placebo. Furthermore, an analysis of resistance provided the first clear information on what has become known as RAL signature mutations: N155, Q148 and Y143, usually in combination with at least one additional mutation, especially in the case of the Q148 pathway, which favors a second G140 mutation to rescue viral fitness.[45–49]

The treatment-naïve patient STARTMRK Phase 3 trial was of non-inferiority design and compared RAL with the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz, both as part of a three-drug regimen that included the two nucleoside RT inhibitors (NRTIs) tenofovir and emtricitabine. This study showed non-inferiority of RAL, with the INI and NNRTI arms achieving 81 and 79% efficacy (<50 copies mL^{-1}) at 96 weeks.[50,51] Similar levels of $CD4^+$ cell increase were also observed.

The above studies clearly establish RAL as a bid option for the treatment of naive or experienced patients and investigators at Merck sought to evaluate further the potential of their new agent. The SWITCHMRK study was an attempt to show efficacious non-inferiority to switching from a protease inhibitor (PI) to the INI RAL.[52] Since PIs have a long history of deleterious effects on lipid profiles, albeit in the face of tremendous efficacy and high genetic barrier to resistance, it would be desirable to have a similar virological outcome without the lipid changes. However, RAL was shown to be inferior to lopinavir/ritonavir at 24 weeks. *Post hoc* analysis showed that if previous failure was taken into account, RAL performed similarly to the PI; unfortunately, this was not considered in the trial designs. The effects on cholesterol and triglycerides, however, were significantly more favorable for the RAL arm. Thus, from an efficacy standpoint, there was still interest in further demonstration of the ability to change from a PI to an INI. A slightly redesigned and smaller study called SPIRAL was undertaken in Spain to revisit the switch challenge. Ultimately, this study did show non-inferior efficacy and improved lipids in a 48 week trial, when patients with sustained suppression for more than 6 months were chosen to switch regimens.[53]

These switch studies, along with the levels of resistance observed, particularly in the BENCHMRK studies, began to create concerns about the genetic barrier to resistance for RAL and perhaps, more broadly, for the class in general.[54] The final major clinical study of note involving RAL was an attempt to gain approval for once-daily dosing.[55] The QDMRK study was designed to compare 400 mg bid with 800 mg qd, with a common backbone of tenofovir/emtricitabine. A fully powered Phase 3 study was planned through 96 weeks of dosing, with primary endpoints at both 48 and 96 weeks. The 48 week analysis showed a slightly inferior performance of the qd arm of the study when all participants were included, with an apparent worsening situation for patients with high viral loads of $>100\,000$ copies mL^{-1} or low $CD4^+$ cell count.

It is interesting to compare the above results with early clinical and preclinical data around the PK profile of RAL. From the healthy volunteer studies, RAL showed a rapid initial (α) elimination phase ($t_{\frac{1}{2}} = 1$ h) and a longer terminal (β) elimination ($t_{\frac{1}{2}} = 7$–12 h).[56] Similar PK was observed in the Phase 2a study, which established antiviral efficacy after 10 days of monotherapy