was assumed that no event occurred in the respective outcome at Week 52.
c. Outcomes of the categories of morbidity and health-related quality of life: Cochran-Mantel-Haenszel method, stratified by induction therapy (use vs. non-use), p-value from Wald test; outcomes of the category of side effects: Cochran-Mantel-Haenszel method, unstratified, p-value from Wald test.
d. Peto odds ratio (for proportions of events ≤ 1% or ≥ 99% in at least one treatment arm).
e. The following events occurred in study MK-8228-002: gastrointestinal disorders and pneumonia, each in connection with CMV detection and confirmed by a blinded Clinical Adjudication Committee
f. Defined as the first occurrence of diabetes after kidney transplantation, according to WHO (World Health Organization) and ADA (American Diabetes Association) guidelines.
g. Proportion of patients with score increase by ≥ 15 points from baseline to Week 52, at a scale range of 0 to 100. Higher (increasing) values indicate an improvement in health status.
h. Proportion of patients with improvement: increase in PCS score by ≥ 9.4 points from baseline to Week 32 (corresponds to 15% of the scale range; normalized scale with a minimum of approx. 7 and a maximum of approx. 70).
i. Proportion of patients with improvement: increase in MCS score by ≥ 9.6 points from baseline to Week 32 (corresponds to 15% of the scale range; normalized scale with a minimum of approx. 6 and a maximum of approx. 70).

AE: adverse event; CI: confidence interval; CMV: cytomegalovirus; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; NODAT: new-onset diabetes mellitus after transplantation; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form 36-version 2 Health Survey; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see also Section I 4.2).

Mortality

All-cause mortality

No statistically significant difference between treatment groups was shown for the outcome of all-cause mortality. There is no hint of an added benefit of letermovir in comparison with valganciclovir for the outcome of all-cause mortality; an added benefit is therefore not proven.

Morbidity

Graft loss

No statistically significant difference between treatment groups was shown for the outcome of graft loss. There is no hint of an added benefit of letermovir in comparison with valganciclovir for the outcome of graft loss; an added benefit is therefore not proven.

Severe CMV disease

No statistically significant difference between treatment groups was shown for the outcome of severe CMV disease. There is no hint of an added benefit of letermovir in comparison with valganciclovir for the outcome of severe CMV disease; an added benefit is therefore not proven.

NODAT

No statistically significant difference between treatment groups was shown for the outcome of NODAT. However, there is an effect modification by the characteristic of age (< 65 versus ≥ 65 years). For patients ≥ 65 years of age, there is a hint of an added benefit of letermovir compared with valganciclovir. For patients < 65 years of age, there is no hint of an added benefit of letermovir compared with valganciclovir; an added benefit is therefore not proven for this patient group (see Section I 4.4).

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was shown for the outcome of health status. There is no hint of an added benefit of letermovir in comparison with valganciclovir; an added benefit is therefore not proven.

Health-related quality of life

SF-36v2 – Physical and Mental Component Summary

Health-related quality of life outcomes were recorded using the SF-36v2.

Statistically significant differences between treatment groups were shown neither for the Physical nor for the Mental Component Summary. There is no hint of an added benefit of letermovir in comparison with valganciclovir; an added benefit is therefore not proven.

Side effects

SAEs

No statistically significant difference between treatment groups was shown for the outcome of SAEs. There is no hint of greater or lesser harm from letermovir in comparison with valganciclovir; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference between treatment groups in favour of letermovir was shown for the outcome of discontinuation due to AEs. However, there is an effect modification by the characteristic of sex (male versus female). For men, there is a hint of lesser harm from letermovir in comparison with valganciclovir. For women, there is no hint of greater or lesser harm from letermovir in comparison with valganciclovir; greater or lesser harm is therefore not proven for women (see Section I 4.4).

Specific AEs

General disorders and administration site conditions

A statistically significant difference to the disadvantage of letermovir was shown for the outcome of general disorders and administration site conditions (SOC, SAEs). There is a hint of greater harm from letermovir in comparison with valganciclovir.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- induction therapy (use versus non-use of a highly cytolytic, anti-lymphocyte immunotherapy)

In the present benefit assessment, the subgroup characteristic of induction therapy was taken into account because the use of a highly cytolytic, anti-lymphocyte immunotherapy increases the risk of CMV infection [13] and thus represents a characteristic for kidney transplant recipients with a high immunological risk.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there have to be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Table 13 summarizes the subgroup results of the comparison of letermovir with valganciclovir for prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor.

Table 13: Subgroups (morbidity, side effects) – RCT, direct comparison: letermovir vs. valganciclovir

Study Outcome Characteristic Subgroup	Letermovir N	Letermovir Patients with event n (%)	Valganciclovir N	Valganciclovir Patients with event n (%)	Letermovir vs. valganciclovir RR [95% CI]	Letermovir vs. valganciclovir p-value
MK-8228-002						
NODAT						
Age [years]						
< 65	242	18 (7.4)	242	16 (6.6)	1.14 [0.57; 2.30][a]	0.708
≥ 65	47	0 (0)	55	4 (7.3)	0.12 [0.02; 0.88][a]	0.037
Total					Interaction:	0.024[b]
Treatment discontinuation due to AEs						
Sex						
Male	213	6 (2.8)	209	31 (14.8)	0.19 [0.08; 0.45][c]	0.028[d]
Female	79	6 (7.6)	88	9 (10.2)	0.74 [0.28; 1.99][c]	0.597[d]
Total					Interaction:	0.038[e]

a. RR and CI according to Wald from 2x2 table, p-value from Cochran-Mantel-Haenszel test; Peto odds ratio for event rates of ≤ 1% in at least one cell, p-value from Wald test.
b. Generalized linear model, stratified by use of induction therapy (use vs. non-use), with treatment and subgroup as covariates and interaction between treatment and subgroup (p-value using the likelihood ratio test).
c. Institute's calculation of RR and CI (asymptotic).
d. Institute's calculation (unconditional exact test, CSZ method according to [14]).
e. Institute's calculation of Q test for heterogeneity.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; NODAT: new-onset diabetes mellitus after transplantation; RCT: randomized controlled trial; RR: relative risk

Morbidity

NODAT

For the outcome of NODAT, there was a statistically significant interaction by the characteristic of age. A statistically significant difference in favour of letermovir was shown for patients ≥ 65 years of age. For patients ≥ 65 years of age, there is a hint of an added benefit of letermovir compared with valganciclovir.

For patients < 65 years of age, there is no hint of an added benefit of letermovir compared with valganciclovir; an added benefit is therefore not proven for this patient group.

Side effects

Discontinuation due to AEs

There was an effect modification by the characteristic of sex for the outcome of discontinuation due to AEs. A statistically significant difference in favour of letermovir compared with valganciclovir was shown for men. For men, there is a hint of lesser harm from letermovir in comparison with valganciclovir.

For women, there is no hint of greater or lesser harm from letermovir in comparison with valganciclovir; greater or lesser harm is therefore not proven for women.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 14).

Determination of the outcome category for outcomes on morbidity and side effects

The dossier does not provide any details as to whether the outcomes regarding morbidity and side effects were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

NODAT

Concurring with the company, the outcome of NODAT is assigned to the outcome category of serious/severe symptoms/late complications in the present therapeutic indication. The outcome is defined as the first occurrence of diabetes after kidney transplantation, according to WHO (World Health Organization) and ADA (American Diabetes Association) guidelines [13]. These criteria correspond to manifest diabetes mellitus. The ADA guideline also describes new-onset diabetes mellitus as a severe complication after solid organ transplantation [15].

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, the available severity data are insufficient for a classification as serious/severe. The outcome of discontinuation due to AEs was therefore assigned to the outcome category of non-serious/non-severe side effects.

Table 14: Extent of added benefit at outcome level: letermovir vs. valganciclovir (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Letermovir vs. valganciclovir** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration (Week 52)		
Mortality		
All-cause mortality	1.4 vs. 1.0 RR: 1.41 [0.32; 6.33]; p = 0.651	Lesser/added benefit not proven
Outcomes		
Morbidity		
Graft loss	0.7 vs. 2.0 Peto OR: 0.37 [0.09; 1.51]; p = 0.167	Lesser/added benefit not proven
Severe CMV disease	12.1 vs. 11.4 RR: 1.06 [0.68; 1.65]; p = 0.796	Lesser/added benefit not proven
CMV end-organ disease	2.1 vs. 0.3 Peto OR: 4.42 [0.99; 19.61]; p = 0.051	Lesser/added benefit not proven
NODAT Age (years) < 65	7.4 vs. 6.6 RR: 1.14 [0.57; 2.30] p = 0.708	Lesser/added benefit not proven
≥ 65	0 vs. 7.3 Peto OR: 0.12 [0.02; 0.88]; p = 0.037 Probability: “hint”	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ Added benefit, extent: “considerable”
Health status (EQ-5D VAS)	35.2 vs. 33.3 RR: 1.06 [0.84; 1.32]; p = 0.639	Lesser/added benefit not proven

Table 14: Extent of added benefit at outcome level: letermovir vs. valganciclovir (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Letermovir vs. valganciclovir** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
SF-36v2, Physical Component Summary (PCS)		
Improvement by ≥ 9.4 points	42.3 vs. 34.6 RR: 1.22 [0.99; 1.50]; p = 0.061	Lesser/added benefit not proven
SF-36v2, Mental Component Summary (MCS)		
Improvement by ≥ 9.6 points	11.6 vs. 15.1 RR: 0.77 [0.51; 1.18]; p = 0.227	Lesser/added benefit not proven
Outcomes with shortened observation period (Week 30)		
Side effects		
SAEs	36.3 vs. 38.1 RR: 0.95 [0.77; 1.18]; p = 0.661	Greater/lesser harm not proven
Discontinuation due to AEs Sex Male	2.8 vs. 14.8 RR: 0.19 [0.08; 0.45]; p = 0.028 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: "considerable"
Female	7.6 vs. 10.2 RR: 0.74 [0.28; 1.99]; p = 0.597	Greater/lesser harm not proven
General disorders and administration site conditions (SAEs)	4.5 vs. 1.4 RR: 3.31 [1.09; 10.02]; RR: 0.30 [0.10; 0.92][c]; p = 0.025 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; MCS: Mental Component Summary; NODAT: new-onset diabetes mellitus after transplantation; PCS: Physical Component Summary; Peto OR: Peto odds ratio; RR: relative risk; SAE: serious adverse event

I 5.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of letermovir in comparison with valganciclovir

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Morbidity Serious/severe symptoms/late complications ▪ NODAT ▫ Age (≥ 65 years): hint of added benefit – extent: "considerable"	–
Outcomes with shortened observation period	
–	Serious/severe side effects ▪ General disorders and administration site conditions (SAE): hint of greater harm – extent: "minor"
Non-serious/non-severe side effects ▪ Discontinuation due to AEs ▫ Sex (male): hint of lesser harm – extent "considerable"	–
AE: adverse event; NODAT: new-onset diabetes mellitus after transplantation; SAE: serious adverse event	

Overall, both positive and negative effects were shown, each with the probability of hint, but of different extents, and on the positive-side only in subgroups.

On the side of positive effects, there is a hint of considerable added benefit in the outcome category of serious/severe late complications for the outcome of NODAT, but only for adults ≥ 65 years. In men, there is an additional hint of lesser harm of considerable extent in the outcome category of non-serious/non-severe side effects for the outcome of discontinuation due to AEs. On the other hand, there is a hint of greater harm of minor extent in the outcome category of serious/severe side effects for the SAE of general disorders and administration site conditions. Overall, there is no added benefit of letermovir in comparison with the ACT.

In summary, there is no hint of an added benefit of letermovir in comparison with the ACT for prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor.

Table 16 summarizes the result of the assessment of added benefit of letermovir in comparison with the ACT.

Table 16: Letermovir – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor	Ganciclovir or **valganciclovir**	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

ACT: appropriate comparator therapy; CMV: cytomegalovirus; G-BA: Federal Joint Committee

The assessment described above deviates from that by the company, which derived an indication of major added benefit.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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