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# Early formulation development of CKD-519, a new CETP inhibitor, for phase 1 clinical study based on *in vitro* and *in vivo* evaluation

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ABSTRACT

CKD-519, a potent cholesteryl ester transfer protein (CETP) inhibitor, is a clinical candidate being developed for the treatment of dyslipidemia. It is considered a Biopharmaceutical Classification System II compound with low solubility and high permeability. The objective of this study was to develop early formulations focusing on the dissolution rate of the compound to achieve dose-dependent exposure. High performance formulation strategies including solid dispersion (SD) and a self-microemulsifying drug delivery system (SMEDDS) were investigated and their *in vivo* and *in vitro* correlations were also evaluated in monkeys along with dose optimization in human volunteers. The SD granules were prepared in a fluid bed granulator using microcrystalline cellulose and mannitol as carriers. Poloxamer 407 and Eudragit E PO were each found to be a suitable solubilizing agent and polymer for the improvement of the CKD-519 dissolution rate. Pharmacokinetic studies in monkeys showed that the SD tablets exhibited better absorption than the SMEDDS in a dose-dependent manner from 1.5 mg to 100 mg. The mannitol-based SD tablet formulations were bioequivalent. However, pharmacokinetics studies in humans showed that the dose was saturable above 100 mg of CKD-519. This study was performed to determine how to develop early formulations for clinical studies and to identify rational formulation development strategies for CKD-519 to establish the pharmaceutical proof-of-concept in humans.

## 1. Introduction

New drug development is a complicated and challenging process with multiple stages, which may each last for several years (Settleman and Cohen, 2016). Pharmaceutical scientists are involved in multiple lines of investigation including diverse disciplines, often with conflicting goals and the need to integrate data to achieve balanced clinical candidates. Even with extensive research, the success rate for new molecule development from the early stages to marketing is extremely low (1 in 10,000) (De Boer and Gaillard, 2007). Additionally, a large number of leading candidates end up with a wide range of undesirable physicochemical and biopharmaceutical properties despite extensive optimization of discovery leads. In the case of small molecular leads, the solid state of a drug, for instance, can impact key attributes of the final product including stability, bioavailability, and manufacturability (Neervannan, 2006). Scientists from diverse disciplines are involved in many stages of drug development, from new drug discovery to formulation development and clinical studies.

As many clinical candidates have poor pharmaceutical properties, they may result in a lot of obstacles during the initial and late stages of development. There has been a lot of argument on the importance of optimizing the absorption, distribution, metabolism, and elimination (ADME) of candidate compounds to increase the success rate of new molecular entities. Moreover, the pharmaceutical profile, for instance, melting point, solubility, partition coefficient, permeability, and stability may affect the ADME and needs to be considered carefully in early development stages (Alsenz and Kansy, 2007; Arnott and Planey, 2012). Furthermore, pharmaceutical profiling can aid both the drug discovery and development processes for all institutes, maximizing the efficiency of the drug development process. Pharmaceutical profiling is also beneficial for companies that produce generic drugs, as it provides fundamental understanding of rational formulation approaches that can be employed to make the final products bioequivalent or even better.

Cardiovascular disease is the leading cause of mortality worldwide (Kim et al., 2016; Ohira and Iso, 2013). The major risk for cardiovascular events is associated with elevated low density lipoprotein cholesterol (LDL-C) and a low level of high density lipoprotein cholesterol (HDL-C) (Expert Panel on Detection, 2001; Gordon et al., 1977; Sharrett

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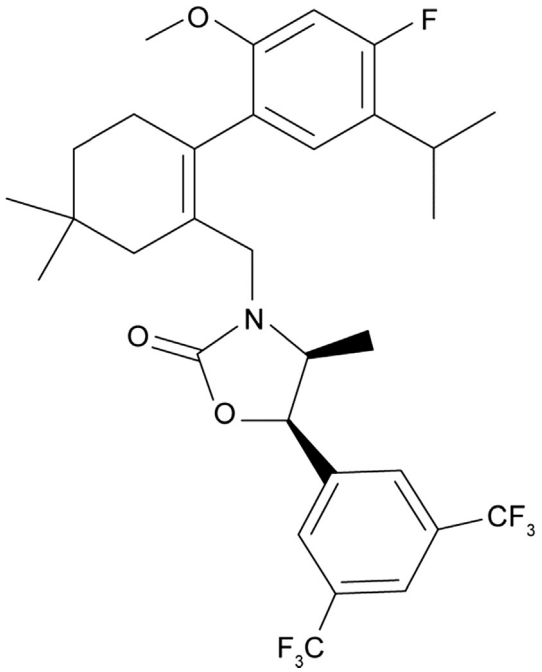


**Fig. 1.** Chemical structure of CKD-519 ($C_{31}H_{34}F_7NO_3$, mw 601.60), a selective and potent cholesteryl ester transfer protein (CETP) inhibitor for the treatment of dyslipidemia.

et al., 2001). One mechanism being investigated as a potential approach to minimize LDL-C while increasing HDL-C is related to the cholesteryl ester transfer protein (CETP) (Krishna et al., 2009; Tall, 1993). CETP transfers cholesterol from HDL cholesterol to very low density or low density lipoproteins (VLDL or LDL). Therefore, CETP inhibitors can reduce the risk of atherosclerosis by improving blood lipid levels. CKD-519 is a potent CETP inhibitor newly developed for the treatment of dyslipidemia (Fig. 1).

Preformulation studies are very important for the characterization of clinical candidates before formulation design. These studies help researchers understand the critical properties of new molecules that need to be determined during the formulation development process. Several technical and practical aspects should be considered when choosing the formulation technology, especially for poorly soluble candidates, because it is not common that only one formulation technology can achieve the targeted pharmacokinetic profiles of the given molecules. Among the various formulation strategies available, solid dispersion (SD) and liquid formulation (self-emulsifying drug delivery system) could be considered as a promising method to obtain high bioavailability of poorly soluble active pharmaceutical ingredients (API) (Chiou and Riegelman, 1971; Karwal et al., 2016; Sakai et al., 2018; Vo et al., 2013).

Due to the poor aqueous solubility of CKD-519, special formulation considerations are required to increase the dissolution rate, which may eventually improve the bioavailability. In the present study, we investigated a rational formulation strategy to improve the dissolution of CKD-519 using SD and a self microemulsifying drug delivery system (SMEDDS) and evaluated the effect of the pharmacokinetic (PK) parameters of the resulting formulations in monkeys. Finally, a clinical study was carried out with healthy volunteers to determine the linear exposure of the selected clinical formulation.

## 2. Materials and methods

### 2.1. Materials

CKD-519 was kindly supplied by Chong Kun Dang Corp. (Seoul, Korea). Plasdone® S-630 was purchased from Ashland Inc. (Wilmington, USA). Povidone K-17 (Kollidon® 17), Poloxamer 407 (Kolliphor® P407), Poloxamer 188 (Kolliphor® 188), polyoxyl castor oil (Kolliphor® EL), polyethylene glycol 6000 (PEG 6000), crospovidone (Ludiflash®), and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (Soluplus®) were obtained from BASF (Ludwigshafen, Germany). Colloidal silicon dioxide (Aerosil® 200) and Eudragit® E PO were purchased from Evonik Degussa AG (Essen, Germany). Microcrystalline cellulose (MCC, Avicel® 102) was obtained from Asahi Kasei Corporation (Tokyo, Japan). Croscarmellose sodium (Acdisol®) was obtained from DMV Fonterra Excipients GmbH & Co. KG (Goch, Germany). Glyceryl palmitostearate (Precirol® ATO5), glyceryl behenate (Compritol® 888 ATO), propylene glycol monocaprylate (Capryol® PGMC), and Gelucire® 50/13 were purchased from Gattefosse (Nanterre, France). Mannitol was obtained from Roquette Freres (Lestrem, France). Meglumine (MEG), ethanol, propylene carbonate, and butylated hydroxyanisole (BHA) were purchased from Sigma–Aldrich Co. (St. Louis, MO, USA). All other reagents were of analytical or HPLC grade.

### 2.2. Solubility of CKD-519 in selected excipients

*In vitro* solubility test was conducted according to the melting method to obtain suitable solubilizing agents. Briefly, physical mixture of CKD-519 with selected excipients at 1:3 ratio was prepared by trituration in mortar and pestle for 10 min. The blend was heated at 10 °C above the melting point of excipients in a glass vial. The mixture was allowed to cool down slowly to room temperature. The solidified melt was milled and sieved. An excess amount of SDs prepared was weighed and added into 2 mL distilled water in screw capped glass vial. The suspension was shaken at 100 rpm in a thermostatic water bath at 25 °C. After 48 h, 1 mL of supernatant was withdrawn, centrifuged at 12,000 rpm for 10 min, and then filtered through 0.45 syringe filter and the samples were mixed with 1 mL 75% acetonitrile. The samples were analyzed using the validated HPLC system with UV detection at 278 nm. 10 μL of each sample was injected into a Waters Sunfire $C_{18}$ column (5 μm particle size, 4.6 × 150 mm) adjusted to 30 °C with a flow rate of 1.0 mL/min. The mobile phase contained a mixture of 1 mL of acetic acid with 1 L of 100% acetonitrile.

### 2.3. Preparation of CKD-519 solid dispersion

Various CKD-519 SD formulations were prepared using MEG, Poloxamer 407 (P 407), Eudragit EPO (EEPO EPO), and BHA. In the formulations, the amount of CKD-519 was kept constant. Briefly, Poloxamer 407, Eudragit EPO, MEG, and BHA were dissolved in 80.0 w/w % ethanolic solution to which CKD-519 was added and agitated until completely dissolved. Mannitol was added to a fluidized-bed granulator (FBCG-1, Chung Jin Tech., Seoul, Korea), and the granules were prepared by spraying the liquid using the top-spray mode. The operating conditions for the fluid bed process were as follows: inlet air temperature 40–50 °C, exhaust air temperature maximum 35 °C, product temperature 25–35 °C, and atomization air pressure 1.5–2.5 bar. CKD-519 SD was prepared by passing the mixture through a 20-mesh sieve. Crospovidone and calcium silicate previously sieved through a 30-mesh screen were added to the above CKD-519 SD and mixed manually for 10 min. Finally, sodium stearyl fumarate (sieved through 30 mesh) was added to the mixture and lubricated for 2 min. The resulting powder was tightly packed in a plastic container and stored in a desiccator until further use. Fig. 2 depicts the flow diagram of the manufacturing process for SD tablets. Tablets were compressed on a single punch tablet press (XP 1, Korsh AG, Germany) with TSM B-type and resulting tablets had the hardness of 4–5 kP.