doses. Volumes of distribution are moderate. Owing to mechanism-based inhibition of human CYP3A and consequent self-inhibition of their clearance, the absorption potential in humans is the more relevant PK parameter for cobicistat and ritonavir. The absorption potential was evaluated in both portal vein-cannulated dogs and rats. The results indicated that the absorption of cobicistat is above 50% in these species, comparable to that of ritonavir. Cobicistat was therefore expected to have high absorption potential in humans.

All of these studies have shown that cobicistat is a potent and selective CYP3A inhibitor that lacks significant anti-HIV activity. *In vitro* studies also suggest that cobicistat may have a lower potential for causing undesired drug–drug interactions and lipid disorders than ritonavir. Based on these results, cobicistat was selected as a clinical candidate for further development.

13.6 Cobicistat as a Pharmacoenhancer in HIV Therapy

13.6.1 Cobicistat Boosting the PK Profile of CYP3A Substrate

Cobicistat was investigated in clinical Phase 1 studies for its safety, tolerability, pharmacokinetics and pharmacodynamics with single- and multiple-escalating oral doses in healthy subjects.[48] Studies showed that cobicistat is generally safe and well tolerated, with mild-grade headache, somnolence and abnormal dreams the most frequently reported drug-related adverse events. It is well absorbed and its PK showed non-linearity, with apparent clearance approaching a nadir after single or multiple dosing at doses >200 mg. More importantly, pharmacodynamic studies confirmed the prediction from the preclinical *in vivo* and *in vitro* investigations that cobicistat is a potent and persistent CYP3A inhibitor. In this Phase 1 study using the CYP3A substrate midazolam as a probe, the CYP3A inhibitory activities of cobicistat and ritonavir were compared. Midazolam maleate was administered at the steady state of cobicistat (50, 100, 200 mg) and ritonavir (100 mg). Cobicistat reduced the clearance of midazolam by 95% when dosed at 200 mg once daily, comparable to that achieved with ritonavir dosed at 100 mg once daily (96%). The persistence of the inhibitory effect of cobicistat was confirmed by the sustained suppression of the formation of the CYP3A-mediated metabolite of midazolam, 1′-hydroxymidazolam. In two independent Phase 1 studies in healthy subjects, the pharmacoenhancing effects of cobicistat on atazanavir and darunavir were compared with that of ritonavir. Atazanavir and darunavir were bioequivalent when administered concomitantly with 150 mg of cobicistat once daily or 100 mg of ritonavir.[56,57] These studies demonstrated that cobicistat is comparable to ritonavir in enhancing the PK profile of a CYP3A substrate.

13.6.2 Cobicistat as a Pharmacoenhancer for Anti-HIV Agents

After demonstrating favorable PK/PD results from Phase 1, cobicistat was investigated in Phase 2 and 3 clinical studies as a pharmacoenhancer for drugs