Introduction
Nifedipine, a drug of dihydropyridine class, inhibits calcium uptake of myocardial and smooth muscle cells. Several nifedipine controlled release tablets were developed because nifedipine is rapidly inactivated through oxidative biotransformation and the pharmacodynamics of the drug is closely related to its kinetics [1].

Adalat CR® tablet, which was started to be marketed in 1998 in Japan, is expected to increase the drug compliance by enabling once-daily dosing. We developed a population pharmacokinetic model to describe the plasma concentration profiles following administration of Adalat CR®.

Material and methods
4 clinical pharmacology studies in Japanese healthy adult male subjects were used. Two studies were performed under fasting conditions and the other ones under non-fasting conditions. A single oral dose of Adalat CR® tablet 20 mg was given to a subject. 3 mL of blood were drawn at predefined sampling points and plasma concentrations were determined by a validated LC-MS/MS assay. Totally, 1314 plasma concentrations from 92 healthy male subjects were obtained. The pharmacokinetic analyses were performed using nonlinear mixed effect modeling (FO method) with the NONMEM [2] program version V on a validated Linux server farm environment.

Concept of drug formulation
The formulation of Adalat CR® consists of a fast-dissolving core surrounded by a slowly-dissolving coat; this tablet was designed in order to combine the dissolution characteristics of the outer coating controlling the release of nifedipine at a constant rate with the characteristics of the inner core showing a faster drug release than the outer coat in order to counteract a decrease in nifedipine plasma concentrations towards the end of the release from the coat.

Population PK model
According to the concept, 3 compartments were assumed; a 1st compartment for the coat part, which releases nifedipine slowly to the central (2nd) compartment, and a 3rd compartment for the core part, which releases nifedipine faster to the 2nd compartment after a lag time. By the combination of the estimated drug concentrations from the 1st compartment and the 3rd compartment, estimated total plasma concentrations can be fitted well to the observed concentrations.

Results and Discussion
The final population PK model parameters and their precision estimates are given in Table. In the goodness-of-fit plots, there were no trends and biases. The IWRES vs IPRED were symmetrically distributed. As seen from the individual curve fitting, observed plasma concentrations in almost patient were fitted well, but the curves for some patients still seem to be underestimated.

Food effect was found to be a covariate on F1, K12 and Lag1. If the drug is taken with food, plasma concentration time profiles show a larger lag time, then increasing to Cmax more rapidly and showing overall a higher bioavailability.

Variability in estimated PK parameters, especially K32 and Lag3 was very large, being most probably related to the sampling approach; there were only few sampling points between first peak and second peak.

Conclusion
Although this evaluation was based on limited healthy volunteer data, population pharmacokinetic structural model for nifedipine controlled release formulation reflecting the drug release concept was established. The population approach accounts for covariate effects and inter-individual variability, which is difficult to access by a non-compartment evaluation approach.

Furthermore, this structural population pk model is planned to be enhanced with PK/PD evaluation in patients data.

Reference
2. Reul SL, Shenker LB. NONMEM users guide, NONMEM project groups. San Francisco: University of California, 1992