CLINICAL TRIAL REPORT SUMMARY

Name of Sponsor/Company: AiCuris GmbH & Co. KG

Name of finished product: Letermovir

Name of active ingredient: (S)-{8-fluoro-2-[4-(3-methoxyphenyl)- piperazin-1yl]-3-(2- methoxy-5-trifluoromethyl-phenyl)- 3,4-dihydro-4- quinazolinyl} acetic acid

Title of the study: A randomized, double-blind, placebo controlled trial to evaluate the safety, tolerability and antiviral activity of 12 weeks' treatment with a new antiviral HCMV drug

Coordinating Investigator: Gerhard Ehninger, MD, PhD, University Clinic Carl Gustav Carus Dresden, Fetscherstraße 74, 01304 Dresden, Germany.

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Study center(s): Twenty-three (23) sites in Germany and the United States of America (USA) participated in this trial. Of the 23 sites, 19 enrolled patients in this trial.

Publication (reference):

Chemaly, R.F., et al., Letermovir for cytomegalovirus prophylaxis in hematopoietic-cell transplantation. N Engl J Med, 2014. 370(19): p. 1781-9.

22nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID): Letermovir (AIC246) for prevention of HCMV infections in patients after human blood precursor cell transplantation: a randomised, double-blind, placebo-controlled trial to evaluate the safety, tolerability and antiviral activity of 12 weeks treatment. Poster by H Zimmerman; April 2012.

EBMT, Geneva: Presentation by G Ehninger, MD, PhD – April 2012.

Studies period (years): 30 March 2010 (First patient, first visit) to 17 October 2011 (Last patient, last visit)	**Phase of development:** 2

Objectives: The primary objective of this trial was to compare the safety and efficacy of 3 different doses of letermovir with matching placebo. The incidence and time to onset of "human cytomegalovirus (HCMV) prophylaxis failure" for the prevention of an active HCMV replication within an 84-day treatment period in HCMV seropositive allogeneic human blood precursor cell (HBPC) transplant recipients was compared between each active treatment group versus (vs.) placebo.

The secondary objective of this trial was to compare 3 different doses of letermovir vs. matching placebo with regard to:

- the pharmacokinetics (PK) of letermovir at steady-state to establish an exposure-effect relationship;
- investigate the effect of letermovir on co-administered cyclosporine, tacrolimus, sirolimus, and everolimus;
- the incidence and time to onset of HCMV end-organ disease alone;
- the incidence and time to onset of systemic detectable HCMV replication alone;
- the incidence and time to onset of discontinuation of trial medication within the 84-day treatment period.

Methodology: This was a multi-center, randomized, double-blind, placebo-controlled, dose-ranging trial to investigate 3 different doses of letermovir given orally for 84 days in comparison to matching placebo in patients after HBPC transplantation for the prevention of active replication by re-infection or reactivation in HCMV-seropositive patients. Nineteen (19) investigational sites (transplant clinics) located in Germany and the USA enrolled patients in this trial.

Eligible allogeneic HBPC recipients received 1 of 3 once daily (od) doses of letermovir (60 mg, 120 mg, or 240 mg) or placebo od. Patients were enrolled sequentially to the different dose groups, starting with the lowest dose group. Patients were then randomized to letermovir or placebo in a 3:1 ratio.

For the ongoing safety evaluation of each dose group and to ensure safe conduct of the trial, an independent Safety Monitoring Committee (SMC) was established. This SMC evaluated all available safety information together with data for exposure to trial medication when every 22 patients had been randomized.

At the scheduled weekly visits, a central and a local HCMV laboratory tested patients' blood samples in order to detect active HCMV replication. A central HCMV laboratory tested HCMV deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) in plasma. Local laboratories performed evaluations according to their standards by HCMV DNA PCR or pp65 antigenemia testing.

The trial primarily evaluated the primary endpoint of "HCMV prophylaxis failure" within the 84-day treatment period as a prevention of an active replication in HCMV seropositive patients.

"HCMV prophylaxis failure" was defined as:

- If the patient developed systemic detectable HCMV replication, defined by:
  - Two HCMV blood samples tested positive in the local laboratory, which were drawn at separate consecutive time-points (ie, no negative samples at any intervening time point) and which have led to the discontinuation of the trial medication and to the initiation of treatment with an alternative HCMV antiviral medication.
  - In addition, 1 HCMV blood sample from either of the 2 time-points that tested positive in the local laboratory must have tested positive in the central laboratory.

Or

- If the patient developed HCMV end-organ disease as defined by Ljungman et al. "Definitions of Cytomegalovirus Infection and Disease in Transplant Recipients" (Clinical Infectious Diseases 2002; 34: 1094-7).

Number of subjects (planned and analyzed): It was planned to enroll 132 patients, with each active dose group consisting of 44 eligible patients (to ensure 33 patients were randomly assigned to letermovir 60 mg, 120 mg, and 240 mg, plus 11 patients randomly assigned to placebo). One hundred and thirty-three (133) patients were randomized (33 patients in the 60 and 120 mg/day letermovir and placebo groups and 34 patients in the 240 mg/day letermovir group) and all were included in the Full Analysis Set (FAS) with the exception of 2 patients in the 120 mg/day letermovir group who did not receive trial medication.

Diagnosis and main criteria for inclusion: All patients were required to meet the following criteria at Screening to be enrolled in this trial:

1. Male or female patients of any ethnic group aged ≥18 years on the day informed consent was given.
2. Seropositive for HCMV immunoglobulin G (IgG) antibodies as tested by the local laboratory within 1 year before transplantation (if the patient had received HCMV IgG antibody treatment, the test must

have been performed ≥30 days after HCMV IgG antibody administration). If repeated tests were performed, 1 positive HCMV test confirmed the patient as HCMV IgG seropositive.
3. First allogeneic HBPC transplantation performed within 40 days before randomization for 1 of the following diagnoses: leukemia, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, myelodysplastic, and myeloproliferative disorder.
4. Allogeneic human leukocyte antigen A, B, C, DR identical related or unrelated donor bone marrow or peripheral blood progenitor cell transplant recipient using high resolution typing.
5. Evidence of post-transplantation engraftment (absolute neutrophil count remaining ≥500/mm3 for at least 3 consecutive sampling days documented by a minimum of 2 tests by the local laboratory).
6. An active HCMV replication not detectable by the HCMV standard evaluation of local laboratory (pp65 or HCMV PCR) within 5 days before starting trial medication.
7. Able to swallow tablets.
8. Male patients who were surgically sterile (eg, after vasectomy) or who agreed to use an adequate method of contraception during participation in the trial and for at least 2 complete months after the final trial visit and final examination. An adequate method of contraception was defined as sexual abstinence or single barrier method with their sexual partner.
   Female patients who were surgically sterile (eg, 2-sided tubal resection or ovariectomy) or post-menopausal (defined as >50 years of age or who had a history of no menses for at least 24 months).
   or
   Female patients of childbearing potential who agreed to use an adequate method of contraception during participation in the trial and for at least 1 complete month after the final trial visit and final examination. An adequate method of contraception was defined as sexual abstinence, single-barrier method, adequate hormonal contraception (to have started at least 7 days prior to screening), or an intra-uterine device (to have been in place for at least 2 months prior to screening).
9. Negative beta-human chorionic gonadotropin blood test for women.
10. Written informed consent provided to participate in this trial.

Test product, dose and mode of administration, batch number(s):

Test Product	Dose and Mode of Administration	Batch Number
Letermovir	60 mg od oral tablets (60 mg cohort)	4184701T
	120 mg od oral tablets (120 mg cohort)	4184801T
	2 x 120 mg od oral tablets (240 mg cohort)	4304001T

Duration of Treatment:

The treatment period was 12 weeks (84 days).

Reference therapy, dose and mode of administration, batch number(s): Patients assigned to the placebo group received no letermovir treatment, but received matching placebo which was taken orally od (batch number: 4206301T).

Criteria for evaluation:

Efficacy: The efficacy analyses were performed for the FAS, with the PPS a secondary supportive analysis population.

The primary efficacy endpoints were:

- incidence of "HCMV prophylaxis failure" within the 84-day treatment period;
- time to onset of "HCMV prophylaxis failure" within the 84-day treatment period.

The test of equal incidences was conducted with pairwise Fisher's exact tests for each active treatment group vs. placebo (alpha=0.05). The test of equal times to onset was conducted with pairwise log rank tests and

Kaplan-Meier estimates for the median times. Patients were censored at the date of last trial medication if the endpoint had not been met. Sensitivity analyses of the primary endpoints were performed for the Per Protocol Set (PPS). In addition, Cochran-Mantel-Haenszel (CMH) tests for the incidences were calculated to take into account the country effect and immunosuppressant dosage adjustments for both the FAS and PPS.

The secondary efficacy endpoints were:

- Incidence and time to onset of HCMV end-organ disease alone within the 84-day treatment period.
- Incidence and time to onset of systemic detectable HCMV replication alone within the 84-day treatment period.
- Incidence and time to onset of discontinuation of trial medication within the 84-day treatment period.

The same analyses as described for the primary endpoints were carried out for both the FAS and PPS for the secondary endpoints.

Pharmacokinetics: Pharmacokinetic analysis utilized a population pharmacokinetic (POPPK) approach using a sparse sampling regime. All PK analyses were performed on the pharmacokinetic Set (PKS). The PKS consisted of all patients who received trial medication and had a single plasma concentration time point included in the PK analysis.

The secondary PK endpoints were:

- Trough levels of letermovir.
- PK sampling for letermovir with documentation of date and time on Day 8 or 15, corresponding to steady-state conditions.
- Pre-dose blood levels of the immunosuppressant cyclosporine, tacrolimus, sirolimus, and everolimus and their dose-adjustments.

The following parameters were reported and were obtained by utilization of a 1-compartment model which best fitted model stability criteria: Clearance (CL), volume distribution (VD), absorption rate constant (KA), CL between subject variability (BSV-%CV), VD between subject variability (BSV-%CV), KA between subject variability (BSV-%CV), proportional residual error (%CV), additive residual error (%CV), and model predicted maximum plasma concentration (Cmax), steady-state plasma concentration (C_{ss}), minimum plasma concentration (Cmin), and area under the curve at steady-state (AUCss). Furthermore the influence of patient-specific covariates; age, body weight, body mass index, creatinine clearance on the PK parameters were assessed.

Likewise, the following categorical covariates were also assessed: gender (male/female), race, concomitant medications, if applicable (coadministered cyclosporine, tacrolimus, sirolimus, everolimus, aciclovir, valaciclovir, or famciclovir). Top-line POPPK results are presented, with full details of all POPPK analysis and parameters reported in a separate report.

Safety: All safety analyses were performed for the Safety Set (SS).

Secondary safety endpoints were:

- Nature, frequency, duration, severity and causality of adverse events (AEs).
- Safety laboratory parameters.
- Vital signs (systolic and diastolic blood pressure, pulse rate, body temperature), standard 12-lead

electrocardiogram (ECG) and physical examination.

All safety and tolerability parameters (AEs, the percentage of patients requiring adjustment of coadministered immunosuppressive medication [ie, cyclosporine and tacrolimus], physical examinations, vital signs, ECG results, laboratory safety tests [hematology, coagulation, biochemistry, and urinalysis], prior and concomitant medications) were listed by patient and treatment group. Safety data were also tabulated by treatment group. The incidence of "predefined change abnormal" (PCA) was tested for statistical significance using Fisher's exact test (as per the primary endpoint) to test each active dose vs. placebo for the incidence of abnormalities.

Statistical methods: All statistical outputs were produced using SAS v8.2.

The FAS was the primary analysis population and consisted of all randomized patients who received trial medication at least once and had at least 1 HCMV (either local or central) evaluation after randomization.

The PPS was a secondary supportive analysis population and consisted of a subset of the FAS patients without major protocol violations.

The SS consisted of all randomized patients who received trial medication at least once. The SS was used for the safety analyses.

- For the primary efficacy endpoints, the hypothesis of equality of incidences between each active treatment and placebo was tested using the Fisher's exact test and the time to onset was compared between each active treatment group and placebo using the log-rank test (FAS and PPS).
- For the secondary efficacy endpoints, incidence endpoints were analyzed using Fisher's exact test, and time to onset endpoints were analyzed with log-rank test (FAS and PPS).
- For both the primary and the secondary endpoints, pairwise comparisons between the active treatment groups were performed using Fisher's exact test and log-rank test, as was performed between each active treatment group and placebo (FAS and PPS).
- The incidence of "HCMV prophylaxis failure" was analyzed by a CMH test, stratified for the effect of country and immunosuppressant dose adjustments (FAS and PPS).
- Sensitivity analyses: The relationship between the dose used and the response obtained in terms of incidence of "HCMV prophylaxis failure" was explored by means of a logistic regression, with dose as a continuous variable (FAS and PPS). The analysis was repeated with non-completers omitted (FAS).
- The relationship between dose and response, in terms of time to "HCMV prophylaxis failure", was explored by a log-rank test for trend (FAS).

A model predicted steady-state exposure parameters such as Css, Cmax, Cmin, and area under the concentration time curve during a dosing interval (AUC(0-τ)) were computed from the POSTHOC parameter estimates under the final NONMEM® software program for NONlinear Mixed-Effects Modeling (ICON, Hanover MD) covariate model. The relationships between model predicted letermovir exposure (at steady-state) and the primary endpoints (incidence of and time to onset of "HCMV prophylaxis failure") as well as safety endpoints were assessed using statistical models.

SUMMARY AND CONCLUSIONS

Efficacy results:

Following an 84-day treatment period, the incidence of HCMV prophylaxis failure (defined as all patients who developed systemic detectable HCMV replication and/or HCMV end-organ disease, or discontinued treatment prior to Day 84 due to other reasons [AE, death, protocol non-compliance, withdrew consent, or other]) appeared to decrease across increasing letermovir dose groups (48.5%, 32.3%, and 29.4% of

patients in the 60, 120, and 240 mg/day groups, respectively) and was highest in the placebo group (63.6% of patients). In the comparison of active treatment groups vs. placebo, a statistically significant reduction in the incidence of HCMV prophylaxis failure was observed in the 120 mg/day letermovir (p=0.014) and 240 mg/day letermovir (p=0.007) groups. Sensitivity analysis in the PPS showed a statistically significant reduction in the incidence of HCMV prophylaxis failure in the 240 mg/day letermovir group (p = 0.019). Similar results were observed when non-completers due to reasons other than prophylaxis failure were removed from the analysis (p=0.046 and p=0.001 in the 120 and 240 mg/day letermovir groups, respectively, although borderline statistically significant for the 120 mg/day letermovir group), and when controlling for center (p<0.001 and p<0.001, respectively) and country effects (p=0.011 and p=0.005, respectively).

Analysis of incidence of HCMV prophylaxis failure within the 84-day treatment period (non-completers considered as failure; FAS)

	Letermovir 60 mg/day N = 33	Letermovir 120 mg/day N = 31	Letermovir 240 mg/day N = 34	Placebo N = 33
Failed, n (%)				
Yes[a]	16 (48.5)	10 (32.3)	10 (29.4)	21 (63.6)
HCMV prophylaxis failed	7 (21.2)	6 (19.4)	2 (5.9)	12 (36.4)
Other discontinuation	9 (27.3)	4 (12.9)	8 (23.5)	9 (27.3)
No	17 (51.5)	21 (67.7)	24 (70.6)	12 (36.4)
Odds ratio (95% CI)[b]	0.538 (0.179, 1.603)	0.272 (0.085, 0.857)	0.238 (0.075, 0.739)	
p-value[c]	0.321	0.014	0.007	

Abbreviations: HCMV = human cytomegalovirus; CI = confidence interval.

[a] Failed was defined as all patients who developed systemic detectable HCMV replication, developed HCMV end-organ disease or discontinued treatment prior to Day 84 due to other reasons (AE, death, protocol non-compliance, withdrew consent or other).

[b] Active dose vs. placebo.

[c] Fisher's exact test of active dose vs. placebo.

Note: For the analysis, patients who discontinued early without the event were counted in the "yes" category.
Patient [redacted] in the 240 mg/day group has reason for discontinuation from trial medication of Adverse Event (GI-GVHD); however, this patient met the criteria for systemic detectable HCMV Replication prior to discontinuation and was therefore counted as a true failure.

Patients [redacted] in the 240 mg/day group and [redacted] in the placebo group discontinued from trial medication due to initiation of alternative anti-HCMV medication; however they did not meet the criteria for systemic detectable HCMV Replication and were therefore counted as other discontinuations.

Sensitivity analysis of the incidence of HCMV prophylaxis failure in the FAS showed a statistically significant reduction of this incidence between the 240 mg/day letermovir and placebo groups with non-completers due to reasons other than prophylaxis failure removed from the analysis (5.9% vs. 36.4%, respectively; p=0.003).

When the definition of HCMV prophylaxis failure was amended to "2 HCMV blood samples tested positive in the local laboratory or the central laboratory at any timepoint with no intervening negative sample which led to the initiation of alternative HCMV antiviral medication within 9 days of the last sample and who received exposure to trial medication for at least 7 days prior to a positive HCMV replication event", the incidence of HCMV prophylaxis failure was statistically significantly lower in the 240 mg/day letermovir group compared to placebo (0% vs. 33.3%; p=0.004). Of note a sensitivity

analysis of incidence of HCMV prophylaxis failure for patients treated for at least 7 days prior to a positive HCMV replication event within the 84-day treatment period (non-completers omitted, FAS) showed statistically significant difference (p=0.019) between 60 mg qd and 240 mg qd, although the trial was not powered for this pairwise comparison between the active treatment groups.

Analysis of time to onset of HCMV prophylaxis failure showed that a decrease in time to onset of HCMV prophylaxis failure was statistically significant for the 240 mg/day letermovir group (p=0.002) compared to placebo. It was therefore considered unlikely that the difference observed was due to a coincidence of random sampling and the null hypothesis that the 240 mg/day letermovir and placebo groups had identical time to event characteristics was rejected. Results were supported by sensitivity analyses, firstly when defining failure as "2 HCMV blood samples tested positive in the local laboratory or the central laboratory at any timepoint with no intervening negative sample which led to the initiation of alternative HCMV antiviral medication within 9 days of the last sample" (p=0.003) and secondly when including only those patients treated for at least 7 days prior to a positive HCMV replication event within the 84-day treatment period (p=0.004). Of note a sensitivity analysis of time to onset of HCMV prophylaxis failure for patients treated for at least 7 days prior to a positive HCMV replication event within the 84-day treatment period (non-completers omitted, FAS) showed statistically significant difference (p=0.022) between 60 mg qd and 240 mg qd, although the trial was not powered for this pairwise comparison between the active treatment groups.

Analysis of time to onset of HCMV prophylaxis failure within the 84-day treatment period (FAS)

	Letermovir 60 mg/day	**Letermovir 120 mg/day**	**Letermovir 240 mg/day**	**Placebo**
	N = 33	**N = 31**	**N = 34**	**N = 33**
Time (days) to onset of HCMV prophylaxis failure, n (%)				
Patients assessed	33	31	34	33
Number (%) with event	7 (21.2)	6 (19.4)	2 (5.9)	12 (36.4)
Number (%) censored	26 (78.8)	25 (80.6)	32 (94.1)	21 (63.6)
KM median (95% CI)	NC	NC	NC	NC
Min - Max	1-85	1-86	1-88	1-85
Min - Max (patients with event)	1-42	1-15	1-8	1-21
p-value[a]	0.148	0.126	0.002	

Abbreviations: CI = confidence interval; HCMV = human cytomegalovirus; KM = Kaplan-Meier, NC = non-calculable.

Note: Time to onset of event was calculated from date of randomization and therefore it was possible that the time to onset of event was greater than 84 days.

[a] Pairwise comparison of active dose vs. placebo, log-rank test.

In order to meet the definition of the primary efficacy endpoint, HCMV prophylaxis failure, patients had to have either systemic detectable HCMV replication, end organ disease, or discontinue treatment prior to Day 84 for other reasons. The incidence and time to onset of HCMV systemic detectable HCMV replication alone and the incidence of discontinuation of trial medication were consistent with the primary efficacy analyses; time to discontinuation of trial medication was statistically significantly longer in both the 120 mg/day and 240 mg/day letermovir groups (p=0.014 and p=0.006, respectively) compared to placebo. No patients were reported with HCMV end-organ disease alone. A single patient had HCMV end-organ disease, ie, CMV syndrome with systemic detectable HCMV replication, fever and neutropenia in the 120 mg/day letermovir group.

Sensitivity analysis evaluating the relationship between letermovir dose and incidence of HCMV prophylaxis failure within the 84-day treatment period when stratifying patients by whether they took ciclosporin, tacrolimus, or another immunosuppressant showed that results were not influenced by which immunosuppressant was taken; a CMH analysis showed a statistically significantly lower incidence of HCMV prophylaxis failure in the 120 mg/day letermovir group (32.3%; p=0.006) and 240 mg/day letermovir group (29.4%; p=0.005) compared with placebo (63.6%).

Both primary efficacy endpoints (incidence and time to onset of HCMV prophylaxis failure) in both the FAS and PPS demonstrated statistically significant efficacy of letermovir at a dose of 240 mg/day, which was confirmed by all sensitivity analyses. Statistically significant efficacy of letermovir at a dose of 120 mg/day was also observed for the incidence of HCMV prophylaxis failure in the FAS, which was supported by some of the sensitivity analyses of this primary endpoint (eg, non-completers omitted).

The odds for the incidence and time to onset of HCMV prophylaxis failure were not statistically significantly related to the letermovir exposure, though the odds were about 10 to 29% lower with the doubling of letermovir exposure.

Additional sub-analyses not outlined in the statistical analysis plan were performed.

Safety results:

All patients in the 240 mg/day letermovir group and the placebo group and the majority of patients in the 60 and 120 mg/day letermovir groups (31 [93.9%] and 30 [96.8%] patients, respectively) were reported with at least 1 AE. The majority of AEs were treatment-emergent (all patients in the 240 mg letermovir and placebo groups and 31 [93.9%] and 29 [93.5%] patients in the 60 and 120 mg/day letermovir groups, respectively).

Treatment-emergent adverse events (TEAEs) were reported in the majority of patients during the study (907 events in 95.9% of patients receiving letermovir and 238 events in 100% of patients receiving placebo). At the System Organ Class level, the most frequent TEAEs were gastrointestinal disorders (162 events reported in 66.3% of patients receiving letermovir and 52 events reported in 60.6% of patients receiving placebo; mostly diarrhea, nausea, and vomiting) and infections and infestations (91 events reported in 59.2% of patients receiving letermovir and 35 events reported in 75.8% of patients receiving placebo; mostly CMV infection).

A smaller proportion were considered by the Investigator to be possibly, probably, or definitely related to trial medication (58 events in 17.3% of patients receiving letermovir and 20 events in 33.3% of patients receiving placebo).

Across letermovir dose groups, there was a decrease in the percentage of patients with related TEAEs from 33.3% in the 60 mg/day group to 5.9% in the 240 mg/day group.

The majority of TEAEs reported were mild or moderate TEAEs; 23.5% of patients receiving letermovir and 30.3% of patients receiving placebo were reported with severe TEAEs.

Treatment-emergent AEs leading to permanent discontinuation of trial medication were reported in a higher percentage of patients receiving placebo (57.6%) compared with letermovir (25.5%). The most commonly reported TEAEs leading to discontinuation of trial medication were infections and infestations, reported in 15.2%, 19.4%, and 8.8% of patients in the 60, 120, and 240 mg/day letermovir groups, respectively, compared with 39.4% of patients in the placebo group.

Supporting the efficacy analyses, which demonstrated a significant reduction in HCMV prophylaxis failure in the 120 mg and 240 mg letermovir dose groups compared with placebo during the 84-day

treatment period, TEAEs of CMV infection occurred in fewer patients receiving treatment with letermovir compared with placebo (17.3% and 33.3%, respectively). In addition, more patients discontinued trial medication following TEAEs of CMV infection in the placebo group than the combined letermovir group (30.3% and 13.3% of patients, respectively).

A slightly higher percentage of patients were reported with treatment-emergent serious AEs (TESAEs) in the placebo group (36.4%) compared with those receiving letermovir (30.6%). Treatment-emergent serious AEs led to permanent discontinuation of trial medication in 15.2% of patients in the placebo group, compared with 6.1% of patients receiving letermovir.

Four patients were reported with a TESAE leading to death: 1 patient in the 60 mg/day letermovir group with acute graft vs. host disease in intestine, 1 patient in the 60 mg/day letermovir group with acute myeloid leukemia, 1 patient in the 240 mg/day letermovir group with pneumonia, and 1 patient in the placebo group with bacterial pneumonia. One patient in the 120 mg/day letermovir group died following respiratory failure secondary to bilateral progressive pneumonia; this event was not classed as a TESAE leading to death as it occurred more than 7 days after the last dose of trial medication; however, pneumonia was reported as a non-TESAE leading to death.

Overview of treatment-emergent AEs (SS)

	Letermovir 60 mg/day	Letermovir 120 mg/day	Letermovir 240 mg/day	Letermovir overall treatment	Placebo
	N = 33	N = 31	N = 34	N = 98	N = 33
Number of patients with at least 1, n (%)					
TEAE	31 (93.9)	29 (93.5)	34 (100)	94 (95.9)	33 (100)
TESAE	9 (27.3)	12 (38.7)	9 (26.5)	30 (30.6)	12 (36.4)
TEAE leading to permanent discontinuation of trial medication	9 (27.3)	9 (29.0)	7 (20.6)	25 (25.5)	19 (57.6)
TESAE leading to permanent discontinuation of trial medication	2 (6.1)	2 (6.5)	2 (5.9)	6 (6.1)	5 (15.2)
TEAE leading to death	2 (6.1)	0	1 (2.9)	3 (3.1)	1 (3.0)
TESAE leading to death	2 (6.1)	0	1 (2.9)	3 (3.1)	1 (3.0)
Severe TEAE	8 (24.2)	9 (29.0)	6 (17.6)	23 (23.5)	10 (30.3)
Possibly, probably, or definitely related TEAE	11 (33.3)	4 (12.9)	2 (5.9)	17 (17.3)	11 (33.3)

Abbreviations: TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Note: Treatment-emergent adverse events were defined as those adverse events that started or worsened on or after initiation of trial medication and within 7 days after the last dose of trial medication. Percentages were based on the number of patients in each treatment group.

There were no statistically significant differences between treatment groups in the incidence of PCAs in laboratory parameters or vital signs.

Electrocardiogram results indicate the absence of relevant electrocardiographic effects, including QT/QTcF, of letermovir up to a once daily dose of 240 mg.

Overall, letermovir was safe and well-tolerated, raising no safety concerns and having an AE profile at least comparable to placebo.

Pharmacokinetics results:

The PK of letermovir given for prophylaxis of HCMV replication in HBPC transplanted recipients at risk of developing HCMV replication, and therefore disease, are best described by a 1-compartment model with linear absorption and elimination.

The final base model was a 1-compartment model with first order absorption and elimination and BSV on clearance, volume of distribution, and relative bioavailability. There were 2 proportional residual errors; 1 for the serial samples and 1 for the trough and follow-up samples.

In the covariate analysis, cyclosporine was found to have a significant effect on letermovir clearance and was included in the final covariate model. The clearance of letermovir decreased 43% when letermovir was dosed concomitantly with cyclosporine. The other covariates were not found to be statistically significant.

Following oral administration of an oral solid dosage form, letermovir is absorbed with a time to maximum plasma concentration (tmax) of about 1.5 hours independent of the letermovir dose. Following Cmax, the letermovir concentrations decline in an apparently monoexponential manner.

A dose-proportionality analysis on the letermovir PK parameters indicated that the mean predicted peak (Cmax) and total (AUC(0-τ)) exposure of letermovir increased in a dose-proportional manner for the 60 to 240 mg doses (demonstrated by slope estimates close to 1). However, the wide confidence interval for the slope estimates, due to high BSV in these parameters, precludes making definitive statistical conclusions on dose proportionality.

Conclusions:

The results of this Phase 2 trial support development of letermovir in a Phase 3 program to further demonstrate the potential of letermovir as prophylaxis of HCMV replication, and therefore disease:

- Letermovir is effective at doses of 120 and 240 mg od, showing highly statistically significant efficacy results in terms of incidence and time to onset of "HCMV prophylaxis failure" within the 84-day treatment period.
- Analysis of the FAS and PPS and all sensitivity analysis showed that letermovir at a dose of 240 mg od is highly and consistently effective.
- Letermovir is safe, with no evidence of safety concerns in any dose group.
- The PK of letermovir given for prophylaxis of HCMV replication in HBPC transplanted recipients at risk of developing HCMV replication, and therefore disease, are best described by a 1-compartment model with linear absorption and elimination.
- Following administration of an oral solid dosage form, letermovir is absorbed with a tmax of about 1.5 hours independent of the letermovir dose. Following Cmax, the letermovir concentrations decline in an apparently monoexponential manner.
- Letermovir exposure appears to be dose-proportional in the 60 to 240 mg od dose range in HBPC patients, though the wide CIs precluded definitive conclusions of dose proportionality.
- Cyclosporine had a statistically significant effect on the clearance of letermovir with the clearance being 43% lower when patients are on concomitant cyclosporine.

Date of AIC246-01-II-02 final clinical trial report: 05 July 2012