## MODULE 2.2 - INTRODUCTION

Integrase inhibitors (INIs) are a class of antiretroviral agents designed to block the action of the Human Immunodeficiency Virus (HIV) integrase (IN) viral enzyme, which is responsible for insertion of the viral genome into host cell DNA. Dolutegravir (DTG, GSK1349572) is an orally administered, 2-metal binding integrase inhibitor (INI) being developed for the treatment of HIV infection. Dolutegravir is owned by ViiV Healthcare, who are working with GlaxoSmithKline LLC (GSK) to develop the product.

The proposed tradename for dolutegravir is TIVICAY™. To date, TIVICAY has not received marketing approval for any indication in any market. This marketing application is for TIVICAY 50 mg tablets. The proposed indication for dolutegravir is for the treatment of HIV infection in adults and children (aged 12 to 18 years and weighing ≥ 40kg) in combination with other antiretroviral agents.

The Sponsor obtained advice from the Committee for Medicinal Products for Human Use (CHMP) on the DTG development program on three separate occasions ( , and ). Advice from CHMP was obtained on the , and . More recently, pre-submission meetings were held with the Rapporteur [Sweden, Medical Products Agency (MPA)] and co-Rapporteur [France, National Security Agency of Medicines and Health Products (ANSM)] in . A Paediatric Investigation Plan (PIP), which includes and , has been agreed with the Paediatric Committee (PDCO).

The Sponsor engaged FDA's Division of Antiviral Products (DAVP) to discuss the DTG development program on multiple occasions. Major regulatory milestones occurred as .

The DTG submission package contains data supporting the benefit risk assessment across the treatment spectrum, from integrase inhibitor (INI)-experienced adults with few treatment options, through moderately treatment experienced adults (INI-naive) and treatment naive adults to treatment experienced, INI-naive adolescents.

Results of clinical studies to date show that dolutegravir provides a significant improvement compared to currently marketed products. Summary points of the clinical data are provided below.

- The dose of DTG is 50 mg once daily in treatment naive and treatment experienced, INI-naive, HIV-infected adults. The DTG dose is 50 mg twice daily in INI-resistant subjects.
- The dose of DTG in INI-naive children 12 to 18 years old, weighing ≥40 kg, is 50 mg once daily.

- Dolutegravir can be taken with or without food based on results from a food effect study and the accumulated safety data in Phase IIb and III studies which permitted DTG dosing without regard to food.
- Dolutegravir is primarily metabolized via UGT1A1 with a minor CYP3A component (approximately 10-15% in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged drug is low (<1% of the dose). Dolutegravir is highly protein bound.
- The pharmacokinetic (PK) variability of DTG is low to moderate leading to predictable exposures in HIV-infected patients, including key sub-populations.
- Dolutegravir has been evaluated in a series of drug interaction studies and does not require dose adjustment for most co-administered drugs. Strong inducers of UGT1A1 and/or CYP3A4 (efavirenz, tipranavir/ritonavir, and rifampin) reduced the plasma concentrations of DTG; the recommended dose of DTG is 50 mg twice daily when co-administered with these drugs. The effect of etravirine, another potent inducer of DTG, is mitigated by co-administration of lopinavir/ritonavir, atazanavir/ritonavir and darunavir/ritonavir.
- Dolutegravir 50 mg QD has been studied in 2 Phase III, double-blind, double-dummy non-inferiority studies in treatment-naive subjects, ING113086 and ING114467.
    - In ING113086, DTG, administered with two nucleoside reverse transcriptase inhibitors (NRTIs), demonstrated non-inferiority to raltegravir (RAL) at Week 48; 88% vs. 85%, of DTG and RAL subjects, respectively, achieved the primary endpoint of HIV-1 RNA <50 copies/mL (c/mL) (FDA "Snapshot" algorithm).
    - ING114467 compared DTG co-administered with ABC/3TC to Atripla™ [efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF)]. The DTG regimen demonstrated superiority compared to Atripla, 88% vs. 81% (p=0.003), based on proportion of subjects achieving the primary endpoint. The statistically significant difference in response rates noted in ING114467 was primarily due to fewer discontinuations due to adverse events (AEs) on the DTG regimen.
    - Sensitivity and subgroup analyses were supportive of the primary analyses in each study and did not identify subgroups at risk of diminished benefit on DTG.
- In ING111762, DTG was administered once daily compared to RAL 400mg twice daily both in combination with a background regimen consisting of one to two (1-2) fully active agents in HIV-1 infected, INI-naïve, therapy-experienced subjects. The primary efficacy analysis will be conducted at 48 weeks. Secondary safety and efficacy objectives were analyzed at 24 weeks. There was a statistically significant difference in response rates in favor of DTG (79%) over RAL (70%) using the Snapshot (MSDF) algorithm for the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 [adjusted treatment difference (DTG-RAL): 9.7%; 95% CI: (3.4, 15.9), p=0.003]. Additional subgroup and sensitivity analyses were consistent and supportive of this result, with the exception of subgroups who experienced particularly high responses on RAL [e.g., PI-sensitive subjects receiving darunavir/ritonavir (DRV/r)].
- Dolutegravir 50 mg once daily has a higher barrier to resistance in INI-naïve patients.

  - In treatment-naive population: Data from two studies including over 1600 treatment-naïve patients are supportive of DTG's higher barrier to resistance, given that no subjects on the DTG regimen developed resistance to either the INI or the background NRTIs, whereas resistance to both the third agent and the background NRTIs was observed in both the RAL and EFV-based comparator arms. In addition, no treatment emergent resistance has been observed (to 96 weeks) on DTG 50mg in the dose-ranging Phase IIb study.
  - In the treatment-experienced (INI-naïve) population: significantly fewer virologic failures and significantly fewer subjects with INI resistance (in addition to less treatment-emergent resistance to the background regimens) were observed when compared with RAL.
- Dolutegravir showed activity in most subjects with INI resistance.
  - ING112574 was a single arm study of DTG in integrase resistant patients with the primary endpoint comprised of the change from baseline in plasma HIV-1 RNA at Day 8 and an assessment of the proportion of subjects with <50 c/mL HIV-1 RNA at Week 24. In subjects who had the opportunity to reach Week 24 before the data cut-off, 63% of this Week 24 ITT-E population (N=114) achieved viral suppression to <50 c/mL based on the Snapshot algorithm.
  - In ING112574, genotypic grouping based on the 148 pathway was more predictive of response to DTG than phenotypic fold change.
- The safety profile for DTG including adverse events (AEs), drug related discontinuations, serious adverse events and deaths is favorable when compared across all treatment populations and comparator antiretroviral agents (ARVs) and at higher (i.e., 50 mg twice daily) doses. The most frequently observed AEs across patient populations were diarrhea, nausea, and headache, which were typically Grade 1 or 2 in severity and typically did not lead to discontinuation from studies.
  - For subjects with hepatitis B or C co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses, along with inadequate therapy for hepatitis B co-infected subjects, likely contributed to an imbalance in significant elevations in liver chemistries in study ING111762. As several subjects were allowed to restart DTG or continued DTG without progression of liver enzyme elevations, drug-induced liver injury in this setting seems less likely as the cause of the imbalance in liver chemistry elevations in this patient population.
- The safety profile in children 12-18 years old was comparable to that in adults.
- Dolutegravir causes predictable, reversible increases in serum creatinine without affecting glomerular filtration. The mechanism for this likely benign clinical finding is the inhibition of the creatinine secretion at the OCT-2 transporter in the proximal tubule. There has been no increase in clinical renal events associated with this finding or laboratory signs of proximal tubular nephropathy regardless of NRTI backbone.
- The results from four pivotal studies (studies ING113086, ING114467, ING112574 and ING111762) provide substantial evidence of the safety and effectiveness of dolutegravir as a treatment for HIV-1infection in combination with other antiretroviral agents.