were given 50 mg qd on top of their existing background regimen for 10 days, followed by OBT on day 11 onwards. A second cohort of 24 patients were dosed under similar conditions, but with 50 mg bid to increase DTG drug levels further and a requirement for at least one fully active background agent. After 10 days with Cohort 1, 21/27 (78%) patients met the primary endpoint of <400 copies mL^{-1} whereas 23/24 (96%) of the Cohort 2 patients achieved the endpoint successfully. After 24 weeks, 41 and 52% of patients in the qd cohort and 75 and 83% of patients in bid cohort achieved plasma HIV RNA levels below either 50 or 400 copies mL^{-1}, respectively.[106,107] These data are critical in addressing the ability of DTG to treat integrase-resistant viruses in an actual clinical environment and serves to validate the preclinical virological data presented above.

Phase 3 evaluation of DTG is well under way at the time of drafting this chapter. Two pivotal trials looking at the treatment-naive population (SPRING-2 and SINGLE) have been reported thus far. SPRING-2 demonstrated that DTG was non-inferior to RAL through 48 weeks of treatment; 88% of study participants on the dolutegravir regimen were virologically suppressed (<50 copies mL^{-1}) *versus* 85% of participants on raltegravir [2.5% adjusted treatment difference, with 95% confidence interval (CI) -2.2% to $+7.1\%$].[108] SINGLE is an ongoing double-blind, double dummy study designed to compare the efficacy and safety of two antiretroviral regimens: dolutegravir 50 mg plus abacavir/lamivudine (Kivexa/Epzicom) *versus* Atripla (tenofovir/emtricitabine/efavirenz). The study demonstrated superiority of the dolutegravir-based regimen over Atripla: at 48 weeks, 88% of study participants on the dolutegravir regimen were virologically suppressed (<50 copies mL^{-1}) *versus* 81% of participants on Atripla [difference 7.4% and 95% CI $+2.5\%$ to $+12.3\%$; the difference in the primary endpoint was statistically significant, $p = 0.003$].[109]

There are also two ongoing studies in the treatment-experienced population. The SAILING study compares DTG 50 mg qd OBT with RAL plus OBT in treatment-experienced patients who are failing in their current therapy. A fourth Phase 3 study, VIKING-3, will explore the effect of DTG treatment (plus OBT) in INI-resistant patients. At this point, DTG is in late-stage clinical evaluation, but sufficient data exist to consider the goals of the discovery program to have been robustly achieved.

6.3.9 Long-acting Parenteral INI – S/GSK744

The potency and resistance profile[110] of S/GSK744 also makes it a very intriguing drug. A multipart Phase 1 study was conducted that included a cohort of HIV patients and also healthy volunteers to assess both efficacy and human pharmacokinetics, in addition to safety and tolerability data. In this study, subjects were given doses of 5, 10 and 25 mg once daily for 14 days and showed a near 30 h half life, with robust coverage of the $PAIC_{90}$ value determined as 166 ng mL^{-1}. Even at the 5 mg dose, several multiples of exposure over the clinical target were observed through 72 h. In the monotherapy cohort,