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Preliminary population PK-PD of dalcetrapib: an agent targeting CETP to raise HDL-C and prevent cardiovascular morbidity and mortality

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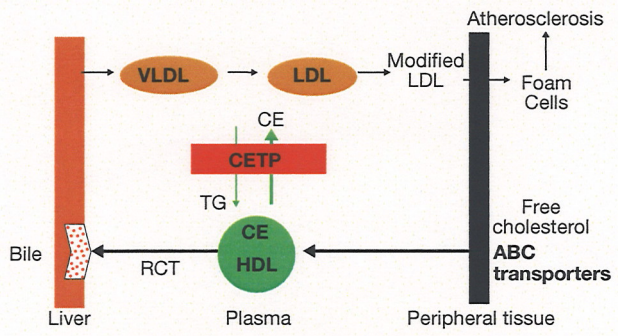
Introduction

- Cardiovascular disease (CVD) is a leading cause of death.[1]
- Strong epidemiological evidence links low levels of serum high-density lipoprotein cholesterol (HDL-C) to increased coronary heart disease (CHD) morbidity and mortality.[2-4] A strategy to further decrease cardiovascular (CV) risk is to increase HDL-C levels.
- Cholesteryl ester transfer protein (CETP) is a plasma protein that transfers cholesteryl ester (CE) from HDL to triglyceride (TG) rich lipoproteins such as low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). Inhibiting the transfer of CE from HDL is expected to result in an increase in HDL-C which may protect against atherosclerosis and potentially reduce the risk of CV events (Figure 1).

Figure 1. Role of CETP in cholesterol metabolism.



- Dalcetrapib has been shown to effectively decrease CETP activity and increase HDL-C in clinical studies.[5,6]
- By understanding the relationship between dalcetrapib plasma concentration and pharmacodynamic parameters such as CETP activity and HDL-C, it is possible to fully characterize the relationships between CETP activity and HDL-C levels prior to obtaining data on clinical endpoints i.e., CV mortality and morbidity.

Objectives

- The first objective is to establish the correlation between dalcetrapib exposure, CETP inhibition and HDL-C increase as part of the characterization of a new mechanism of action.
- The second objective is to establish the relationship between dalcetrapib exposure and HDL-C increase, omitting the mediator role of CETP activity in order to anticipate the Phase 3 analysis where CETP activity is not measured.

Methods

- Data were obtained from a Phase 2 randomized study in which patients received dalcetrapib 300, 600, or 900 mg/day or placebo, in combination with pravastatin 40 mg for 12 weeks (84 days).
- Plasma was obtained from all patients for PK analysis on days 14, 28, 56, and 81 before drug administration and between 1.5 and 5 h post-dose on day 84. HDL-C levels and CETP activity were measured in trough samples during pre-randomization, on days 0 (baseline), 14, 28, 56 and 84, and at follow-up on day 112 for HDL-C.
- A population PK-PD analysis was performed using a sequential PK-PD approach in NONMEM V6.1 using Foce interaction. First, a model describing the cascade of events i.e., dose-exposure-CETP activity-HDL-C was developed. Thereafter, a simplified model of dose-exposure-HDL-C was developed to investigate if change in HDL-C level could be predicted directly from drug exposure data. The robustness of the PK-PD population models were then assessed using a VPC method.

Results

Patient demographics

- A total of 942 plasma samples from 204 patients were collected for dalcetrapib measurement; 1195 samples from 276 patients (72 control arm) were collected for CETP activity and 1485 samples for HDL-C measurements.
- Baseline demographics show that the 4 treatment groups in the study were evenly matched in terms of CETP activity, HDL-C levels (Table 1).

Table 1. Demographic characteristics

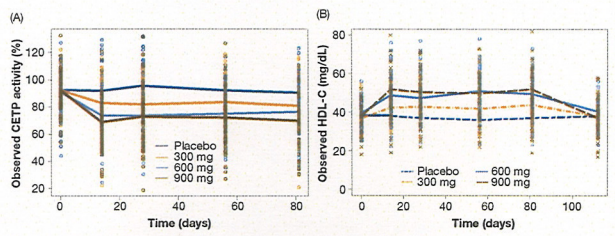
Characteristic	Placebo	300 mg	600 mg	900 mg
N	72	71	64	69
Male sex, n (%)	57 (80)	59 (83)	51 (80)	53 (77)
Age, y	57 (28-74)	56 (30-74)	57 (29-75)	56 (24-76)
Weight, kg	87 (57-127)	91 (66-138)	89 (68-141)	87 (49-117)
Total cholesterol, mg/dL	175 (124-306)	165 (98-216)	172 (122-295)	167 (53-296)
HDL-C, mg/dL	38.2 (27-54)	37.6 (25-55)	39.0 (25-56)	37.3 (18-52)
CETP activity, %	91.7 (51-116)	92.5 (44-122)	90.9 (44-127)	92 (54-133)
Diabetes, n (%)	6 (8.1)	6 (7.9)	9 (13)	3 (4.0)
Hypertension, n (%)	32 (43)	32 (42)	30 (44)	26 (35)
Smoking, n (%)	65 (88)	67 (80)	60 (88)	63 (85)

Values are mean (range) unless otherwise stated

Effect of treatment on CETP activity and HDL-C level

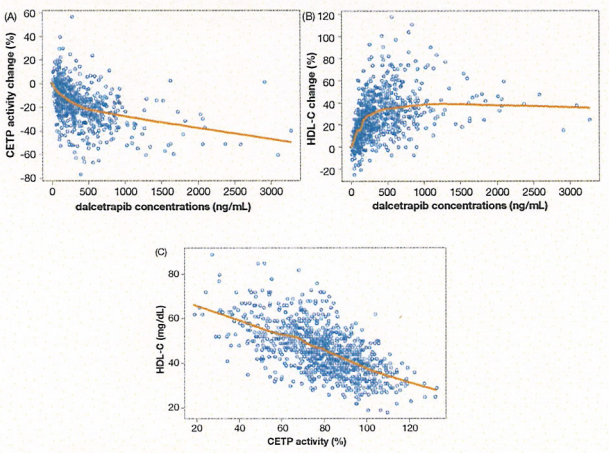
- The time course of the PD parameters showed that the plateau of the effect is reached by 2 weeks with a clear dose-response relationship (Figure 2).

Figure 2. Time course of (A) CETP activity and (B) HDL-C level.



- CETP activity decreases gradually with dalcetrapib exposure. Treatment with dalcetrapib resulted in an increase in HDL-C with a maximum of around 35% (Figure 3).
- A marked relationship was observed between CETP activity and HDL-C levels (Figure 3).

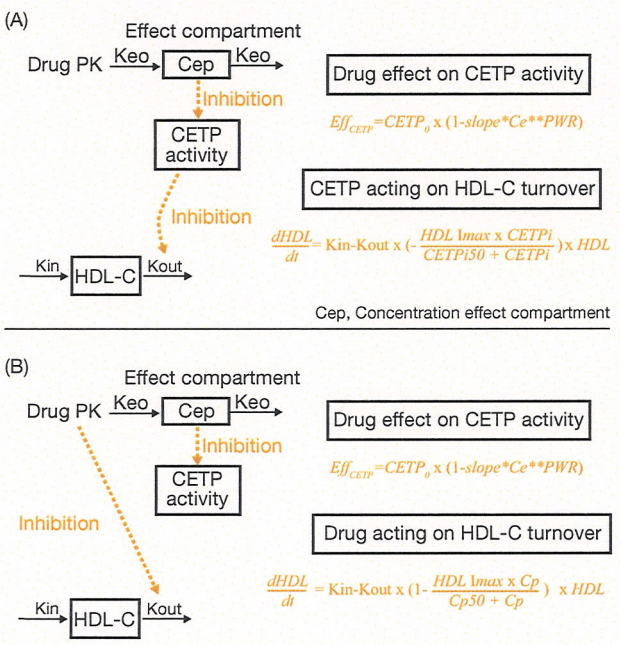
Figure 3. Relationship between (A) dalcetrapib exposure and CETP activity, (B) dalcetrapib exposure and HDL-C level, and (C) CETP activity and HDL-C level.



PK-PD model development

- The PK-PD models characterizing HDL-C increases as a function of CETP activity (full model) or dalcetrapib exposure (simplified model) are illustrated in Figure 4.
- The relationship between dalcetrapib plasma concentrations and CETP activity was described by a power model. An effect compartment was used to take into account the delay between the time course of the PK and the PD.
- The relationship between CETP activity and HDL-C level or dalcetrapib and HDL-C was described using an indirect type II 'turnover' model incorporating an inhibition Emax model with a baseline.

Figure 4. HDL-C increase as a function of (A) CETP activity (full model) and (B) dalcetrapib exposure (simplified model).



- The parameter estimates for the full and the simplified models are presented in Table 2 and 3, respectively. The parameters are well estimated with precision of estimation <25% for the structural parameters and <40% for the random effect.
- Both models described the data correctly as assessed by the goodness of fit and the outcomes of the VPC (Figures 5 and 6, respectively).

Table 2. PK-PD parameter estimates for the full model

Parameter	Estimate	CV (%)	IIV (%)	CV (%)
Base CETP activity (%)	90.9	1.05	13	15.8
Slope	0.103	8.03	40.5	17
Keo	0.0075	17.5	-	-
Power	0.623	9.5	-	-
Residual error (%)	10.3	3.53	-	-
Base HDL-C (mg/dL)	37.6	1.1	16.6	11.1
Kout (1/h)	0.285	23	60.7	44.4
Imax (%)	68.7	14.3	-	-
CETPi50 (%)	33.6	21.6	-	-
Residual error (mg/dL)	4.06	4.56	-	-

Table 3. PK-PD parameter estimates for the simplified model

Parameter	Estimate	CV (%)	IIV (%)	CV (%)
Base CETP activity (%)	90.9	1.06	13.5	16.5
Slope	0.109	8.91	39.4	27.9
Keo	0.0944	37.5	-	-
Power	0.572	11.6	-	-
Residual error (%)	10.2	3.52	-	-
Base HDL-C (mg/dL)	37.8	1.08	16.9	11.3
Kout (1/h)	0.00984	2.87	80.9	22
Imax (%)	43.8	4.27	-	-
Cp50 (ng/mL)	412	9.66	47.7	33.6
Residual error (mg/dL)	4.06	4.56	-	-

Comparison of the full and simplified models

- The between-subject variability on the removal rate of HDL-C decreases from 80 to 60% between the simplified and the full model. It suggests that part of the variability on this parameter is influenced by the level of CETP activity.

Figure 5. Goodness of fit plots for (A) the full model and (B) the simplified model.

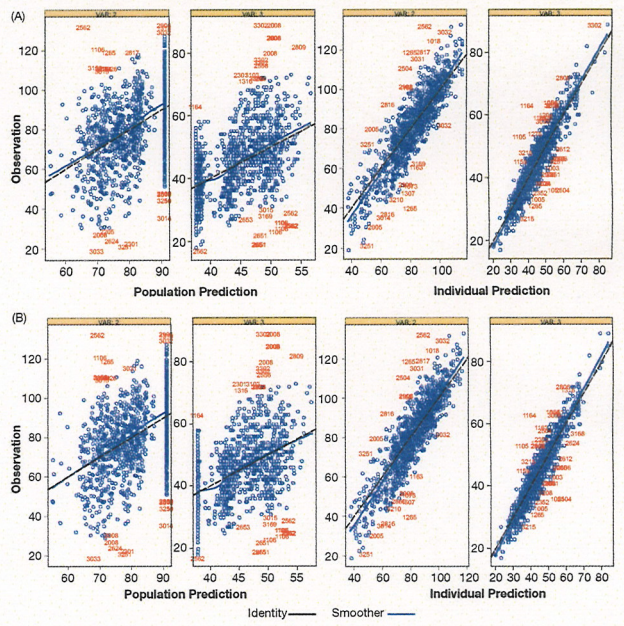
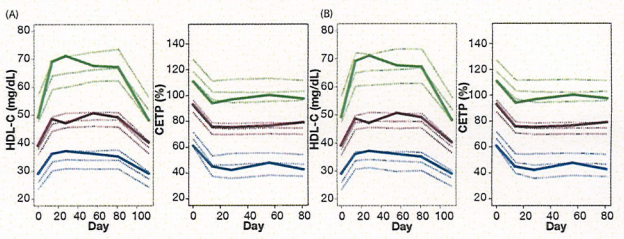
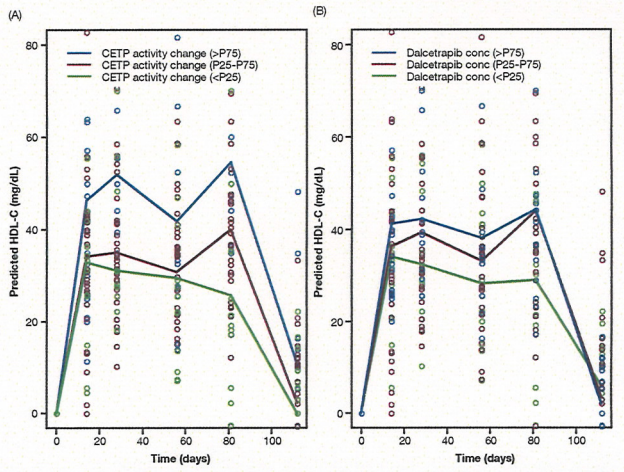


Figure 6. VPC outcomes for (A) the full model and (B) the simplified model.



- For the full model, no between-subject variability could be estimated for the level of CETP activity inhibition that decreases the rate of HDL-C removal by 50%. It suggests that dalcetrapib consistently reduces CETP activity, resulting in small fluctuations of CETP activity in all patients.
- Based on these two findings, CETP activity is expected to explain part of the variability in HDL-C changes. This is supported by the observed data. In Figure 7, the time course of the observed HDL-C change is plotted by the category of CETP activity change or dalcetrapib concentration. It shows that the range of HDL-C changes within one dose group is largely influenced by the change in CETP activity compared with dalcetrapib exposure.

Figure 7. Predicted time course of HDL-C level, with dalcetrapib 900 mg by (A) change in CETP activity and (B) dalcetrapib exposure.



Conclusions

- The two models adequately described the observed HDL-C time course caused by 12 weeks of treatment with dalcetrapib.
- The PK-PD model established the correlation between exposure data, CETP activity decreases and HDL-C increases.
- The variability in HDL-C changes is partly explained by the changes in CETP activity.
- The model describing HDL-C as a function of CETP activity could be used to describe HDL-C changes where dalcetrapib is not measured (imaging study).
- The model describing HDL-C as a function of exposure could be used to describe dalcetrapib-induced HDL-C changes where CETP activity is not measured. The characterization of this relationship will facilitate the use of HDL-C as an early biomarker of efficacy for CV morbidity and mortality outcomes as measured in Phase 3.

References

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Disclosure information

F. Hourcade-Potelleret is an employee of F. Hoffmann-La Roche Ltd.