MODULE 2.2 - INTRODUCTION

A once-daily fixed-dose combination (FDC) single-tablet regimen (STR) that combines the integrase inhibitor (INI) dolutegravir (DTG) with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir sulfate (abacavir, ABC) and lamivudine (3TC) is being developed for use in the treatment of human immunodeficiency virus (HIV) infection.

Dolutegravir is a novel INI owned by ViiV Healthcare, who is working with GlaxoSmithKline (GSK) to develop the product. It is a potent, low nanomolar inhibitor of HIV integrase that provides the excellent antiviral activity and tolerability demonstrated for the INI class, while also offering once-daily dosing without the need for pharmacokinetic (PK) boosting. Co-formulated ABC 600 mg/3TC 300 mg is already available as a once-daily FDC indicated for the treatment of HIV infection as part of antiretroviral combination therapy, which is marketed as KIVEXA (EPZICOM in the US and Japan).

The new STR being developed is a FDC of DTG 50 mg + ABC 600 mg + 3TC 300 mg with once-daily dosing for antiretroviral therapy (ART)-naïve and ART-experienced (INI-naïve) patients, and is referred to in this document as the DTG/ABC/3TC FDC.

The proposed tradename for DTG/ABC/3TC FDC is TRIUMEQ™. To date, DTG/ABC/3TC FDC has not received marketing approval for any indication in any market. This marketing application is for DTG/ABC/3TC FDC 50/600/300 mg tablets. The proposed indication is for DTG/ABC/3TC FDC as a complete regimen for the treatment of HIV infection in adults without known mutations associated with resistance to any of the three antiretroviral agents. In regions where ABC/3TC FDC is approved in adolescents, an indication for DTG/ABC/3TC FDC is also sought in adolescents 12-18 years weighing greater than 40kg.

The Sponsor obtained advice from the Committee for Medicinal Products for Human Use (CHMP) on the DTG development program which encompassed the DTG/ABC/3TC FDC on three separate occasions ([redacted], [redacted] and [redacted]). Advice from CHMP was obtained on the [redacted], [redacted] and [redacted] More recently, pre-submission meetings were held with the EMA ([redacted]), the Rapporteur [Sweden, Medical Products Agency (MPA)] and co-Rapporteur [Netherlands, (Medicines Evaluation Board)] in [redacted] A Paediatric Investigation Plan (PIP), which includes [redacted] and [redacted] has been agreed with the Paediatric Committee (PDCO).

The Sponsor engaged FDA's Division of Antiviral Products (DAVP) to discuss the DTG/ABC/3TC FDC development program on multiple occasions. Major regulatory milestones occurred as [redacted] and [redacted], [redacted] ([redacted]).

The DTG/ABC/3TC FDC submission package contains data supporting the benefit: risk assessment across the treatment spectrum, from antiretroviral treatment (ART)-naïve adults to ART-experienced, INI- naïve adults and adolescents.

Results of clinical studies to date show that DTG/ABC/3TC FDC provides a significant improvement compared to currently marketed products. Summary points of the clinical data are provided below.

For ART-naïve patients, efficacy data in this submission establish the following:

- Superiority of DTG + ABC/3TC over EFV/TDF/FTC (Atripla), the recommended first-line therapy in US Department of Health and Human Services (DHHS), European AIDS Clinical Society (EACS), World Health Organization (WHO), and other treatment guidelines for HIV-1-infected, ART-naïve subjects, was demonstrated at both Week 48 and 96 in ING114467, the pivotal trial supporting efficacy for the DTG/ABC/3TC FDC.
    - Differences in efficacy were primarily driven by a lower rate of discontinuation due to AEs on the DTG + ABC/3TC arm.
    - ING114467 Week 48 (the time point for the primary endpoint analysis) treatment differences between DTG + ABC/3TC and EFV/TDF/FTC were consistent across the Baseline stratification factors.
    - The results from the pivotal study ING114467 demonstrate that a treatment regimen with an ABC/3TC NRTI backbone is at least as effective as treatment regimens with TDF/FTC, including subjects with a Baseline viral load >100,000 c/mL.
- Data from the subgroups of subjects in ING113086 and ING114915 who initiated DTG + ABC/3TC support the pivotal study data, with response rates at Week 48 that were similar to those observed for the DTG + ABC/3TC arm of ING114467.
- In studies ING113086 and ING114915, the efficacy at Week 96 and Week 48, respectively, was consistent when the investigator selected either ABC/3TC or TDF/FTC as the NRTI backbone.

For ART-experienced, INI-naïve patients, efficacy data in this submission establish the following:

- ING111762 provides efficacy support for the use of DTG-based therapy in the ART-experienced (INI-naïve) patient population, however <10 patients received the DTG+ABC/3TC regimen in this study.
    - Efficacy in ING111762 was driven by DTG vs. RAL. There was a wide range of OBR selected for use with either drug; however, DTG paired with any effective OBR demonstrated efficacy in this patient population.
    - Data from ING111762 are supportive of an indication in ART-experienced patients for DTG alone.
- Abacavir and lamivudine single entity products and the ABC/3TC FDC are all indicated in multiple markets for the treatment HIV infection in ART-experienced patients
- The broad indication of the constituent antiretroviral agents combined with confirmatory bioequivalence data (ING114580) establishes the efficacy of

DTG/ABC/3TC FDC across all patients with HIV infection without resistance to the components.

- Based on this information, in treatment-experienced subjects without INI or ABC resistance, the DTG/ABC/3TC FDC should provide effective therapy.

The DTG/ABC/3TC 50/600/300 mg FDC comprises a new chemical entity, DTG, plus two well-established marketed products, ABC and 3TC. The safety and efficacy profile of the component drug DTG has been established through the DTG clinical program. The safety and efficacy profiles of ABC and 3TC are well defined and supported by years of post-marketing experience and extensive clinical trial data. As found in the ING114580 bioequivalence study, there is no difference in exposure of component drugs when they are dosed as an FDC. The data collected in the clinical program suggests that in INI-naïve (treatment-naïve or treatment-experienced) adult patients without resistance to its components, DTG/ABC/3TC FDC dosed once daily is safe and effective.