respectively; C_{trough} was improved to a great extent, whereas the AUC and C_{max} were less affected.[69] More importantly, the asymptomatic grade 4 ALT elevation observed with danoprevir at a dose of 900 mg bid was associated with a high AUC and C_{max}, while its efficacy corresponded with the C_{trough}. Co-administration with ritonavir allows a lower dose of danoprevir to achieve inadequate C_{trough} for therapy but with a much lower AUC and $C_{max.}$ With the standard-of-care PEG-IFNα-2α/ribavirin, danoprevir/ritonavir 200/100 mg twice daily exhibited more potent antiviral activity than danoprevir 900 mg bid.[66] The ritonavir-boosted, low-dose danoprevir regimen is undergoing further clinical studies.

Ritonavir is also used as a pharmacoenhancer for several investigational drugs, including the HIV-1 non-nucleoside reverse transcriptase inhibitor BILR 355 and the HCV NS3 protease inhibitor ABT-405, although no detailed PK data are yet available for either of these two drugs. In the COPILOT study, ABT-450/r, plus ABT-333 and ribavirin administered for 12 weeks showed a sustained virologic response at 12 weeks post-treatment (SVR12) in 93 and 95% of treatment-naïve genotype 1 (GT1) patients. In a separate study, known as PILOT, 91% of GT1-infected, treatment-naive patients taking ABT-450/r and ABT-072 combined with ribavirin, administered for 12 weeks, achieved a sustained viral response at 24 weeks (SVR24).

13.7.2 Novel Pharmacoenhancers

Any novel pharmacoenhancers entering development that can maintain the boosting efficacy of ritonavir but overcome its liabilities, such as anti-HIV activity, adverse lipid profile and poor physical properties, are highly desirable. The development of a new chemical entity as a pharmacoenhancer was first explored with cobicistat, as the benefit of cobicistat (a pharmacoenhancer) can only be demonstrated when it is combined with a therapeutic drug, as itself it has no therapeutic effect. Ritonavir is widely used off-label as a pharmacoenhancer in the treatment of HIV infection, although it was not originally developed as a pharmacoenhancer but as an HIV PI. Cobicistat is now under regulatory review. The current challenge facing the development of a pharmacoenhancer is that a well-defined pathway is not available for advancing it through different stages of clinical studies. Also, if a pharmacoenhancer has successfully obtained regulatory approval for co-administration with a therapeutic drug, it remains unclear what type of clinical studies need to be carried out to secure indications for enhancing the same class therapeutic drugs (the 'boostees') with a similar metabolic pathway. Additionally, it is critical that the novel pharmacoenhancer has a clean chronic safety profile.

There are a number of companies engaged in the discovery and development of novel pharmacoenhancers (Figure 13.14); several are in advanced preclinical stages or in clinical studies. SPI-452 (exact structure not disclosed), a structural derivative of amprenavir, is a novel PK enhancer designed to improve the exposure of co-administered HIV medications to permit less-frequent antiviral drug dosing. Phase 1 clinical studies in combination with HIV medications