Letermovir (CMV prophylaxis after stem cell transplantation, < 18 years)

Addendum to Project A25-67 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
APaT	all-participants-as-treated
CMV	cytomegalovirus
FAS	full analysis set
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)
SmPC	summary of product characteristics

1 Background

On 23 September 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-67 (Letermovir – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprised the assessment of the analyses submitted by the pharmaceutical company (hereinafter referred to as 'the company') in the commenting procedure [2], taking into account the information provided in the dossier [3], on:

- The comparison of the paediatric study MK-8228-030 and the adult study MK-8228-001 (study characteristics, study populations and intervention characteristics, operationalization and results of the relevant outcome of clinically significant cytomegalovirus [CMV] infection at 24 weeks)
- The analysis of the subgroup for the adjacent age group of the adult study MK-8228-001 (≥ 18 to < 25-year-olds) for the outcome of clinically significant CMV infection
- The description of the paediatric study MK-8228-030 and presentation of the results (in the appendix as necessary)

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

2 Assessment

For the assessment of the added benefit of letermovir, the company sought to transfer study results from adult patients in the therapeutic indication to the paediatric population relevant for this benefit assessment. To this end, the company drew on the single-arm study MK-8228-030 [4] in paediatric patients and the randomized controlled trial (RCT) MK-8228-001 in adults, which it had already presented in the procedure for the benefit assessment of letermovir in adults in the therapeutic indication [5].

As already described in benefit assessment A25-67 [1], the data presented by the company were not suitable for drawing conclusions on the added benefit of letermovir compared with the appropriate comparator therapy (ACT) for the present research question in paediatric patients. This is due in particular to the fact that the company did not present any studies or other information that could be used to assess the course of the disease under the ACT (watchful waiting) for the present research question in paediatric patients. Additionally, the outcome of severe CMV reactivation/CMV disease (operationalized as readmission to hospital due to CMV reactivation or CMV disease) was not recorded in MK-8228-030 on paediatric patients, although the added benefit of letermovir for the adult population is largely based on this outcome [6]. These 2 central points of criticism remained unchanged following the commenting procedure [2,7]. It was therefore not possible to transfer the added benefit from adult patients to the paediatric population.

In accordance with the commission, the analyses and information subsequently submitted by the company in the commenting procedure are assessed below, taking into account the details in the dossier, and the results of MK-8228-030 are presented.

2.1 Comparison of the study and patient characteristics of MK-8228-030 and MK-8228-001

Within the commenting procedure, the company addressed the criticism regarding the lack of comparative analysis of the study and patient characteristics of the 2 studies MK-8228-030 and MK-8228-001. For this purpose, it presented a comparison of the operationalization and the results of the outcome clinically significant CMV infection 24 weeks after transplantation (composite outcome consisting of the components CMV end-organ disease and start of pre-emptive therapy against CMV) and the study, intervention and patient characteristics in tabular form. In addition, for the outcome clinically significant CMV infection, it provided the results from the adjacent age group of ≥ 18- to < 25-year-olds from MK-8228-001 in adults. The company described that the tabular comparison showed that the outcome clinically significant CMV infection was operationalized identically in both studies, and that the proportions of events while on letermovir were comparable in the overall populations of the 2 studies as well as in the age group of ≥ 18 to < 25-year-olds. Thus, from the company's point

of view, there were no reasons that would argue against the comparability of the studies and thus against the transfer of evidence. The company did not remark on the other tabular comparisons (study, intervention and patient characteristics) in the comments. There remained a lack of information regarding the ACT in paediatric patients, so that it was not possible to assess how the disease progresses in those patients while using the ACT. The studies are briefly described below and their characteristics compared.

Study description

Study MK-8228-030 is a completed single-arm study investigating treatment with letermovir in patients < 18 years. The study enrolled paediatric recipients of an allogeneic haematopoietic stem cell transplant (N = 65). The primary outcome of MK-8228-030 was the pharmacokinetics of letermovir. Secondary outcomes were clinically significant CMV infections consisting of the components CMV end-organ disease and initiation of pre-emptive therapy against CMV as well as outcomes in the side effects category. A detailed description of the study can be found in dossier assessment A25-67 [1].

MK-8228-001 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 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 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. A detailed description of the study can be found in dossier assessment A23-139 [6].

Study and intervention characteristics

The studies differ fundamentally in that MK-8228-001 is a comparative study in adults, while MK-8228-030 is a single-arm study. The intervention characteristics of both studies were very similar. In both studies, the intervention was administered without any relevant deviation from the summary of product characteristics (SmPC) [8-10]. In both studies, treatment with letermovir was started within 28 days after a stem cell transplant and continued until 100 days (14 weeks) after a stem cell transplant. According to the current SmPC, prolonged letermovir prophylaxis beyond 100 days after a stem cell transplant may be of benefit in some patients at high risk for late CMV reactivation [8-10]. The option to extend the prophylaxis, however, was neither in MK-8228-030 nor in MK-8228-001 available. In both studies, in the event of CMV end-organ disease or initiation of pre-emptive therapy due to documented CMV viraemia and the clinical condition of the patient, treatment with the study medication was discontinued and treatment according to local practice could be initiated.

The primary outcome of the paediatric study was pharmacokinetics; of the study on adults the primary outcome was clinically significant CMV infection consisting of the components CMV end-organ disease and initiation of anti-CMV pre-emptive therapy. The patient-relevant morbidity outcome severe CMV infection (operationalized as readmission to hospital due to CMV reactivation or CMV disease), which was relevant for the benefit assessment A23-139, was not recorded in MK-8228-030. No data were available for this outcome in paediatric patients (see also Section 2.2).

Study populations

In both studies, a negative test for CMV DNA was a prerequisite for study inclusion, but patients who had CMV viraemia before starting treatment were also randomized in both studies [6]. Patients who already have CMV viraemia before starting treatment with letermovir are no longer eligible for prophylaxis and generally require pre-emptive therapy. These patients are therefore no longer covered by the given therapeutic indication. The company addressed this in its analyses by defining 2 analysis populations. An all-participants-as-treated (APaT) population, defined as all included patients who had received at least 1 dose of the study medication and thus also included patients with CMV viraemia at the start of treatment, and a full analysis set (FAS) population, defined as all included patients who had received at least 1 dose of the study medication and in whom no CMV viraemia was detected at the start of treatment.

In the comparison of the patient characteristics of the 2 studies subsequently provided in the comments, the company presented the FAS population for the study on adults, but the APaT population for MK-8228-030 on paediatric patients, which included 7 patients (11%) with CMV viraemia before the start of treatment. In addition, as already described in the benefit assessment, MK-8228-030 included a total of 7 (11%) seronegative stem cell transplant recipients in the analysis population who are not covered by the therapeutic indication to be assessed. The company did not submit data for MK-8228-030 for paediatric patients that relate solely to patients in the therapeutic indication to be assessed.

While in the intervention arm of MK-8228-001 the proportion of both sexes was almost equal (54.2% male, 45.8% female), in MK-8228-030 the majority of the study population (69.8%) was male. In both studies, around 50% of patients were recruited in Europe, while the proportions of other countries (Asia-Pacific, Latin America, North America) varied between the studies. In MK-8228-030, 66.7% of patients received concomitant therapy with ciclosporin A and 27.0% with tacrolimus, while in the intervention arm of MK-8228-001, 49.8% received ciclosporin A and 50.2% another immunosuppressive drug (tacrolimus, sirolimus, everolimus, systemic steroids, leflunomide or mycophenolate). While almost all children and adolescents included in MK-8228-030 received myeloablative treatment as conditioning for stem cell transplantation (87.3%), this only applied to around half of the adult patients in the

intervention arm of MK-8228-001 (47.4%). There, around 26% had received reduced-intensity conditioning and around 26% had not received myeloablative conditioning. The reasons for the stem cell transplant performed were not presented by the company for either of the 2 studies.

2.2 Comparison of the results of the studies MK-8228-030 and MK-8228-001

In accordance with the commission, the results of the paediatric study MK-8228-030 are presented in Table 2 of Appendix A.

As described above, the company addressed the criticism of the comparative analysis of the results of the 2 studies MK-8228-030 and MK-8228-001 and the presentation of the results of the adjacent age group of ≥ 18 to < 25-year olds in the commenting procedure. However, the company limited its comments to the results on the outcome clinically significant CMV infection. A comparative analysis of the results on mortality and side effects was lacking. The results of the adult study MK-8228-001 reported by the company in the comments are also shown in Table 2 for comparison.

The outcome of severe CMV reactivation/CMV disease was not recorded in MK-8228-030 on paediatric patients, although the added benefit of letermovir for the adult population is largely based on this outcome [6] (see Section 2.1). A comparison of the results of this outcome for the assessment of transferability was therefore not possible.

Outcome of clinically significant CMV infection

The operationalization of the composite outcome clinically significant CMV infection was identical in both studies and comprised 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.

The component occurrence of CMV end-organ disease was considered to be sufficiently relevant to patients. The component initiation of anti-CMV pre-emptive therapy was not considered to be relevant to patients. 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 given situation. Possible advantages and disadvantages resulting from the initiation of pre-emptive therapy should be reflected in other patient-relevant outcomes, such as adverse events (AEs), however. In

addition, results on the outcome initiation of anti-CMV pre-emptive therapy were only available until Week 14 and 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.

Since the composite outcome clinically significant CMV infection was largely determined by the events of the component initiation of pre-emptive therapy (not directly patient relevant; part of the therapeutic strategy; see above), the results on this outcome alone are not sufficient to support the evidence transfer sought by the company.

2.3 Summary

The data presented by the company were not suitable to dispel the points of criticism described in the benefit assessment regarding the lack of information on the course of the disease in children and adolescents under watchful waiting, and the missing recording of the patient-relevant outcome severe CMV disease or reactivation in children and adolescents.

The data subsequently submitted by the company in the commenting procedure did not alter the conclusion on the added benefit of letermovir from dossier assessment A25-67.

The following Table 1 shows the result of the benefit assessment of letermovir, taking into account dossier assessment A25-67 and this 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 paediatric patients with a body weight of at least 5 kg who are CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant	Watchful waiting[b]	Added benefit not proven
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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Appendix A Supplementary presentation of the results of study MK-8228-030 and comparison with the results of study MK-8228-001

Table 2: Results (mortality, morbidity and side effects, dichotomous) – supplementary presentation: study MK-8228-030 and results from study MK-8228-001 used for comparison by the company in its comments

Outcome category Outcome	Study MK-8228-030		Study MK-8228-001							
	Total population letermovir		≥ 18- to < 25-year-olds letermovir arm		≥ 18- to < 25-year-olds placebo arm		Total population letermovir arm		Total population placebo arm	
	N[a]	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
Mortality (until Week 48 after stem cell transplantation)										
Overall survival[b]	63	6 (9.5)	ND	ND	ND	ND	ND	ND	ND	ND
Morbidity (until Week 24 after stem cell transplantation)										
Clinically significant CMV infection at Week 24[c]	56	6 (10.7)	11	2 (18.2)	9	3 (33.3)	325	57 (17.5)	170	71 (41.8)
Initiation of PET[c]	56	6 (10.7)	11	2 (18.2)	9	3 (33.3)	325	52 (16.0)	170	68 (40.0)
Onset of CMV end-organ disease[c]	56	0 (0.0)	11	0 (0.0)	9	0 (0.0)	325	5 (1.5)	170	3 (1.8)
Side effects[d] (until Week 18 after stem cell transplantation)										
AEs	63	63 (100.0)	ND	ND	ND	ND	ND	ND	ND	ND
SAEs	63	38 (60.3)	ND	ND	ND	ND	ND	ND	ND	ND
Discontinuation due to AEs	63	8 (12.7)	ND	ND	ND	ND	ND	ND	ND	ND

a. All-participants-as-treated population of the company, defined as all enrolled patients who received at least 1 dose of the study medication.
b. The company does not provide any information on the median time to event.
c. Values refer to the full analysis set population of the company, defined as all enrolled patients who received at least 1 dose of the study medication, and in whom no CMV viraemia was detected at the start of treatment.
d. In study MK-8228-030, side effects were only recorded up to 4 weeks after the end of treatment (no longer than until Week 18 after stem cell transplantation).

AE: adverse event; CMV: cytomegalovirus; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; PET: pre-emptive therapy; SAE: serious adverse event