

ARTICLE

Intravenous Hydroxypropyl β -Cyclodextrin Formulation of Letemovir: A Phase I, Randomized, Single-Ascending, and Multiple-Dose Trial

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Letemovir is a novel antiviral in clinical development for prophylaxis against human cytomegalovirus in immunocompromised transplant recipients. This two-part, single-center, randomized, double-blind, placebo-controlled trial evaluated the safety and pharmacokinetics of a hydroxypropyl β -cyclodextrin (HP β CD)-based intravenous formulation of letemovir in healthy women. Subjects received single, escalating doses (120, 240, 480, 720, and 960 mg; 6 letemovir, 2 placebo per cohort) or multiple, once-daily doses (240 mg; 8 letemovir, 4 placebo) of HP β CD-formulated letemovir and the associated pharmacokinetic profiles and adverse events were investigated. Single-dose and multiple-dose regimens were generally well tolerated. Single-dose escalation resulted in a slightly more-than-dose-proportional increase in the area under the letemovir plasma concentration-time curve (AUC), whereas increase in the maximal observed letemovir plasma concentration (C_{max}) was dose proportional. After once-daily dosing, accumulation ratios in AUC and C_{max} were 1.22 and 1.03, respectively. The terminal half-life was 28.3 h, supporting once-daily dosing (EudraCT Number: 2012-001603-20).

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Conventional anti-HCMV prophylactic treatments for immunocompromised patients are nucleoside analogs that act via inhibition of viral DNA polymerase and are associated with significant toxicity. Letemovir is a mechanistically distinct prophylactic and therapeutic against HCMV that targets DNA processing and has demonstrated a favorable safety profile and efficacy in clinical trials to date.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ This study investigated the safety, tolerability, and PKs of single ascending and multiple once-daily i.v. doses of the HP β CD-based formulation of letemovir. HP β CD was

used as an excipient to reduce local irritation at the site of injection.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ The results indicated that the HP β CD-based i.v. formulation of letemovir is well tolerated and were supportive of a once-daily dosing regimen.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

✓ The results demonstrate the influence of HP β CD as a vehicle for letemovir i.v. formulation on local tolerability. The extensive investigation of local i.v. tolerability may serve as a baseline for other trials/publications.

Human cytomegalovirus (HCMV) disease is commonly reported in immunocompromised individuals, notably in transplant recipients. In the absence of appropriate prophylactic treatment during allogeneic hematopoietic stem-cell transplant (HSCT), 80% of patients with HCMV-positive disease develop symptoms of HCMV disease.¹ The most serious clinical manifestation of this infection is HCMV pneumonia, with an associated mortality rate >50%.¹ In addition to pneumonia, other clinical manifestations of HCMV disease include gastrointestinal complications that render the ingestion and absorption of oral drugs difficult, further complicating treatment.¹

Currently, pre-emptive anti-HCMV treatments rely on the use of nucleoside analogs, such as ganciclovir and valganciclovir,

which act as DNA polymerase inhibitors and are associated with significant toxicity and the potential of drug resistance development.² Therefore, there is a need to develop new antivirals with a novel mode of action to nucleosides and a lower toxicity, while maintaining activity against resistant strains. This need was compounded by recent findings regarding two candidate anti-HCMV agents, maribavir and brincidofovir (CMX001), that failed to demonstrate efficacy in clinical phase III trials.^{3,4}

Letemovir (AIC246) is a novel drug being initially developed for prophylactic treatment against HCMV in HSCT recipients. It belongs to a class of anti-HCMV agents (terminase inhibitors) that inhibit the formation and release of infectious virus particles by targeting viral DNA processing.^{5–9}

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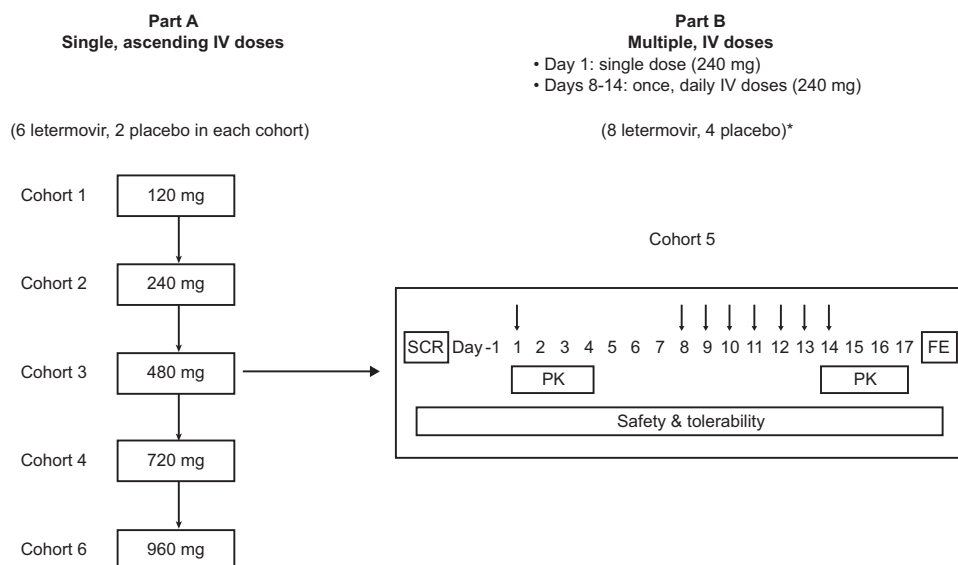


Figure 1 Study design. *Two subjects discontinued during washout period (day 7) and one subject discontinued during multiple dosing (day 12). All discontinuations were for personal reasons. FE, final examination; PK, pharmacokinetic; SCR, screening.

Nucleosides have to be phosphorylated by a viral enzyme to be activated;¹⁰ but this type of HCMV inhibitor does not require intracellular activation and, hence, is highly active and protective for uninfected cells. Furthermore, as terminase inhibitors address a different target than polymerase inhibitors, they are also active against viruses that have become resistant to the latter treatment. In a 12-week, phase IIb trial, oral letermovir 120 mg and 240 mg demonstrated an acceptable safety profile and efficacy as prophylaxis against HCMV in HSCT recipients.¹¹ Letermovir also showed antiviral activity as a pre-emptive therapy in viremic kidney transplant recipients¹² and demonstrated efficacy in the treatment of one case of HCMV disease caused by multitreatment-resistant HCMV in a subject with bilateral lung transplant for cystic fibrosis.¹³ Letermovir recently met the primary end points of a phase III trial and has demonstrated safety and efficacy as a prophylactic in recipients of HSCT.^{11,14}

To aid in the administration of letermovir, a novel hydroxypropyl β -cyclodextrin (HP β CD)-based formulation has been devised for i.v. use, which would enable the start of prophylaxis immediately after transplantation. HP β CD is an excipient characterized by a favorable safety profile using the parenteral route of delivery and has been demonstrated to increase the solubility of drugs and reduce irritation at the injection site.¹⁵ As this treatment has yet to be fully assessed *in vivo*, the aim of this study was to investigate the safety, tolerability, and pharmacokinetics (PKs) of single ascending and multiple once-daily i.v. doses of the HP β CD-based formulation of letermovir in healthy women.

METHODS

Study design

This single-center, randomized, double-blind, placebo-controlled trial (Protocol number: AIC246-01-I-14; EudraCT Number: 2012-001603-20) comprised two parts (**Figure 1**). The study was conducted with the approval of the

relevant ethics committee and in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All subjects provided written informed consent. In part A, subjects received letermovir in single, ascending i.v. doses (120 mg, 240 mg, 480 mg, 720 mg, and 960 mg; 6 letermovir, 2 placebo per cohort) to characterize the PK, safety, and tolerability of the single dose. In part B, letermovir was administered as a single i.v. dose on day 1, followed by a once-daily regimen for a week between days 8 and 14 (8 letermovir, 4 placebo) to characterize safety and tolerability after multiple administrations and to assess the single-dose vs. steady-state PK (**Figure 1**).

Study population

Eligible subjects were healthy women, aged 18–45 years, with a normal body weight (body mass index ≥ 18.0 and ≤ 28.0 kg/m²). Only women were included in this healthy subject trial due to an early finding in toxicology studies, although the relevance of which to humans was unknown. Participants' health status was assessed based on a screening examination, including a physical examination and evaluation of medical history, blood pressure, pulse rate, electrocardiogram (ECG), and clinical laboratory results.

Dosing

In part A, subjects received i.v. letermovir in ascending single doses or placebo in the fasted state (120 mg, 240 mg (30-min infusions in 150 mL 0.9% saline); 480 mg, 720 mg, and 960 mg (60-min infusions in 300 mL 0.9% saline). Within each cohort, six subjects received letermovir and two received placebo. Drug administration within each cohort was undertaken in a staggered fashion such that two subjects (one on letermovir and one on placebo) were treated on the first day of dosing, followed by three subjects on the second day (at least 24 h after treatment of the first two subjects), then the last three subjects were treated on the third day (at least 48 h after treatment of the first subjects).

Same-day infusions in subsequent patients were separated by at least 1 h to allow for monitoring of potential immediate tolerability issues. Subsequent subjects were dosed only if considered safe based on the experience with the preceding subjects. Safety, tolerability, and PK data available from preliminary analyses of the previous cohort were reviewed by a dose escalation committee consisting of the investigator and sponsor experts with medical, safety, and PK expertise before dose increase and results were used to estimate exposure for the next cohort. Doses were escalated based on a comprehensive review of all available data and consensus decisions of the dose escalation committee.

Part B of the study was only allowed to proceed after results from the 480-mg dose arm of part A were available, reviewed, and approved (consensus decision) by the dose escalation committee. Part B comprised one cohort of 12 subjects of whom 8 received a single, i.v.-infused (30-min) 240-mg dose of letermovir under fasting conditions in the morning of day 1, followed by a once-daily regimen of the same dose for 1 week between day 8 and day 14, and the remaining 4 subjects received placebo according to the same schedule. Letermovir administration was performed according to a staggered schedule whereby 4 subjects received the drug on the first day of dosing, followed by 4 subjects on the second day at least 24 h after treatment of the first 4 subjects, and the last 4 subjects on the third day (at least 48 h after treatment of the first subjects). On each day of dosing, at least one subject received placebo. The interval between the start of infusion in subsequent patients was at least 1 h. Subsequent subjects were dosed only if considered safe based on the experience with the preceding subjects.

Sampling

In part A and in the single-dose period of part B, blood samples were collected on day 1 predose and after letermovir infusion (postdose 0.08 (5 min), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, and 96 h after the start of infusion). In the multiple-dose period of part B, blood sampling took place predose daily on days 8–14 and postdose on day 14 (0.08 (5 min), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, and 96 h after the start of infusion).

Pharmacokinetics

Letermovir plasma concentrations were determined from plasma samples using ultrahigh performance liquid chromatography with tandem mass spectroscopy by A&M Labor für Analytik und Metabolismusforschung Service GmbH, Bergheim, Germany. The linear calibration range was 1.00–1000 ng/mL and the lower limit of quantification was 1.00 ng/mL. The inter-batch precision of the assay was $\leq 5.4\%$, whereas the accuracy was -3.29 to -3.41% . Non-compartmental PK and statistical analyses were performed by Kinesis Pharma B.V., Breda, The Netherlands. PK parameters were derived from the letermovir plasma concentrations and actual collection times using Phoenix WinNonlin and dose normalization was performed by dividing the relevant PK parameter by the corresponding dose. For single-dose treatments in parts A and B, the primary PK variables calculated included area under the analyte concentration-time curve (AUC) from time of administration to infinity ($AUC_{0-\infty}$),

dose-normalized $AUC_{0-\infty}$ ($AUC_{0-\infty}/D$), maximal observed analyte concentration (C_{max}), dose-normalized C_{max} (C_{max}/D), time of maximum plasma concentration (T_{max}), clearance (CL), total systemic volume of distribution (V_d), and mean residence time (MRT). Secondary PK variables were the apparent terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2z}$), AUC from time of administration up to the time of the last quantifiable concentration (AUC_{0-last}), and dose-normalized AUC_{0-last} (AUC_{0-last}/D). Dose proportionality was assessed by comparing C_{max}/D , $AUC_{0-\infty}$, and AUC_{0-last} among the cohorts.

For the multiple-dose treatment (part B), PK variables were assessed under steady-state conditions. Primary variables were area under the analyte concentration-time curve over a dosing interval τ at steady state ($AUC_{\tau,ss}$; dose-normalized $AUC_{\tau,ss}$ ($AUC_{\tau,ss}/D$), predose analyte concentration (C_{0h}), minimal observed analyte concentration (C_{min}), dose-normalized minimal observed analyte concentration (C_{min}/D), maximal observed analyte concentration at steady state ($C_{ss,max}$), and dose-normalized maximal observed analyte concentration at steady state ($C_{ss,max}/D$). Secondary variables were T_{max} , average steady-state analyte concentration over the dosing interval τ ($C_{ss,av}$), fluctuation index, λ_z , $t_{1/2z}$, CL, total systemic volume of distribution at steady state, MRT, accumulation ratio after multiple-dose administration for C_{max} ($R_{A(CMAX)}$), and accumulation ratio after multiple-dose administration for AUC ($R_{A(AUC)}$).

Safety assessments

Adverse events (AEs) were monitored and categorized based on nature, frequency of occurrence, duration, severity, causality, and dose-dependence in relation to treatment. Other safety measures included clinical laboratory parameters, vital signs (blood pressure and heart rate), and standard 12-lead and Holter ECG.

Local tolerability was evaluated using a visual analogue scale (VAS) score for the assessment of pain at the infusion site, a Visual Infusion Phlebitis (VIP) score for the assessment of the signs and stage of phlebitis/thrombophlebitis, and by ultrasound of the arm veins. In part A and in the single-dose phase of part B, assessment of pain by the VAS was undertaken on day 1 at predose (after indwelling of the i.v. catheter), at specific times postdose on day 1 (0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, 48, and 72 h), and at the post-trial examination. Additionally, subjects in part B rated their pain once-daily on days 8–13 and predose and postdose on day 14 at the same times described above for day 1. Subjects rated their perception of pain during infusion by drawing a vertical line on a 100-mm horizontal axis representing a scale of pain from 0 mm (no pain) to 100 mm (unbearable pain). Signs of phlebitis/thrombophlebitis were evaluated by the investigator using the VIP score.¹⁶ In part A and in the single-dose phase of part B, assessments were conducted on day 1 predose (after indwelling of the i.v. catheter), at specific times postdose on day 1 (0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 h), and at the post-trial examination. Additional assessments were performed in the multiple-dose phase of part B, whereby subjects were examined for signs of phlebitis on days 8–13 and predose and postdose on day 14 at the same times described for day 1. The scoring was performed on a scale of

Table 1 Participant baseline demographics

	Part A						Part B	
	Letermovir 120 mg (N = 6)	Letermovir 240 mg (N = 6)	Letermovir 480 mg (N = 6)	Letermovir 720 mg (N = 6)	Letermovir 960 mg (N = 6)	Placebo (N = 10)	Letermovir 120 mg (N = 8)	Placebo (N = 4)
Race (% white)	100	100	100	100	100	100	100	100
Mean age, years [range]	29.0 [20–45]	28.8 [19–34]	32.8 [20–44]	33.5 [21–43]	28.0 [23–41]	32.2 [20–42]	36.1 [24–45]	31.5 [24–42]
Mean body height, m	1.69	1.64	1.73	1.74	1.67	1.69	1.71	1.66
Mean body weight, kg	69.9	68.0	71.4	72.2	65.1	65.4	71.7	70.5
Mean body mass index, kg/m ²	24.7	25.2	23.8	23.9	23.6	23.0	24.5	25.4

0–5, with the zero score indicating no signs of phlebitis and a score of 5 indicating advanced stage thrombophlebitis. During the ultrasound assessment, veins of both infusion and noninfusion arms were examined by a third party specialist. Findings were categorized as normal or abnormal and abnormal results were rated as clinically significant or not clinically significant (NCS) per investigator's assessment. In part A and at the single-dose phase of part B, ultrasound examinations were performed at screening, day 1 (24, 48, and 72 h postinfusion), and at the final examination. During the multiple dose phase of part B, ultrasound examinations were performed at readmission on day 7 and on days 9–14 (predose). After dosing on day 14, ultrasound examinations were conducted 24, 48, and 72 h postdose and at the final examination.

Data analysis and statistics

Descriptive statistics were calculated for plasma concentrations of letermovir and derived PK parameters. Mean plasma concentration-time profiles were plotted. For a general overview of letermovir PK, parameters were subjected to an exploratory graphical analysis, including appropriate transformations of the data. For a statistical assessment of dose proportionality, dose-normalized C_{max} , $AUC_{0-\infty}$, and AUC_{0-last} values were analyzed in part A.

AEs and other physical and clinical examinations were listed by subject and analyzed by descriptive statistics. Holter ECG data of the two single-dose cohorts with the highest doses and the multiple-dose cohort were evaluated by an external cardiologist and will be reported separately.

RESULTS

Study population

Subject demographics at baseline are summarized in **Table 1**. Three subjects withdrew from the study for personal reasons following randomization to part B; two subjects discontinued after completion of the single-dose treatment of part B; and one subject withdrew during the multiple-dose period (**Figure 1**).

Pharmacokinetics

Plasma concentration-time curves of letermovir for parts A and B are shown in **Figure 2**. After the single i.v. dose, mean letermovir plasma concentration increased with dose escalation and C_{max} was attained in all subjects after the end of infusion (**Figure 2a**). This was followed by a rapid initial drop in plasma levels and a less steep terminal elimination phase. Letermovir plasma concentrations were still

quantifiable up to 96 h postdosing in all subjects in the 480 mg, 720 mg, and 960 mg dose cohorts. In the 120 mg and 240 mg cohorts, drug levels were quantifiable at least until 48 h post-dose.

PK parameters (arithmetic means) after single and multiple once-daily i.v. doses of letermovir are described in **Table 2**. In addition, individual C_{max}/D values and dose-normalized $AUC_{0-\infty}/D$ after single, ascending doses are shown in **Figure 3**. After single-dose administration, both C_{max} and T_{max} were observed immediately after the end of infusion. Mean C_{max}/D values ranged between 61.9 and 65.6 ng/mL/mg for the 120 and 240 mg doses (30-min infusion), and between 54.3 and 59.6 ng/mL/mg for the 480–960 mg doses (60-min infusion; **Table 2**). The C_{max} exhibited a dose-proportional increase (**Table 2** and **Figure 3**). Across the 120-mg to 960-mg dose increase, the observed increase in total exposure $AUC_{0-\infty}$ was more than dose proportional (**Table 2** and **Figure 3**). Mean total systemic drug CL and V_d values decreased with increasing dose and ranged between 4.0–9.4 L/h and 74.0–192.7 L, respectively. Mean apparent $t_{1/2}$ ranged from 10.7–16.7 h. The MRT values were similar between dose groups.

Following once-daily i.v. administration of letermovir (240 mg) for a week, steady state was reached after 7 days according to C_{0h} values (**Table 2**). At steady state, the mean $t_{1/2}$ value was 28.3 h, compared with 16.7 h for the single dose. The observed difference in $t_{1/2}$ values between the 240 mg single-dose and multiple-dose regimens was mainly driven by a single subject whose $t_{1/2}$ at day 14 was 69 h, compared with a value of 28.7 h on day 1. Other subjects showed similar or modestly higher $t_{1/2}$ at steady state relative to day 1. When excluding the subject with uncharacteristically high $t_{1/2}$, the steady state mean value of $t_{1/2}$ decreased to 18 h which is comparable with $t_{1/2}$ after single-dose treatment. Accumulation to steady-state exposure was modest, as shown by the $R_{A(AUC)}$ and $R_{A(CMAX)}$ values of 1.22 and 1.03, respectively. $AUC_{\tau,ss}$ was slightly higher compared with $AUC_{0-\infty}$ after a single dose (33,609 h.ng/mL vs. 27,475 h.ng/mL), but this was not the case for each individual subject. The arithmetic mean $AUC_{0-\infty}$ vs. $AUC_{\tau,ss}$ ratio was 0.93 and individual ratio values ranged between 0.62 and 1.18. Based on comparison of exposure, there was no consistent time dependency in letermovir PK.

Safety

In part A, treatment emergent adverse events (TEAEs) were reported by 60% of subjects (18/30) who received

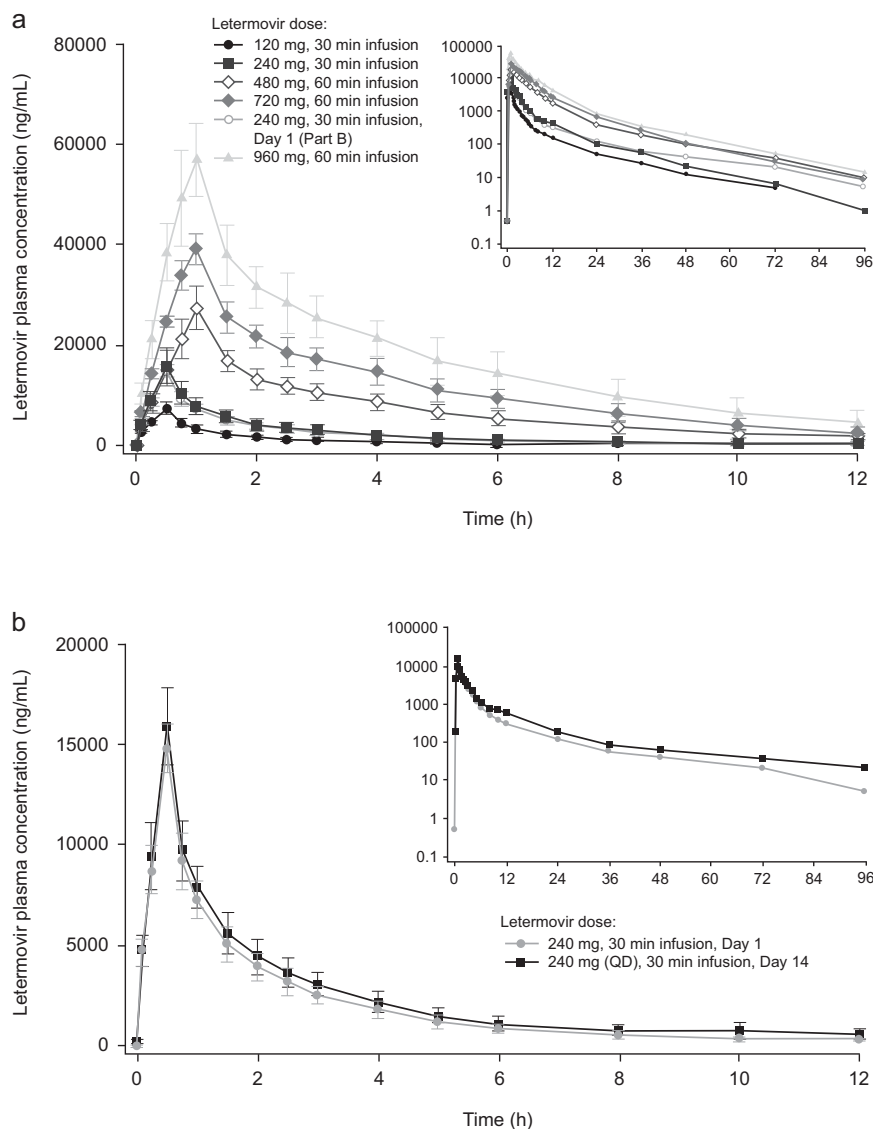


Figure 2 Letermovir plasma concentration-time curves for parts A (a) and B (b) on linear (main figures) and logarithmic scales (inset).

single-dose letermovir and 50% of those who received placebo (5/10). After single-dose letermovir administration, eight subjects (26.7%) reported AEs that were deemed possibly or probably related to treatment per investigator’s assessment. The most common of these treatment-related AEs were vomiting (2 subjects), headache (2 subjects), and nausea (2 subjects). In part B, TEAEs were reported by 75% of subjects (6/8) who received letermovir, compared with 50% of subjects in the placebo cohort (2/4). Among participants who received multiple-dose letermovir, five subjects experienced treatment-related AEs, the most common of which were dizziness (2 subjects) and headache (2 subjects). TEAEs associated with letermovir were predominantly mild or moderate in intensity (17 subjects and 6 subjects in parts A and B, respectively). One subject in the single, 960-mg dose group reported severe TEAEs (nausea and vomiting); however, there were no discontinuations due to

AEs throughout the study. The most frequently reported TEAEs are shown in **Table 3**. In part A, the most common TEAEs (reported by at least 2 subjects in the letermovir total group) were nausea (4 subjects), vessel puncture site pain (4 subjects), vomiting (2 subjects), headache (2 subjects), diarrhea (2 subjects), dizziness (2 subjects), infusion site reaction (2 subjects); reported as “pain, swelling, and tenderness” and “palpable, hardened venous cords in the cubitus on both sides, comprising both infusion and blood withdrawal sites”, neck pain (2 subjects), vessel puncture site hematoma (2 subjects), and vessel puncture site reaction (2 subjects). In part B, the most frequent TEAEs in letermovir-treated subjects were headache (3 subjects) and dizziness (2 subjects). No dose-dependent AEs or clinically significant findings in safety laboratory values, vital signs, or ECG parameters were observed in any of the dose groups.

Table 2 Pharmacokinetic parameters after single or once daily i.v. doses of letermovir

Dose	Part A					Part B		
	Single 120 mg (30-min infusion) (N = 6)	Single 240 mg (30-min infusion) (N = 6)	Single 480 mg (60-min infusion) (N = 6)	Single 720 mg (60-min infusion) (N = 6)	Single 960 mg (60-min infusion) (N = 6)	Single 240 mg day 1 (30-min infusion) (N = 8)	240 mg q.d. day 14 (30-min infusion) (N = 5)	
C_{max} of $C_{max,ss}$, $\mu\text{g/mL}$	7.44 ± 1.35	15.75 ± 3.51	27.33 ± 4.42	39.06 ± 3.06	57.21 ± 7.62	14.73 ± 1.21	15.88 ± 1.95	
$AUC_{0-\infty}$, $\text{h}^* \mu\text{g/mL}$	13.64 ± 3.82	32.51 ± 9.27	105.66 ± 21.55	167.58 ± 23.15	250.08 ± 59.15	30.14 ± 5.48	-	
V_d or V_{ss} , L	158.5 ± 44.59	124.3 ± 44.61	86.91 ± 25.28	74.08 ± 32.00	79.02 ± 42.40	192.7 ± 64.16	60.32 ± 26.69	
CL , L/h	9.417 ± 2.706	7.965 ± 2.482	4.7073 ± 0.9807	4.361 ± 0.5644	4.042 ± 1.043	8.233 ± 1.722	7.350 ± 1.314	
$t_{1/2}$, h	12.19 ± 4.324	10.77 ± 1.906	13.05 ± 4.096	11.56 ± 4.108	12.94 ± 4.503	16.72 ± 6.270	28.31 ± 23.78	
C_{max}/D , $\mu\text{g/mL/mg}$	0.06 ± 0.01	0.07 ± 0.01	0.06 ± 0.01	0.05 ± 0.00	0.06 ± 0.01	0.06 ± 0.01	-	
$AUC_{0-\infty}/D$, $\text{h}^* \mu\text{g/mL/mg}$	0.11 ± 0.03	0.14 ± 0.04	0.22 ± 0.04	0.23 ± 0.03	0.26 ± 0.06	0.13 ± 0.02	-	
MRT, h	6.144 ± 1.842	5.613 ± 1.222	7.205 ± 1.709	6.717 ± 1.072	6.741 ± 1.212	7.312 ± 3.315	8.364 ± 3.866	
$AUC_{0-\text{last}}$, $\text{h}^* \mu\text{g/mL}$	13.57 ± 3.80	32.48 ± 9.28	105.42 ± 21.33	167.40 ± 23.27	249.71 ± 59.37	29.98 ± 5.41	-	
$AUC_{0-\text{last}}/D$, $\mu\text{g/mL/mg}$	0.11 ± 0.03	0.14 ± 0.04	0.22 ± 0.04	0.23 ± 0.03	0.26 ± 0.06	0.12 ± 0.02	-	
$AUC_{0-\text{last}}/D$, $\mu\text{g/mL/mg}$	0.06246 ± 0.01936	0.06578 ± 0.009723	0.05708 ± 0.01530	0.06612 ± 0.0213	0.05870 ± 0.01837	0.04691 ± 0.01765	0.03728 ± 0.02199	
λ_z , 1/h	0.50 (0.50–0.50)	0.50 (0.50–0.50)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.75–1.00)	0.50 (0.50–0.50)	0.50 (0.50–0.50)	
T_{max} , h ^a	-	-	-	-	-	-	193.2 ± 86.23	
C_{0h} , ng/mL	-	-	-	-	-	27.48 ± 4.44	33.61 ± 6.73	
$AUC_{0-\text{last}}$, $\text{h}^* \mu\text{g/mL}$	-	-	-	-	-	-	1143 ± 189.9	
FI, %	-	-	-	-	-	-	1.215 ± 0.3299	
$R_A(AUC)$	-	-	-	-	-	-	1.033 ± 0.09772	
$R_A(C_{max})$	-	-	-	-	-	-	-	

$AUC_{0-\infty}$, area under the analyte concentration-time curve from time of administration to infinity; $AUC_{0-\text{last}}/D$, dose-normalized $AUC_{0-\infty}$; $AUC_{0-\text{last}}$, area under the analyte concentration-time curve over a dosing interval τ at steady state; $AUC_{0-\text{last}}$, area under the analyte concentration-time curve from time of administration up to the time of the last quantifiable concentration; $AUC_{0-\text{last}}/D$, dose-normalized $AUC_{0-\text{last}}$; CL , total systemic drug clearance; C_{max} , maximal observed analyte concentration; C_{max}/D , dose-normalized C_{max} ; $C_{max,ss}$, C_{max} at steady state; C_{0h} , pre-dose analyte concentration; FI, fluctuation index; MRT, mean residence time; q.d., once daily; $R_A(AUC)$, accumulation ratio after multiple-dose administration for AUC; $R_A(C_{max})$, accumulation ratio after multiple-dose administration for C_{max} ; $t_{1/2}$, apparent terminal elimination half-life; T_{max} , time to reach the maximal observed analyte concentration; V_d , total systemic volume of distribution; V_{ss} , V_d at steady state; λ_z , apparent terminal elimination rate constant. ^a T_{max} values are shown as median with a range (minimum-maximum). Values are mean ± SD.

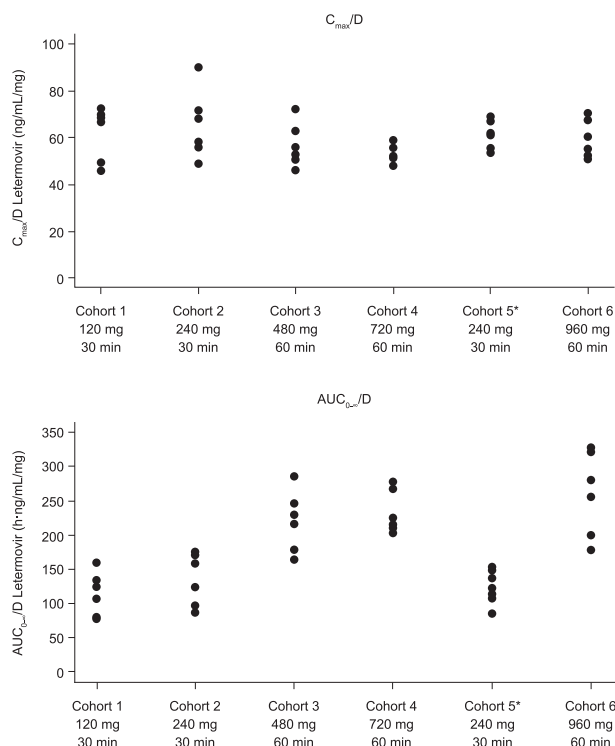


Figure 3 Individual dose-normalized C_{max} (C_{max}/D) and area under the analyte concentration-time curve (AUC) from time of administration to infinity ($AUC_{0-\infty}/D$) after administration of a single i.v. dose of letermovir. *Part B, day 1 $AUC_{0-\infty}/D$; C_{max}/D , observed analyte concentration; i.v., intravenous.

The HP β CD-based formulation of letermovir was locally well tolerated, as evidenced by the VAS score, the VIP score, and the ultrasound of arm veins.

Table 4 shows the mean maximum increase in VAS from baseline for the letermovir group and for the placebo group. In part A, the mean maximum increase of VAS from baseline was 0.73 mm for the total letermovir-treated subjects

and 0.5 mm for the placebo-treated subjects. Across the letermovir single doses, VAS values ranged from 0.17 mm in the 720 mg letermovir group to 1.17 mm in the 120 mg letermovir group. No dose-dependent effects were observed as the highest mean of the area under the VAS-time curve (2.74 h*mm) for letermovir-treated subjects was observed following the administration of the lowest single dose (120 mg). In part B, following multiple daily administrations of 240 mg letermovir, assessment of pain was less in the letermovir-treated group (mean VAS = 0.83 mm) than the placebo group (mean VAS = 5.75 mm). Overall, observed VAS values were small relative to the 100 mm maximum.

No signs of phlebitis were recorded for the majority of subjects participating in this study. In part A, among the 30 letermovir-treated subjects, higher VIP scores were recorded for one subject in the 120 mg letermovir group, with scores of 2 (early-stage phlebitis with “swelling, pain, and tenderness”) and 1 (possibly first sign of phlebitis) at 4 h and 72 h postinfusion, respectively. Another subject treated with 240 mg letermovir developed a VIP score of 1 at 24 h postinfusion. In the placebo group, a VIP score of 1 was recorded for a single subject 1 h after drug administration. In part B, VIP assessment of local tolerability was 0 throughout the study for all participants, except for one letermovir-treated subject who had a VIP score of 1 from predose on day 14 until 72 h postdose.

In the ultrasound assessments of part A, one subject in the letermovir-treated group demonstrated an NCS abnormal finding in the infusion site arm at follow-up and one subject in the placebo group showed an NCS abnormal finding at all assessments throughout the trial. Both subjects also had NCS abnormal findings for the noninfusion site arm. In part B, no abnormal findings were recorded in the infusion site arm.

DISCUSSION

This study investigated the safety, tolerability, and PK characteristics of a novel HP β CD-based formulation of letermovir

Table 3 Treatment emergent adverse events^a

	Part A						Part B		
	No. of subjects						No. of subjects		
	Letermovir 120 mg (N = 6)	Letermovir 240 mg (N = 6)	Letermovir 480 mg (N = 6)	Letermovir 720 mg (N = 6)	Letermovir 960 mg (N = 6)	Letermovir total (N = 30)	Placebo (N = 10)	Letermovir total (N = 8)	Placebo (N = 4)
Nausea	2	–	–	1	1	4	1	–	–
Vessel puncture site pain	1	–	–	–	3	4	–	–	–
Vomiting	–	–	1	–	1	2	–	–	–
Headache	–	–	2	–	–	2	1	3	–
Diarrhea	1	1	–	–	–	2	–	–	–
Dizziness	–	1	–	1	–	2	–	2	–
Infusion site reaction	1	–	1	–	–	2	–	1	–
Neck pain	1	–	1	–	–	2	–	1	–
Vessel puncture site hematoma	1	–	–	–	1	2	–	1	–
Vessel puncture site reaction	–	–	1	1	–	2	–	1	–

^aReported by at least two subjects in the letermovir total group in Part A or in any single-dose group.

Table 4 VAS assessment of pain at infusion site

	Part A						Part B					
	Single dose			Multiple dose			Single dose			Multiple dose		
	Letermovir 120 mg (N = 6)	Letermovir 240 mg (N = 6)	Letermovir 480 mg (N = 6)	Letermovir 720 mg (N = 6)	Letermovir 960 mg (N = 6)	Letermovir total (N = 30)	Placebo (N = 10)	Letermovir 240 mg (N = 8)	Placebo (N = 4)	Letermovir 240 mg (N = 8)	Placebo (N = 4)	
No.	6	6	6	6	6	30	10	8	4	6	4	
Mean (SD)	1.17 (2.40)	1.17 (0.75)	0.5 (0.84)	0.17 (0.41)	0.67 (1.63)	0.73 (1.36)	0.5 (1.08)	0.00	0.25 (0.5)	0.83 (0.41)	5.75 (10.84)	
Median	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.5	
Range	0.00–6.00	0.00–2.00	0.00–2.00	0.00–1.00	0.00–4.00	0.00–6.00	0.00–3.00	0.00	0.00–1.00	0.00–1.00	0.00–22.00	
	Maximum increase from baseline (mm VAS)											
No.	6	6	6	6	6	30	10	8	4	5	4	
Mean (SD)	2.74 (6.55)	0.83 (0.61)	0.24 (0.42)	0.39 (0.95)	0.26 (0.64)	0.89 (2.94)	0.32 (0.72)	0.00	0.10 (0.20)	24.58 (30.23)	250.82 (501.40)	
Median	0.00	0.83	0.00	0.00	0.00	0.00	0.00	0.00	0.00	23.95	0.18	
Range	0.00–16.10	0.00–1.67	0.00–1.02	0.00–2.33	0.00–1.57	0.00–16.10	0.00–2.13	0.00	0.00–0.39	0.00–74.33	0.00–1002.92	

AUC, area under the VAS-time curve; VAS, Visual Analog Scale, subjects rated their perception of pain during infusion by drawing a vertical line on a 100 mm horizontal axis representing a scale of pain from 0 mm (no pain) to 100 mm (unbearable pain).

intended for i.v. administration to enable prophylaxis treatment in transplant recipients immediately after the transplant procedure. Over the investigated range of single i.v. doses (120–960 mg), the trend for increasing total exposure of letermovir AUC_{0-last} and $AUC_{0-\infty}$ was more than dose proportional. Dose-doubling generally resulted in a threefold increase in exposure. In contrast, C_{max} increased approximately proportionally to the dose. Individual dose-normalized C_{max} values were in the same range for the 120 mg and 240 mg dose levels (30-min infusions) and for the 480 mg, 720 mg, and 960 mg dose levels (60-min infusions). The C_{max}/D values for the 120-mg and 240-mg dose groups trended slightly higher compared with higher dose groups due to shorter infusion duration.

After multiple once-daily administrations of letermovir (240 mg) for 1 week, there was little change in C_{max} relative to C_{max} after a single-dose administration. The mean $t_{1/2}$ value showed a substantial increase from 17 to 28 h, which was mainly due to a single subject with an outlying $t_{1/2}$ of 69 h on day 14 compared with a value of 28.7 h on day 1. This also caused an increased intersubject variability in $t_{1/2}$ at steady state compared with the single dose. The atypically prolonged half-life derived from this single participant may have not been determined accurately because the predefined criteria for the accurate calculation of $t_{1/2}$ were not met. Typically, PK sampling should continue for at least three half-lives in order to accurately estimate $t_{1/2}$. As PK sampling was performed to 96 h postdose and the outlying $t_{1/2}$ value for this subject was 69 h, the estimate should be interpreted with caution. When this subject was excluded, the mean $t_{1/2}$ decreased to 18 h, which is comparable with the value observed following single-dose administration. The observed $t_{1/2}$ is supportive of a once-daily dosing.

Letermovir was generally well tolerated at all doses with no dose-dependent TEAEs. No clinically significant findings in safety laboratory values, vital signs, or ECG parameters were observed. Furthermore, the HPβCG-based formulation of letermovir demonstrated good local tolerance across the range of single doses investigated in addition to the 240 mg repeated infusion. After letermovir or placebo administration, very few participants reported minimal infusion site pain, and there were no signs of local intolerance as assessed by VIP and ultrasound examinations.

Previous studies (AIC246-01-I-12 and AIC246-01-I-13, data not published) investigated an arginine-phosphate buffered formulation of letermovir (AiCuris Anti-infective Cures GmbH, unpublished data on file (2012)). After administration of a single dose of arginine-phosphate-buffered letermovir (480 mg), subjects reported mild-to-moderate infusion site pain and indications of local intolerance were documented in the ultrasound examination of arm veins (AIC246-01-I-12). Furthermore, daily-dosing of 240 mg arginine-phosphate-buffered letermovir was also associated with poor local tolerance (AIC246-01-I-13). In the current study, the HPβCD-based formulation of letermovir was locally well tolerated and no signs of local intolerance were observed. This is likely the result of the formation of cyclodextrin-letermovir inclusion complexes.¹⁵

This study is potentially limited by the fact that the population of healthy women may not be representative of immunosuppressed transplant recipients for whom this treatment is intended. The PK characteristics of the drug might substantially differ in the intended clinical population because of interactions with co-drugs such as cyclosporine A, an immunosuppressant commonly administered in this clinical population, which has been shown to increase the exposure of letermovir (Kropeit, D., von Richter, O., Stobernack, H.P., Rubsamens-Schaeff, H. & Zimmermann, H. Pharmacokinetics and safety of letermovir co-administered with cyclosporine A or tacrolimus in healthy subjects; submitted 2016).

In conclusion, single doses up to 960 mg and multiple, once-daily doses (240 mg) of the HPβCD-based i.v. formulation of letermovir were generally safe and well tolerated in healthy female subjects. The results were consistent with the solubilizing properties and reduction of irritation associated with HPβCD. After once-daily dosing, accumulation to steady-state exposure was modest and steady-state conditions were attained within 7 days. The $t_{1/2}$ observed in this study supports the once-daily dosing regimen.

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Conflict of Interest. K.E.-Z. is a current employee of clinphase, Hanau, Germany, and a former consultant of AiCuris Anti-infective Cures GmbH. D.K., H.-P.S., H.Z., and H.R.-S. are former or current employees of AiCuris Anti-infective Cures GmbH. J.S. is a current employee of Merck Biopharma, Darmstadt, Germany. E.G.J.H. is a former employee of Merck Sharp & Dohme, The Netherlands. A.v.S. is a current employee of Quantitative Solutions BV, Oss, The Netherlands, a former employee, and a current consultant of Merck Sharp & Dohme, The Netherlands.

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