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Results of a Phase I study to evaluate the safety, tolerability, pharmacokinetics (with and without ritonavir) and food-effect of VCH-286

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Purpose of the study

VCH-286 is being developed as a novel drug for the treatment of human immunodeficiency virus (HIV). VCH-286 (IC90 HIV-$1_{Ba\text{-}L}$ ~0.21 nM) targets the chemokine co-receptor CCR5 on the cell surface and specifically blocks the entry of CCR5-tropic strains of HIV-1 into host cells. The primary objective of the study was to evaluate the safety/tolerability of VCH-286 following oral administration of single ascending doses (from 25 to 800 mg) in healthy subjects. The secondary objectives were; 1) to determine the pharmacokinetic (PK) profile of VCH-286 under fasting conditions; 2) to evaluate the effect of food on the exposure of 400 mg VCH-286; and 3) to evaluate the effect of 100 mg ritonavir on the exposure 25 mg VCH-286 under fasting conditions.

Methods

The study design involved a single centre, Phase I, sequential ascending dose study, with crossover food-effect and ritonavir-effect arms. The study was divided into three parts: dose escalation – part A; evaluation of the food-effect – part B; and evaluation of the effect of ritonavir – part C. Each cohort of parts A and B were dosed following a randomized, double-blind and placebo-controlled design (six active: two placebo) (2-way crossover for part B). Part C included one treatment with open-label (six subjects).

Summary of results

The most frequently reported adverse events (AEs) were dermatitis contact, back pain, blood pressure decrease, headache and nausea. The majority of AEs were mild in intensity with few moderates and no severe. No increase in AEs was observed in relation to increasing dose. The PK analysis indicated that the AUC and C_{max} increase in a more than dose proportional manner over the 25 to 600 mg doses with the AUC and C_{max} at 600 mg being respectively 62- and 92-fold higher than at the 25 mg dose. Proportionality in AUC and C_{max} was noticed between the 600 and 800 mg doses. The elimination half-life, for all cohorts, was *ca.* 5 hours. At the 400 mg dose, there was no significant food-effect on any of the measured PK parameters. There was a ritonavir-effect as the PK parameters for terminal half-life, AUC and C_{max} were 3-, 19- and 6-fold higher, respectively, when 25 mg VCH-286 was co-administered with 100 mg ritonavir. This observation is consistent with the fact that VCH-286 is a CYP3A4 substrate.

Conclusion

VCH-286 was safe and well tolerated up to 800 mg as a single oral dose. Food did not influence the PK profile at a 400 mg dose. These results supported the initiation of a multiple-dose 14-day study in HIV-1 infected subjects.