MODULE 2.6.1. INTRODUCTION

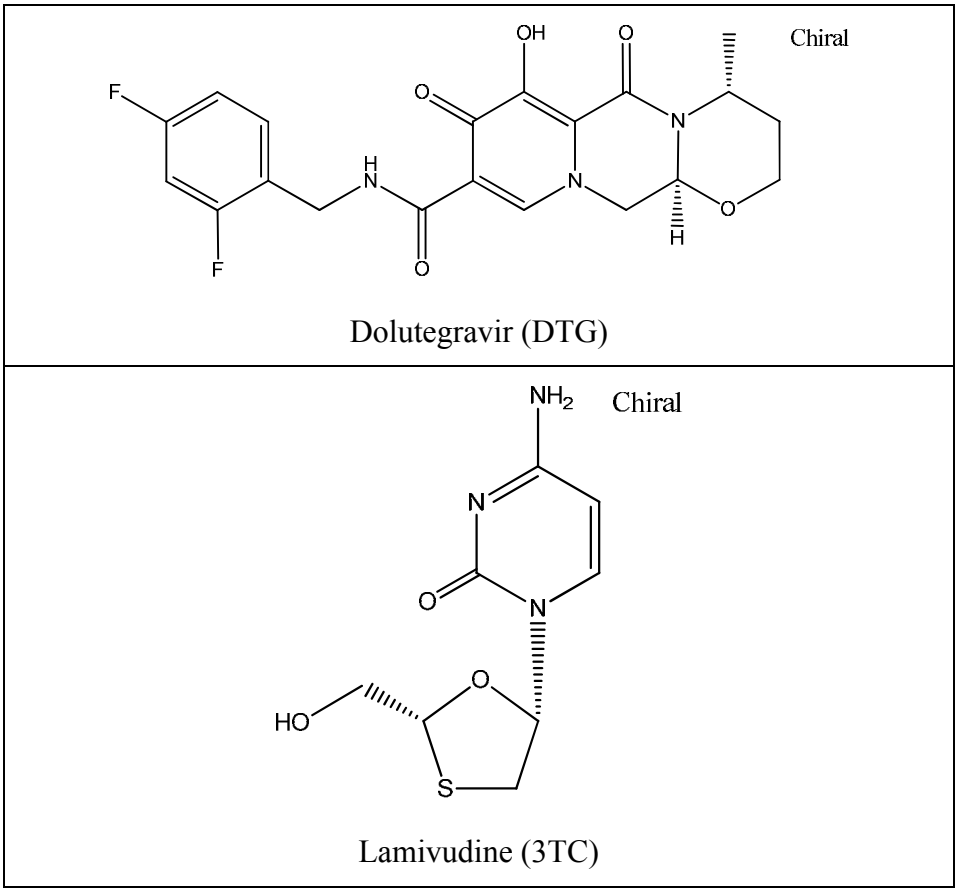
Dolutegravir (DTG; GSK1349572) is a human immunodeficiency virus (HIV-1) integrase strand transfer inhibitor (INSTI) approved for use in antiretroviral treatment-naïve and treatment-experienced HIV-infected adults and children weighing at least 30 kg (TIVICAY®). Lamivudine (3TC; GR109714X) is a nucleoside reverse transcriptase inhibitor (NRTI), also approved for treatment of HIV-1 infection in combination with other antiretroviral therapy (ART) (EPIVIR®), in adults and children weighing at least 14 kg (see Table 1).

DTG is a potent, selective and novel INSTI and 3TC is a potent cytidine NRTI. The DTG/3TC fixed dose combination (FDC) is a two-drug regimen for use as a complete regimen for the treatment of HIV-1 infection, differing from the current standard of care, which typically includes 2 NRTIs plus a third agent from the protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or INSTI classes. The proposed new combination treatment regimen of DTG and 3TC targets HIV at the early and late stage of the virus life cycle, respectively, resulting in suppression of HIV-1 replication in a substantial proportion of infected cells. See Figure 1 for the structures of DTG and 3TC.

Table 1 FDA Approvals of Dolutegravir and Lamivudine

Product	Approval Date	NDA Number
TIVICAY (Dolutegravir 50 mg)	12 August 2013	NDA 204790
EPIVIR (Lamivudine 300 mg)	17 November 1995	NDA 020564

Figure 1 Structure of DTG and 3TC



Where dolutegravir and lamivudine have been approved as monotherapies or in combination in the treatment of HIV-1, comprehensive packages of nonclinical pharmacodynamic, pharmacokinetic and toxicological evaluations have been submitted along with nonclinical study reports (see Table 1 for NDA numbers).

In agreement with ICH Guidance M3 (R2), nonclinical combination studies have not been conducted with DTG/3TC.

Studies described in m2.6 were performed using either the sodium salt form of dolutegravir or base (parent) of lamivudine. All dosages and concentrations quoted are expressed in terms of the parent compounds (referred to simply as dolutegravir or DTG and lamivudine or 3TC).

The new pharmacokinetic study summaries are provided in m2.6.4 and m2.6.5 and the corresponding company reports are located in m4.2, Study Reports.

Filing Strategy

The nonclinical pharmacokinetic study summaries presented in m2.6.4 and m2.6.5 are new monotherapy nonclinical studies which have not been previously submitted.