



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	TB292
Study number	MOX-JOR-T0512/869
Title of the study	Comparative Randomized, Single Dose, Two-Way Crossover Open Label Study To Determine The Bioequivalence Of The Jordanian Pharmaceutical Manufacturing Co. (JPM) AVORES® 400 (400 mg Moxifloxacin as Moxifloxacin Hydrochloride Per Film Coated Tablet) Relative To INNOVATOR product, After An Oral Administration Of 400 mg To Healthy Adults Under Fasting Conditions.
Clinical Part of the study: Name and address of the organization	Sport City Circle, Amman, Jordan. P.O Box: 963166 Amman 11196 Jordan E-mail: iprc@iprc.com.jo
Bio-analytical laboratory: Name and address	Same as above
Date of inspection	13 – 16 May 2015

Part 2: Summary

General information about the site(s)

The site was started in 1997 and the first BE study was submitted in Europe in 2000. According to the opening meeting presentation, there were 60 beds on 2 floors. The data management unit was subdivided into the pharmacokinetics and statistics unit. The company had conducted more than 1100 bioequivalence, bioavailability & pharmacokinetics studies (1997-2014), submitted in the Middle East and North Africa (MENA) region (Jordan, Lebanon, Syria, Turkey), South Africa, Australia, New Zealand, Europe and the USA. It had developed and validated over 250 LC-MS/MS and HPLC methods of analysis, issued more than 50 Toxicology Reports and engaged in Phase II-IV trials in different therapeutic areas.

History of WHO and/or regulatory agency inspections

In 2003, the site was inspected for the 1st time by the US FDA. In 2007, the site was inspected for the 1st time by the Irish Medicines Board and also received its 2nd US FDA inspection. In 2009, it received the 1st Turkish Ministry of Health inspection. In

2010, it was inspected for the 3rd time by the US FDA and for the 1st time by the MCC – South Africa.

It received its 4th USFDA inspection in 2012.

In 2013, IPRC received the 2nd and 3rd EMA inspections by Spain and Austria (based on a national request) as well as the 2nd Turkish Ministry of Health inspection.

Focus of the inspection

The focus was on the clinical and bioanalytical parts of the BE study conducted for TB292 Moxifloxacin 400 mg tablets (Study No. MOX-JOR-T0512/869).

Inspected Areas

Day 1

After the opening meeting, inspectors focused on the following items:

Bioanalytical data verification, with a focus on verification of subject sample concentrations relative to the electronic chromatograms. Method validation was also verified. The bioanalytical laboratory was inspected on site.

Day 2

After providing a summary of the observations from Day 1, inspectors focused on the following items:

- Bioanalytical method validation;
- Subject data concentration verification;
- Calibration curve verification;
- Adequacy of integrations verification;
- Data integrity verification through counter verification of the audit trails relative to the raw data;
- Case report forms (CRFs) for subjects screening No. 057, enrolment No. 15 and others;
- Translation of the study-specific informed consent form for MOX-T003.

Day 3

After providing a summary of the deficiencies from day 2, inspectors proceeded to the following:

- Inspection of the clinic;
- Pharmacy: verification of temperature monitoring, line clearance procedures and accountability;
- Diagnostic laboratory inspection and verification of the electronic data management system;
- CRF verification: CRFs for subjects No. 2, 14, 20, 22, 28 were reviewed;
- Electrocardiograms (ECGs);
- Statistics: the confidence interval was statistically verified from the point estimates.

Day 4

Statistical verification was continued with calculation of the point estimates.

Ultra-deep freezers were verified. Equipment qualification and maintenance was verified for one of the HPLCs (ID: LC-012A) used for the study that had been moved in 2009.

The raw data generated for the 5th, 6th and 7th blood samples for periods 1 and 2, were verified relative to the randomization code. All of the values matched those that were used for verification of the statistical part. The subject 28 which had an AE was not extracted.

On the sample extraction forms, they referred to a working standard for the reference standard batch number.

The CRO master file claimed that there were 30 beds on each clinic, but only 28 beds were permanently placed in the rooms of the clinic – the 2 other beds were added to the remaining space (e.g. Entertainment Room). The alarms located at the beds, were not showing where the alarms came from. Since there were 28 beds on each side, this should be improved if possible for future studies.

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

No deviations on the part of the Sponsor or CRO were noted. Ethics approval was obtained first from the ethics committee, and then from the Jordanian FDA as per local regulation.

2.2 THE PROTOCOL

The protocol was found compliant to applicable WHO-GCP regulations; no discrepancies between the protocol and the informed consent were noted. The study was found to have been conducted in accordance with the protocol.

2.3 PROTECTION OF TRIAL SUBJECTS

The informed consent was reviewed and did not cause concern. The trial subjects were apparently sufficiently and appropriately informed about the trial, the drug their compensation and the duties they were supposed to have.

2.4 RESPONSIBILITIES OF THE INVESTIGATOR

The principal investigator was generally not present during the study but a comprehensive delegation log was in place. The delegation log was reviewed and was found satisfactory. Delegation took place prior to the study.

2.5 RESPONSIBILITIES OF THE SPONSOR

As per GCP regulations, the sponsor had transferred the trial-related responsibility to the CRO via a contract.

2.6 RESPONSIBILITIES OF THE MONITOR

This area was not inspected due to time constraints.

2.7 MONITORING OF SAFETY

There were only two recorded adverse events (AEs) in the entire study. One subject experienced an AE (elevated liver enzymes) after period one, which resulted in disqualification. The AE was not mentioned in the main text of the study report but was mentioned in the tabulated overview of safety. It was suggested to the CRO to

always keep correspondence between the tables and text and to ensure that all AEs are properly mentioned in the text body of the reports. This was solely a matter of reporting AEs, and not recording them. There were no concern about the actual care of subjects. Emergency procedures were reviewed and found acceptable.

2.8 RECORD KEEPING AND HANDLING OF DATA

Generally, the CRO was vigilant towards maintaining properly filled documents. Apart from the single incident mentioned under 2.7, the inspection team did not note discrepancies between records and reported data.

2.9 STATISTICS AND CALCULATIONS

The confidence intervals reported in the study report were recalculated from the raw data listings using WinBE5.0 and matches was found for both Cmax and AUCt.

2.10 HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

The IMP was handled appropriately, incl. line clearance. Records of drug accountability during and after the study were reviewed, and quantities re-calculated. Records of empty blisters were reviewed for the Reference product and matched the drug accountability records.

2.11 ROLE OF THE DRUG REGULATORY AUTHORITY

Apart from approving studies, the Jordanian FDA will come on occasional unannounced visits; records for those visits, including inspection reports, were not reviewed. There is a computerized interface to a server hosted by the Jordanian FDA for which subject can be queried for eligibility. The functionality of this system was reviewed with a non-eligible subject and the system responded appropriately.

2.12 QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

SOPs were in place which covered the necessary quality assurance aspects of the trial. The SOPs appeared to be understood by all employees interviewed and were followed.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the study MOX-JOR-T0512/869 was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at *IPRC Jordan, Sport City Circle, Amman, Jordan*.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the CRO, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.