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Preemptive treatment of Cytomegalovirus infection in kidney transplant recipients with letermovir: results of a Phase 2a study

Susanne Stoelben,[1] Wolfgang Arns,[2] Lutz Renders,[3] Jürgen Hummel,[4] Anja Mühlfeld,[5] Manfred Stangl,[6] Michael Fischereder,[7] Wilfried Gwinner,[8] Barbara Suwelack,[9] Oliver Witzke,[10] Michael Dürr,[11] Dietrich W. Beelen,[12] Detlef Michel,[13] Peter Lischka,[1] Holger Zimmermann,[1]* Helga Rübsamen-Schaeff[1]* and Klemens Budde[11]*

1 AiCuris GmbH & Co. KG, Wuppertal, Germany
2 Transplantationszentrum, Kliniken der Stadt Köln, Klinikum Merheim, Germany
3 Department of Nephrology, Klinikum Rechts der Isar, Technical University Munich, Munich, Germany
4 PPD, Bellshill, UK
5 Department of Nephrology and Clinical Immunology, University Clinic of the RWTH Aachen University, Aachen, Germany
6 Chirurgische Klinik und Poliklinik der TU München, Klinikum rechts der Isar, München, Germany
7 Schwerpunkt Nephrologie, Klinik und Poliklinik für Innere Medizin I – Campus Grosshadern, München, Germany
8 Department of Nephrology, Medical School Hannover, Hannover, Germany
9 Transplantationszentrum, Universitätsklinikum Münster, Münster, Germany
10 Klinik für Nephrologie, Universitätsklinikum Essen, Essen, Germany
11 Department of Nephrology, Charité Universitätsmedizin Berlin, Berlin, Germany
12 Klinik für Knochenmarkstransplantation, Universitätsklinikum Essen, Essen, Germany
13 Institut für Virologie, Universitätsklinikum Ulm, Ulm, Germany

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Correspondence
Dr. rer. nat. Holger Zimmermann, AiCuris GmbH & Co. KG, Friedrich Ebert Straße 475, 42117 Wuppertal, Germany.
Tel.: +49 202 31763 1176;
fax: +49 202 31763 1177;
e-mail: Holger.Zimmermann@AiCuris.com

Conflicts and interest
SS, PL, HZ, and HR-S are all employees of AiCuris. KB acted as an advisory board member for AiCuris and received a consultant fee, has consultancy agreements and/or has received grants from Astellas, Bristol-Myers Squibb, Hexal, LifeCycle Pharma, Novartis Pharma, TCL Pharma, Roche AG, Siemens, and Pfizer.

*These two authors contributed equally to this study.

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Summary

Cytomegalovirus (CMV) infection remains a significant cause of morbidity and mortality in transplant recipients. Letermovir (AIC246), is a novel anti-HCMV drug in development, acting via a novel mechanism of action. In this proof-of-concept trial with first administration of letermovir to patients, 27 transplant recipients with active CMV replication were randomly assigned to a 14-day oral treatment regimen of either letermovir 40 mg twice a day, letermovir 80 mg once a day, or local standard of care (SOC) in a multicenter, open-label trial. Efficacy, safety, and limited pharmacokinetic parameters were assessed. All groups had a statistically significant decrease in CMV-DNA copy number from baseline (40 mg BID: $P = 0.031$; 80 mg QD: $P = 0.018$; SOC: $P = 0.001$), and comparison of viral load reduction between treatment groups showed no statistically significant differences. Viral clearance was achieved for 6 of 12 patients (50%) in the letermovir groups versus two of seven SOC patients (28.6%). Letermovir treatment was generally well tolerated, no patient developed CMV disease during the trial. Both letermovir treatment regimens resulted in equally high trough level plasma concentrations. The efficacy, safety, and pharmacokinetics observed in these viremic transplant recipients indicate that letermovir is a promising new anti-CMV drug.

Introduction

Human cytomegalovirus (CMV) is a significant threat for immunocompromised patients [1–3]. Up to 60% of high-risk (D+/R-) kidney transplant recipients may develop viremia, and 45% of patients if left untreated may develop CMV disease [4–6].

Two main strategies are currently being followed to prevent active CMV disease in kidney transplanted patients: antiviral prophylaxis or preemptive therapy [7–9]. Despite international guidelines on patient management, a common management approach across transplantation centers does not exist and clinics weigh the risks and benefits of treatment regimens according to the individual risk for the patient [8]. Present first-line anti-CMV therapies rely on ganciclovir or its oral prodrug valganciclovir. Second-line treatments include foscarnet and cidofovir. Although efficacious, current treatments are limited by severe dose-related toxicities such as bone marrow suppression and renal toxicity or the development of drug resistance, which may lead to cross-resistance among available agents. The latter is because of their common mode of action as all are inhibitors of the viral DNA polymerase [7,10,11].

Recently, compounds with novel modes of action were discovered, targeting the viral terminase, an enzyme complex that plays a key role in cleavage and packaging of CMV progeny DNA into capsids [12–14]. As there is no counterpart of the viral terminase in humans, it is expected that compounds targeting this viral enzyme will not show target-related toxicities that are seen with the marketed anti-CMV polymerase inhibitors. In addition, the different mode of action should provide new treatment options for patients infected with resistant virus strains [14–17] Letermovir (AiCuris GmbH & Co. KG, Wuppertal, Germany), from the novel chemical class, the 3,4 dihydroquinazolinyl-acetic acids, targets the viral terminase and is the only terminase inhibitor in late stage clinical development.

Letermovir demonstrated a profound and significantly higher antiviral activity than ganciclovir *in vitro* and high activity against viruses resistant to currently available agents including successful treatment of a multi-resistant infection [14–17]. Phase I studies conducted in healthy subjects found that letermovir administration was safe and well tolerated without any drug-specific adverse effects [18]. Pharmacokinetic analysis identified that letermovir maximum plasma concentrations were achieved approximately 1.5 h after oral administration and had a mean terminal elimination half life of about 10 h. Letermovir is highly protein bound and is eliminated mainly unchanged from the human body into feces [18]. Here, we report proof- of-concept data of the first letermovir administration to transplant patients with active CMV replication.

Materials and methods

This is a Phase 2 randomized, controlled, multicenter, open-label trial of letermovir (40 mg twice daily or 80 mg once daily) compared with local standard of care for a 14-day treatment period conducted in adults with active CMV replication at German transplant centers. The trial was registered at the European Clinical Trials Database (EudraCT-number: 2006–006148–69), approved by the responsible Independent Ethics Committee and conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation (ICH).

Initially, the trial was set up in CMV viremic bone marrow transplanted patients. However, after the inclusion of a single bone marrow recipient, the protocol was amended (because of very slow enrollment of suitable bone marrow transplanted patients) to only enroll kidney and kidney/pancreas transplanted patients. To allow timely enrollment after a positive CMV test, patients were enrolled based on a positive local laboratory test result at screening if they were eligible for preemptive therapy according to the local practice. For data analysis purposes, only the central laboratory CMV-DNA results were used, this avoided issues from site to site differences in test sensitivity or specificity, allowing consistent results from a single, certified, accredited laboratory. These data were not communicated to the clinics.

Major exclusion criteria were evidence of current severe systemic infection or symptomatic end-organ CMV disease, graft-versus-host disease (Grade 3 4) at enrollment, evidence of liver or renal dysfunction, a positive Hepatitis B or human immunodeficiency virus evaluation, uncontrolled diarrhea or severe gastrointestinal disease, previous CMV treatment with valganciclovir within 4 days prior to enrollment or with cidofovir or foscarnet within 30 days prior to enrollment and treatment with CYP3A4 inducers or inhibitors.

All patients were randomly assigned to one of the three treatment groups using an interactive voice response system (IVRS). They were treated for 14 days with oral letermovir 40 mg twice a day (BID), 80 mg once a day (QD) or local standard of care (SOC) as control.

Dose selection with respect to length of treatment and total daily doses for letermovir were based on nonclinical pharmacokinetic and pharmacodynamic data as well as on the available data in healthy subjects (incl. safety data) at the start of the trial. The pharmacokinetic target, the human efficacious dose, was selected as the concentration above the effective concentration producing 90% of maximum response (EC_{90}) for the entire dosing interval. The average letermovir EC_{50} and EC_{90} values obtained *in vitro* by different antiviral assays were 4 and 6.1 nM, respectively [14]. Given the steep dose response curve of the drug in these *in vitro* assays, it was assumed that viral replication is

fully inhibited at concentrations above EC_{90} corrected for protein binding. Trough levels exceeding 6.1 nM plasma concentration were reached in healthy subjects with letermovir doses of 40 mg BID or 80 mg QD.

The primary objective for this first trial in patients was to determine the efficacy of letermovir defined as a decline in CMV-DNA versus baseline within a 14-day treatment period. For this, CMV-DNA load was assessed centrally by quantitative polymerase chain reaction (qPCR) from patient plasma samples (measured in log10 genome copies/ml). The lower limit of quantification (lq) of the in-house assay was 500 genome copies/ml, and the limit of detection (ld) was 200 genome copies/ml. Exact details of the performance of the assay were reported recently [19]. Retrospectively, a conversion factor of 0.63 for translation of genome copies/ml into international units (IU) was calculated and applied based on the 1st WHO international standard for HCMV for nucleic acid amplification techniques. Secondary objectives included the assessments of the safety, tolerability, and pharmacokinetics of letermovir.

Local evaluations of CMV-DNA level were performed at screening, and all safety parameters (adverse events (AEs), vital signs, ECG, safety laboratory determinations such as hematology, serum chemistry parameters and urinalysis) were recorded at regular intervals. AEs were coded according to MedDRA version 12.0 and classified using the preferred term by body system.

On Day 1, blood samples were taken for predose (baseline) measurement of pharmacodynamic (central qPCR assessment of CMV-DNA load), safety and pharmacokinetic parameters. Further evaluations of these variables were performed on Days 4, 8, 11, 15, and 22. Following the conclusion of the trial period, all patients underwent end-of-trial assessments on Day 29.

The central evaluation of qPCR CMV-DNA values was performed at the Institute of Virology, University of Ulm, Germany according to a validated method described in [19]. Central evaluation of the letermovir plasma trough levels was performed by HPLC/MS/MS at Bayer HealthCare AG, Wuppertal, Germany; the lower limit of quantification was 2 μg/l.

Statistical methods

The sample size was chosen based on clinical feasibility rather than statistical evaluation. Thus, because of the small sample size, data were reported as descriptive statistics; however, a supportive statistical analysis and power calculation was performed with nQuery Advisor v 4.0 (Statistical Solutions, Cork, Ireland; 2000) to obtain information on the magnitude of the difference that could be observed with the chosen sample size. All statistical outputs were produced in SAS® v8.2 (SAS Institute Inc., Cary, NC, USA).

It was assumed that the primary efficacy endpoint was normally distributed. Owing to the absence of any data on letermovir, the standard deviation (SD) was estimated using data from valganciclovir and ganciclovir from 2 different publications [20,21]. In both cases, the SD for the primary endpoint was derived from information on the range, leading to a pooled SD of 0.8 log10 copies/ml. A sample size of eight patients per group had 80% power to detect a mean reduction in CMV-DNA load from baseline to Day 15 of 0.93 log10 copies/ml. As this was a proof-of-concept trial, no adjustment was made for multiplicity. All statistical tests were 2-sided and were performed using a 5% significance level.

For all analyses, the latest recorded value prior to the first dose of trial medication was used as baseline. Patients grouped to the per-protocol (PP) population fully complied with the requirements of the protocol, had more than 75% trial medication compliance, and had central laboratory CMV assessment collected on Day 15. Patients assigned to any letermovir treatment group were included in the PK population (PKS).

Decline of CMV-DNA load data (on the logarithmic scale) from baseline was analyzed using a repeated measures ANCOVA model. Decline from baseline values was compared with zero (indicating no change from baseline) for each time point within each treatment group and the SOC group.

Results

Of 47 patients screened, 27 patients (including $n = 1$ bone marrow transplant recipient) from 10 different investigational sites were randomly assigned and equally distributed to one of the three treatment groups between April 2007 and April 2009. In total, 25 patients completed 14 days of treatment. All randomized patients were included in the safety population and the ITT. No letermovir-treated patients were excluded from the PKS. Two patients in the letermovir 40 mg BID dosing group were prematurely discontinued from trial treatment because of the decision of the investigator (one patient with dyspnea; one patient with positive HCMV results) and were excluded from the per-protocol population. Investigator's decisions to discontinue treatment were based on the need to minimize risk to the patients and reflect the lack of clinical experience with this new compound. Of these, 1 patient received 11 days and the other 9 days of treatment. All nine patients in the SOC group received 14 days of treatment with oral valganciclovir according to the respective hospital dosing regimen (daily doses: two patients <450 mg, three patients 450 mg, three patients 900 mg, one patient 1800 mg). Intergroup differences in serotype were observed: D+R- was more common

Table 1. Demographics and background characteristics (Safety and ITT populations).

	Letermovir 40 mg BID (*N* = 9)	Letermovir 80 mg BID (*N* = 9)	Standard of care (*N* = 9)	Total (*N* = 27)
Age (years)				
Mean (SD)	55.9 (14.3)	60.2 (11.9)	57.2 (11.2)	57.8 (12.2)
Median	60	66	55	60
Min, Max	35, 7	45, 8	41, 7	35, 8
Sex, *n* (%)				
Male	7 (78)	4 (44)	7 (78)	18 (67)
Female	2 (22)	5 (56)	2 (22)	9 (33)
Race, *n* (%)				
Caucasian	9 (100)	9 (100)	9 (100)	27 (100)
Type of transplantation, *n* (%)				
Kidney	8 (89)	8 (89)	9 (100)	25 (92)
Kidney/pancreas	0	1 (11)	0	1 (4)
Bone marrow	1 (11)	0	0	1 (4)
Serology status *n* (%)*				
D+/R-	1 (11)	3 (33)	6 (67)	10 (37)
D+/R+	4 (45)	4 (45)	3 (33)	11 (41)
D-/R-	2 (22)	0	0	2 (7)
D-/R+	1 (11)	1 (11)	0	2 (7)
Missing	1 (11)	1 (11)	0	2 (7)
Concomitant immunosuppressive medication, *n* (%)				
Calcineurin Inhibitors	9 (100)	7 (78)	7 (78)	23 (86)
Cyclosporine	6 (67)	6 (67)	3 (33)	15 (56)
Tacrolimus	3 (33)	1 (11)	4 (45)	8 (30)
Glucocorticoids	9 (100)	9 (100)	9 (100)	27 (100)
Methylprednisolone	4 (44.4)	3 (33)	3 (33)	10 (37.0)
Prednisolone	2 (22.2)	4 (45)	5 (56)	11 (40.7)
Prednisone	4 (44.4)	2 (22)	1 (11)	7 (25.9)
Selective Immunosuppressants	7 (78)	7 (78)	7 (78)	21 (78)
Everolimus	1 (11)	0	0	1 (4)
Leflunomide	0	1 (11)	0	1 (4)
Mycophenolate mofetil	2 (22)	1 (11)	2 (22)	5 (18)
Mycophenolic acid	4 (45)	5 (56)	5 (56)	14 (52)

BID, twice daily; QD, once daily; D, donor; R, recipient.

Percentages are based on the number of patients in each treatment group. Patients may have more than 1 medication per drug class and preferred term. At each level of patient summarization, a patient was counted once if the patient reported 1 or more medications.

*Donor/recipient serotypes were not assessed as having an impact on trial analysis because of the small sample size of the trial and enrollment of only 4 patients < 6 months after transplantation.

in the SOC group (67%) vs 40 mg BID (33%) or 80 mg QD (11%), while D+/R+ was more common in the letermovir groups: 40 mg BID (45%) and 80 mg QD (45%) vs placebo (33%). Detailed demographic characteristics, transplantation type, CMV serology status, and concomitant immunosuppressant medications of the 27 randomized patients are displayed in Table 1. All patients were treated with glucocorticoids, 23 of 27 (86%) patients received calcineurin inhibitors, and 19 of 27 (70%) were treated with mycophenolate.

Efficacy results

No patient developed CMV disease during the trial. Patients in all treatment groups showed a statistically significant decrease in CMV-DNA load (primary endpoint) during the treatment period. A summary of the plasma CMV-DNA load and the change from baseline (log10 copies/ml) for each treatment group (PP population) is presented in Table 2. The change from baseline to Day 15 for each individual patient is depicted in Fig. 1a. While in each group the difference versus baseline was statistically significant, the differences between the letermovir and SOC groups were not statistically significant. A sharp decline in the CMV-DNA load was seen after Day 4 in the SOC treatment group, whereas a comparable decrease in DNA copy number in the letermovir treatment groups was observed between days 11 and 15 (compare Table 2), which is attributed to the difference in mechanism of action for letermovir and the diagnostic procedure (see discussion).

Table 2. Log-transformed HCMV-DNA copy numbers in plasma actual and change from baseline (Log_{10} copies/ml) (PP population).

	Letermovir 40 mg BID (*N* = 7)		Letermovir 80 mg QD (*N* = 9)		Standard of Care (*N* = 9)	
	Actual	Change	Actual	Change	Actual	Change
Day 1 (Baseline)						
Mean	3.171	–	3.856	–	3.878	–
(SD)	(1.067)		(1.256)		(1.081)	
Day 4						
Mean	3.286	0.114	4.078	0.222	3.178	−0.700
(SD)	(1.268)	(0.677)	(1.234)	(0.504)	(0.931)	(0.776)
P value	–	0.9	–	0.268	–	0.018
Day 8						
Mean	3.114	−0.057	3.798	−0.058	2.900	−0.925
(SD)	(0.928)	(0.493)	(1.306)	(0.568)	(0.550)	(0.899)
P value	–	0.481	–	0.981	–	0.005
Day 11						
Mean	3.357	0.186	3.711	−0.144	3.063	−0.763
(SD)	(0.941)	(0.781)	(1.734)	(0.876)	(0.872)	(1.127)
P value	–	0.908	–	0.754	–	0.02
Day 15						
Mean	2.671	−0.500	3.164	−0.691	2.788	−1.038
(SD)	(0.506)	(0.860)	(1.437)	(0.990)	(0.473)	(1.078)
P value	–	0.031	–	0.018	–	0.001

BID, twice daily; QD, once daily; PP, per protocol.

Data below the limit of quantification (LoQ) (500 copies/ml) were included in the analysis using half the LoQ (on the logarithmic scale). Unscheduled visits were not included in the analysis. The *P* value is from a repeated measures analysis of covariance (ANCOVA) model with time point, treatment, and time point by treatment interaction included as fixed factors, baseline CMV-DNA load as a covariate and patient as a random effect.

As patients were allowed to enter the trial with any baseline viremia level as detected by the local laboratory, two additional subgroup analyses based on central readings were performed: (i) Patients were removed from the subgroup efficacy analysis shown in Fig. 1b if they had no detectable baseline viremia by the central laboratory measurement (three patients in the letermovir 40 mg BID group, one patient in the letermovir 80 mg QD group, and 2 patients in the SOC group). (ii) Patients were separated into two subgroups based on baseline (Day 1) CMV-DNA copy number: high copy number (≥4 log10) compared with lower copy number (<4 log10). Fig. 1c depicts CMV-DNA log reduction between Day 1 and Day 15 of all individual patients with a CMV-DNA copy number >4 log10 at baseline (Day 1). Data analyses revealed that the number of patients with high DNA copy numbers (>4 log10) at baseline differed markedly between treatment groups as only 1 of 7 patients (letermovir 40 mg BID), 4 of 9 patients (letermovir 80 mg QD), and 5 of 9 patients (SOC) had CMV copy numbers >4 log10. This is noteworthy, as patients with a higher CMV-DNA load at baseline may experience a greater decrease in CMV-DNA load compared with patients with a low CMV-DNA load [22].

In summary, although based on only a small patient number, comparable efficacy of letermovir and valganciclovir in terms of CMV-DNA log reduction was demonstrated. As a secondary endpoint, viral clearance within the 14-day treatment period was evaluated for each treatment group. As depicted in Table 3, viral clearance was reached in 2 of 4 (50%) patients in the letermovir 40 mg BID group, 4 of 8 (50%) patients in the letermovir 80 mg QD group, and in 2 of 7 (28.6%) patients in the SOC group.

Pharmacokinetics

Stable trough levels of letermovir were reached on Day 4. Letermovir treatment with either 40 mg BID or 80 mg QD resulted in similar trough levels (Fig. 2). The intraindividual variability in letermovir trough levels was low, resulting in relatively constant trough values over the entire treatment duration. In all patients, the measured mean letermovir trough levels were consistently above the EC_{90} level derived from *in vitro* experiments and corrected for plasma protein binding.

Safety results

There were 62 treatment-emergent adverse events (TEAEs) which occurred in 20 patients (74.1%). The majority of TEAEs were considered to be mild in intensity, and none were considered severe. Table 4 shows a summary of

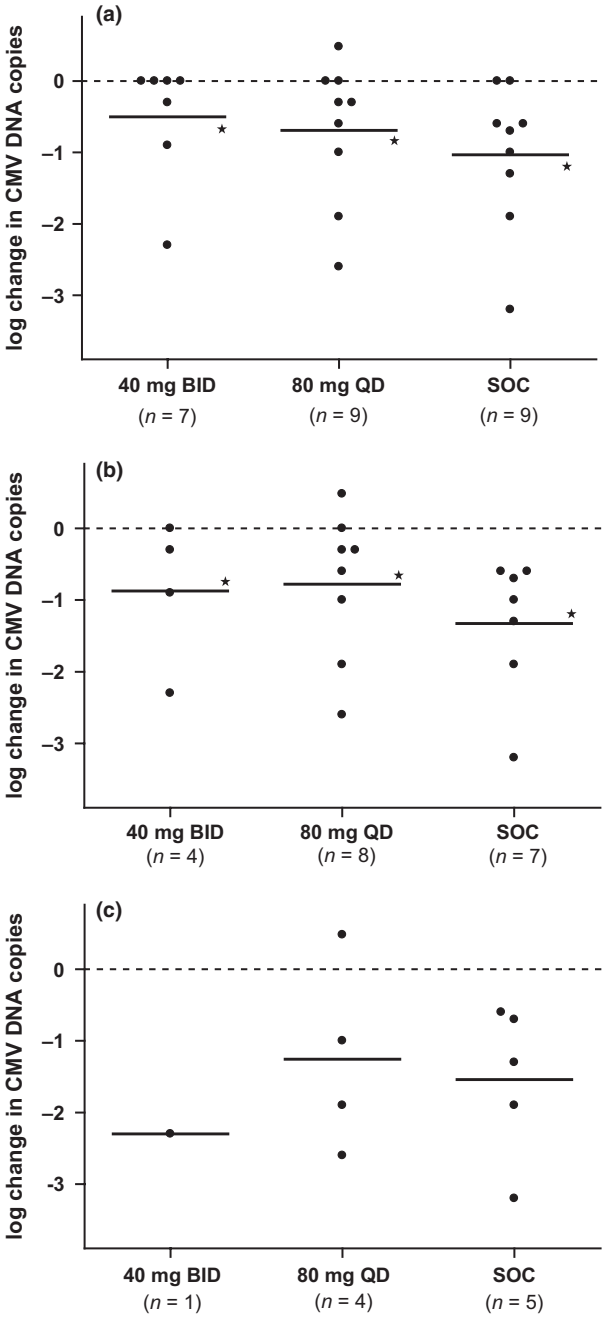

Figure. 1 Individual CMV-DNA load change from baseline to Day 15 (Log10 copies/ml) displayed by dots plus means (bars) for treatment groups for the per-protocol (PP) population (excludes patients with low treatment compliance or no central laboratory evaluation for baseline or Day 15). *, $P < 0.05$; the P value is from a repeated measures analysis of covariance (ANCOVA) model with time point, treatment and time point by treatment interaction included as fixed factors, baseline CMV-DNA load as a covariate and patient as a random effect. Note: Data below the limit of quantification (BLQ; <500 DNA copies/ml) were included in the analysis using half the BLQ. BID, twice daily; QD, once daily for letermovir treatment groups; N = number of patients. (a) Individual CMV-DNA load change from baseline to Day 15 for the entire PP population. (b) Individual CMV-DNA load change from Baseline to Day 15 excluding individuals with either a zero or BLQ (below limit of quantification, 500 DNA copies/ml) value at Day 1(baseline). (c) Individual CMV-DNA load change from baseline to Day 15. Depicted are all patients of the individual treatment groups with baseline CMV-DNA copies ≥4 log10.

Table 3. Viral clearance at Day 15 for the PP population excluding all individuals with either zero or BLQ HCMV counts at baseline.

	Letermovir 40 mg BID (N = 4)	Letermovir 80 mg QD (N = 8)	Standard of care (N = 7)
Patients with viral clearance, n (%)	2 (50.0)	4 (50.0)	2 (28.6)
Patients without viral clearance, n (%)	2 (50.0)	4 (50.0)	5 (71.4)

BID, twice daily; QD, once daily.
Percentages are based on the number of patients with data on the parameter of interest in each treatment group. Viral clearance is defined as CMV-DNA qPCR values below the limit of quantification (BLQ).

TEAEs by system organ class and preferred term for the safety population.

The majority of reported AEs were considered to be unrelated to trial medication. Only five AEs in three patients were considered possibly related to trial medication: four AEs in two patients in the letermovir 40 mg BID group (gastroenteritis, nasopharyngitis, dyspnea, and plasma creatinine increased) and one AE in one patient in the letermovir 80 mg QD group (dyspepsia). No TEAEs were considered probably or definitely related to trial medication.

The laboratory (hematology and serum chemistry) value changes over time were within the normal range. No clinically significant abnormalities in vital signs or ECG evaluations were identified.

Discussion

To obtain first efficacy data for letermovir as preemptive treatment in viraemic kidney and kidney/pancreas transplant patients, this trial was designed as an exploratory proof-of-concept trial, and as such, the sample size was small. Thus, not all factors such as immunosuppressant comedication, viral load at baseline, or serology status were equally distributed between treatment groups. While their influence upon responses to antiviral therapy cannot be excluded, the small population size precluded meaningful investigation of such effects. The limited preclinical and clinical data on letermovir available at start of trial allowed dosing for a maximum of 80 mg letermovir per day for 14 days. For logistical and safety reasons, it was necessary

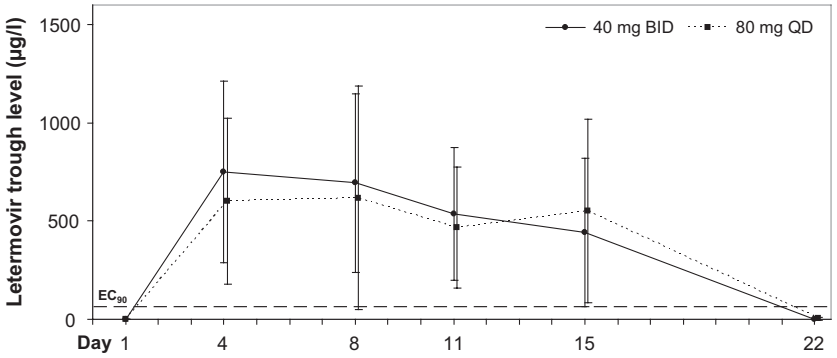

Figure 2 Mean and SD letermovir trough levels (linear scale) versus time (pharmacokinetic population). BID, twice daily; QD, once daily.

to include patients based on CMV results from the local laboratory. However, central randomization as the most important method for bias control was implemented, and evaluations for the primary endpoint were based on central laboratory results only.

In spite of the limitations mentioned above, the primary endpoint of the trial was met. A statistically significant decrease in the biomarker CMV-DNA was seen for all treatment groups between baseline and Day 15 (Table 2). Nine of 12 patients (75%) with a measurable CMV-DNA level by the central laboratory at the start of letermovir treatment showed a reduction in CMV-DNA copies on Day 15 with a maximum reduction of 2.6 log10 (mean 0.81 log10) (Fig. 1b). Moreover, although the difference was not statistically significant, a higher proportion of patients treated with letermovir 50% (6/12) compared with SOC 30% (2/7) achieved viral clearance within the 14-day treatment period (Table 3). Finally, none of the viremic patients developed CMV disease during the trial. Taken together, these data support the efficacy of letermovir for preemptive treatment and clearance of CMV viremia in kidney and kidney/pancreas transplant patients.

Overall, the decrease in plasma CMV-DNA load tended to be greater in the SOC group treated with valganciclovir although the difference versus the letermovir groups was not statistically significant. The higher decrease in viral load in the SOC group might be explained by the differences in baseline characteristics at randomization, with more patients in the SOC group having high CMV-DNA values and thus able to show a larger log DNA reduction [22] (compare Fig. 1b,c). When analyzing only patients with high copy numbers at baseline (>4 log10), the CMV-DNA decline of approximately 1 log10 within the 14-day treatment period (Fig. 1c) is comparable to published efficacy data for valganciclovir [20]. This ambiguity reflects the restrictions of a small sample size and the need for more data in larger cohorts to confirm these conclusions.

Differences in the time course of CMV-DNA decrease were identified between SOC and letermovir treatment groups during the 2-week treatment period (Table 2). In the SOC group, a decline in CMV-DNA values was seen by Day 4 (the first data point after baseline), whereas in both letermovir groups, the decline occurred later, mainly after Day 11. This finding is likely due to the novel mode of action of letermovir. The difference in mechanism of action between letermovir and valganciclovir (SOC) impacts the CMV-DNA value differently as letermovir interferes with maturation and packaging of viral particles but does not inhibit DNA synthesis [14,15]. While letermovir treatment leads to an immediate cessation of the production of infectious viral particles, it allows DNA synthesis to occur, thus providing DNA copies that are measured by the CMV-DNA assay. Valganciclovir, in contrast, is a DNA polymerase inhibitor and thus has an immediate effect on the production of DNA copies. Based on *in vitro* data and the initial clinical evidence from this small trial, letermovir efficacy measured by CMV-DNA reduction might therefore be underestimated during the first 8–10 days of preemptive treatment and clinical judgment should guide treatment decisions. Although not of relevance in a prophylactic setting, diagnostic tests detecting viral surrogate markers expressed with a late kinetic-like pp67 late mRNA [23] might be more suitable when monitoring letermovir efficacy, especially in the first 10 days of preemptive therapy. Ganciclovir or it's prodrug valganciclovir are currently the most widely used antiviral drugs for CMV treatment. However, ganciclovir-resistant virus strains are associated with increased mortality and morbidity because of limited treatment options based on cross-resistance with second-line treatments, as all licensed CMV agents address only one viral target, the viral DNA polymerase [7,8,24,25]. As discussed above, cross-resistance between letermovir and currently available agents does not occur [14,15,17]. In this respect, it is noteworthy that retrospective sequence analyses of samples from the present trial revealed that three patients in the letermovir groups were infected with a virus encoding confirmed GCV resistance mutations [26]; two patients in the 40 mg BID group and one patient in the

Table 4. Summary of Treatment-Emergent Adverse Events, by system organ class and preferred term (Safety Population).

	Letermovir 40 mg BID (*N*=9)		Letermovir 80 mg QD (*N*=9)		Observational control (*N*=9)	
	n (%) Patients	Total Events	*n* (%) Patients	Total Events	*n* (%) Patients	Total Events
Number of patients with >1 TEAE	8 (88.9)	21	6 (66.7)	27	6 (66.7)	14
Blood and lymphatic system disorders	1 (11.1)	1	1 (11.1)	1	1 (11.1)	1
Leukopenia	0	0	1 (11.1)	1	1 (11.1)	1
Lymphopenia	1 (11.1)	1	0	0	0	0
Congenital, familial and genetic disorders	0	0	1 (11.1)	1	0	0
Hydrocele	0	0	1 (11.1)	1	0	0
Ear and labyrinth disorders	1 (11.1)	1	0	0	0	0
Vertigo	1 (11.1)	1	0	0	0	0
Eye disorders	1 (11.1)	1	0	0	0	0
Vision blurred	1 (11.1)	1	0	0	0	0
Gastrointestinal disorders	1 (11.1)	1	2 (22.2)	3	0	0
Abdominal pain upper	1 (11.1)	1	0	0	0	0
Dyspepsia	0	0	1 (11.1)	1	0	0
Periodontitis	0	0	1 (11.1)	1	0	0
Vomiting	0	0	1 (11.1)	1	0	0
General disorders and administration site conditions	2 (22.2)	3	1 (11.1)	1	2 (22.2)	2
Asthenia	1 (11.1)	1	0	0	0	0
Edema	0	0	0	0	1 (11.1)	1
Edema peripheral	1 (11.1)	2	1 (11.1)	1	1 (11.1)	1
Infections and infestations	3 (33.3)	4	3 (33.3)	4	3 (33.3)	4
Central line infection	0	0	0	0	1 (11.1)	1
Gastroenteritis	1 (11.1)	1	0	0	0	0
Nasopharyngitis	2 (22.2)	2	1 (11.1)	1	1 (11.1)	1
Oral herpes	0	0	1 (11.1)	1	0	0
Rhinitis	0	0	0	0	1 (11.1)	1
Urinary tract infection	1 (11.1)	1	2 (22.2)	2	1 (11.1)	1
Injury, poisoning and procedural complications	0	0	1 (11.1)	2	2 (22.2)	2
Arteriovenous fistula aneurysm	0	0	1 (11.1)	1	0	0
Complications of transplanted kidney	0	0	1 (11.1)	1	0	0
Postoperative wound complication	0	0	0	0	1 (11.1)	1
Renal lymphocele	0	0	0	0	1 (11.1)	1
Investigations	1 (11.1)	1	0	0	0	0
Blood creatinine increased	1 (11.1)	1	0	0	0	0
Metabolism and nutrition disorders	1 (11.1)	1	3 (33.3)	4	1 (11.1)	1
Gout	0	0	1 (11.1)	1	1 (11.1)	1
Hyperuricemia	1 (11.1)	1	1 (11.1)	1	0	0
Hypoglycemia	0	0	1 (11.1)	1	0	0
Hypokalemia	0	0	1 (11.1)	1	0	0
Musculoskeletal and connective tissue disorders	1 (11.1)	1	2 (22.2)	9	0	0
Arthralgia	0	0	1 (11.1)	1	0	0
Bone pain	0	0	1 (11.1)	1	0	0
Gouty tophus	0	0	1 (11.1)	4	0	0
Muscle spasms	0	0	1 (11.1)	1	0	0
Myalgia	1 (11.1)	1	0	0	0	0
Pain in extremity	0	0	1 (11.1)	2	0	0
Nervous system disorders	2 (22.2)	3	0	0	0	0
Dizziness	1 (11.1)	1	0	0	0	0
Headache	1 (11.1)	1	0	0	0	0
Tremor	1 (11.1)	1	0	0	0	0
Renal and urinary disorders	0	0	2 (22.2)	2	0	0
Renal disorder	0	0	1 (11.1)	1	0	0
Renal impairment	0	0	1 (11.1)	1	0	0

Table 4. continued

	Letermovir 40 mg BID (*N*=9)		Letermovir 80 mg QD (*N*=9)		Observational control (*N*=9)	
	n (%) Patients	Total Events	*n* (%) Patients	Total Events	*n* (%) Patients	Total Events
Respiratory, thoracic and mediastinal disorders	1 (11.1)	1	0	0	0	0
Dyspnea	1 (11.1)	1	0	0	0	0
Vascular disorders	3 (33.3)	3	0	0	2 (22.2)	4
Hot flush	0	0	0	0	1 (11.1)	1
Hypertension	2 (22.2)	2	0	0	2 (22.2)	3
Hypotension	1 (11.1)	1	0	0	0	0

BID, twice daily; QD, once daily; TEAE treatment-emergent adverse event.
This table displays nonserious and serious adverse events (AEs). The total number of events counts all AEs for patients. At each level of patient summarization, a patient is counted once if the patient reported 1 or more events. Percentages are based on the number of patients in each treatment group.

80 mg BID group exhibited GCV mutations in either the viral kinase UL97 or in both UL97 and the viral polymerase UL54 (mediating cidofovir and foscarnet cross-resistance). All three patients responded to letermovir treatment.

This observation concurs with another recent publication demonstrating the successful treatment of a lung transplant recipient suffering from a multidrug-resistant cytomegalovirus disease using letermovir [16].

As the viral terminase complex is an essential and unique viral target without a mammalian counterpart, letermovir was expected to have a favorable toxicity profile because of the absence of mechanism-based side effects. The good safety and tolerability profile of letermovir seen in this trial is in accordance with this hypothesis.

With respect to pharmacokinetics, all patients had letermovir trough concentrations above the targeted EC_{90} value. This suggests that a convenient once-daily regimen with a tablet formulation of letermovir is possible. However, the present trial was not intended to be a dose finding trial, and as such, only 80 mg as total daily dose was investigated.

In conclusion, letermovir treatment of CMV viremia in kidney and kidney/pancreas transplant patients was comparable in efficacy to the SOC and met the primary endpoint, a statistically significant reduction in CMV virus load versus baseline. In addition, patients with nucleoside-resistant viruses were treated successfully. Letermovir has potential as a well-tolerated, efficacious and novel anti-CMV drug, and these data support its further development for prevention and treatment of HCMV infections in transplant recipients.

Authorship

SS was responsible for the design, conduct management, and analysis of the trial. PL, HZ, and HR-S were involved in the design of the trial, the analyses of the trial data and in the preparation of the manuscript. WA has been the responsible coordinating investigator of the trial and consulted the trial design, conduct, and analysis. WA, LR, AM, MS, MF, WG, BS, OW, MD, DWB, and KB: have been investigators for the trial and were paid for trial activities. JH was the responsible statistician for the trial. JH provided statistical and methodological input for the trial design, analyzed the data, and assisted in preparation of the manuscript. DM performed CMV-DNA evaluations of the trial and assisted in preparation of the manuscript.

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