SCIENTIFIC DISCUSSION SUPPLEMENT

1. Introduction

A new BE study was necessitated due to a Notice of Concern (NOC) issued by WHO Prequalification Unit relating to the implementation status of Good Clinical Practices standards at Panexcell Clinical Lab Private Limited, Navi Mumbai on October 2020.

WHO/PQT has requested applicants of the affected products to review the impact of these findings and take actions to confirm bioequivalence of their products.

This supplement therefore includes the submission and review outcome of a new BE study for HA731.

2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

There have been no material changes to the Quality aspects and the content remains unchanged.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2021 according to internationally accepted guidelines.

An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period cross-over, oral bioequivalence study comparing Dolutegravir tablets 50mg of Strides Pharma Science Limited, India with Tivicay® (dolutegravir) tablets 50mg of Viiv HealthCare, Research triangle park, NC 27709, United States in healthy, adult, human subjects under fasting conditions (study 009-20).

The objective of the study was to compare the bioavailability of the stated Dolutegravir 50 mg tablet manufactured by/for Strides Pharma Science Limited, India (test drug) with the reference formulation Tivicay® 50 mg tablet (Viiv HealthCare) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Dolutegravir 50 mg (dolutegravir 50 mg) Batch no. 7245252.
Treatment R:	Reference – 1 tablet Tivicay® 50 mg (dolutegravir 50 mg) Batch no. E76Y.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 29 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug

concentrations for dolutegravir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 20 ng/ml for dolutegravir.

The study was performed with 72 participants; data generated from a total of 71 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for dolutegravir as well as statistical results are summarised in the following table:

Dolutegravir

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	2.81 ± 1.35	3.08 ± 2.02	–	–
C_{max} (ng/mL)	2853 ± 1062 (2667)	3093 ± 1219 (2875)	92.8	86.1 – 99.9
AUC_{0-t} (ng·h/mL)	57733 ± 23125 (53278)	60570 ± 23043 (56856)	93.7	87.6 – 100.3
AUC_{0-inf} (ng·h/mL)	61629 ± 25612 (56515)	64458 ± 25031 (60306)	93.7	87.7 – 100.2

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding dolutegravir. Accordingly, the test Dolutegravir 50 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Tivicay® 50 mg tablet (Viiv Health Care).

4. Summary of product safety and efficacy

[HA731 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [HA731 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Tivicay® (Viiv Health Care) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA731 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [HA731 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA731 trade name] has been shown to be bioequivalent with Tivicay® (Viiv Health Care).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA731 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA731 trade name] was acceptable for the following indication: 'in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infection in patients weighing at least 20kg', and would allow inclusion of [HA731 trade name], manufactured at Strides Pharma Science Limited KRS Gardens 36/7,Suragajakkanahalli, Indlawadi cross Anekal Taluk, Bangalore, Karnataka, 562 106, India in the list of prequalified medicinal products.