15 November 2023
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Prevymis (letermovir)
Prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk
EU/3/11/849

Sponsor: Merck Sharp & Dohme B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted

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1. Product and administrative information

Product	
Designated active substance(s)	(S)-{8-fluoro-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3,4-dihydro-4-quinazolinyl} acetic acid
Other name(s)	-
International Non-Proprietary Name	Letermovir
Tradename	Prevymis
Orphan condition	Prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk
Sponsor's details:	Merck Sharp & Dohme B.V. Waarderweg 39 2031 BN Haarlem Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	AiCuris GmbH & Co. KG
COMP opinion	12 January 2011
EC decision	15 April 2011
EC registration number	EU/3/11/849
Post-designation procedural history	
Transfer of sponsorship	Transfer from AiCuris GmbH & Co. KG to Merck Sharp & Dohme Limited – EC decision of 15 March 2013 2nd transfer from Merck Sharp & Dohme Limited to Merck Sharp & Dohme B.V. – EC decision of 25 June 2018
COMP opinion on review of orphan designation at the time of marketing authorisation	17 November 2017
Type II variation procedural history	
Rapporteur / Co-rapporteur	Filip Josephson / Aaron Sosa Mejia
Applicant	Merck Sharp & Dohme B.V.
Application submission	7 March 2023
Procedure start	25 March 2023
Procedure number	EMA/H/C/0004536/II/0033/G
Invented name	Prevymis
Proposed therapeutic indication	PREVYMIS is indicated for prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor [D+/R-]. Further information on can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Prevymis
CHMP opinion	12 October 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Elisabeth Johanne Rook
Sponsor's report submission	5 April 2023
COMP discussion	3-5 October 2023

COMP opinion (adoption via written procedure)	23 October 2023

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2011 designation was based on the following grounds:

- "the population of patients eligible for prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk (hereinafter referred to as "the condition") was estimated to be approximately 3.1 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating and life threatening due to complications such as pneumonitis, hepatitis, inflammation of the gastrointestinal tract and reduced graft survival in transplanted patients;
- although satisfactory methods of prevention of the condition have been authorised in the European Union, sufficient justification has been provided that (S)-{8-fluoro-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3,4-dihydro-4-quinazolinyl} acetic acid may be of significant benefit to the population at risk of developing the condition. This appears justified in particular with regards to a potential clinically relevant advantage based on the new mechanism of action which may confer improved efficacy in resistant CMV strains. This is in line with the preclinical studies and preliminary clinical data presented".

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2017 was based on the following grounds:

"The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the population of patients eligible for prevention of cytomegalovirus disease (hereinafter referred to as "the condition") was estimated to be approximately 3.8 in 10,000 persons in the European Union, at the time the application was made;
- the condition is life-threatening due to frequent development of acute severe hepatitis, pneumonitis, colitis, haemorrhagic cystitis and encephalitis. Disseminated disease can be rapidly fatal, with mortality rates reported to be as high as 80%;
- although satisfactory methods of prevention of the condition have been authorised in the European Union, the assumption that Prevymis may be of potential significant benefit to the population at risk of developing the condition still holds. The sponsor has provided clinical data which supported a reduction in the number of patients in need of pre-emptive therapy. The COMP considered that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Prevymis, (S)-{8-fluoro-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3,4-dihydro-4-quinazolinyl} acetic acid, letermovir, EU/3/11/849 for prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk is not removed from the Community Register of Orphan Medicinal Products".

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor is proposing that Cytomegalovirus disease in patients with impaired mediated immunity deemed at risk is a distinct medical entity which was the indication that they obtained in their orphan designation in 2010. As for the initial marketing authorisation the COMP agreed to expand this orphan condition to just cytomegalovirus disease. Human CMV or human herpesvirus 5 is a ubiquitous double-stranded DNA virus belonging to the Betaherpesvirinae. There is a large heterogeneity of CMV strains. The seroprevalence of CMV in the general population ranges from 30%-97% and increases with age. CMV can be transmitted through saliva, urine, sexual contact, placental transfer, breastfeeding, blood transfusion, solid-organ transplantation, or hematopoietic stem cell transplantation. After primary infection, the virus establishes a lifelong latency within the host. Periodical reactivation with production and shedding of lytic virus occurs in both immunocompetent and immunocompromised individuals.

In an immunocompetent host, primary CMV infection often is asymptomatic, although it can manifest as a mononucleosis-like syndrome. In contrast, in immunocompromised hosts, primary CMV infection, reactivation of latent infection, or reinfection with a different strain usually causes CMV disease (Am J Kidney Dis. 2011;58(1):118-126). The diagnosis of CMV disease is made based on the presence of "typical" clinical signs and symptoms combined with the detection of CMV in blood and/or the involved organs as shown in Table 2 below, taken from Clin Infect Dis.2002;34(8):1094-1097. The term disease is generally used in the context of patients who have developed a cytomegalovirus infection within the context of the latent virus becoming active due to the immune system becoming compromised under one of 4 underlying conditions namely, i) HIV infection, ii) haematopoietic stem cell transplantation, iii) solid organ transplantation and iv) primary immune deficiency disease. The term infection is not used as this would also encompass latent infection in both healthy and immunocompromised patients as noted above. The two tables below highlight the differences between infection and disease.

Table 1. Definitions of CMV Infection

Type of Infection	Definition
CMV infection	Isolation of CMV virus or detection of viral proteins or nucleic acid in any body fluid or tissue specimen
Viremia	Isolation of CMV using conventional tube cell cultures or shell vial assays
Antigenemia	Detection of CMV pp65 in peripheral-blood leukocytes
DNAemia	Detection of CMV DNA in plasma, whole blood, isolated peripheral-blood leukocytes, or buffy-coat specimens
Primary CMV infection	1. Detection of CMV infection in a seronegative patient 2. Appearance of de novo specific antibodies in a seronegative patient (provided that passive transfer of antibodies through immunoglobulin or blood products is excluded)
Recurrent CMV infection	New detection of CMV infection in a patient with previously documented infection and in whom no virus has been detected for an interval of at least 4 weeks during active surveillance

Abbreviations: CMV, cytomegalovirus; pp65, phosphoprotein 65.
Based on definitions provided in Ljungman et al.[12]

Table 2. Definitions of CMV Disease

Type of Disease	Definition
CMV syndrome	Fever (temperature >38°C) for at least 2 d within a 4-d period + neutropenia and/or thrombocytopenia + detection of CMV infection in blood
CMV pneumonia	Signs and/or symptoms of pulmonary disease + detection of CMV infection in BAL fluid or a lung biopsy specimen
CMV GI disease	Symptoms from the upper or lower GI tract + macroscopic mucosal lesions on endoscopy + detection of CMV infection in GI tract biopsy specimen
CMV hepatitis	Increased bilirubin and/or liver enzyme levels + absence of another documented cause of hepatitis + detection of CMV infection in a liver biopsy specimen
CMV encephalitis	Central nervous system symptoms + detection of CMV infection in CSF or a brain biopsy specimen
CMV retinitis	Symptoms of retinitis + typical retinal lesions on dilated eye ophthalmoscopy
CMV nephritis	Signs and/or symptoms of kidney dysfunction + detection of CMV infection + identification of conventional histologic features of CMV infection in a kidney biopsy specimen
CMV cystitis	Signs and/or symptoms of cystitis + detection of CMV infection + identification of conventional histologic features of CMV infection in a bladder biopsy specimen
CMV myocarditis	Signs and/or symptoms of myocarditis + detection of CMV infection + identification of conventional histologic features of CMV infection in a heart biopsy specimen
CMV pancreatitis	Signs and/or symptoms of pancreatitis + detection of CMV infection + identification of conventional histologic features of CMV infection in a pancreatic biopsy specimen

Abbreviations: BAL, bronchoalveolar lavage; CMV, cytomegalovirus; CSF, cerebrospinal fluid; GI, gastrointestinal.
Based on definitions provided in Ljungman et al.[12]

Cytomegalovirus disease is an acute condition in immunocompromised patients and is different from cytomegalovirus infection which can occur in normal individuals because it does not manifest in the same manner nor present with the same morbidity and mortality.

The approved extension of indication "*PREVYMIS is indicated for prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor [D+/R-]"* falls within the scope of the designated orphan condition "prevention of cytomegalovirus disease".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor did not identify any major changes in the chronically debilitating or life-threatening nature of the condition ("prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk"). Since the grant of the original designation and/or approval of the MA, no new therapies have been approved for the prevention of CMV in immunosuppressed patients. However, the sponsor does note that maribavir was approved (November 2022) for an indication in the treatment of CMV infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, VGCV, cidofovir, or foscarnet in adult patients who have undergone an HSCT or SOT.

CMV is a problematic infection in many transplant patients. It can be acquired by seronegative patients from seropositive organ donors or via reactivation of latent infections in seropositive transplant recipients upon immunosuppression. CMV-related disease manifests differently depending on which organ is transplanted. CMV is known to damage various organs, including the lung, liver, gastrointestinal tract, bone marrow, and retina. It has been noted that CMV disease is associated with substantial increases in the risk of graft rejection and mortality (Hakimi Z et al, Transplant Infection Disease July 2017). In bone marrow recipients, CMV disease occurs often as an interstitial pneumonia with high mortality.

The COMP can agree that CMV disease remains a chronically debilitating and life-threatening condition.

Number of people affected or at risk

The sponsor has not identified any change in prevalence since the initial marketing authorisation application assessed by the COMP in 2018. A prevalence of 3.8 in 10,000 is still proposed.

Notably, the prevalence has to be calculated for the entirety of the orphan condition, and not the subset of patients receiving a kidney transplant, which is part of the extension of the therapeutic indication.

The four patient populations with impaired cell-mediated immunity considered to be at risk of developing CMV disease and therefore eligible for prevention of CMV disease are:

1. Haematopoietic stem cell transplant recipients (HSCTs) (previously referred to as human blood precursor cell transplant (HBPCT) recipients);
2. Solid organ transplant recipients (SOTs);
3. HIV patients with a CD4 T-cell count of not more than 50 cells/µl;
4. Patients with primary immune deficiency diseases (PIDDs).

These four patient populations are considered for prevalence estimates of the orphan condition at the time of the current application in 2023. The MAH considers these patient populations to be at risk for CMV disease and that may benefit from a therapy to prevent CMV disease.

A risk calculation of CMV disease for each of the four targeted patient populations has been provided by the applicant and is summarised in table 3.

Table 3.

	Calculations in 2010		**Updated calculations in 2017**	
Patients	N	Prevalence per 10,000	N	Prevalence per 10,000
SOT Recipients	26,671	0.5	31,165	0.6
HBPCT* Recipients	23,333	0.6	36, 469	0.7
allogeneic HSCT recipients	-		15,765	0.3
autologous HSCT recipients	-		20,704	0.4
HIV Patients (with CD4 <= 50 cells/mL)	-	1.5	96,000	1.9
CCL (Oncology patients receiving alemtuzumab	-	0.5	-	-
Primary immunodeficiency diseases (PIDD)	-	-	30,952	0.6
Total	-	**3.1**	***194,586***	***3.8***

* HBPCT, human blood precursor cell transplant, which is the term used previously for HSCTs in the report in 2010.

This calculation indicates that reporting has increased since 2010 in HIV patients, SOT patients and HSCT patients. These assumptions are based on recent publications and reports from European databases.

It was already acknowledged at the initial marketing authorization, that the incidences submitted by the sponsor offer a more current calculation of the situation in Europe, than the one at the designation, because there has been an increase in the number of CMV disease cases reported since 2010. The assumptions for acquired immune deficiency patients focus primarily on oncology patients who have received alemtuzumab, a treatment that had been associated with a high risk of CMV reactivation (Clinical Lymphoma & Myeloma, Vol. 7, No. 2, 125-130, 2006). In view that alemtuzumab for the treatment of patients with CLL had been withdrawn from the EU market in 2012, this subset has been removed from the updated prevalence estimation, which is supported by the COMP.

Primary immunodeficiency diseases (PIDD) are indicated as one of the causes of CMV disease in several publications and has been highlighted in the condition section. The incidence of these conditions in 2004 was reported to be 1 in 10,000 (Lim M et al, Journal of Molecular Diagnostics, Vol. 6, No. 2, May 2004). According to this publication the reporting rates increased. The sponsor showed that primary immunodeficiency diseases comprised of more than 200 rare, inherited chronic diseases that result in defects in the immune system. As stated by the sponsor, the European Society for Immunodeficiencies (ESID) registry reported 19,355 cases in 2014. The prevalence ranges across

Europe varied from 0.023 in 100,000 in Croatia to 6.2 in 100,000 in France. The sponsor has proposed to use the higher prevalence of 0.6 in 10,000 for the overall European prevalence. This has been added to the prevalences of the other three conditions linked to CMV disease.

The COMP concluded that the proposed prevalence of 3.8 in 10,000 is acceptable for the purpose of maintaining the orphan designation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Currently there are three products authorised for the prevention of cytomegalovirus disease in Europe. These are maribavir, ganciclovir and valganciclovir.

Maribavir *(LIVTENCITY) is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT).*

The therapeutic indication for maribavir has an element of prevention of CMV disease as it is for the treatment of CMV infection which can be considered as prevention of the disease. However, maribavir is not considered a satisfactory method that would be a relevant comparator for establishing the Significant Benefit of Prevymis, since this product is authorised in a later line treatment setting.

Valganciclovir (VGCV) is available as a 450mg tablet which is taken bid. Ganciclovir (GCV) is only available as an IV formulation. The use of either of these products are authorised for the prevention of the CMV disease as described in the Summary of Product Characteristics of each product. In the case of valganciclovir section 4.1 limits the use to "the prevention of CMV disease in CMV-negative adults and children (aged from birth to 18years) who have received a solid organ transplant from a CMV-donor".

In the case of ganciclovir, the Summary of Product Characteristics states in section 4.1: "prevention of CMV disease in patients with drug-induced immunosuppression (for example following organ transplantation or cancer chemotherapy)".

Current reviews and guidelines support the recommendation of the use of either of these antiviral agents in the management of CMV disease. (Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation; Contemporary management of cytomegalovirus infection in transplant recipients: guidelines from an IHMF workshop, 2007(external link); 2008 prevention of opportunistic infections in HIV-infected adolescents and adults guidelines: recommendations of GESIDA/National AIDS Plan AIDS Study Group. Since 2013 primarily valganciclovir is used in the prophylaxis of the condition as it is delivered as an oral formulation as opposed to the iv infusion of ganciclovir. As recently reported, by the working group for solid organ transplant in Europe, among solid organ patients at high risk for CMV disease e.g. D+/R- kidney transplant recipients, 90% of respondents provide their patients with CMV prophylaxis and VGCV was the drug most frequently utilized in prophylaxis regimens. By drug category, respondents reported that ~90% of patients received VGCV (the pro-drug of GCV and available for oral use), while ~10% of patients might also require intravenous GCV because some patients were unable to take the oral

formulation in the early postoperative period. According to 80% of respondents, prophylaxis commenced within the first week after transplantation, and 8% reported the addition of CMV Ig for D+/R− patients or those receiving ATG, but that CMV Ig was only used as an add-on therapy during prophylaxis. [Grossi, P. A., et al 2022].

For the propose of this assessment both VGCV and GCV are considered satisfactory methods of treatment.

Significant benefit

The sponsor confirms that protocol assistance (PA) for the justification of significant benefit has not been sought for the use of letermovir (LET) prophylaxis in the kidney transplant population. Two maintenance reports were submitted by the sponsor (one draft in April 2023 and a revised one in June 2023) and in the end, both were considered for the assessment as they had slightly different claims and supportive discussions, while still being based on the same data.

The following claims for significant benefit of LET were put forward by the sponsor in maintenance report from June 2023:

a) A clinically relevant advantage in terms of improved efficacy due to i) the absence of cross-resistance with other approved therapies used for used for CMV treatment, and ii) the observed low rate of anti-viral resistance development, thus allowing one therapy for prophylaxis (LET) and a different therapy without cross-resistance for treatment (VGCV).

b) A clinically relevant advantage in terms of improved efficacy due to dosing independent of kidney function, thus improving compliance and reducing early CMV infection and disease.

c) A clinically relevant advantage in terms of improved efficacy due to reduced rate of prophylaxis discontinuation of LET compared with VGCV, thus allowing more LET prophylaxed patients to receive a complete course of prophylaxis.

From the maintenance report submitted in April 2023 the following claim for significant benefit was assessed by the COMP:

- LET brings a clinically relevant advantage due to an improved safety profile as measured by myelotoxicity (rate of neutropenia/leukopenia), lower rates of prophylaxis discontinuations and drug-related adverse events.

To support these claims the sponsor has submitted data from their clinical trial P002 and data which has been published in the literature.

Of note: VGVC and GCV are the same class of drug and has shown similar efficacy in a randomised study, therefore, the COMP considered that it is possible to extrapolate from the data available on VGVC from the control arm of the pivotal study to GCV (Clin J Am Soc Nephrol. 2015 Feb 6; 10(2): 294–304).

A Phase III pivotal study (P002) was conducted to evaluate the efficacy and safety of letermovir (LET) versus VGCV for the prevention of human CMV disease in adult kidney transplant recipients. P002 enrolled 586 CMV-seronegative recipients ≥18 years of age who received a primary or secondary allograft kidney from a CMV-seropositive donor within 7 days prior to randomization. The population enrolled was representative of adult kidney transplant recipients at risk for CMV disease.

Clinical data from P002 show that 200 days of LET prophylaxis is non-inferior to VGCV in preventing CMV disease through 52 weeks post-transplant. LET is also associated with a significantly lower incidence of leukopenia and neutropenia compared with VGCV and is generally well tolerated.

LET met the pre-defined non-inferiority criterion for efficacy versus VGCV, as measured by the proportion of participants with adjudicated CMV disease through Week 52 post-kidney transplant. The upper bound of the 2-sided 95% CI for the difference in proportion of participants with adjudicated CMV disease (LET – VGCV) was ≤+/- 10%, the pre-defined non-inferiority margin.

Table 4. Analysis of Proportion of Participants with CMV Disease Through Week 52 Post-Transplant (Observed Failure Approach, Full Analysis Set Population)

Parameter	LET Arm (N=289) n (%)	VGCV Arm (N=297) n (%)
Failures	**30 (10.4)**	**35 (11.8)**
CMV Disease[a] Through Week 52	30 (10.4)	35 (11.8)
CMV Syndrome	24 (8.3)	34 (11.4)
CMV End-organ Disease	6 (2.1)	1 (0.3)
Stratum-adjusted Treatment Difference (LET Arm-VGCV Arm)[b]		
Difference (95% CI)	-1.4 (-6.5, 3.8)	
Conclusion[c]	Non-inferior	

Approach to handling missing values: Observed failure (OF) approach. With OF approach, participants who discontinue prematurely from the study for any reason are not considered failures.

[a] CMV disease cases confirmed by an independent adjudication committee.

[b] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction).

[c] LET is concluded non-inferior to VGCV if the upper bound of the two-sided 95% CI for difference in proportion of participants with adjudicated CMV disease (LET – VGCV) is no higher than 10%. LET is concluded superior to VGCV if the upper bound of the two-sided 95% CI for difference in proportion of participants with adjudicated CMV disease (LET – VGCV) is less than 0.

Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.

Source: [P002MK8228: adam-adsl; adeff]

Secondary Efficacy Endpoints in P002

- CMV Disease Through Week 28 Post-transplant
    - No participants (0.0%) in the LET group experienced CMV disease through Week 28 post-kidney transplant; 5 (1.7%) participants in the VGCV group experienced CMV disease through Week 28.
- Time to Onset of CMV Disease Through Week 52 Post-transplant
    - The time to onset of CMV disease was comparable in the LET and VGCV groups through Week 52 post-kidney transplant.
- Subgroup Analyses for P002
    - The treatment difference in the incidence of CMV disease by intervention group through Week 52 post-transplant was comparable across the subgroups of sex, age, race, geographic region, and induction therapy.

Safety

The analysis of safety followed a tiered approach. In P002, the proportion of participants with events of leukopenia (defined as an AE of leukopenia or a total WBC count <3,500 cell/µL) or neutropenia (defined as an AE of neutropenia or an ANC <1,000 cell/µL) was pre-specified as a Tier 1 safety endpoint. The proportion of participants with Tier 1 events of leukopenia (defined as an AE of leukopenia or a total WBC count <3,500 cell/µL) or neutropenia (defined as an AE of neutropenia or an ANC <1,000 cell/µL) during the treatment phase was significantly lower in the LET arm compared with the VGCV arm (26.0% vs 64.0%; $p<0.0001$). Adverse events of leukopenia and neutropenia were reported by lower proportions of participants in the LET arm compared with the VGCV arm (leukopenia: 11.3% vs 37.0%; neutropenia: 2.7% vs 16.5%) [Table 5].

The proportion of participants with drug-related AEs was lower in the LET arm compared with the VGCV arm (19.9% vs 35.0%) [Table 20], primarily due to fewer participants in the LET arm compared with the VGCV arm with drug related AEs of leukopenia (6.8% vs 22.9%) and neutropenia (2.1% vs 8.1%).

The proportions of participants who discontinued study intervention were lower in the LET arm compared with the VGCV arm due to an AE (4.1% vs 13.5%) or a drug-related AE (2.7% vs 8.8%)

Clinically relevant advantage claim a):

Concerning the first claim namely: *A clinically relevant advantage in terms of improved efficacy due to i) the absence of cross-resistance with other approved therapies used for CMV treatment, and ii) the observed low rate of anti-viral resistance development, thus allowing one therapy for prophylaxis (LET) and a different therapy without cross-resistance for treatment (VGCV).*

Viral resistance through week 52 post-transplant revealed that the proportion of participants with resistance-associated substitutions was 0% in the LET group (LET resistance-associated substitution) and 12.1% in the VGCV group (VGCV resistance-associated substitution).

In P002, genotypic resistance testing was performed on blood plasma collected from participants with suspected CMV disease. Among these, 118 participants had sequence data available; 52 participants in the LET arm and 66 participants in the VGCV arm. Analysis of sequence data showed that none of the participants (0/52) in the LET arm had a known resistance-associated substitution at any of the three regions (pU51, pUL56, pUL89) detected at a frequency above the validated assay limit (5% allele frequency) through week 52. In contrast, among the 66 participants in the VGCV arm, 2/66 (3.0%) had a previously characterized resistance-associated substitution in the UL54 gene and 7/66 (10.6%) had resistance-associated substitutions in the UL97 gene. In total 8 participants (12.1%) in the VGCV arm had one or more VGCV resistance-associated substitution detected.

All 8 of these VGCV participants received CMV treatment (8 VGCV and 2 additionally received foscarnet) following the CMV disease visit at which the viral resistance sample was obtained. These 8 participants included 3 participants who experienced CMV DNAemia during the prophylaxis period, 1 participant who experienced CMV DNAemia within 2 weeks after completion of prophylaxis and 4 participants who experienced CMV DNAemia later in the follow-up period, between weeks 30-40 post-transplant.

The COMP considered these observations, but as the primary outcome of CMV disease through Week 52 showed non-inferiority of LET to VGCV, the clinical relevance of these claims by the sponsor on improved drug-resistance were not considered fully substantiated.

Clinically relevant advantage claim b) and c):

b) A clinically relevant advantage in terms of improved efficacy due to dosing independent of kidney function, thus improving compliance and reducing early CMV infection and disease.

c) A clinically relevant advantage in terms of improved efficacy due to reduced rate of prophylaxis discontinuation of LET compared with VGCV, thus allowing more LET prophylaxed patients to receive a complete course of prophylaxis.

The COMP noted that points b) and c) were not exclusively a clinically relevant advantage but aspects of the claims could be considered as claims for a major contribution to patient care.

Dosing that is dependent upon kidney function in kidney transplant recipients is a limitation of both VGCV and GCV (when IV is needed) prophylaxis. Patients are frequently inadequately dosed due to noncompliance and/or not adjusting doses in a timely manner to match changing CrCL. The consequence of inadequate dosing of prophylaxis is increased risk for CMV infection, disease, and resistance, as was observed in P002. LET, which is dosed independent of kidney function, provides a clinically relevant advantage compared with VGCV in high-risk D+/R- kidney transplant recipients, as demonstrated by the comparative results of P002.

The sponsor further claims that this is further supported by evidence that demonstrates that requirements for dose modification based on CrCL is a clinical issue in the effective prophylaxis of CMV disease in kidney transplant recipients, placing patients at risk for low rates of compliance and CMV infection and disease.

The complex dosing recommendation for VGCV is reflected in the number of dosing modifications (doses that were not the same two days consecutively). In P002, dose modification due to CrCL was entered as "Physician Decision to Titrate" which was found to be the most common reason for dose modification. [Table 6] shows that "Physician Decision to Titrate" was lower for participants receiving LET and VGVC placebo (0%) compared with participants receiving VGCV (62.6%) or LET placebo (56.8%).

The number of dose modifications for each participant during the treatment phase ranged from none to more than 10 [Table 6].

Table 5. Reason for Dose Modification Through Week 28 Post-Transplant
(All Participants as Treated Population)

	LET Arm N=292						VGCV Arm N=297					
	LET		ACV*		VGCV Placebo		LET Placebo		ACV Placebo		VGCV	
Reason for Dose Modification	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Adverse Event	27	(9.2)	28	(9.6)	28	(9.6)	46	(15.5)	49	(16.5)	48	(16.2)
General Compl	64	(21.9)	103	(35.3)	77	(26.4)	70	(23.6)	97	(32.7)	75	(25.3)

iance Problems												
Inability to Swallow Medication	3	(1.0)	4	(1.4)	4	(1.4)	3	(1.0)	3	(1.0)	3	(1.0)
Other	31	(10.6)	38	(13.0)	34	(11.6)	32	(10.8)	34	(11.4)	27	(9.1)
Physician Decision to Titrate	0	(0.0)	50	(17.1)	166	(56.8)	0	(0.0)	46	(15.5)	186	(62.6)

*ACV: acyclovir

Table 6. Participants with "Physician Decision to Titrate" Dose Modifications for Either VGCV Placebo or VGCV Through Week 28 Post-Transplant (All Participants as Treated Population)

	LET Arm N=292 VGCV Placebo		VGCV Arm N=297 VGCV	
Number of dose modifications for Physician Decision to Titrate	n	(%)	n	(%)
0	126	(43.2)	111	(37.4)
1	21	(7.2)	27	(9.1)
2	18	(6.2)	22	(7.4)
3	9	(3.1)	13	(4.4)
4-10	41	(14.0)	45	(15.2)
>10	77	(26.4)	79	(26.6)

The proportion of participants with compliance <90% was lower in the LET arm compared with the VGCV arm (<2% vs >20%). However, there is no data provided by the sponsor to support that the higher compliance resulted in either a clinically relevant advantage (as the study showed non-inferiority) or a major contribution to patient care.

The sponsor also claimed that the P002 data support that CMV prophylaxis with LET compared with VGCV/GCV in D+/R- kidney transplant recipients is a more effective prophylaxis agent due to a decreased rate of prophylaxis discontinuation; thus patients who receive LET prophylaxis are more likely to complete a full course of prophylaxis. However, in line with the above comment on compliance, there is, as the study showed non-inferiority of LET vs VGCV, no evidence to support this assumption.

The COMP concluded that the data, while interesting, is not sufficient to support the basis of MCPC or CRA.

Clinically relevant advantage based on a better safety profile:

Leukopenia/neutropenia is a particular characteristic of treatment with VGCV. Prophylaxis with VGCV for 200 days in D+/R- kidney transplant recipients was adopted by guidelines and practitioners following the IMPACT trial published in 2010 [Humar, A., et al 2010]. Although the IMPACT trial demonstrated that 200 days of VGCV prophylaxis compared with 100 days of VGCV prophylaxis significantly reduced the rate of CMV disease in high risk (D+/R-) kidney transplant recipients, high rates of prophylaxis discontinuations were observed as well as SAEs, myelosuppressive events, and hospitalizations among patients receiving 200 days of VGCV prophylaxis compared with 100 days of VGCV prophylaxis. Patients receiving 200 days of VGCV prophylaxis were 4 times more likely than those receiving 100 days of prophylaxis to discontinue due to neutropenia.

The proportion of participants with an event of leukopenia or neutropenia (reported as either an AE or laboratory criteria [AE of leukopenia, WBC count <3,500 cell/µL, AE of neutropenia, ANC <1,000 cell/µL]) was significantly lower in the LET arm (26%) compared with the VGCV arm (64.0%) (estimated difference of -37.9; with a 95% CI of (-45.1, -30.3), p-value <0.0001) [Table 5].

Furthermore, additional details demonstrate that leukopenia and neutropenia were both less common and less severe in the LET arm compared with the VGCV arm. The proportion of participants who reported an AE of leukopenia was lower in the LET arm compared with the VGCV arm (11.3% vs 37.0%). Similarly, the proportion of participants who reported an AE of neutropenia was lower in the LET arm compared with the VGCV arm (2.7% v 16.5%) [Table 5]. Drug-related AEs also occurred at a lower rate in the LET arm compared with the VGCV arm (19.9% vs 35.0%), primarily due to fewer participants with drug related AEs of leukopenia (6.8% vs 22.9%) and neutropenia (2.1% vs 8.1%) [Table 20]. The rate of drug-related SAEs due to leukopenia was also lower in the LET arm compared with the VGCV arm. Laboratory evaluations showed that the proportion of participants with Grade 3 or Grade 4 decreases of leukocytes or neutrophils was lower in the LET arm compared with the VGCV arm (leukocytes: 2.7% vs 6.6%; neutrophils: 2.1% vs 7.9%).

The consequences of leukopenia and neutropenia in the trial included the use of hematopoietic growth factors for clinical treatment of leukopenia/neutropenia (i.e. GCSF), and higher rates of prophylaxis discontinuation. GCSF use was lower in the LET arm compared with the VGCV arm (1.7% vs 7.1%) below. The proportion of participants discontinuing prophylaxis due to leukopenia was lower in the LET arm compared with the VGCV arm (1.0% vs 5.4%). The proportion of participants discontinuing prophylaxis due to neutropenia was similar in the LET arm compared with the VGCV arm (1.4% vs 1.7%).

The sponsor also noted that there was a reduced drop-out rate for the LET group as opposed to VGCV (4.1 vs 13.5%), mainly because of neutropenia, which translates into a difference of 90% CI 4.9-14.1.) as well as a reduced use of rescue medication with Granulocyte colony-stimulating factor (GCSF).

Table 7. Analysis of Participants with Leukopenia or Neutropenia (by Adverse Event Preferred Term or Laboratory Criteria) Treatment Phase (All Participants as Treated)

	LET Arm		VGCV Arm		Total		Difference in % vs VGCV	
	n	%	n	%	n	%	Estimate (95% CI)[a]	p-valuea
Participants in population	292		297		589			
With no leukopenia or neutropenia (preferred term or laboratory criteria) events	216	(74.0)	107	(36.0)	323	(54.8)		
With one or more leukopenia or neutropenia (preferred term or laboratory criteria) events	**76**	**(26.0)**	**190**	**(64.0)**	**266**	**(45.2)**	**-37.9 (-45.1, -30.3)**	**<0.0001**
Leukopenia (preferred term)	33	(11.3)	110	(37.0)	143	(24.3)	-25.7 (-32.3, -19.1)	
Leukopenia (WBC <3500 cells/µL)	66	(22.6)	172	(57.9)	238	(40.4)	-35.3 (-42.5, -27.7)	
Neutropenia (preferred term)	8	(2.7)	49	(16.5)	57	(9.7)	-13.8 (-18.7, -9.3)	
Neutropenia (ANC <1000 cells/µL)	12	(4.1)	58	(19.5)	70	(11.9)	-15.4 (-20.7, -10.5)	

[a] Based on Miettinen & Nurminen method.

Source: [P002MK8228: adam-adsl]

Conclusion: The COMP considered that particularly in the treatment setting of kidney transplantation where patients use multiple immunosuppressive agents, the avoidance of neutropenia is of importance.

Neutropenia is a well-known risk with VGCV, which is subsequently linked with dose adjustments and disruption in the prophylaxis treatment. The sponsor provided data from the comparative study P002 showing a statistically significant, and clinically relevant reduction of neutropenia of LET as compared to VGCV treated patients.

The COMP concluded, exceptionally, that a clinically relevant advantage is supported by improved safety.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 23 October 2023

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 3.8 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening due to frequent development of acute severe hepatitis, pneumonitis, colitis, haemorrhagic cystitis and encephalitis. Disseminated disease can be rapidly fatal, with mortality rates reported to be as high as 80%;
- although satisfactory methods for the prevention of the condition have been authorised in the European Union for all the patients covered by Prevymis, the assumption that Prevymis may be of potential significant benefit still holds. The sponsor has provided data which show a significant reduction in neutropaenia, a critical complication of treatment with valganciclovir in kidney transplantation, as shown in a direct comparison.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Prevymis, letermovir for prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk (EU/3/11/849) is not removed from the Community Register of Orphan Medicinal Products.