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 TB195.

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.

Study title: A randomized, open label, balanced, single dose, two treatment, two period, two sequence, two way crossover oral bioequivalence study comparing of fixed dose combination of Rifampin and Isoniazid tablets 150mg/150mg (2 x 150mg/150mg tablets) manufactured by Lupin Limited, India with of Rimactan (rifampicin) capsules 300mg (01 capsule) manufactured by Sandoz Farmaceutica S.A., Spain & Isozid (isoniazid) tablets 100mg (3 x 100mg tablets) manufactured by Fatol Arzneimittel Gmbh, AG in healthy adult human male subjects, under fasting conditions (study no. SLS-CL-0123-17).

The objective of the study was to compare the bioavailability of the stated Isoniazid/Rifampicin 150/150 mg FDC tablet manufactured for/by Lupin Ltd., India (test drug) with the reference formulations Isozid 100 mg (Fatol Arzneimittel Gmbh) and Rimactan 300 mg capsule (Sandoz Farmaceutica S.A.) 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 treatments in a randomized fashion:

Treatment T:	Test – 2 tablets Isoniazid/Rifampicin 150/150 mg (isoniazid 300 mg + rifampicin 300 mg) Batch no.: A704550
Treatment R:	References – 3 tablets Isozid 100 mg (isoniazid 300 mg)

Batch no. 002114
– 1 capsule Rimactan 300 mg (rifampicin 300 mg)
Batch no. FX6116

A 11-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 48 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for isoniazid and rifampicin were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 30 ng/ml for isoniazid and about 26 ng/ml for rifampicin.

The study was performed with 36 participants; data generated from a total of 35 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	0.70 ± 0.45	0.82 ± 0.44	-	-
C_{max} (µg/ml)	7.58 ± 2.50 (7.19)	7.38 ± 2.59 (6.92)	103.8	95.0 – 113.5
AUC_{0-t} (µg.h/ml)	27.4 ± 9.4 (25.6)	27.8 ± 10.3 (25.6)	99.7	97.4 – 102.1
AUC_{0-inf} (µg.h/ml)	30.3 ± 11.3 (28.1)	30.9 ± 12.5 (28.1)	99.8	97.4 – 102.3

* geometric mean

Rifampicin

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)	1.92 ± 0.67	1.82 ± 0.59	-	-
C_{max} (µg/ml)	5.90 ± 1.63 (5.70)	6.54 ± 1.94 (6.26)	91.1	84.4 – 98.3
AUC_{0-t} (µg.h/ml)	32.1 ± 7.4 (31.3)	35.6 ± 9.3 (34.4)	91.0	86.2 – 96.2
AUC_{0-inf} (µg.h/ml)	32.4 ± 7.4 (31.6)	36.0 ± 9.3 (34.8)	91.1	86.2 – 96.2

* 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 isoniazid and rifampicin. Accordingly, the test Isoniazid/Rifampicin 150/150 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the references Isozid 100 mg tablet (Fatol Arzneimittel GmbH) and Rimactan 300 mg capsule (Sandoz Farmaceutica S.A.).

4. Summary of product safety and efficacy

[TB195 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, [TB195 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products Isozid 100 mg tablets (Fatol Arzneimittel GmbH) and Rimactan 300 mg capsule (Sandoz Farmaceutica S.A.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB195 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 safetyBenefit risk assessment of bioequivalence study.

5. Bioequivalence

[TB195 trade name] has been shown to be bioequivalent with Isozid 100 mg tablets (Fatol Arzneimittel Gmbh) and Rimactan 300 mg capsule (Sandoz Farmaceutica S.A.).