was not a case of everything being equal. Different PK properties and C_{trough} efficacy targets led us to consider whether perhaps one of these compounds did have an advantage that we had not yet accounted for in preclinical studies. Consequently, both compounds continued to proceed. In the end, the lower clinical target of **3** made it the priority and it quickly gained speed over the remaining compound **4**. There were some concerns about the protein shift and higher C_{trough} target for **4**, but these properties have thus far proven to be significant attributes, albeit with far fewer data in hand than for **3**. A description of how **4** is being developed is described in the next section. Compound **3** ultimately became what is known as dolutegravir (DTG, S/GSK1349572) and compound **4** is known as S/GSK1265744 (S/GSK744).

6.3.8 Clinical Development of Dolutegravir

Early Phase 1 clinical data for DTG demonstrated a 15 h half-life while producing a 25-fold coverage of the $PAIC_{90}$ *versus* C_{trough} from a 50 mg once-daily dose, without the need for a boosting agent.[96] These data were translated into a study design whereby once-daily doses of 2, 10 and 50 mg were given for 10 days as monotherapy to HIV-infected patients who were treatment-naive or off-therapy experienced during a Phase 2a proof-of-concept study. The results from these doses showed $\log_{10}$ viral load decreases in HIV-1 RNA copies per milliliter of plasma of 1.51, 2.03 and 2.46, respectively (Figure 6.10).[97] DTG was well tolerated during these studies while delivering an excellent impact on

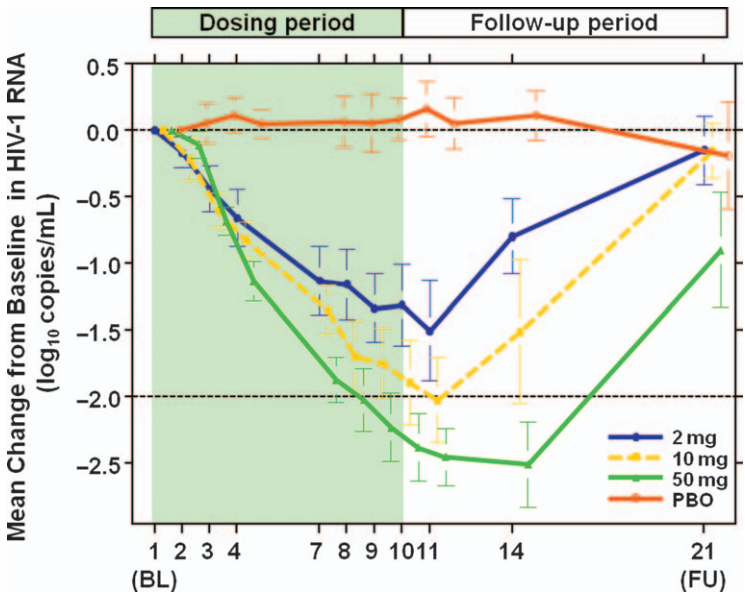

Figure 6.10 Phase 2a 10 day monotherapy viral load data for DTG.