

Phase I Safety and PK Data of the novel anti-HCMV terminase inhibitor AIC246

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Introduction

Human Cytomegalovirus (HCMV) remains a serious threat for immunocompromised individuals including transplant recipients and newborns. To date, all drugs licensed for the treatment of HCMV infection and disease target the viral DNA-polymerase. Although effective, several drawbacks are associated with the use of these drugs including toxicity and emergence of drug resistance.

Hence, new and improved antivirals with novel molecular targets are urgently needed. AIC246 belongs to a novel class of anti-CMV agents. Its mode of action differs from Ganciclovir as it targets the processing of the viral DNA thereby inhibiting the formation and release of infectious virus particles.

AIC246 was shown to exhibit excellent *in vitro* inhibitory activity against HCMV laboratory-strains and clinical isolates and to be highly active against viruses resistant to current treatments.

AIC246 underwent comprehensive Phase I investigations and is currently in Phase IIb clinical development. Phase IIa data from kidney and kidney/pancreas transplanted patients who were treated preemptively for 14 days revealed good tolerability and an efficacy comparable to Valganciclovir.

Importantly AIC246 exhibited sustained activity against GCV-resistant and multiresistant HCMV (GCV, foscarnet, cidofovir) strains in patients, including a patient with multiorgan HCMV disease.

Methods

Phase I single dose and multiple dose data, food effect, and effect of gender have been investigated in several Phase I trials: Trials A and B were double-blind, placebo-controlled single dose escalation trials in male subjects using 2 different formulations.

In trial A and B 28 and 48 male subjects received AIC246 as a solution (5-80 mg) and as tablets (80-320 mg), respectively, 24 subjects received placebo.

Trial C (open, no placebo, cross-over design) investigated the effect of food. 11 male subjects received a 20 mg AIC246 tablet under fasted in one period and under fed conditions (high fat, high caloric) in the other period.

Trial D was a double-blind, placebo-controlled multiple dose escalation trial. 6 males and 6 females each received placebo as well as 120 mg bid, 180 mg bid, and 240 mg bid AIC246 for 2 weeks.

Results

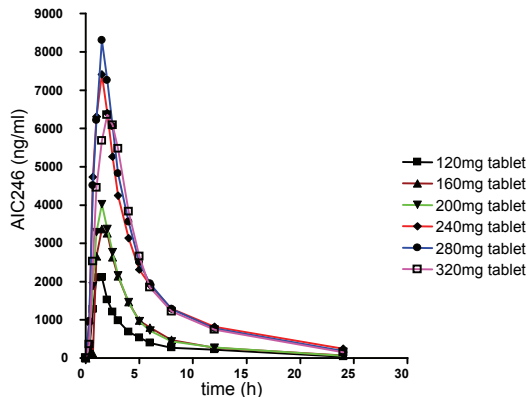
Trials A and B:

Figure 1 shows the plasma concentration time curves of Trial B

Main results are:

- Over-proportional increase in AIC246 exposure up to 240 mg
- No further increase of exposure at higher doses between 240 and 320 mg
- Median t_{max} 1.5 h
- Mean terminal t_{1/2} 10 h

Figure 1: Plasma concentration time curves from Trial B



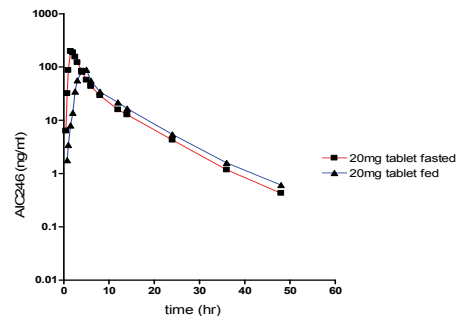
Trial C:

Figure 2 shows the plasma concentration time curves of Trial C

Main results are:

- Food intake led to decrease in rate (median t_{max} 4 h) and extent of absorption (C_{max} reduced by 24%)
- However AUC_{0-∞} not effected by intake of food

Figure 2: Plasma concentration time curves from Trial C



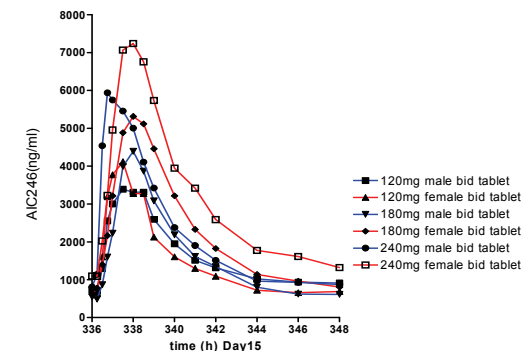
Trial D:

Figure 3 shows the plasma concentration time curves of Trial D

Main results are:

- Mean terminal t_{1/2} and median t_{max} values do not change as compared to single dose administration
- Accumulation factors for bid administration was approximately 1.2 at steady state
- Females exhibited higher plasma concentrations compared to males in the 180 and 240 mg dose groups.

Figure 3: Plasma concentration time curves (Day15) from Trial D



Safety Results

AIC246 was administered in trials A to D to 123 healthy volunteers. In these trials as well as in additional trials (not shown here) AIC246 was generally well tolerated.

No dose-dependent adverse events occurred, no effects on safety laboratory, vital signs and ECG parameters were detected.

Conclusions

AIC246 has a favorable PK profile allowing once daily dosing and has been generally well tolerated in >200 healthy volunteers in all Phase I trials.

This good tolerability combined with the convenience of a once daily dosing, high efficacy and resistance breaking properties based on a new mode of action, makes AIC246 a very promising candidate for significantly improving future HCMV treatment.