*Macedonian pharmaceutical bulletin, 68 (Suppl 1) 541 - 542 (2022)*
*Online ISSN 1857 - 8969*
*DOI:10.33320/maced.pharm.bull.2022.68.03.259*
*Short communication*

# Pharmacovigilance in clinical trials

# Experience from bioequivalence Studies and further perspectives

Gordana Damjanovska[1*], Emilija Atanasovska[2*], Nikola Labacevski[2], Svetlana Neceva[1]

*[1]REPLEK FARM Ltd, Kozle 188, 1000 Skopje, Republic of North Macedonia*
*[2]Medical Faculty of Ss. Cyril and Methodius University, Department of Preclinical and Clinical Pharmacology with Toxicology, 50 Divizija 6, 1000 Skopje, Republic of North Macedonia*

## Introduction

According to the GUIDELINE FOR GOOD CLINICAL PRACTICE ICH E6 (R2): Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

Section 4.11 “Safety Reporting”; Section 5.16 “Safety Information”; and Section 5.18.4 “Monitor's Responsibilities” of this Guideline define responsibilities for safety evaluation and adverse drug reaction reporting.

These stipulated responsibilities regarding safety apply to Bioequivalence studies (BES) too.

## Objective

The aim of this paper is to present the safety outcome (appearance of adverse drug events, their assessment, reporting and actions undertaken) from two Bioequivalent studies conducted in the period 2018/2021.

## Material and methods

Two comparative, randomized, single-dose, 2-way crossover bioavailability studies for determining bioequivalence (similarity in terms of safety and efficacy) between Test and Reference medicinal product were

assessed for safety outcomes in 80 healthy female and male volunteers in total.

The clinical part of both studies was conducted at the Medical Faculty of Ss. Cyril and Methodius University,

Department of Preclinical and Clinical Pharmacology & Toxicology as Clinical Study Center.

REPLEK FARM LTD Skopje was a sponsor of the both studies.

The studies were monitored in standard (on-site) and hybrid way (on-site and by using questionnaire in compliance with protocols for conducting clinical trials during COVID-19 pandemic).

The first study was a pre-marketing study and has compared the bioavailability of Test medicinal product Sildenafil 100 mg film-coated tablets, manufactured by REPLEK FARM LTD Skopje, Republic of North Macedonia with Reference medicinal product Viagra® 100 mg film-coated tablets, manufactured by Fareva Amboise, Poce-sur-Cisse, France, Marketing Authorization Holder: Pfizer Limited, Sandwich Kent, UK.

Thirty six volunteers from this study were assessed for safety outcomes.

*gordana.damjanovska@replek.mk

The second study was a post-marketing study and has compared bioavailability of Test medicinal product AZIMED 500 mg film-coated tablets, manufactured by REPLEK FARM LTD Skopje, Republic of North macedonia with Reference medicinal product ZITHROMAX 500 mg film-coated tablets, manufactured by Laboratórios Pfizer, Lda., Porto Salvo Portugal, EU. Marketing Authorization Holder: Laboratorios Pfizer Lda, Portugal, EU.

Forty four volunteers from this study were assessed for safety outcomes.

## Results and discussion

There were four different adverse events noted in the first study, all known as undesirable effects of sildenafil and therefore all assessed as 'probably' or 'possibly' related to the study medication, i.e., erection increased, flushing, vision color distortion (cyanopsia) and headache, occurring with various frequency.

After 70 administrations of study medications to 36 subjects, 14 cases of post-dose adverse events were reported.

Most frequently reported AE was 'erection increased', which occurred in 5 subjects (13.89 %) who received treatment A and 6 subjects (17.65 %) who received treatment B. Other three AEs, were reported with lesser frequency: headache occurred in 1 subject (2.78%) who received treatment A, flushing occurred in 1 subject (2.78%) who received treatment A and vision color distortion (cyanopsia) occurred in 1 subject (2.78%) who received treatment B.

The severity of all 14 AEs was graded as "mild".

All AEs experienced during this study resolved completely by the end of the study.

In the second post-marketing study, a total of 10 post-dose AEs were reported by 6 (13.64%) of the 44 subjects. Three AEs (nausea-3) were reported by 6.98% (n=3) of the 43 subjects who received Treatment A.

Seven AEs (headache-2, vomiting-2, anxiety-1, nausea-1, abdominal pain-1) were reported by 9.09% (n=4) of the 44 subjects who received Treatment B.

The most commonly reported AE was nausea, reported by 9.09% (n=4) of subjects who constituted the safety population. Of the 10 AEs reported, 8 were graded as mild and 2 were graded as moderate.

All AEs experienced during this study resolved completely by the end of the study.

No severe adverse events, expected or non-expected serious adverse events or deaths occurred during both studies. These adverse events were included in the Final report submitted to the regulatory authority.

All adverse events that occurred while conducting both studies were included in Sponsor's Monitoring report as well as in the Annual and Periodic Safety Report submitted to the regulatory authority.

## Conclusion

Although Bioequivalence studies are based on bioavailability comparison towards Reference product with known safety profile, adverse events with different intensity, frequency and/or relationship of adverse events to study drug can occur.

Pharmacovigilance in clinical trials, including the bioequivalence studies should be part of Risk based quality trial management and integrated monitoring based on identification of critical risks with focus on already known serious adverse events, risk assessment, defined risk control mechanisms as systematic end-to-end risk control.

Thinking about further perspectives of monitoring in Bioequivalence studies (including pharmaco-vigilance) in light of intensive overall digitalization and technology applied, as well as the accumulated experience from conducting trials during COVID-19 pandemic, hybrid (on-site and centralized) and centralized (remote) monitoring are imposed as possible future forms, mostly due to cost containment and possibility of daily-based subject centered monitoring.

Additionally, cognitive models that analyze safety data obtained from safety examination, such as algorithm driven automated alerts with embedded Artificial Intelligence/ Machine learning are also imposed as possible future tools for monitoring and managing the studies, clinical site and subject data, including safety outcomes.

## References

EMA/CHMP/ICH/135/1995. ICH Topic E6: Guideline for Good Clinical Practice (R2). London, June 2017.

WMA Declaration of Helsinki –Ethical Principles for Medical Research Involving Human Subject as amended: http://www.wma.net/en/30publications/10policies/b3.