CLINICAL TRIAL REPORT SUMMARY

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

Name of Finished Product: AIC-001

Name of Active Ingredient: (S)-{8-Fluoro-2-[4-(3-methoxyphenyl) piperazin-1-yl]-3-[2- methoxy-5- trifluoromethylphenyl]-3,4-dihydroquinazolin-4-yl} acetic acid

Title of study: Phase 2a Randomized, Controlled, Multi-center, Open-label, Dose Ranging Proof of Concept Study to Evaluate the Safety, Tolerability and Antiviral Activity of AIC-001 Over 14 Days of Dosing in Patients With Positive HCMV Viremia Under the Conditions of a Pre-emptive Strategy

Coordinating investigator: Wolfgang Arns, MD, Kliniken der Stadt Köln, Klinikum Merheim, Ostmerheimer Straße 200, 51109 Köln, Germany.

Ten investigators in Germany.

Study site(s): This was a multi-center study conducted at 10 sites in Germany.

Publication (reference): Stoelben, S., et al., Preemptive treatment of Cytomegalovirus infection in kidney transplant recipients with letermovir: results of a Phase 2a study. Transpl Int, 2014. **27**(1): p. 77-86.

Studied period (years): 2 years: 10 April 2007 (First patient, first visit) to 15 May 2009 (Last patient, last visit)	Phase of development: 2a

Objectives: The primary objective of this study was to determine the decline in human cytomegalovirus (HCMV) DNA load after a 14-day treatment for each AIC-001 dosing regimen and to compare this to an observational control group.

The secondary objective of this study was to assess the safety, pharmacokinetics, tolerability, and efficacy of the AIC-001 dosing regimens and to compare this to an observational control group.

Methodology: Overall, there were 3 protocol amendments for this study. One patient was recruited under the original protocol and 1 patient was recruited under Protocol Amendment 2. Protocol Amendment 1 was not implemented. The majority of patients (25 of 27 patients) were recruited under Protocol Amendment 3.

This was a randomized, controlled, multi-center, open-label study with a 14-day treatment period in 3 parallel groups of kidney and kidney/pancreas transplant patients with positive HCMV viremia. Under the original protocol and Protocol Amendment 1, bone marrow (autologous and allogeneic) transplant patients were also eligible for enrollment and in Protocol Amendment 2, autologous bone marrow transplant patients were eligible for enrollment. The study was conducted at investigational sites (transplant clinics) located in Germany.

After signing informed consent eligible patients, they were randomly assigned to one of the 3 treatment groups using an interactive voice response system (IVRS). The treatment groups were: AIC-001 40 mg twice daily (BID); AIC-001 80 mg once daily (QD); and observational control (local standard of care).

At Screening, the patient entered the study and all safety parameters (including vital signs) were recorded. On Day 1, blood samples were taken for a predose (baseline) measurement of pharmacodynamics (assessment of HCMV DNA load/HCMV pp65 levels) for all enrolled patients and pharmacokinetics (plasma concentrations) for all patients assigned to the AIC-001 treatment groups. In addition, a urine sample was taken for HCMV virus isolation. Following this, patients who were assigned to receive investigational treatment received either 40 mg BID or 80 mg QD of AIC-001 on Days 1 to 14, inclusive, depending on their treatment allocation.

Under the original protocol, patients assigned to the AIC-001 treatment groups were to have blood samples for pharmacokinetic assessments taken before dosing and at 1 to 4 hours after dosing on Days 1, 4, 8, and 11, and in the morning on Day 15. Under Protocol Amendment 2, a more extensive pharmacokinetic sampling schedule was used and patients assigned to the AIC-001 treatment groups were to have blood samples for pharmacokinetic assessments taken on Days 1, 4, and 14 at the following time points: predose, 0.5, 1, 1.5, 2, 4, 8, 12, and 24 hours. Under Protocol Amendment 3, patients assigned to the AIC-001 treatment groups had a blood sample for pharmacokinetic assessments taken under fasting conditions before dosing on Days 1, 4, 8, and 11, and in the morning of Days 15 and 22.

As there was a possibility of drug-drug interactions between AIC-001 and standard coadministered drugs for the

maintenance of the transplant, which are also cytochrome P450 (CYP) 3A4 substrates (ie, cyclosporine, tacrolimus, and everolimus), the investigator assessed the levels of coadministered drugs before dosing on Days 1, 4, 8, and 11, and in the morning on Days 15 and 22. Assessment of the immunosuppressant levels using validated assays was carried out at the local laboratory. Trough values of coadministered immunosuppressive drugs and resulting dose adjustment were documented in the case report form (CRF).

Before dosing on Days 1, 4, 8, and 11, and in the morning on Day 15, all patients had a blood sample taken for pharmacodynamic assessment. Adverse events (AEs) were also monitored.

On Day 15 (or on day of withdrawal, if applicable), a second urine sample was taken for HCMV virus isolation.

Following the conclusion of the study period, all patients underwent end-of-study assessments on Day 29. Patients who were still positive for virus at Day 15, or had signs and symptoms of HCMV infection or HCMV syndrome, were switched to standard treatment for HCMV according to usual practice for the site.

Number of patients (planned and analyzed): It was planned to enroll up to 30 patients to ensure that approximately 24 patients had an evaluable Day 15 viral load assessment. In total, 27 patients were enrolled and randomly assigned to one of the following treatment groups: AIC-001 40 mg BID; AIC-001 80 mg QD; or observational control (local standard of care).

Diagnosis and main criteria for inclusion: Patients who were positive for HCMV (in blood measured at the local laboratory) and who were eligible for pre-emptive therapy according to local practice qualified for enrollment. All patients were required to meet the following criteria at Screening to be enrolled in this study:

1. Signed written informed consent form;
2. Able and willing to comply with protocol requirements;
3. At least 18 years of age at Screening;
4. Male patients who agreed to use an acceptable form of contraception, ie, double barrier methods, with their sexual partner during participation in the study and for 3 months after the end-of-study visit; or
5. Female patients who were postmenopausal (older than 50 years of age who had a history of no menses for at least 24 months) or surgically sterile;
   In the original protocol, patients were to additionally have a follicle-stimulating hormone level over the upper limit of normal for reproductive aged women.
6. Positive for HCMV in blood (tested at the local laboratory) and eligible for pre-emptive therapy according to local practice;
7. Transplant recipient for kidney or kidney/pancreas.
   In the original protocol and Protocol Amendment 2, recipients for bone marrow transplants could also be enrolled (autologous or allogenic in the original protocol and autologous in Protocol Amendment 2).

Test product, dose, and mode of administration, batch number:

Test Product	Dose and Mode of Administration	Batch Number
AIC-001	40-mg BID oral tablets (administered as 20-mg tablets)	BX0284S
AIC-001	80-mg QD oral tablets(administered as 20-mg tablets)	BX0284S

Duration of treatment: The treatment period was 14 days.

Reference therapy, dose, and mode of administration, batch number: Patients assigned to the observational control group received no AIC-001 treatment, but received the local standard treatment for HCMV according to usual practice for the site. Following enrollment into the study, the subsequent 14 days of local standard treatment was used to provide the comparison for the 14-day AIC-001 treatment period.

Criteria for evaluation:

Efficacy: Analysis was performed for both the per-protocol (PP) and intent-to-treat (ITT) populations. For all analyses, the latest recorded value prior to the first dose of study medication was used as Baseline unless otherwise specified.

The primary efficacy endpoint was the reduction in HCMV DNA load (assessed by PCR [polymerase chain

reaction]) from Baseline to Day 15.

The secondary efficacy endpoints included:

- Reduction in HCMV DNA load from Baseline on Days 4, 8, and 11;
- Reduction in HCMV pp65 levels from Baseline on Days 4, 8, 11, and 15;
- Time to viral clearance (defined as the time from Day 1 to the first time point where HCMV DNA load is below the limit of detection, with samples at all subsequent time points below the limit of detection);
- Time to viral clearance (defined as the time from Day 1 to the first time point where HCMV pp65 levels are below the limit of detection, with samples at all subsequent time points below the limit of detection);
- Percentage of patients with no detectable viral load at Day 15 (defined by HCMV DNA load);
- Percentage of patients with no detectable viral load at Day 15 (defined by HCMV pp65 levels);
- Percentage of patients requiring salvage therapy based on clinical evidence of commonly accepted signs and symptoms of HCMV infection or HCMV syndrome together with increases in viral load from Days 4 to 8 (or Day 11, according to quantification by the local laboratory, in which case, the local standard therapy usually used at the site was to be implemented).

Pharmacokinetics: Analysis was performed for the pharmacokinetic population. The pharmacokinetic endpoints were plasma trough levels of AIC-001, cyclosporine, tacrolimus, and everolimus in patients. The plasma trough levels of everolimus were not evaluated because none of the patients were coadministered everolimus.

Safety: Analysis was performed for the safety population. The safety endpoints were: AEs, the percentage of patients requiring adjustment of coadministered immunosuppressive treatment medication (ie, cyclosporine and tacrolimus); and discontinuation of study medication. Clinical safety evaluations, performed at all postrandomization visits, included physical examinations, vital sign measurements, electrocardiogram results, laboratory safety tests (hematology, serum chemistry, and urinalysis), prior and concomitant medications, and all reported AEs.

Statistical methods: HCMV DNA load University of Ulm central laboratory data and corresponding decline from baseline data (on the logarithmic scale) were summarized separately for each time point within each treatment group. Depending on local practice (and therefore if collected), HCMV DNA load local laboratory data and corresponding decline from baseline data (on the logarithmic scale) were summarized separately for each time point within each treatment group and site. The primary focus was the University of Ulm central laboratory data.

As an additional supportive analysis, the decline from Baseline in HCMV DNA load University of Ulm central laboratory data (on the logarithmic scale) was analyzed using a repeated measures analysis of covariance model with time point, treatment, and time point by treatment interaction included as fixed factors, baseline HCMV DNA load (on the logarithmic scale) included as a covariate and patient included as a random effect. Decline from baseline values were compared to zero (indicating no change from Baseline) for each time point within each treatment group (primary comparison) as well as between each dose of AIC-001 and the control group and between the dosing schedules for AIC-001 for each time point (secondary comparison). The overall decline from baseline values were compared between each dose of AIC-001 and the control group and between the dosing schedules of AIC-001. For each comparison, the point estimate, associated 95% confidence interval and *P* value were presented. The primary hypothesis tested was whether the mean reduction from Baseline in HCMV DNA load for each dose of AIC-001 was equal to zero.

HCMV DNA load data below the limit of quantification (LoQ) were included in the analysis using half the LoQ (on the logarithmic scale). The assumptions of normality and homogeneity of variance were assessed by inspection of normal probability plots and residual plots. As there is no direct nonparametric equivalent to the proposed approach, the results were to be interpreted with some caution if these assumptions were clearly not met.

HCMV pp65 University of Ulm central laboratory and local laboratory data and corresponding decline from baseline data were summarized in a similar manner to the HCMV DNA load data, but without the use of a logarithmic transformation. Decline of HCMV pp65 from Baseline was also analyzed in a similar manner to that of the HCMV DNA load decline from Baseline, again without the use of a logarithmic transformation.

Time to viral clearance was compared between treatment groups using the log-rank test. Patients without viral clearance were included as censored observations. In addition, Kaplan-Meier graphs were produced, separately by treatment group.

The percentage of patients with no detectable viral load (summarized for each variable) at the end of the study and the percentage of patients requiring salvage therapy were summarized by treatment group.

No formal pharmacokinetic analysis was performed. Plasma concentration data of AIC-001 were summarized by dose level and time point as well as by dose level, time point, and type of coadministered drug (ie, cyclosporine or tacrolimus). Plasma concentration data of the primary immunosuppressive drug (cyclosporine and tacrolimus) were summarized by treatment group and time point.

AIC-001 trough levels were compared with historical data from healthy volunteers.

All other efficacy, safety, and demographic endpoints were summarized only.

Summary and Conclusions:

Efficacy results: Although the sample size was small in this exploratory proof of concept study, no patients treated during the study developed HCMV disease. Of the 17 patients treated with AIC-001 for 14 days, 13 patients had a measurable HCMV viral load in the plasma HCMV PCR evaluation on Day 1, and 10 of these 13 patients showed a reduction in plasma HCMV PCR on Day 15; the maximum reduction in plasma HCMV PCR on Day 15 was 2.6 $\log_{10}$. Furthermore, AIC-001 was used to successfully treat a patient harboring a multi-resistant HCMV strain for the marketed anti-HCMV drugs ganciclovir, cidofovir, and foscarnet. Thus, it can be concluded that proof of concept was shown for AIC-001.

The efficacy in reducing HCMV DNA levels during 14-days of treatment of AIC-001 in this open design trial was comparable to observational treatment.

In the observational control group, a sharp decline in the viral load mean change from Baseline was seen at Day 4 and the viral load remained similar between Days 4 and 15. In the AIC-001 treatment groups, the viral load remained similar between Days 1 and 11 and a sharp decline in the viral load mean change from Baseline was seen between Days 11 and 15. At Day 15, a statistically significant viral load decline from Baseline was seen in both the AIC-001 and observational control treatment groups.

Pharmacokinetic results: Treatment with either the AIC-001 40-mg BID or 80-mg QD dosing regimen resulted in equally high AIC-001 predose levels. Steady-state trough levels were reached at Day 4. Between Days 4 and 15, the AIC-001 predose values under steady-state conditions ranged from 130.97 µg/L to 1504.41 µg/L in the AIC-001 40-mg BID treatment group and from 25.80 µg/L to 1796.51 µg/L in the AIC-001 80-mg QD treatment group. The mean AIC-001 predose values were higher in the kidney and kidney/pancreas transplant patients in both the AIC-001 40-mg BID and 80-mg QD treatment groups than those measured in healthy subjects in Phase 1 trials. The intra-individual variability in AIC-001 predose levels was low, resulting in relatively constant predose values over the entire treatment duration.

No major adjustments in the immunosuppressant doses were required when coadministered with AIC-001.

Safety results: Overall, both AIC-001 40-mg BID and 80-mg QD 14-day treatments were well tolerated.

There were no deaths reported during the study. A total of 3 treatment-emergent SAEs (renal disorder, arteriovenous fistula aneurysm, and renal lymphocele) were reported in 2 patients during the study and none was considered related to study treatment by the investigator.

The most frequently reported AEs occurring in more than 1 patient in any treatment group were urinary tract infection, hypertension, nasopharyngitis, and edema. None of the most frequently reported AEs were reported in more than 2 patients per treatment group and no other AEs were reported in more than 1 patient per treatment group.

The majority of AEs reported were considered by the investigator to be unrelated to study medication and mild in intensity. None of the AEs reported were considered by the investigator to be severe in intensity. Only 5 AEs reported in 3 patients were considered possibly related to study medication: 4 AEs in 2 patients in the AIC-001 40-mg BID group (gastroenteritis, nasopharyngitis, dyspnea and blood creatinine increased) and 1 AE in 1 patient in the AIC-001 80-mg QD group (dyspepsia).

For the majority of patients, the largest shift from Baseline in laboratory hematology and serum chemistry values were within the normal range.

There were no changes in vital signs, physical examinations, or ECG results from Baseline that were considered clinically relevant by the investigator.

Conclusions: In this exploratory study, the oral administration of AIC-001 to a limited number of patients clearly demonstrated a successful proof-of-concept outcome. Of the 17 patients treated with AIC-001 for 14 days, 13 patients had a measurable HCMV viral load in the plasma HCMV PCR evaluation on Day 1, and 10 of these 13 patients showed a reduction in plasma HCMV PCR on Day 15; the maximum reduction in plasma HCMV PCR on Day 15 was 2.6 $\log_{10}$. Furthermore, AIC-001 was used to successfully treat a patient haboring an HCMV strain multi-resistant to the marketed anti-HCMV drugs ganciclovir, cidofovir, and foscarnet. No patients treated during the study developed HCMV disease.

For all the treatment groups, a statistically significant decrease in HCMV PCR plasma viral load was seen between Days 1 and 15 and no statistically significant difference was observed between the observational control group and the AIC-001 treatment groups at Day 15. It is therefore concluded that the efficacy of AIC-001 in this open design trial was comparable to observational treatment.

Treatment with either of the AIC-001 treatment groups resulted in similar and equally high AIC-001 predose plasma concentration. Steady state trough levels were reached at Day 4. The intra-individual variability in AIC-001 predose levels was low, resulting in relatively constant predose values over the entire treatment duration.

In all patients the measured mean trough levels with the daily dose of 80 mg AIC-001 were consistently higher than the AIC-001 EC_{90} level derived from in vitro experiments and corrected for plasma protein binding. From this it is concluded that the design of further dose optimization trials using the once-daily regimen of AIC-001 treatment is warranted.

Overall, AIC-001 40 mg BID and 80 mg QD administered over 14 days has been shown to be generally safe and well tolerated in this patient population of bone marrow-, kidney-, and kidney/pancreas-transplanted patients. This is demonstrated by the low number of AEs and clinically relevant changes in laboratory parameters and no clinically relevant changes in vital signs, physical examinations and ECG parameters.

Within the limits of a small sample size and treatment duration of 14 days, the results support a favorable risk/benefit ratio for AIC-001.

Date of report: Date of AIC001-02-001 final clinical trial report: 09 December 2009