SCIENTIFIC DISCUSSION SUPPLEMENT

1. Introduction

A Notice of Concern was issued by WHO Prequalification Unit relating to the implementation status of Good Clinical Practices standards at Semler Research Centre Private Ltd, Bangalore, India

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 TB199.

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 2017 according to internationally accepted guidelines:

An open label, randomized, balanced, single dose, two treatment, two period, two sequence, two-way crossover oral bioequivalence study comparing Fixed dose combination of Rifampin 150 mg, Isoniazid 75 mg and Ethambutol Hydrochloride 275 mg tablets (1 x 4 tablets) of Lupin Limited, India with separate formulation of Rifamate® (rifampin 300 mg and isoniazid 150 mg) capsules (1 x 2 capsules) of Sanofi Aventis, USA and Myambutol® (ethambutol hydrochloride) tablets 400 mg (1 x 3 tablets) of Riemser Arzneimittel, Germany, in healthy adult human male subjects, under fasting conditions (study no. SLS-CL-0126-17).

The objective of the study was to compare the bioavailability of the stated Ethambutol/Isoniazid/Rifampin 275mg/75mg/150mg FDC tablet manufactured by/for Lupin Limited, India (test drug) with the reference formulations Myambutol® (Riemser Arzneimittel) and Rifamate® (Sanofi Aventis) 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 – 4 tablets Ethambutol/Isoniazid/Rifampin 275mg/75mg/150mg (ethambutol 1100 mg + isoniazid 300 mg + rifampin 600 mg) Batch no. A702281.
Treatment R:	Reference – 3 tablets Myambutol® (ethambutol 1200 mg)

Batch no. D851
– 2 capsules Rifamate®
(isoniazid 300 mg + rifampin 600 mg)
Batch no. 3141415.

A 7-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 21 samples within 48h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for ethambutol, isoniazid and rifampin were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 30 ng/ml for ethambutol, 60 ng/ml for isoniazid and 26 ng/ml for rifampin.

The study was performed with 60 participants; data generated from a total of 56 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for ethambutol, isoniazid and rifampin as well as statistical results are summarised in the following tables:

Ethambutol

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	3.56 ± 1.00	3.22 ± 0.92	-	-
C_{max} (µg/ml)	3.09 ± 1.20 (2.90)	3.34 ± 1.09 (3.16)	91.5	85.3 – 98.1
AUC_{0-t} (µg.h/ml)	17.1 ± 4.3 (16.6)	18.0 ± 4.0 (17.6)	94.4	91.1 – 97.8
AUC_{0-inf} (µg.h/ml)	19.1 ± 4.6 (18.6)	20.1 ± 4.3 (19.6)	94.8	91.8 – 97.9

* geometric mean (dose normalised)

Isoniazid

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	1.15 ± 0.70	0.88 ± 0.64	-	-
C_{max} (ng/ml)	6266 ± 2210 (5839)	6914 ± 2580 (6411)	91.1	83.6 – 99.3
AUC_{0-t} (ng.h/ml)	25054 ± 14177 (20770)	25639 ± 14807 (21163)	98.1	95.2 – 101.2
AUC_{0-inf} (ng.h/ml)	25537 ± 14455 (21188)	26168 ± 15105 (21592)	-	-

* geometric mean

Rifampin

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	2.64 ± 0.91	2.25 ± 1.02	-	-
C_{max} (µg/ml)	10.61 ± 2.56 (10.24)	11.31 ± 2.94 (10.91)	93.8	88.8 – 99.1
AUC_{0-t} (µg.h/ml)	78.6 ± 23.3 (75.7)	82.4 ± 22.0 (79.3)	95.4	91.1 – 99.9
AUC_{0-inf} (µg.h/ml)	80.2 ± 24.6 (76.9)	83.7 ± 23.0 (80.5)	-	-

* geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding ethambutol, isoniazid and rifampin. Accordingly, the test Ethambutol/Isoniazid/Rifampin 275mg/75mg/150mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations Myambutol® (Riemser Arzneimittel) and Rifamate® (Sanofi Aventis).

4. Summary of product safety and efficacy

[TB199 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, [TB199 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products Myambutol® (Riemser Arzneimittel) and Rifamate® (Sanofi Aventis). for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB199 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

[TB199 trade name] has been shown to be bioequivalent with Myambutol® (Riemser Arzneimittel) and Rifamate® (Sanofi Aventis).