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

Addendum to Project A23-139 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CMV	cytomegalovirus
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 23 April 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-139 (Letermovir – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the following outcomes presented by the pharmaceutical company (hereinafter referred to as "the company" in the dossier [2]:

- overall survival until Week 24
- initiation of pre-emptive therapy
- composite outcome of clinically significant cytomegalovirus (CMV) infection

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is sent to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The randomized controlled trial (RCT) MK-8228-001 was used for the benefit assessment of letermovir in comparison with watchful waiting as appropriate comparator therapy (ACT) used for prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant. A detailed description of the study can be found in dossier assessment A23-139 [1].

In compliance with the commission, the analyses for the outcomes of overall survival until Week 24, initiation of pre-emptive therapy, and clinically significant CMV infection are assessed below.

Notes on outcomes and analyses

Overall survival

As dossier assessment A23-139, this addendum considers the analyses on the outcome of overall survival including the data on survival status collected subsequently after study discontinuation. Even with the same observation periods, time-to-event analyses are generally preferable for the outcome of overall survival in the present therapeutic indication, in which there is a relevant risk of death for the patients. The time-to-event analysis until Week 48 used in dossier assessment A23-139 is the longest available observation period, which also includes events until Week 24. This analysis is used for the benefit assessment.

In compliance with the commission, the result of the time-to-event analysis for the outcome of overall survival until Week 24 is presented in Appendix A. The relative risk for the outcome of overall survival until Week 24 and until Week 48 is additionally presented in the results in Appendix A, showing no statistically significant differences between the treatment arms at either Week 24 or Week 48. No subgroup analyses are available for the operationalizations considered here, including the subsequently collected data on survival status.

Composite outcome of clinically significant CMV infection (including the component of initiation of pre-emptive therapy)

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

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

As described in dossier assessment A23-139, to be eligible for inclusion in the benefit assessment, the individual components of the outcome must be patient relevant. Patient-relevance is not given for the component of initiation of anti-CMV pre-emptive therapy (see dossier assessment A23-139 for reasons). No further relevant information on the patient

relevance of this component was submitted in the commenting procedure [3]. In compliance with the commission, the results for the outcome of clinically significant CMV infection (including the component initiation of pre-emptive therapy) at Week 14 and Week 24 are presented in Appendix A.

In its main analysis, the company imputed the missing values using the prespecified Non-Completer = Failure (NC = F) approach. As a result, the main analysis of the company not only includes patients who had an event, but also patients who had discontinued the study prematurely or who had a missing value for other reasons (see also A23-139). In the MK-8228-001 study, the most common reasons for study discontinuation until Week 24 were death, discontinuation at the patient's request, and the investigator's decision. The assumption made in the NC = F approach that patients with missing values had an event until the relevant date is not appropriate. Due to the high proportion of patients with missing values compared with patients with actually observed events (at Week 24: 65 [20.0%] versus 57 [17.5%] in the intervention arm, and 32 [18.8%] versus 71 [41.8%] in the comparator arm; at Week 14: 37 [11.4%] versus 25 [7.7%] in the intervention arm, and 18 [10.6%] versus 67 [39.4%] in the comparator arm), the analyses based on the N = F approach used by the company cannot be interpreted meaningfully. Analogous to the procedure in A23-139, the analyses for the composite outcome of clinically significant CMV infection (including the individual components of initiation of anti-CMV pre-emptive therapy and onset of CMV end-organ disease) are therefore presented on the basis of the events that actually occurred. There are no subgroup analyses on the operationalizations considered here.

2.1 Summary

The present addendum does not change the conclusion on the added benefit of letermovir from dossier assessment A23-139.

The following Table 1 shows the result of the benefit assessment of letermovir, taking into account dossier assessment A23-139 and the present addendum.

Table 1: 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 G-BA decides on the added benefit.

3 References

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

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4. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://doi.org/10.1016/0167-9473(94)90148-1.

Appendix A Supplementary presentation of results on mortality and morbidity

Table 2: Results (mortality, morbidity, dichotomous) – RCT, direct comparison: letermovir vs. placebo

Study Outcome category Outcome Time point	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					
Mortality					
Overall survival[c] (Week 48 post-transplant)	325	76 (23.4)	170	46 (27.1)	0.86 [0.63; 1.19]; 0.422
Overall survival[c] (Week 24 post-transplant)	325	40 (12.3)	170	32 (18.8)	0.65 [0.43; 1.001]; 0.052 HR[d]: 0.62 [0.39; 0.98]; 0.042
Morbidity (Week 24 post-transplant)					
Clinically significant CMV infection	325	57 (17.5)	170	71 (41.8)	0.42 [0.31; 0.56]; < 0.001
Initiation of pre-emptive therapy	325	52 (16.0)	170	68 (40.0)	0.40 [0.29; 0.55]; < 0.001
Onset of CMV end-organ disease[e]	325	5 (1.5)	170	3 (1.8)	0.87 [0.21; 3.60]; 0.879
Morbidity (Week 14 post-transplant)					
Clinically significant CMV infection	325	25 (7.7)	170	67 (39.4)	0.20 [0.13; 0.30]; < 0.001
Initiation of pre-emptive therapy	325	24 (7.4)	170	65 (38.2)	0.19 [0.13; 0.30]; < 0.001
Onset of CMV end-organ disease[e]	325	1 (0.3)	170	2 (1.2)	0.26 [0.02; 2.86]; 0.312

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 on Day 1.
b. Institute's calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [4]).
c. No data on survival status after study discontinuation are available for 10 patients in the intervention arm and 4 patients in the comparator arm. It is unclear how many of these patients discontinued the study before Week 24.
d. Cox proportional hazards model stratified by CMV risk group (high vs. low), p-value from Wald test; the median survival time was not achieved in either treatment group.
e. In the MK-8228-001 study, all events occurring until Week 24 were gastrointestinal disorders.

CI: confidence interval; CMV: cytomegalovirus; CSZ: convexity, symmetry, z-score; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk