Letermovir (prophylaxis of CMV reactivation and disease after stem cell transplantation)

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

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Letermovir (Prophylaxe einer CMV-Reaktivierung und -Erkrankung nach Stammzelltransplantation) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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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

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent and the mpn-netzwerk e. V. (Myeloproliferative Neoplasm Network) for participating in the written exchange and for their support. The respondent and the mpn-netzwerk e.V. were not involved in the actual preparation of the 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
AE	adverse event
APaT	all participants as treated
CMV	cytomegalovirus
CSR	clinical study report
DNA	deoxyribonucleic acid
FACT-BMT	Functional Assessment of Cancer Therapy – Bone Marrow Transplantation
FAS	full analysis set
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GVHD	graft-versus-host disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

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 watchful waiting as appropriate comparator therapy (ACT) used for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant.

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]**
Prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant	Watchful waiting[b]
a. Presented is the ACT specified by the G-BA. b. It is assumed that pre-emptive therapy is initiated if a CMV infection occurs. ACT: appropriate comparator therapy; CMV: cytomegalovirus; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

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 RCT MK-8228-001 is used for the benefit assessment of letermovir. The company also used the retrospective observational study CELESTIAL for the outcome of overall survival. The data of the CELESTIAL study for the outcome of overall survival presented by the company are not suitable for the benefit assessment, however.

The MK-8228-001 study is a completed, double-blind, randomized multicentre study comparing letermovir with placebo. Adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant were enrolled. The stem cell transplantation had to be

performed within 28 days before randomization. A negative test for CMV deoxyribonucleic acid (DNA) by the central laboratory from a plasma sample collected within 5 days prior to randomization was required for inclusion in the study.

The study included a total of 570 patients who were randomly allocated in a 2:1 ratio either to prophylaxis with letermovir (N = 376) or to placebo (N = 194).

The primary outcome of the study was the composite outcome of clinically significant CMV infection consisting of the components of CMV end-organ disease and initiation of anti-CMV pre-emptive therapy. Patient-relevant secondary outcomes were overall survival as well as outcomes from the categories of morbidity, health-related quality of life, and side effects. The primary outcome was to be observed until Week 24 post-transplant, and further outcomes on morbidity, health-related quality of life and overall survival were observed until Week 48. In Module 4 A, the company presented analyses on outcomes in the categories of mortality, morbidity and health-related quality of life for different observation periods (until Week 24 and additionally until Week 14 and/or until Week 48 post-transplant). If available, the analyses on outcomes in the categories of mortality, morbidity and health-related quality of life until Week 48 are used in the present benefit assessment, as these cover the longest available observation periods. Adverse events (AEs), on the other hand, were only recorded up to 2 weeks after the end of treatment (no longer than until Week 16 after stem cell transplantation).

Analysis populations

The company presented analyses on 2 analysis populations in Module 4 A of the dossier. The primary analyses of the benefit outcomes were conducted based on the full analysis set (FAS) population. Compared with the all-participants-as-treated (APaT) population, which consists of all randomized patients who received at least one dose of study medication, the FAS population excludes 70 patients diagnosed with CMV viraemia by the central laboratory before starting treatment. Patients who already have CMV viraemia before starting treatment with letermovir or placebo are no longer eligible for prophylaxis and generally require pre-emptive therapy. These patients are therefore no longer comprised by the present therapeutic indication. The exclusion of these patients is appropriate. This benefit assessment therefore uses the analyses based on the FAS population if available.

The analyses on outcomes in the side effects category presented by the company in the dossier are based on the APaT population, however. Since the proportion of patients in the APaT population diagnosed with CMV viraemia before starting treatment, who are thus not included in the therapeutic indication, is comparable in both study arms and is < 20%, the discrepancy in the analysis populations is of no consequence for the present benefit assessment.

Duration of treatment with letermovir is not in compliance with the SPC

Treatment with letermovir was started within 28 days after stem cell transplantation and continued until 100 days (14 weeks) after stem cell transplantation. According to the current Summary of Product Characteristics (SPC), prolonged letermovir prophylaxis beyond 100 days after stem cell transplantation may be of benefit in some patients at high risk for late CMV reactivation. However, prolonged prophylaxis was not possible in the MK-8228-001 study. It can be assumed that prolonged prophylaxis would have been an option for a relevant proportion of patients in the intervention arm. The resulting uncertainty is taken into account in the assessment of the certainty of conclusions. No more than hints can be derived for all outcomes.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes for the MK-8228-001 study is rated as low.

The risk of bias of the results for the outcome of overall survival is rated as low. Due to the high proportion of missing values at the relevant date of analysis, the risk of bias is rated as high for the results of the outcomes of onset of CMV end-organ disease, severe CMV reactivation/CMV disease, and acute graft-versus-host disease (GVHD). For the results of the patient-reported outcomes of health status (EQ-5D visual analogue scale [VAS]) and health-related quality of life (Functional Assessment of Cancer Therapy – Bone Marrow Transplantation [FACT-BMT]), the high risk of bias results from the high proportion of patients excluded from the analysis. With the exception of the outcome of discontinuation due to AEs, the risk of bias of the results is rated as high for the outcomes of the side effects category due to incomplete observations for potentially informative reasons. 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. Consequently, after treatment discontinuation for other reasons, AEs which would have led to discontinuation may have occurred, but the criterion of discontinuation can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

As prolonged prophylaxis beyond 100 days would have been an option for a relevant proportion of patients in the study, these patients did not receive letermovir treatment in compliance with the SPC. Overall, this reduces the certainty of conclusions of the study results for the present research question. Based on the MK-8228-001 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

Results

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. There is no hint of an added benefit of letermovir in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Onset of CMV end-organ disease

No statistically significant difference between treatment groups was shown for the outcome of onset of CMV end-organ disease. There is no hint of an added benefit of letermovir in comparison with watchful waiting; an added benefit is therefore not proven.

Severe CMV reactivation/CMV disease

A statistically significant difference between treatment groups in favour of letermovir was shown for the outcome of severe CMV reactivation/CMV disease. There is a hint of an added benefit of letermovir in comparison with watchful waiting.

Acute GVHD

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

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status surveyed with the EQ-5D VAS. There is no hint of an added benefit of letermovir in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

FACT-BMT

No statistically significant difference between treatment groups was shown for the outcome of FACT-BMT total score. There is no hint of an added benefit of letermovir in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs

No statistically significant difference between treatment groups was shown for the outcome of SAEs. However, there is an effect modification by the characteristic of sex. For women, there is a hint of lesser harm from letermovir in comparison with watchful waiting. For men,

however, there is no hint of greater or lesser harm from letermovir in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm from letermovir in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Nervous system disorders (SAEs)

A statistically significant difference between treatment groups to the disadvantage of letermovir was shown for the outcome of nervous system disorders (serious adverse events [SAEs]). There is a hint of greater harm from letermovir in comparison with watchful waiting.

Renal and urinary disorders (SAEs)

A statistically significant difference between treatment groups in favour of letermovir was shown for the outcome of renal and urinary disorders (SAEs). There is a hint of lesser harm from letermovir in comparison with watchful waiting.

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, there are both positive and negative effects of letermovir in comparison with watchful waiting.

On the positive effects side, there is a hint of considerable added benefit in the outcome category of serious/severe symptoms/late complications for the outcome of severe CMV reactivation/CMV disease. In addition, there are hints of lesser harm in the outcome category of serious/severe side effects. For the overall rate of SAEs, there is a hint of lesser harm with the extent “considerable” in the subgroup of women. For the outcome of renal and urinary disorders, there is a hint of lesser harm with the extent “minor”. On the other hand, there is

[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].

a hint of greater harm of non-quantifiable, but no more than considerable extent for the outcome of nervous system disorders in the category of serious/severe side effects.

In comparison with the other outcomes, the observation period for the outcomes in the category of side effects was much shorter. They therefore do not reflect the therapeutic strategies of the 2 study arms, including pre-emptive therapy in patients with CMV reactivation. It is unclear whether an adequate observation period would have potentially shown further or other positive/negative effects in the category of side effects. Overall, this uncertainty does not entirely call into question the positive effects observed. However, it is not possible to quantify the added benefit of letermovir compared with watchful waiting on the basis of the available data.

In summary, there is a hint of a non-quantifiable added benefit of letermovir in comparison with the ACT "watchful waiting" for prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant.

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

Table 3: Letermovir – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant	Watchful waiting[b]	Hint of non-quantifiable added benefit
a. Presented is the ACT specified by the G-BA. b. It is assumed that pre-emptive therapy is initiated if a CMV infection occurs. 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 watchful waiting as ACT used for prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant.

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]
Prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant	Watchful waiting[b]
a. Presented is the ACT specified by the G-BA. b. It is assumed that pre-emptive therapy is initiated if a CMV infection occurs. ACT: appropriate comparator therapy; CMV: cytomegalovirus; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

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 18 September 2023)
- search in trial registries/trial results databases for studies on letermovir (last search on 21 September 2023)
- search on the G-BA website for letermovir (last search on 21 September 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.

The company did not conduct an information retrieval for further investigations, but nevertheless presented additional results of the observational study CELESTIAL on the outcome of overall survival and considered these in the derivation of the added benefit [3]. However, the data from this study are not suitable for the benefit assessment of letermovir. The CELESTIAL study is described below and the reasons for the unsuitability of this study are presented.

CELESTIAL study

The CELESTIAL study is a retrospective observational study on letermovir prophylaxis of CMV reactivation and disease. Adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant were enrolled. The patients were enrolled at 6 centres in Germany. In the study, patients who received prophylaxis with letermovir were compared with a retrospectively selected control group.

A total of 200 patients each were included in the letermovir arm and in the control group of the CELESTIAL study. Patients in the letermovir arm were enrolled between 17 August 2021 and 20 September 2023. The control group included patients who had received an allogeneic haematopoietic stem cell transplant between 1 January 2016 and 31 December 2017, prior to the approval of letermovir. In order to achieve comparability of the patient populations in the 2 study arms, one patient from the same centre was included in the control group for each patient in the letermovir arm. The selection of patients for the control group was based on their risk of CMV disease and their age. The criteria for the risk of CMV disease corresponded

to the criteria used in the MK-8228-001 study (see Table 8). In addition, the patients had to be free of CMV viraemia at least until that day post-transplant when the corresponding patient in the letermovir arm started taking letermovir. If several patients were eligible for selection on the basis of these criteria, further selection criteria (e.g. calendar day of the stem cell transplantation, sex, or underlying disease of the stem cell transplantation) were used. The patients were observed up to 48 weeks after stem cell transplantation. The primary objective of the study was to prevent a clinically significant CMV infection, defined as onset of CMV end-organ disease or initiation of pre-emptive therapy based on the detection of CMV viraemia.

The data of the CELESTIAL study for the outcome of overall survival presented by the company are not suitable for the benefit assessment. The company took various patient characteristics into account when compiling the control group in order to achieve structural equality between the treatment groups despite the lack of randomization. A systematic identification of potential confounders is not described in the clinical study report (CSR) for the CELESTIAL study, however. It is therefore not guaranteed that all relevant confounders were identified and taken into account when compiling the control group. Furthermore, procedures for adjusting for confounders that can adequately take into account a possible distorting effect (e.g. propensity score weighting) [4] were not carried out in the CELESTIAL study. In addition, the comparability of the patient populations in the 2 study arms is limited by the fact that patients in the letermovir arm received a stem cell transplant between 2021 and 2023, while patients in the control group received a stem cell transplant between 2016 and 2017. Therefore, the study arms may potentially differ in terms of their health care context. Irrespective of the company's approach, there are no effects in the present scenario for which it can be ruled out with sufficient certainty that they result solely from systematic bias due to confounders.

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. watchful waiting

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 and other sources[c] (yes/no [citation])
MK-8228-001	Yes	Yes	No	Yes [5-7]	Yes [8,9]	Yes [10-12]

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.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The MK-8228-001 study is used for the benefit assessment. The study pool corresponds to that of the company, which, however, additionally used the results of the CELESTIAL study for the outcome of overall survival (see Chapter I 3).

I 3.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MK-8228-001	RCT, double-blind, parallel	Adult CMV-seropositive[b] recipients of an allogeneic HSCT[c]	Letermovir (N = 376)[d, e] Placebo (N = 194)[d, e]	Screening: ▪ 15 days before HSCT to 28 days post-HSCT Treatment[f]: ▪ Start within 28 days post-HSCT until Week 14 post-HSCT (up to 100 days) Observation[g]: ▪ Until Week 48 post-HSCT	67 centres in: Austria, Belgium, Brazil, Canada, Finland, France, Germany, Italy, Japan, Korea, Lithuania, New Zealand, Peru, Poland, Romania, Spain, Sweden, Turkey, United Kingdom, United States 6/2014–11/2016 Data cut-offs: ▪ 12 Sep 2016 (Week 24 post-HSCT)[h] ▪ 28 Jan 2017 (Week 48 post-HSCT)[i]	Primary: clinically significant CMV infection until Week 24 post-HSCT[j] 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. Seropositive test for CMV within one year prior to allogeneic HSCT
c. Receipt of a first allogeneic HSCT (bone marrow, peripheral blood stem cell, or cord blood transplant) within 28 days prior to randomization. A negative test for CMV DNA by the central laboratory from a plasma sample collected within 5 days prior to randomization was required for inclusion in the study.
d. For the primary analysis of the efficacy outcomes, the company used the FAS population, defined as all randomized patients who received at least one dose of the study medication, and in whom no CMV viraemia was detected by the central laboratory at the start of treatment.
e. 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.
f. The duration of treatment was 10-14 weeks, depending on the time of the first study medication. If the first study medication was administered on the day of HSCT, the treatment duration was 14 weeks (this corresponds to Week 14 after HSCT). If the treatment was administered 28 days after HSCT, the treatment duration was 10 weeks (this also corresponds to Week 14 after HSCT).
g. Observation of the primary study outcome was until Week 24 post-HSCT. AEs were observed up to 2 weeks after the end of treatment (no longer than until Week 16 post-HSCT).
h. Database lock after reaching the primary outcome (CSR at Week 24).
i. Final database lock (CSR at Week 48).
j. Defined as onset of CMV end-organ disease or initiation of anti-CMV pre-emptive therapy (based on documented CMV viraemia and the patient's clinical condition) by Week 24 post-HSCT.

AE: adverse event; APaT: all participants as treated; CMV: cytomegalovirus; CSR: clinical study report; DNA: deoxyribonucleic acid; FAS: full analysis set; HSCT: haematopoietic stem cell transplantation; 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. placebo (multipage table)

Study	Intervention	Comparison
MK-8228-001	Letermovir ▪ 480 mg once daily, orally or IV[a] or ▪ 240 mg once daily, orally or IV [a], with concomitant use of CsA-containing GVHD prophylaxis	Placebo once daily, orally or IV[a]
	Dose adjustment: ▪ Letermovir arm: If CsA was taken after the start of the treatment phase, the dose was to be decreased from 480 mg to 240 mg. If CsA was discontinued permanently or for the long-term during the treatment phase, the next dose of letermovir (administered up to 24 hours later) was to be increased from 240 mg to 480 mg. ▪ Discontinuation of study medication if the criteria for a clinically significant CMV infection were met[b]	
	Allowed concomitant treatment ▪ standard antimicrobial prophylaxis (e.g. levofloxacin for bacterial infections, fluconazole/voriconazole/posaconazole for fungal infections) ▪ aciclovir, valaciclovir or famciclovir for prophylaxis and treatment of HSV or VZV infections at doses below the doses listed below ▪ all types of conditioning regimens (including myeloablative, non-myeloablative, or reduced-intensity regimens) ▪ prior or ongoing graft manipulation regimens (including various ex-vivo or in-vivo T-cell depletion or selection regimens) ▪ GVHD prophylaxis ▪ Mycophenolate mofetil **Disallowed prior and concomitant treatment** ▪ prior allogeneic HSCT[c] <u>Antiviral drugs or therapies for prevention or treatment of CMV, including[d]:</u> ▪ within 7 days before screening ▫ ganciclovir ▫ valganciclovir ▫ foscarnet ▫ aciclovir (at doses > 3200 mg orally per day or > 25 mg/kg IV per day) ▫ valaciclovir (at doses > 3000 mg orally per day) ▫ famciclovir (at doses > 1500 mg orally per day) ▪ within 30 days before screening ▫ cidofovir ▫ CMV hyperimmune globulin	

Table 7: Characteristics of the intervention – RCT, direct comparison: letermovir vs. placebo (multipage table)

Study	Intervention	Comparison
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. b. The presence of CMV viraemia had to be confirmed by the central laboratory when pre-emptive therapy or treatment of CMV end-organ disease was initiated. If the central laboratory tested negative for CMV DNA, pre-emptive therapy could be discontinued and the study medication restarted. The interruption of therapy was not allowed to last more than 7 days. c. Prior autologous HSCT was allowed. d. If study medication was discontinued due to a clinically significant CMV infection, the patient was to be treated according to the local standard of care. The listed disallowed concomitant anti-CMV treatments could be used in this case. CMV: cytomegalovirus; CsA: ciclosporin A; DNA: deoxyribonucleic acid; GVHD: graft-versus-host disease; HSCT: haematopoietic stem cell transplantation; HSV: herpes simplex virus; IV: intravenous; RCT: randomized controlled trial; VZV: varicella zoster virus		

The MK-8228-001 study is a completed, double-blind, randomized multicentre study comparing letermovir with placebo. Adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant were enrolled. The stem cell transplantation had to be performed within 28 days before randomization. Patients with previous allogeneic haematopoietic stem cell transplantation could not be included in the study, but previous autologous haematopoietic stem cell transplantation was permitted. A negative test for CMV DNA by the central laboratory from a plasma sample collected within 5 days prior to randomization was required for inclusion in the study.

The study included a total of 570 patients who were randomly allocated in a 2:1 ratio either to prophylaxis with letermovir (N = 376) or to placebo (N = 194). Randomization was stratified according to study centre and risk of CMV reactivation or CMV end-organ disease (high risk versus low risk).

In both study arms, the study medication could be administered both orally and as an intravenous infusion and was largely in compliance with the SPC (see below for the duration of treatment) [13,14]. For oral administration, the recommended dose is one 480 mg tablet daily [13]. In deviation from this, administration of two 240 mg tablets was also possible in the study. However, according to the CSR, bioequivalence studies have shown no relevant differences between the 2 dosing regimens [5]. This deviation therefore has no consequence for the benefit assessment. In case of CMV reactivation or CMV end-organ disease, treatment with the study medication was discontinued and pre-emptive therapy or treatment of CMV end-organ disease was started according to local standards of care.

The primary outcome of the study was the composite outcome of clinically significant CMV infection consisting of the components of CMV end-organ disease and initiation of anti-CMV pre-emptive therapy. Patient-relevant secondary outcomes were overall survival as well as outcomes from the categories of morbidity, health-related quality of life, and side effects. The primary outcome was to be observed until Week 24 post-transplant, and further outcomes on morbidity, health-related quality of life and overall survival were observed until Week 48. In Module 4 A, the company presented analyses on outcomes in the categories of mortality, morbidity and health-related quality of life for different observation periods (until Week 24 and additionally until Week 14 and/or until Week 48 post-transplant). If available, the analyses on outcomes in the categories of mortality, morbidity and health-related quality of life until Week 48 are used in the present benefit assessment, as these cover the longest available observation periods. AEs, on the other hand, were only recorded up to 2 weeks after the end of treatment (no longer than until Week 16 after stem cell transplantation).

Analysis populations

The company presented analyses on 2 analysis populations in Module 4 A of the dossier. The primary analyses of the benefit outcomes were conducted based on the FAS population. In addition, the company presented sensitivity analyses based on the APaT population for some of the benefit outcomes. Compared with the APaT population, which consists of all randomized patients who received at least one dose of study medication (letermovir: N = 373, placebo: N = 192), the FAS population excludes 70 patients diagnosed with CMV viraemia by the central laboratory before starting treatment (letermovir: N = 325, placebo: N = 170). Patients who already have CMV viraemia before starting treatment with letermovir or placebo are no longer eligible for prophylaxis and generally require pre-emptive therapy [15]. These patients are therefore no longer comprised by the present therapeutic indication. The exclusion of these patients is appropriate. This benefit assessment therefore uses the analyses based on the FAS population if available.

The analyses on outcomes in the side effects category presented by the company in the dossier are based on the APaT population, however. Since the proportion of patients in the APaT population diagnosed with CMV viraemia before starting treatment, who are thus not included in the therapeutic indication, is comparable in both study arms and is < 20% (48/373 patients [12.9%] in the intervention arm, and 22/192 patients [11.5%] in the comparator arm), the discrepancy in the analysis populations is of no consequence for the present benefit assessment.

Duration of treatment with letermovir is not in compliance with the SPC

Treatment with letermovir was started within 28 days after stem cell transplantation and continued until 100 days (14 weeks) after stem cell transplantation. According to the current SPC, prolonged letermovir prophylaxis beyond 100 days after stem cell transplantation may

be of benefit in some patients at high risk for late CMV reactivation [13,14]. However, prolonged prophylaxis was not possible in the MK-8228-001 study. The risk factors for late CMV reactivation listed in the SPC largely correspond to the criteria for risk stratification used in the study (see Table 8). At baseline, 102 patients (31.4%) in the intervention arm were at high risk for CMV reactivation. In 11 of these patients, prophylaxis with letermovir was discontinued prematurely and anti-CMV pre-emptive therapy was initiated. By Week 14 after stem cell transplantation, 17 patients in the intervention arm had died. Data on the risk status of these patients are not available. For at least 74 patients (22.8%) in the intervention arm, prolonged prophylaxis beyond 100 days would therefore have been an option.

The SPC also mentions use of anti-thymocyte globulin and use of alemtuzumab as further risk factors [13,14]. In the intervention arm of the study, 11 patients received alemtuzumab (3.4%) and 116 patients (35.7%) received anti-thymocyte globulin. It is not clear from the study documents how many of these patients were already at high risk for CMV reactivation at the start of the study. However, it can be assumed that in addition to the at least 74 patients who were already at high risk at the start of the study, other patients in the intervention arm would have been eligible for prolonged prophylaxis due to other factors arising in the course of the study.

In summary, prolonged prophylaxis with letermovir would have been an option for a relevant proportion of patients in the intervention arm according to the SPC, but was not administered in the study. The resulting uncertainty is taken into account in the assessment of the certainty of conclusions. Therefore, at most hints can be derived for all outcomes (see also Section I 4.2).

Implementation of the ACT

The G-BA specified watchful waiting as the ACT. The MK-8228-001 study used placebo as comparator therapy.

According to the G-BA notes on the ACT and the S2k guideline on viral infections in organ and allogeneic stem cell transplant recipients, pre-emptive therapy should be started in this therapeutic indication if CMV viraemia is detected [15]. According to the guideline, the CMV DNA concentration should be determined at least weekly in the first 100 days after stem cell transplantation using quantitative polymerase chain reaction testing [15]. A uniform threshold value that requires therapeutic intervention is not specified. For initiating pre-emptive therapy, threshold values should be used in consultation with the local centre. The guideline recommends the use of valganciclovir or ganciclovir as standard pre-emptive therapy. In case of non-response or neutropenia, foscarnet is recommended as an alternative.

In the MK-8228-001 study, the CMV DNA concentration was determined in all patients by means of quantitative polymerase chain reaction testing by a central laboratory. The tests were conducted weekly until the end of treatment, then every 2 weeks until Week 24, and

finally every 8 weeks until Week 48. Recommendations for threshold values for the initiation of pre-emptive therapy were risk-adapted and depended on the time of the study, but were not mandatory. The study did not specify how the pre-emptive therapy should be carried out. According to the CSR, the drugs valganciclovir, ganciclovir and foscarnet were administered as concomitant medication until Week 48 after stem cell transplantation.

In summary, the ACT was adequately implemented in the MK-8228-001 study.

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. placebo (multipage table)

Study **Characteristic** **Category**	**Letermovir** **N[a] = 325**	**Placebo** **N[a] = 170**
MK-8228-001		
Age [years], mean (SD)	51 (13)	52 (14)
Sex [F/M], %	46/54	39/61
Geographical region, n (%)		
Asia-Pacific	31 (10)	7 (4)
Latin America	4 (1)	2 (1)
Europe	161 (50)	87 (51)
North America	129 (40)	74 (44)
Risk stratum[b], n (%)		
High	102 (31)	45 (26)
Low	223 (69)	125 (74)
Engraftment at baseline, n (%)		
Yes	103 (32)	63 (37)
No	219 (67)	105 (62)
Unknown	3 (< 1)	2 (1)
Immunosuppressants, n (%)		
Ciclosporin A	162 (50)	90 (53)
Tacrolimus	145 (45)	69 (41)
Other	18 (6)	9 (5)
Unknown	0 (0)	2 (1)

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

Study **Characteristic** **Category**	**Letermovir** **N[a] = 325**	**Placebo** **N[a] = 170**
Main reason for transplant, n (%)		
Acute lymphocytic leukaemia	26 (8)	14 (8)
Acute myeloid leukaemia	127 (39)	60 (35)
Aplastic anaemia	7 (2)	10 (6)
Chronic lymphocytic leukaemia	10 (3)	4 (2)
Chronic myeloid leukaemia	17 (5)	6 (4)
Lymphoma	37 (11)	24 (14)
Myelodysplastic syndrome	57 (18)	22 (13)
Myelofibrosis	9 (3)	6 (4)
Plasma cell myeloma	11 (3)	9 (5)
Other	24 (7)	15 (9)
Donor CMV serostatus, n (%)		
Positive	200 (62)	98 (58)
Negative	122 (38)	72 (42)
Unknown	3 (< 1)	0 (0)
Days from transplantation to randomization, median [Q1; Q3]	8.0 [4.0; 17.0]	9.0 [4.0; 19.0]
Treatment discontinuation, n (%)	106 (28%)[c]	112 (58%)[c]
Study discontinuation, n (%)	132 (35%)[d]	75 (39%)[d]

a. Full analysis set population of the company, defined as all randomized patients who received at least one dose of the study medication, and in whom no CMV viraemia was detected by the central laboratory at the start of treatment. Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b. Patients at high risk for CMV reactivation had to fulfil at least 1 of the following criteria: 1) HLA-related (sibling) donor with at least one mismatch at one of the following 3 HLA-gene loci: HLA-A, -B or -DR; 2) unrelated donor with at least one mismatch at one of the following 4 HLA-gene loci: HLA-A, -B, -C and -DRB1; 3) haploidentical donor; 4) use of umbilical cord blood as stem cell source; 5) use of ex vivo T-cell-depleted grafts; 6) grade ≥ 2 GVHD requiring systemic corticosteroids (use of prednisone or equivalent at a dose of ≥ 1 mg/kg/day).
c. Based on the number of randomized patients (letermovir N = 376 and placebo N = 194). Common reasons for treatment discontinuation in the intervention vs. comparator arm were: lack of efficacy (24 vs. 82), adverse event (42 vs. 19), discontinuation at the patient's request (20 vs. 4).
d. Based on the number of randomized patients (letermovir N = 376 and placebo N = 194). Common reasons for study discontinuation in the intervention vs. comparator arm were: death (71 vs. 44), discontinuation at the patient's request (28 vs. 17), decision by the investigator (15 vs. 5).

CMV: cytomegalovirus; F: female; GVHD: graft-versus-host disease; HLA: human leukocyte antigen; M: male; n: number of patients in category; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the patients are largely balanced between both treatment arms of the MK-8228-001 study. The average patient age was about 51 years. In both treatment arms, the

majority of the study population consisted of men (54% and 61% respectively). According to the risk stratification used in the study (see also Section I 3.2), the vast majority of patients had a low risk of CMV reactivation or disease at baseline. Slightly more than half of the patients in both treatment arms received a transplant from a CMV-seropositive donor. In relation to the total number of all randomized patients, treatment discontinuations were markedly more common in the comparator arm (58%) than in the intervention arm (28%). The number of study discontinuations is comparable between the arms (35% vs. 39%).

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. placebo

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			
Study MK-8228-001	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the MK-8228-001 study is rated as low.

Transferability of the study results to the German health care context

According to the company, the MK-8228-001 study results 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 the previous text section on treatment with letermovir and 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
  - overall survival
- Morbidity
  - onset of CMV end-organ disease
  - severe CMV reactivation/CMV disease
  - acute GVHD
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the FACT-BMT
- Side effects
  - SAEs
  - discontinuation due to AEs
  - other specific AEs

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. placebo

Study	Outcomes									
	Overall survival	Onset of CMV end-organ disease	Severe CMV reactivation/CMV disease[a]	Acute GVHD[b]	Health status (EQ-5D VAS)	Health-related quality of life (FACT-BMT)	SAEs[c]	Discontinuation due to AEs[c]	Nervous system disorders (SOC, SAEs)	Renal and urinary disorders (SOC, SAEs)
MK-8228-001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Operationalized as rehospitalization for CMV reactivation or CMV disease.
b. Defined as acute grade ≥ 2 GVHD.
c. Excluding the events of CMV infection, CMV viraemia, GVHD and bacterial and/or fungal infections (see following text section).

AE: adverse event; CMV: cytomegalovirus; FACT-BMT: Functional Assessment of Cancer Therapy – Bone Marrow Transplantation; GVHD: graft-versus-host disease; n: number of patients with event; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on the outcomes

Overall survival

It was not planned in the MK-8228-001 study to record survival status beyond study discontinuation. For the period after study discontinuation, the survival status was only recorded post hoc following a request from the Food and Drug Administration. In Module 4 A of the dossier, the company presented analyses on the outcome of overall survival, taking into account the data on survival status recorded retrospectively after study discontinuation. Data on survival status after study discontinuation were missing for 10 patients in the intervention arm (3.1%) and 4 patients in the comparator arm (2.4%). Since this affected only a small proportion of patients, which was comparable in the study arms, the uncertainty regarding the survival status of the 14 patients is of no consequence for the present benefit assessment. In addition to the analysis until Week 48, the company presented an analysis until Week 24 as well as analyses from the CELESTIAL study until Week 48. The CELESTIAL study is not relevant for the present benefit assessment (see Chapter I 3). As described above, the benefit assessment uses the analysis from the MK-8228-001 study until Week 48, which covers the entire duration of the study and thus a much longer observation period than the analysis until Week 24.

Composite outcome of clinically significant CMV infection

The outcome of onset 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 clinically significant CMV infection. This is justified below.

The composite outcome of clinically significant CMV infection used by the company comprises the following 2 components:

- initiation of anti-CMV pre-emptive therapy
- onset of CMV end-organ disease

For a composite outcome to be eligible for inclusion in a benefit assessment, the individual components of the outcome must be patient relevant.

Initiation of anti-CMV pre-emptive therapy

Patient-relevance is not given for the component of initiation of anti-CMV pre-emptive therapy. In the study, initiation of anti-CMV pre-emptive therapy was based on the detection of CMV viraemia (regular testing over the course of the study, regardless of symptoms) and the patient's clinical condition. Since detected CMV viraemia does not necessarily cause noticeable symptoms for the patient, the outcome of initiation of anti-CMV pre-emptive therapy is not directly patient relevant in the present situation. Possible advantages and disadvantages resulting from the initiation of pre-emptive therapy should be reflected in other patient-relevant outcomes, such as AEs, however. In addition, results on the outcome of initiation of anti-CMV pre-emptive therapy are only available until Week 24 after stem cell transplantation. Furthermore, it should be noted that pre-emptive therapy is an essential component of the ACT "watchful waiting" and is also part of the therapeutic strategy in the intervention arm if prophylaxis with letermovir fails.

Onset of CMV end-organ disease

For the outcome of onset of CMV end-organ disease, the company's dossier presented analyses until Week 14, until Week 24 and until Week 48 after stem cell transplantation. The presence of CMV end-organ disease had to be confirmed by an independent, blinded Clinical Adjudication Committee. Various events involving an organ system were recorded in the component of onset of CMV end-organ disease. CMV-related gastrointestinal disorders (n = 11), CMV pneumonia (n = 1) and CMV retinitis (n = 2) occurred in the MK-8228-001 study. CMV-related gastrointestinal disorders and CMV pneumonia were diagnosed in the study on the basis of symptoms and the detection of CMV in tissue-specific samples. CMV retinitis was diagnosed by an ophthalmologist on the basis of typical retinal lesions. It is unclear whether the 2 cases of CMV retinitis that occurred were accompanied by noticeable symptoms.

Nevertheless, the outcome of onset of CMV end-organ disease is considered with sufficient certainty to be patient relevant and is used for the benefit assessment.

Proportion of missing values and imputation strategies

For the outcome of onset of CMV end-organ disease, the proportion of patients with missing values in both treatment arms is > 30%. The majority of the missing values in both treatment arms can be explained by study discontinuations before Week 48, with death as the most common reason for study discontinuation. No information is available on how many patients have missing values due to study discontinuation for reasons other than death. However, the data on deaths suggest that this proportion is 10 to 15%.

In its main analysis, the company imputed the missing values using the prespecified Non-Completer = Failure (NC = F) approach. This means that for patients who discontinued the study prematurely or for whom no value was available at Week 48, it is assumed that an event occurred. In addition, the company presented supplementary analyses with a descriptive presentation of the events that actually occurred in the study separately from the study discontinuations and the number of missing values at Week 48. Due to the high proportion of patients with missing values compared with the events actually observed (112 [34.5%] versus 8 [2.5%] in the intervention arm and 62 [36.5%] versus 6 [3.5%] in the comparator arm), the analysis based on the N = F approach used by the company cannot be interpreted meaningfully. In the present benefit assessment, the analysis for the outcome of CMV end-organ disease is therefore presented on the basis of the events that actually occurred. The uncertainty resulting from the high proportion of missing values is addressed in the assessment of the risk of bias of the results (see Section I 4.2).

Severe CMV reactivation/CMV disease

The outcome of severe CMV reactivation/CMV disease is defined as rehospitalization for CMV reactivation or CMV disease that occurred after initial discharge from hospital. In Module 4 A of the dossier, the company described that these were inpatient stays regardless of the duration of the stay. No further information is available on the conditions under which hospitalization due to CMV reactivation/CMV disease occurred. 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 additionally assumed not to be short-term hospital stays. Hospitalization for CMV reactivation/CMV disease is used for the present benefit assessment. As previously described for the outcome of onset of CMV end-organ disease, there is a high proportion of patients with missing values at the relevant analysis date at Week 48 after stem cell transplantation. The uncertainty resulting from the high proportion of missing values is addressed in the assessment of the risk of bias of the results (see Section I 4.2).

Bacterial and/or fungal infections

The outcome was defined as the occurrence of an opportunistic bacterial and/or fungal infection, whereby categorization as an opportunistic infection was determined by the investigator. In principle, however, an analysis of all patient-relevant infections would be necessary in this therapeutic indication, regardless of whether they were assessed as opportunistic infections by the investigator. This analysis should also include viral and parasitic infections in order to fully reflect the infections that occurred in the study. In addition, the infections that occurred should be categorized according to severity (AEs and SAEs). It should also be noted that it is not clear from the information provided by the company in the dossier whether the recording in the study was systematic. According to the company, bacterial and/or fungal infections were documented as AEs until Week 16 after stem cell transplantation. Events occurring from Week 17 to Week 48 after stem cell transplantation were only recorded as AEs if they were fatal or classified as treatment-related SAEs. The study documents also show that opportunistic infections until Week 48 were recorded as part of the Health Outcomes Assessment. Overall, it is unclear which events (AEs, SAEs, recordings as part of the Health Outcomes Assessment) were included in the outcome of bacterial and/or fungal infections. The outcome of bacterial and/or fungal infections was therefore disregarded in the present benefit assessment.

Acute and/or chronic GVHD

According to the company's information in Module 4 A of the dossier, the outcome is defined as the occurrence of acute and/or chronic severity grade ≥ 2 GVHD, requiring the use of systemic corticosteroids. In the study, however, only acute GVHD was categorized by severity grades according to the Glucksberg classification, but not chronic GVHD. Based on comparison with the CSR, the results presented in Module 4 A refer to any acute and/or chronic GVHD regardless of severity. However, acute grade 1 GVHD is not necessarily patient relevant, as it is potentially only based on changes in laboratory parameters [16]. The analyses until Week 48 include a relevant proportion of acute grade 1 GVHD (n = 73 in the intervention arm [22.5%] and n = 37 in the comparator arm [21.8%]). For a relevant proportion of patients, it is therefore not ensured that the operationalization of the outcome presented in Module 4 A reflects noticeable symptoms. Furthermore, it is unclear which events (AEs, SAEs, recordings as part of the Health Outcomes Assessment) were included in the outcome of acute and/or chronic GVHD. In the CSR, the company also presented separate analyses on acute GVHD (separated by severity grade) and chronic GVHD. For the present benefit assessment, the analyses on acute severity grade ≥ 2 GVHD are used despite the uncertainty as to which of the events were considered in the analysis. This is due to the fact that it is not assumed that a relevant proportion of acute GVHD events occurred after Week 16.

Health status, recorded with the EQ-5D VAS

The response rates for recording health status using the EQ-5D VAS presented in Module 4 A do not concur with the information in Appendix 4 G of the current dossier or the information provided in the CSR. It is therefore unclear which responses were actually the basis for the responder analyses on the EQ-5D VAS presented in the company's dossier. In the dossier for the G-BA assessment in the context of the market access in 2018, the company provided information on response rates that corresponded to those in the CSR [12]. In the dossier at that time, the company presented responder analyses using the response criterion of 10 points (corresponding to 10% of the scale range) and analyses of continuous data. The responder analyses are not suitable for the benefit assessment due to the response criterion. 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. The analyses of the continuous data from the dossier for the G-BA assessment of 2018 are used for the present benefit assessment.

Health-related quality of life recorded using the FACT-BMT total score

The FACT-BMT is a validated instrument for recording health-related quality of life in adult cancer patients who have received a bone marrow transplant [17]. The current version 4 of the instrument was used in the study. According to the Scoring Manual (Version 4), 37 items, including 10 of the 23 items of the BMT subscale, are to be used to form the total score (scale range 0 to 148 points) [18]. In Module 4 A of the dossier, the company stated that the calculation of the total score was based on 12 items of the BMT subscale (scale range 0 to 156 points) in order to meet the requirements of the G-BA.

The analysis based on 12 items of the BMT subscale, which deviates from the Scoring Manual, is not appropriate. In the dossier for the G-BA assessment of 2018, the company presented both analyses including 10 items of the BMTS subscale, and analyses based on 12 items of the BMT subscale [12]. As part of this initial assessment, the company presented both analyses of continuous data and responder analyses using the response criterion of 5 points (corresponding to 3.4% of the scale range taking into account 10 items of the BMT subscale) for the FACT-BMT total score. The present benefit assessment uses the continuous analyses on the FACT-BMT total score presented in the dossier for the G-BA assessment of 2018, which were conducted according to the specifications of the Scoring Manual on the basis of 10 items of the BMTS subscale. The responder analyses presented at that time are not suitable for the benefit assessment due to the response criterion used. 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.

Outcomes in the category of side effects

Observation period of outcomes in the side effects category

In the MK-8228-001 study, the observation of the side effect outcomes was only planned up to 2 weeks after the end of treatment (no later than Week 16 after stem cell transplantation). Due to treatment discontinuations (the most common reasons were lack of efficacy, AEs and discontinuation at the patient's request), the median observation period for AEs was only 3.2 months in the intervention arm and only 2.3 months in the comparator arm. In the present therapeutic indication, pre-emptive therapy is initiated in case of CMV reactivation (see Section I 3.2). In the comparator arm, pre-emptive therapy was initiated in 40.0% of patients until Week 24 after stem cell transplantation. Pre-emptive therapy is thus an essential component of the ACT "watchful waiting" and is also part of the therapeutic strategy in the intervention arm if prophylaxis with letermovir fails. However, potential AEs as a result of pre-emptive therapy are not recorded (to the full extent) due to the short follow-up observation of 2 weeks after treatment discontinuation. This concerns myelotoxic effects of pre-emptive therapy, for example. The data on AEs recorded in the study therefore do not fully reflect the potentially negative effects of the ACT "watchful waiting", including pre-emptive therapy, in the comparator arm. In addition, it was shown that pre-emptive therapy was also increasingly initiated in the intervention arm after discontinuation of the study medication and thus discontinuation of the follow-up observation of AEs. In the intervention arm, 7.4% of patients initiated pre-emptive therapy by the end of treatment at Week 14 after stem cell transplantation, while 16.0% of patients had already started pre-emptive therapy at Week 24 after stem cell transplantation. However, AEs potentially occurring after the end of treatment with letermovir as a result of pre-emptive therapy were no longer recorded due to the shortened observation period. An adequate comparison of the therapeutic strategy of letermovir with pre-emptive therapy in case of failed prophylaxis versus the ACT "watchful waiting" with pre-emptive therapy in case of CMV reactivation would require a notably longer observation beyond the end of treatment, which also fully covers potential AEs due to pre-emptive therapy. It is overall unclear whether an adequate observation period would have potentially shown further or other positive/negative effects in the AE outcomes. Despite the uncertainties described, the time-to-event analyses on side effects are used in the present benefit assessment, but the existing limitations are addressed in the overall assessment.

SAEs and discontinuation due to AEs

The analyses of side effects presented in Module 4 A of the dossier include CMV infections to a relevant extent (see I Appendix C of the full dossier assessment). However, this event does not reflect a side effect, but rather a prophylaxis failure. In Appendix 4 G of the dossier, the company presented analyses on side effects excluding the events of CMV infections, CMV viraemia, GVHD and bacterial and/or fungal infections. The present benefit assessment uses the analyses on SAEs and discontinuations due to AEs from Appendix 4 G of Module 4

excluding these events to avoid including events that reflect the underlying disease (CMV infection, CMV viraemia). The events of GVHD and bacterial and/or fungal infections are also not included in these analyses, but the comparison between the analyses including and excluding the events shows that the non-consideration of the events of GVHD and bacterial and/or fungal infections does not have a relevant effect on the results for the outcomes of SAEs and discontinuation due to AEs.

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 versus placebo

Study		Outcomes									
	Study level	Overall survival	Onset of CMV end-organ disease	Severe CMV reactivation/CMV disease[a]	Acute GVHD[b]	Health status (EQ-5D VAS)	Health-related quality of life (FACT-BMT)	SAEs[c]	Discontinuation due to AEs[c]	Nervous system disorders (SOC, SAEs)	Renal and urinary disorders (SOC, SAEs)
MK-8228-001	L	L	H[d]	H[d]	H[d]	H[e]	H[e]	H[f]	L[g]	H[f]	H[f]

a. Operationalized as rehospitalization for CMV reactivation or CMV disease.
b. Defined as acute grade ≥ 2 GVHD.
c. Excluding the events of CMV infection, CMV viraemia, GVHD and bacterial and/or fungal infections (see Section I 4.1).
d. Large proportion of patients with missing values.
e. Large proportion of patients not considered in the analysis.
f. Incomplete observations for potentially informative reasons in the presence of differences in follow-up observation periods between the treatment arms.
g. Despite the low risk of bias, the certainty of results is presumably limited for the outcome of discontinuation due to AEs.

AE: adverse event; CMV: cytomegalovirus; FACT-BMT: Functional Assessment of Cancer Therapy – Bone Marrow Transplantation; GVHD: graft-versus-host disease; H: high; L: low; n: number of patients with event; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results for the outcome of overall survival is rated as low.

Due to the high proportion of missing values at the relevant date of analysis, the risk of bias is rated as high for the results of the outcomes of onset of CMV end-organ disease, severe CMV reactivation/CMV disease, and acute GVHD. For the results of the patient-reported outcomes of health status (EQ-5D VAS) and health-related quality of life (FACT-BMT), the high risk of bias results from the high proportion of patients excluded from the analysis (for the outcome of health status, no baseline value was available for 20.6% of patients in the intervention arm and 18.8% in the comparator arm; and for the outcome of health-related quality of life, no baseline value was available for 25.2% of patients in the intervention arm and 20.6% in the comparator arm).

Due to incomplete observations for potentially informative reasons, the risk of bias of the results is rated as high for the outcomes of SAEs, nervous system disorders and renal and urinary disorders. 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 is a competing event for the outcome to be recorded, discontinuation due to AEs. Consequently, after treatment discontinuation for other reasons, AEs which would have led to discontinuation may have occurred, but the criterion of discontinuation can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

Summary assessment of the certainty of conclusions

As already described in Section I 3.2, prolonged prophylaxis with letermovir beyond 100 days after stem cell transplantation was not possible in the MK-8228-001 study. According to the SPC, prolonged prophylaxis may be of benefit in some patients at high risk for late CMV reactivation, however [13,14]. As prolonged prophylaxis would have been an option for a relevant proportion of patients in the study, these patients did not receive letermovir treatment in compliance with the SPC. Overall, this reduces the certainty of conclusions of the study results for the present research question. Based on the MK-8228-001 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

I 4.3 Results

Table 12, Table 13 and Table 14 summarize the results of the comparison of letermovir with placebo used for prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses are presented in I Appendix B of the full dossier assessment, and the tables on common AEs, SAEs, and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment. The results on overall hospitalization are presented as supplementary information in I Appendix D of the full dossier assessment.

Table 12: Results (morbidity, dichotomous) – RCT, direct comparison: letermovir vs. placebo

Study Outcome category Outcome	Letermovir		Placebo		Letermovir vs. placebo
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value[b]
MK-8228-001					
Morbidity (until Week 48 after stem cell transplantation)					
Onset of CMV end-organ disease[c]	325	8 (2.5)	170	6 (3.5)	0.70 [0.25; 1.98]; 0.571[d]
Severe CMV reactivation/CMV disease[e]	325	10 (3.1)	170	15 (8.8)	0.35 [0.16; 0.77]; 0.009
Acute GVHD[f]	325	85 (26.2)	170	48 (28.2)	0.93 [0.69; 1.25]; 0.638[d]

a. Full analysis set population of the company, defined as all randomized patients who received at least one dose of the study medication, and in whom no CMV viraemia was detected by the central laboratory at the start of treatment.
b. Cochran-Mantel-Haenszel method, stratified by CMV risk group (high vs. low), p-value from Wald test.
c. The following events occurred in study MK-8228-001: gastrointestinal disorders (n = 11), pneumonia (n = 1) and retinitis (n = 2).
d. Institute's calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [19]).
e. Operationalized as rehospitalization for CMV reactivation or CMV disease.
f. Defined as acute grade ≥ 2 GVHD.

CI: confidence interval; CMV: cytomegalovirus; GVHD: graft-versus-host disease; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk

Table 13: Results (mortality, side effects) – RCT, direct comparison: letermovir vs. placebo

Study Outcome category Outcome	Letermovir N[a] Median time to event in weeks [95% CI] Patients with event n (%)	Placebo N[a] Median time to event in weeks [95% CI] Patients with event n (%)	Letermovir vs. placebo HR [95% CI]; p-value[b]
MK-8228-001			
Mortality (until Week 48 after stem cell transplantation)			
Overall survival[c]	325 NA 76 (23.4)	170 NA 46 (27.1)	0.79 [0.55; 1.14]; 0.214
Side effects (until Week 16 after stem cell transplantation)			
AEs (supplementary information)[d]	373 0.4 [0.4; 0.6] 357 (95.7)	192 0.6 [0.4; 0.7] 185 (96.4)	–
SAEs[d]	373 15.3 [15.1; 15.6] 145 (38.9)	192 NA [11.1; NC] 72 (37.5)	0.90 [0.67; 1.19]; 0.450
Discontinuation due to AEs[d]	373 NA 47 (12.6)	192 NA 21 (10.9)	1.06 [0.63; 1.78]; 0.818
Nervous system disorders (SOC, SAEs)	373 NA 12 (3.2)	192 NA 0 (0)	NC; 0.020
Renal and urinary disorders (SOC, SAEs)[e]	373 NA 10 (2.7)	192 NA 11 (5.7)	0.39 [0.16; 0.92]; 0.032

a. All-participants-as-treated population of the company, defined as all randomized patients who received at least one dose of the study medication.
b. Outcome of overall survival: Cox proportional hazards model stratified by CMV risk group (high vs. low), p-value from Wald test; outcomes in the side effects category: Cox proportional hazards model without stratification, p-value from Wald test.
c. Values refer to the company's full analysis set population. No data on survival status after study discontinuation are available for 10 patients in the intervention arm and 4 patients in the comparator arm.
d. Excluding the events of CMV infection, CMV viraemia, GVHD and bacterial and/or fungal infections (see Section I 4.1).
e. The main underlying event is acute kidney injury (letermovir: 5 [1.3%] vs. placebo: 9 [4.7%]).

AE: adverse event; CI: confidence interval; CMV: cytomegalovirus; GVHD: graft-versus-host disease; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: letermovir vs. placebo

Study Outcome category Outcome	Letermovir			Placebo			Letermovir vs. placebo
	N[a]	Values at baseline mean (SD)	Change at Week 48 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at Week 48 mean[b] (SE)	MD [95% CI]; p-value[b]
MK-8228-001							
Morbidity (until Week 48 after stem cell transplantation)							
EQ-5D VAS[c, d]	243	62.9 (20.5)	14.0 (1.6)	135	62.3 (19.5)	10.7 (2.1)	3.27 [−0.91; 7.46]; 0.125
Health-related quality of life (until Week 48 after stem cell transplantation)							
FACT-BMT[d, e]							
Total score	258	99.0 (20.3)	8.6 (1.6)	138	99.2 (18.3)	5.5 (2.2)	3.11 [−1.63; 7.84]; 0.198
Physical wellbeing	258	17.6 (6.4)	4.4 (0.5)	138	17.9 (6.4)	3.6 (0.6)	0.86 [−0.32; 2.05]
Social/family wellbeing	258	23.1 (3.9)	−1.5 (0.4)	138	23.0 (4.5)	−1.6 (0.5)	0.09 [−1.01; 1.18]
Emotional wellbeing	258	18.9 (3.8)	0.3 (0.3)	138	18.6 (3.9)	0.1 (0.4)	0.22 [−0.71; 1.15]
Functional wellbeing	258	14.4 (5.8)	2.8 (0.5)	138	14.6 (5.3)	2.1 (0.6)	0.64 [−0.74; 2.03]
Stem cell transplantation-specific subscale	258	25.1 (6.1)	2.6 (0.5)	138	25.1 (5.7)	1.3 (0.7)	1.28 [−0.18; 2.74]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. cLDA model adjusted for CMV risk group (high vs. low) taking into account the dates of recording.
c. Higher (increasing) values indicate improved symptoms; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).
d. The results presented were taken from the dossier of the G-BA assessment of letermovir as part of the 2018 market access [12].
e. Higher (increasing) values indicate better quality of life; positive effects (intervention minus control) indicate an advantage for the intervention (scale range: total score 0 to 148 points; physical wellbeing, social/family wellbeing and functional wellbeing each 0 to 28 points; emotional wellbeing 0 to 24 points; stem cell transplantation-specific subscale 0 to 40 points).

CI: confidence interval; cLDA: constrained longitudinal data analysis; CMV: cytomegalovirus; FACT-BMT: Functional Assessment of Cancer Therapy – Bone Marrow Transplantation; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; 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 Section I 4.2).

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. There is no hint of an added benefit of letermovir in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Onset of CMV end-organ disease

No statistically significant difference between treatment groups was shown for the outcome of onset of CMV end-organ disease. There is no hint of an added benefit of letermovir in comparison with watchful waiting; an added benefit is therefore not proven.

Severe CMV reactivation/CMV disease

A statistically significant difference between treatment groups in favour of letermovir was shown for the outcome of severe CMV reactivation/CMV disease. There is a hint of an added benefit of letermovir in comparison with watchful waiting.

Acute GVHD

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

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status surveyed with the EQ-5D VAS. There is no hint of an added benefit of letermovir in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

FACT-BMT

Health-related quality of life was recorded using the FACT-BMT total score.

No statistically significant difference between treatment groups was shown for the outcome of FACT-BMT total score. There is no hint of an added benefit of letermovir in comparison with watchful waiting; 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 an effect modification for the characteristic of sex, however (see Section I 4.4). For women, there is a hint of lesser harm from letermovir in comparison with watchful

waiting. For men, however, there is no hint of greater or lesser harm from letermovir in comparison with watchful waiting; greater or lesser harm is therefore not proven for men.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm from letermovir in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Nervous system disorders (SAEs)

A statistically significant difference between treatment groups to the disadvantage of letermovir was shown for the outcome of nervous system disorders (SAEs). There is a hint of greater harm from letermovir in comparison with watchful waiting.

Renal and urinary disorders (SAEs)

A statistically significant difference between treatment groups in favour of letermovir was shown for the outcome of renal and urinary disorders (SAEs). There is a hint of lesser harm from letermovir in comparison with watchful waiting.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are taken into account in the present benefit assessment:

- age (< 54 years versus ≥ 54 years)
- sex (women versus men)
- CMV risk group (high versus low)

The company submitted subgroup analyses by age, sex and CMV risk groups for all outcomes listed in the dossier, with the exception of the outcome of acute GVHD. It should be noted that the age cut-off of 54 years represents the median age of the study population. The company did not justify its use of the age cut-off of 54 years, but the use of the median for subgroup analyses on the characteristic of age was prespecified in the planning of the study. In the absence of further analyses on the characteristic of age, these subgroup analyses are therefore considered as an approximation in the present data situation.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also 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 15 summarizes the subgroup results of the comparison of letermovir with placebo used for prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant. Kaplan-Meier curves on the presented time-to-event analyses can be found in I Appendix B of the full dossier assessment.

Table 15: Subgroups (side effects) – RCT, direct comparison: letermovir vs. placebo

Study Outcome Characteristic Subgroup	Letermovir		Placebo		Letermovir vs. placebo	
	N[a]	Median time to event in weeks [95% CI] Patients with event n (%)	N[a]	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI][b]	p-value[c]
MK-8228-001						
SAEs[d]						
Sex						
Women	162	NA [15.1; NC] 53 (32.7)	76	10.0 [6.1; NC] 37 (48.7)	0.52 [0.34; 0.79]	0.002
Men	211	15.3 [13.3; 15.6] 92 (43.6)	116	NA 35 (30.2)	1.33 [0.90; 1.97]	0.152
Total					Interaction[e]:	0.002

a. All-participants-as-treated population of the company, defined as all randomized patients who received at least one dose of the study medication.
b. Cox proportional hazards model.
c. Based on Wald test.
d. Excluding the events of CMV infection, CMV viraemia, GVHD and bacterial and/or fungal infections (see Section I 4.1).
e. Based on likelihood ratio test.

CI: confidence interval; CMV: cytomegalovirus; GVHD: graft-versus-host disease; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event

Side effects

SAEs

For the outcome of SAEs, there is an effect modification by the characteristic of sex. A statistically significant difference between treatment groups in favour of letermovir was shown for women. There is a hint of lesser harm from letermovir in comparison with watchful waiting.

For men, however, no statistically significant difference was shown between treatment groups. There is no hint of greater or lesser harm from letermovir in comparison with watchful waiting; greater or lesser harm is therefore not proven.

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 16).

Determination of the outcome category for the morbidity outcomes

It cannot be inferred from the dossier whether the following symptoms outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Severe CMV reactivation/CMV disease

Events which require inpatient treatment are considered severe or serious. Therefore, the outcome of severe CMV reactivation/CMV disease was assigned to the outcome category of serious/severe symptoms/late complications.

Table 16: Extent of added benefit at outcome level: letermovir vs. watchful waiting (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Letermovir vs. placebo** **Median time to event (weeks) or proportion of events (%) or mean change at Week 48** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration (until Week 48)		
Mortality		
Overall survival	NA vs. NA HR: 0.79 [0.55; 1.14]; p = 0.214	Lesser/added benefit not proven
Morbidity		
Onset of CMV end-organ disease	2.5% vs. 3.5% RR: 0.70 [0.25; 1.98]; p = 0.571	Lesser/added benefit not proven
Severe CMV reactivation/CMV disease	3.1% vs. 8.8% RR: 0.35 [0.16; 0.77]; p = 0.009 Probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
Acute GVHD	26.2% vs. 28.2% RR: 0.93 [0.69; 1.25]; p = 0.638	Lesser/added benefit not proven
Health status (EQ-5D VAS)	14.0 vs. 10.7 MD: 3.27 [-0.91; 7.46]; p = 0.125	Lesser/added benefit not proven
Health-related quality of life		
FACT-BMT total score	8.6 vs. 5.5 MD: 3.11 [-1.63; 7.84]; p = 0.198	Lesser/added benefit not proven
Outcomes with shortened observation period (until Week 16)		
Side effects		
SAEs[c] Sex Women	NA vs. 10.0 HR: 0.52 [0.34; 0.79]; p = 0.002 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Lesser harm; extent: "considerable"
Men	15.3 vs. NA HR: 1.33 [0.90; 1.97]; p = 0.152	Greater/lesser harm not proven

Table 16: Extent of added benefit at outcome level: letermovir vs. watchful waiting (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Letermovir vs. placebo** **Median time to event (weeks) or proportion of events (%) or mean change at Week 48** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs[c]	NA vs. NA HR: 1.06 [0.63; 1.78]; p = 0.818	Greater/lesser harm not proven
Nervous system disorders (SAEs)	NA vs. NA HR: NC; p = 0.020 Probability: "hint"	Outcome category: serious/severe side effects Greater harm, extent: "non-quantifiable", at most "considerable"[d]
Renal and urinary disorders (SAEs)	NA vs. NA HR: 0.39 [0.16; 0.92]; p = 0.032 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale of the outcome, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Excluding the events of CMV infection, CMV viraemia, GVHD and bacterial and/or fungal infections (see Section I 4.1).
d. The p-value is decisive for the derivation of the added benefit. Since the risk is not at least 5% in either of the 2 study arms, the extent is at most "considerable".

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CMV: cytomegalovirus; FACT-BMT: Functional Assessment of Cancer Therapy – Bone Marrow Transplantation; GVHD: graft-versus-host disease; HR: hazard ratio; MD: mean difference; NA: not achieved; NC: not calculable; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of letermovir in comparison with watchful waiting

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration (until Week 48)	
Serious/severe symptoms/late complications ▪ Severe CMV reactivation/CMV disease: hint of greater benefit – extent: “considerable”	–
Outcomes with shortened observation period (until Week 16)	
Serious/severe side effects ▪ SAEs: ▫ Sex (women): hint of lesser harm –extent “considerable” ▪ Renal and urinary disorders (SAEs): hint of lesser harm – extent: “minor”	Serious/severe side effects ▪ Nervous system disorders (SAEs): hint of greater harm – extent: “non-quantifiable”, at most “considerable”
CMV: cytomegalovirus; SAE: serious adverse event	

Overall, there are both positive and negative effects of letermovir in comparison with watchful waiting.

On the positive effects side, there is a hint of considerable added benefit in the outcome category of serious/severe symptoms/late complications for the outcome of severe CMV reactivation/CMV disease. In addition, there are hints of lesser harm in the outcome category of serious/severe side effects. For the overall rate of SAEs, there is a hint of lesser harm with the extent “considerable” in the subgroup of women. For the outcome of renal and urinary disorders, there is a hint of lesser harm with the extent “minor”. On the other hand, there is a hint of greater harm of non-quantifiable, but no more than considerable extent for the outcome of nervous system disorders in the category of serious/severe side effects.

In comparison with the other outcomes, the observation period for the outcomes in the category of side effects was much shorter (see Section I 4.1). They therefore do not reflect the therapeutic strategies of the 2 study arms, including pre-emptive therapy in patients with CMV reactivation. It is unclear whether an adequate observation period would have potentially shown further or other positive/negative effects in the category of side effects. Overall, this uncertainty does not entirely call into question the positive effects observed. However, it is not possible to quantify the added benefit of letermovir compared with watchful waiting on the basis of the available data.

In summary, there is a hint of a non-quantifiable added benefit of letermovir in comparison with the ACT “watchful waiting” for prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant.

Table 18 summarizes the result of the assessment of added benefit of letermovir in comparison with the ACT.

Table 18: Letermovir – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant	Watchful waiting[b]	Hint of non-quantifiable added benefit
a. Presented is the ACT specified by the G-BA. b. It is assumed that pre-emptive therapy is initiated if a CMV infection occurs. 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.

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