MODULE 2.2 – INTRODUCTION

Antiretroviral treatment failure and drug resistance arise from many factors, among them suboptimal drug efficacy and/or variable pharmacokinetics, inadequate compliance to life-long therapy, pre-existing drug resistance and chronic drug toxicities. Novel approaches to improve therapy compliance may address some of these issues. Fixed-dose combinations (FDCs) have greatly advanced human immunodeficiency virus (HIV) treatment by allowing simplification of dosing and reducing pill burden. Among regimens of comparable efficacy, physicians and HIV type1 (HIV-1)-infected subjects who receive antiretroviral therapy (ART) rate total pill burden, dosing frequency, and safety concerns among the greatest obstacles to achieving adherence. Incomplete adherence may lead to the emergence of drug-resistant virus that can lead to the loss of virologic control and reverse the benefits of ART.

Alternative HIV treatment modalities are being developed to help improve adherence and subject outcomes, and to prevent the emergence of resistance and transmission of the virus. Long-acting antiretroviral agents capable of being administered on an infrequent basis (e.g., once a month or once every two months) may improve adherence to therapy and extend opportunities for therapeutic intervention to underserved patient populations. There is also an increasing desire to develop nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimens that avoid long-term NRTI-associated adverse drug reactions, including renal, hepatic, bone, and cardiovascular toxicities. In addition, simplifying treatment has long been a goal to increase treatment compliance and improve the quality of life for subjects with HIV.

ViiV Healthcare, in partnership with GlaxoSmithKline and Janssen, is developing cabotegravir (CAB) and rilpivirine (RPV) oral tablets and long-acting injections for the treatment of HIV-1 infection. CAB is a potent integrase inhibitor (INI) that can be formulated and delivered as a long-acting (LA) parenteral product. RPV, which can also be formulated as a LA product, is a diarylpyrimidine derivative and a non-NRTI (NNRTI) with in vitro activity against wild type HIV-1 and select NNRTI-resistant mutants.

VOCABRIA is the proposed tradename for both formulations of CAB, CAB LA (400mg and 600mg prolonged-release suspensions for injection) and CAB 30 mg film-coated tablets. VOCABRIA tablets should be administered in combination with RPV oral tablets [registered as EDURANT] for oral lead-in (OLI) and oral bridging (referred to as *oral therapy for adults who will miss planned dosing with Vocabria injection plus rilpivirine injection* in labelling) dosing prior to initiating injections. VOCABRIA injection should be administered with RPV injection once a month or once every two months, depending on the dosing regimen, for maintenance therapy.

To support the proposed indication for CAB/RPV oral tablet and injection regimens, Week 48 (primary endpoint) data from two pivotal non-inferiority switch studies, FLAIR and ATLAS, and the Phase IIIb study, ATLAS-2M, are included in the submission package:

- In the Phase III clinical study 201584 (FLAIR), a total of 283 HIV-infected subjects have received CAB 30 mg once daily with RPV 25 mg once daily as oral lead-in therapy prior to initiation of injections. Of these subjects, 278 have also received CAB LA + RPV LA injections (dosed every 4-weeks; Q4W, monthly) during the Maintenance Phase (also referred to as the Continuation Phase) of the study.
- In the Phase III clinical study 201585 (ATLAS), a total of 308 HIV-infected subjects entered the Maintenance Phase and received CAB 30 mg once daily and RPV 25 mg once daily as oral lead-in therapy prior to initiation of monthly injections. Of the 308 subjects who received OLI, 303 transitioned to receive CAB + RPV LA injections (dosed Q4W). Of the 308 subjects that entered the Maintenance Phase, 282 successfully completed and 26 subjects withdrew. Participants in the ATLAS study who completed the Week 52 visit were eligible to enroll into study 207966 (ATLAS-2M; described below).
- In the Phase IIIb study ATLAS-2M, a total of 1049 virologically-suppressed (HIV-1 RNA <50 copies/mL) subjects already enrolled in the ATLAS study, on either an injectable regimen of CAB LA + RPV LA (monthly dosing; subjects transitioned from ATLAS following Week 52) or current antiretroviral regimen (CAR) were randomized 1:1 into the 2-monthly intramuscular (IM) or monthly IM arm.

The following supporting clinical investigations are also included in the submission package:

- In Phase IIb study LAI116482 (LATTE), a total of 181 HIV-infected, antiretroviral-naive subjects received oral CAB 10 mg, 30 mg, or 60 mg with 2 nucleoside background ARTs (ABC/3TC or TDF/FTC).
- In Phase IIb study 200056 (LATTE-2), a total of 309 HIV-infected, antiretroviral-naive subjects have received oral CAB 30 mg with 2 nucleoside background ARTs (ABC/3TC, unless HLA-B*5701 positive). A total of 286 subjects which initiated maintenance treatment and 258 subjects which completed the Maintenance Period.

This Application provides information regarding CAB nonclinical development, as well as a complete body of data for Chemistry, Manufacturing and Controls information to support both the CAB tablets and injections.

In summary, the data generated in the development program suggest that the proposed CAB (in combination with RPV) dosing regimens are safe and effective for the proposed indication.