MODULE 2.2 – INTRODUCTION

The use of nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimens for the long-term treatment of human immunodeficiency virus (HIV) infection has the potential to avoid known NRTI-associated adverse drug reactions and long-term toxicities. Treatment simplification has long been a goal to increase treatment compliance and improve the quality of life for patients with HIV. Currently there are no approved two-drug regimens to maintain suppression.

ViiV Healthcare, in partnership with GlaxoSmithKline (GSK) and Janssen, is developing GSK3365791 (dolutegravir [DTG, GSK1349572] and rilpivirine [RPV, TMC278, GSK1329758] fixed-dose combination [FDC] tablets for the treatment of human immunodeficiency virus-1 (HIV-1) infection in virologically suppressed (HIV-1 <50 copies/mL) adults without known or suspected resistance to either component. As individual agents, both DTG and RPV are currently approved products marketed as TIVICAY (held by ViiV Healthcare) and EDURANT (held by Janssen), respectively. Based on the established tolerability and combined resistance profiles of DTG and RPV, this simplified two-drug regimen offers favorable tolerability and suppression of resistance similar to other DTG-based HIV-1 treatment regimens. At this time, ViiV Healthcare is seeking marketing approval for the combined use of DTG and RPV for the aforementioned indication.

The DTG + RPV regimen currently under development and the subject of this marketing application, is a two-drug, "NRTI-sparing" regimen, differing from the current standard of care, which typically includes 2 NRTIs plus a third agent from the protease inhibitor (PI), NNRTI, or INSTI classes. NRTI-based therapies, while highly effective and largely well-tolerated, have associated long-term toxicities, including lactic acidosis risks and bone and kidney changes [Carr, 2003]. As the population with HIV ages, new treatment options with fewer long-term toxicities are needed. The development of new safe and efficacious drugs continues, with individual profiles being evaluated within the context of combination treatment regimens. The proposed new combination treatment regimen of DTG and RPV targets HIV replication at the early and late stage of the virus life cycle, respectively, and results in suppression of HIV-1 replication in a substantial proportion of infected cells.

The proposed tradename for the DTG/RPV FDC is JULUCA. To date, the DTG/RPV FDC has not received marketing approval for any indication in any market. This marketing application is for DTG and RPV 50/25 mg tablets for the proposed indication of the treatment of human immunodeficiency virus-1 (HIV-1) infection in virologically suppressed (HIV-1 <50 copies/mL) adults without known or suspected resistance to either component.

The Sponsor engaged the US FDA's Division of Antiviral Products (DAVP) on several occasions to discuss the DTG/RPV FDC development program. Major regulatory milestones occurred as [redacted]. [redacted] was agreed with the US FDA in [redacted], and includes [redacted] under the [redacted] in [redacted].

The Sponsor also obtained advice from the Committee for Medicinal Products for Human Use (CHMP) regarding the DTG/RPV FDC development program in [redacted]. Advice was obtained on the [redacted], [redacted] and [redacted]. More recently, pre-submission meetings were held with the EMA ([redacted]), the Rapporteur (Germany, Federal Institute for Drugs and Medical Devices, [BfArM]) and co-Rapporteur (Netherlands, Medicines Evaluation Board [MEB]) in [redacted]. [redacted] ([redacted]), which includes [redacted], has been agreed with the [redacted] ([redacted]).

To support the proposed indication for the DTG + RPV combined regimen, the following pivotal clinical investigations of DTG and RPV used in combination are included in this submission package:

- Phase 3 Clinical Studies 201636 (SWORD-1) and 201637 (SWORD-2), which demonstrated the safety of the DTG + RPV combined regimen as well as the non-inferior antiviral activity of switching to the DTG + RPV combined regimen compared to continuation of current antiviral regimen over 48 weeks in HIV-1 infected antiretroviral treatment-experienced subjects (Week 48 safety and efficacy analysis individual and pooled);
- Sub-study 202094 (DEXA Bone Density Evaluation), which evaluated the change in bone mineral density assessed by areal density in total hip at 48 weeks following switch of subjects from an ART regimen containing tenofovir disoproxil fumarate (TDF) to DTG + RPV once daily compared to continued therapy with the TDF-containing regimen (Week 48 analysis);
- Study 201674 (Relative Bioavailability [RBA] and Food Effect Study), which evaluated the relative bioavailability in the fed and fasted states of a single dose of DTG 50 mg and RPV 25 mg as a FDC tablet compared to co-administration of a single dose of the single-entity DTG and RPV products [Part 1], as well as the effect of food on the bioavailability of selected FDC formulation(s) of DTG and RPV [Part 2];
- Study 201676 (Pivotal Bioequivalence [BE] Study), which demonstrated the bioequivalence of the proposed DTG/RPV FDC to the corresponding DTG and RPV single entities used in Phase III trials 201636 (SWORD-1) and 201637 (SWORD-2).

This submission also provides information regarding the nonclinical development, and includes a complete body of data for Chemistry, Manufacturing, and Controls information to support the DTG/RPV FDC tablet 50mg/25mg.

In summary, the data collected in the development program suggest that the proposed DTG/RPV FDC is safe and effective for the proposed indication.