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 Accutest Research Laboratories (I) Private Limited (Unit-I) Ahmedabad, India in February 2018.

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 HA715.

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 2023 according to internationally accepted guidelines.

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover bioequivalence study of [HA715 trade name] manufactured by Lupin Limited, India with Truvada® (emtricitabine and tenofovir disoproxil fumarate) 200 mg/300 mg tablets manufactured by Gilead sciences Inc., Foster City, CA 94404, in normal, healthy, adult, male and female human subjects under fasting conditions (study no. ARL/23/006).

The objective of the study was to compare the bioavailability of the stated [HA715 trade name] manufactured by/for Lupin Limited, India (test drug) with the reference formulation Truvada® (Gilead Sciences Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, 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 [HA715 trade name] (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) Batch no. M300091.
Treatment R:	Reference – 1 tablet Truvada® (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) Batch no. 0035808.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 samples within 72h post dose) were taken during each study period

to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for emtricitabine and tenofovir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 40 ng/mL for emtricitabine and 5 ng/mL for tenofovir.

The study was performed with 28 participants; data generated from a total of 27 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for emtricitabine and tenofovir as well as statistical results are summarised in the following tables:

Emtricitabine

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)#	1.33 (0.67 – 3.00)	1.33 (1.00 – 3.00)	-	-
C_{max} (ng/mL)	2413 ± 680 (2317)	2543 ± 546 (2481)	93.4	86.5 – 100.9
AUC_{0-t} (ng.h/mL)	11968 ± 2543 (11651)	12626 ± 2187 (12438)	93.7	87.2 – 100.6
AUC_{0-inf} (ng.h/mL)	12345 ± 2542 --	12300 ± 2164 --	-	-

median (min-max)

Tenofovir

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)#	1.00 (0.67 – 2.67)	1.00 (0.67 – 3.00)	-	-
C_{max} (ng/mL)	317 ± 117 (296)	307 ± 91 (290)	102.1	92.2 – 113.1
AUC_{0-t} (ng.h/mL)	2209 ± 693 (2099)	2301 ± 646 (2193)	95.7	88.2 – 103.9
AUC_{0-inf} (ng.h/mL)	2436 ± 723 --	2524 ± 657 --	-	-

median (min-max)

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding emtricitabine and tenofovir. Accordingly, the test [HA715 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Truvada® (Gilead Sciences Inc.).

4. Summary of product safety and efficacy

[HA715 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, [HA715 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Truvada® (Gilead Sciences Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA715 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 of bioequivalence study

Bioequivalence

[HA715 trade name] has been shown to be bioequivalent with Truvada® (Gilead Sciences, Inc.).