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STUDY PROTOCOL

Study Title: "Interaction Between Omeprazole and Gliclazide in CYP2C19 Normal/ Ultrarapid Metabolisers"

Study Acronym: **INTERGLIKOM**

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PROTOCOL APPROVAL

“Interaction Between Omeprazole and Gliclazide in CYP2C19 Normal/ Ultrarapid Metabolisers”

Signature

By signing this document, I am confirming that I have read, understood and approved the protocol for the above study. I accept to perform the study in accordance with this protocol.

Prim. Dr. Dragan Stevanović _____ _____
Principal Investigator Signature Date

Interaction Between Omeprazole and Gliclazide in CYP2C19 Normal/ Ultrarapid Metabolisers

Introduction

Type 2 diabetes (T2D) is a global health problem affecting more than 370 million people worldwide. According to the estimations of the International Diabetes Federation, Bosnia and Herzegovina has one of the highest prevalence of diabetes in Europe, 12.3%.[1] Despite development of novel pharmacological agents, sulfonylureas (SUs) remain the most commonly prescribed drugs after metformin in the treatment of T2D, because of their high efficacy, extensive experience and least cost.[2] Due to their low cost compared to some of the newer agents, SUs are particularly widely used in low and middle income countries, where they have been recommended as treatment of choice for T2D.[3]
The most common and potentially most serious adverse effect of sulfonylurea therapy is hypoglycaemia.[4] Severe hypoglycaemia may result in significant morbidity, including higher risk of dementia, stroke and mortality.[5-7] Among different SUs, gliclazide has been recommended as a first choice in many countries, as it seems to be associated with lower risk of hypoglycaemia and lower morbidity and mortality compared with other SUs.[8,9] Furthermore, gliclazide has been included on the WHO Model List of Essential Medicines, based on safety data in elderly patients. Nevertheless, in a recent population-based cohort study, gliclazide showed a similar risk of hypoglycaemia compared with other SUs.[10]
Gliclazide is extensively metabolised in the liver to inactive metabolites. Although CYP2C9 is involved in the metabolism of gliclazide,[11] the pharmacokinetics (PK) and pharmacodynamics (PD) of gliclazide seem to be affected mainly by *CYP2C19* genetic polymorphisms.[12,13]
Gastrointestinal problems, such as gastroesophageal reflux disease (GERD) are common in T2D.[14] A recent meta-analysis involving 9,067 cases and 81,968 controls showed a significant association between diabetes and the risk of GERD.[15] The prevalence of GERD symptoms in patients with T2D could be as high as 40%.[14] Therefore, millions of individuals are managing blood glucose and GERD concomitantly.[16] Proton pump inhibitors (PPIs) are the medications of choice for GERD, and are primarily metabolised by CYP2C19.[17] The potential for drug-drug interactions is highest for omeprazole and its stereo-isomer esomeprazole, which are metabolised almost entirely by CYP2C19.[17,18] Furthermore, it has been shown that impact of PPIs on the PK, PD, and therapeutic response to drugs metabolised by CYP2C19 could depend on *CYP2C19* genotype, with highest effect seen in CYP2C19 normal metabolisers (extensive metabolisers, EM)[19,20] and ultrarapid metabolisers (UM).[21]

Project aims

Considering the high prevalence of use of PPIs,[22] the greater incidence of GERD in T2D and likely high concomitant use of PPIs with gliclazide, and the possibility of their interaction via CYP2C19, the primary aim of this pilot clinical study is to explore potential drug-drug interaction between gliclazide and omeprazole in CYP2C19 EM/UM metabolisers. The specific aims are:

1. To explore whether gliclazide PK is altered upon co-administration with omeprazole in healthy volunteers, CYP2C19 EM/UM metabolisers
2. To explore whether gliclazide PD is altered upon co-administration with omeprazole in healthy volunteers, CYP2C19 EM/UM metabolisers

Preliminary data

To our knowledge, there have been no studies exploring potential interaction between any PPI and gliclazide, in animals or humans. To explore this possible drug-drug interaction, we performed preliminary observational analyses in the large population-based GoDARTS study (UK). Briefly, our preliminary data suggest that co-treatment with PPIs, especially omeprazole, increases the risk of hypoglycaemia in patients with CYP2C19 EM/UM phenotype treated with gliclazide. This has been confirmed by better glycaemic response (lower HbA1c) associated with PPI use in EM/UM patients treated with gliclazide. These results support a biologically plausible hypothesis of possible interaction between PPIs and gliclazide, in relation to CYP2C19 genotype.

Study population

The study protocol will be approved by the Ethics Committee of the General Hospital "Prim. Dr. Abdulah Nakaš" and the Ethics Committee of the Faculty of Medicine, University of Sarajevo, Sarajevo, Bosnia and Herzegovina (B&H). All procedures will be conducted at the Department of Internal Medicine of the General Hospital in line with the Good Clinical Practice and the Declaration of Helsinki. Prior to inclusion in the study, the nature and purpose of the study will be explained, in both written and verbal form, to each volunteer who will then give the informed written consent to participate in the study.

Volunteers will be initially recruited through advertising by using leaflets, posters and social networks (e.g. Facebook). At least 40 volunteers will be recruited and pre-screened for *CYP2C19* genotype. Based on the frequency of *CYP2C19*2* variant in B&H population of ~17%,[23] we expect that about two-thirds of screened individuals will be non-carriers of the **2* allele. The recruitment will end when the minimal number of 16 individuals, non-carriers of **2* allele, is reached. Only these individuals (CYP2C19 EM/UM metabolisers) will be included in the drug interaction study after confirmation of their health status.

<u>Inclusion criteria for screening (genotyping)</u>

- Men
- Age 18-30 years
- Non-smokers

<u>Exclusion criteria for screening (genotyping)</u>

- medical history of hepatic, renal, gastrointestinal and hematologic disease or any acute or chronic disease
- any chronic drug therapy
- drug allergy to sulfonylureas and/ or PPIs
- history of drug abuse

<u>Genotyping</u>

Genomic DNA will be extracted from blood samples by using commercial DNA extraction kits. Polymorphisms in the *CYP2C19* gene: *CYP2C19*2* (rs4244285) and *CYP2C19*17* (rs12248560), *CYP2C9* gene: *CYP2C9*2* (rs1799853), *CYP2C9*3* (rs1057910) and a variant in the *POR* gene encoding a CYP450 redox partner, enzyme P450 oxidoreductase (POR), *POR*28* (rs1057868), will be genotyped by specific Drug Metabolism SNP genotyping assays. Genetic test results for *CYP2C19* variants will be obtained at the screening, before the randomisation. Only individuals, non-carriers of the *CYP2C19*2* allele will be included further in the clinical study. Results obtained for other three variants in the *CYP2C9* and *POR* genes will be used as covariates in the statistical analysis.[24]

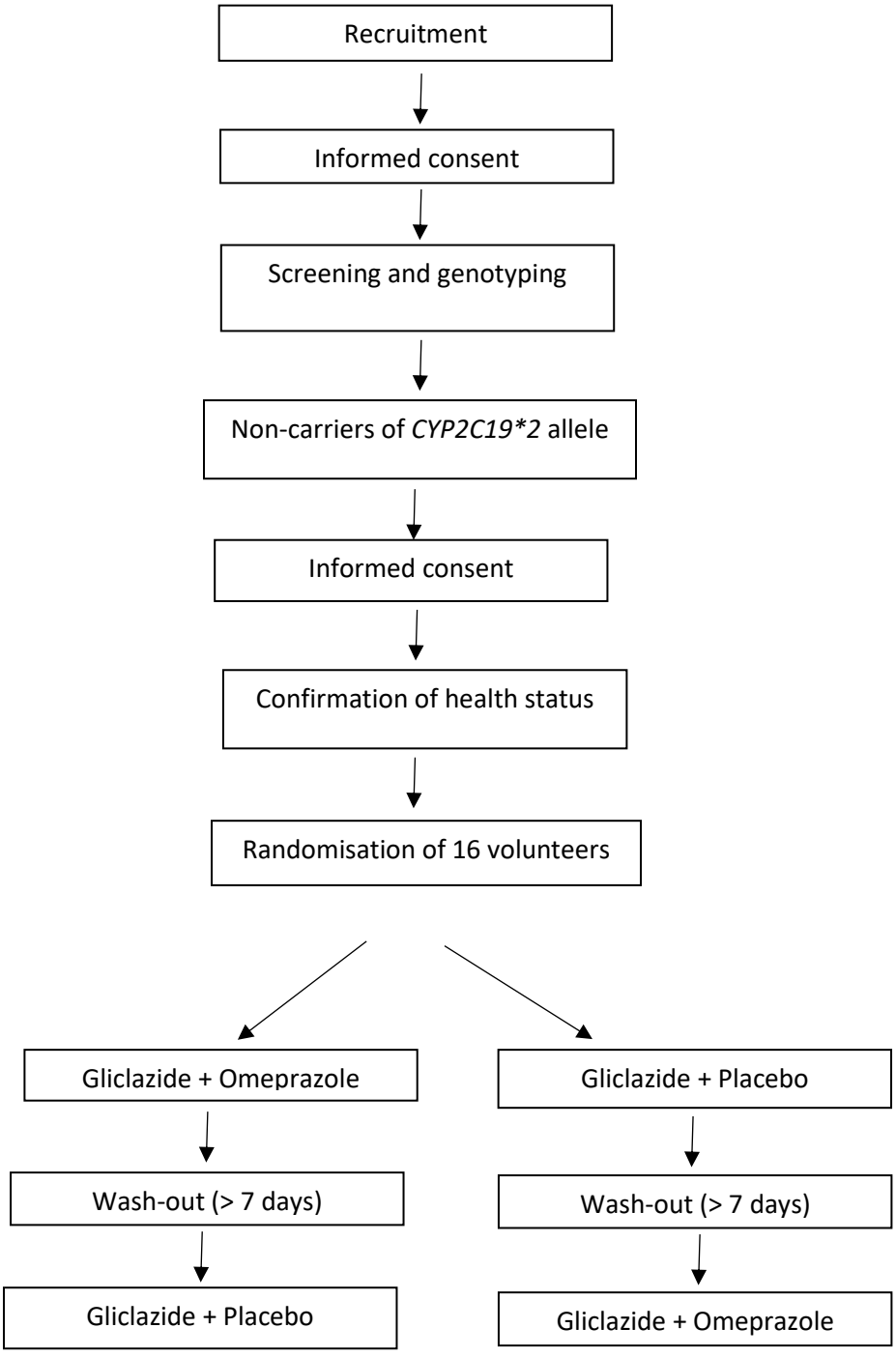
Inclusion criteria for drug interaction study

- CYP2C19 normal/ ultrarapid metabolisers (non-carriers of the *CYP2C19*2* allele)

Exclusion criteria for drug interaction study

- abnormalities in physical examination, ECG and routine clinical laboratory tests (including fasting blood glucose concentration)
- medication use during the 14 days prior and during the study periods
- grapefruit, grapefruit juice, alcohol, beverages or food containing methylxanthines use during 72 h prior and during the study periods

Participants will be randomised to specific treatment sequences using SAS Proc Plan procedure.



Drug interaction study design

A randomised, placebo controlled, two-sequence, two-period crossover study, with at least a 7-day washout period between the study periods will be conducted to compare the effects of gliclazide (40 mg, half of an 80 mg tablet of Diprian®, Hemofarm d.o.o. Banja Luka, B&H, orally) and placebo with those of gliclazide combined with omeprazole (20 mg, Ulcosan®, Bosnalijek d.d. Sarajevo, B&H, orally). Prior to administration of gliclazide, omeprazole or placebo will be administered once daily at 8 AM for 4 days (on day 1 until day 4) to assure PD steady-state. At 8 AM of the day 5, after an overnight fast (last meal at 9 pm of the previous day), the participants will be given a single dose of 40 mg gliclazide with 240 mL of water together with omeprazole or with placebo according to their treatment assignment.

The volunteers will be given both drugs (gliclazide + omeprazole or gliclazide + placebo) in a sitting position and they will not be permitted to lie down or sleep for the next 4 h after taking gliclazide. They will be under direct medical supervision throughout the 24 h following drug administration.

In order to counteract the blood glucose-lowering action of gliclazide, subjects will receive standardized meals: a breakfast at 30 min after gliclazide intake, snacks after 2 and 3 h, a lunch (warm meal) after 4 h, a snack after 6 h, a dinner after 8 h, and additional snacks at 10 h and 12 h after drug administration. The larger meals should be eaten within 10 minutes, and snacks within 5 minutes. No other food and drink (with the exception of water) or strenuous activities will be allowed.

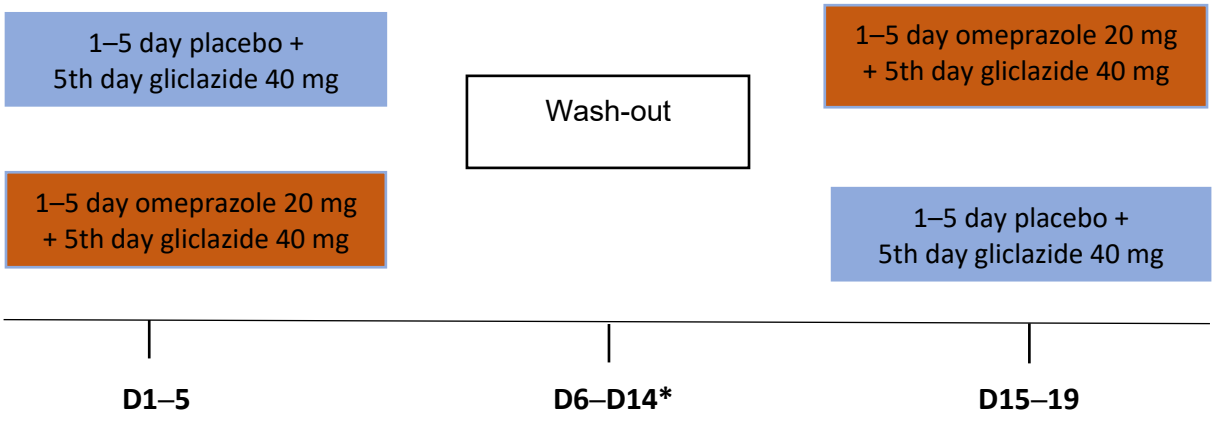
Schematic design of the drug interaction study

- Period 1
  - Eight (8) subjects will receive treatment A on days D 1–5
  - Eight (8) subjects will receive treatment B on days D 1–5
- Wash-out period D6–14
- Period 2
  - Eight (8) subjects will receive treatment B on days D 15–19
  - Eight (8) subjects will receive treatment A on days D 15–19

<u>Treatment</u>

Treatment A: days 1–4, administration of placebo with 240 mL of water
day 5, administration of placebo + 40 mg gliclazide with 240 mL of water

Treatment B: days 1–4, administration of 20 mg omeprazole with 240 mL of water
day 5, administration of 20 mg omeprazole + 40 mg gliclazide with 240 mL of water



*Wash-out period of at least 7 days

Blood collection

Venous blood samples will be collected on day 5 and day 19 for gliclazide, glucose and insulin quantification, through an indwelling intravenous cannula in the arm or by direct venepuncture (in the case of cannula blockage).

A total of 17 blood samples, 5 ml each, will be taken, thus the total blood volume of 85 ml will be taken during 24 hours, which is over 5 times less than the standard 450 ml drawn during voluntary blood donation.

Blood sampling for gliclazide quantification

- gliclazide: pre-dose (0 h), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, and 24 h

Blood sampling for glucose and insulin quantification

- glucose: pre-dose (0 h), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10 and 12 h
- insulin: pre-dose (0 h), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10 and 12 h

Blood glucose levels will be measured immediately after sampling. Serum samples for insulin and gliclazide quantification will be obtained and stored in properly labelled tubes at -80°C until the analysis.

Gliclazide concentration analysis

Serum gliclazide concentration will be analysed at the Biomarker and Drug Analysis Core Facility, School of Medicine, University of Dundee, by using a stable isotope dilution LC-MS method.

Glucose and insulin quantification

Glucose concentrations will be measured at the laboratory of the General Hospital.

Insulin concentrations will be quantified by enzyme-linked immunosorbent assay (ELISA) using commercially available kit.

Pharmacokinetic analysis

- C_{max}: Gliclazide maximum concentration
- t_{max}: Time to reach C_{max}
- AUC_{0-t}: Area under the concentration–time curve (AUC) up to the last concentration measured
- $AUC_{0-\infty}$: Area under the concentration–time curve (AUC) extrapolated to infinity
- $t_{1/2}$: Elimination half-life
- $C_{L/F}$: Apparent oral clearance
- $V_{d/F}$: Apparent volume of distribution

PK parameters will be calculated by a noncompartmental analysis using PKSolver a program for PK and PD data analysis in Microsoft Excel. Gliclazide maximum concentration (C_{max}) and time to reach C_{max} (t_{max}) will be determined by the inspection of the concentration–time data. The area under the plasma gliclazide concentration–time curve (AUC) up to the last concentration measured (AUC_{0-t}) will be determined using the linear trapezoidal rule. The AUC will be extrapolated to infinity ($AUC_{t-\infty}$) using C_t/k_{el}, where C_t is the last measured gliclazide concentration and k_{el} is the elimination rate constant that will be estimated from the slope of the best-fit line determined by linear regression analysis of the log-transformed concentration-time curve. The elimination half-life ($t_{1/2}$) will be calculated using the following equation: $t_{1/2}=\ln(2)/k_{el}$. The apparent oral clearance (CL/F) will be calculated as dose/$AUC_{0-\infty}$. The apparent volume of distribution (Vd/F) will be calculated as dose/AUC x k_{el}.

Pharmacodynamic parameters

- C_{min}: Glucose minimum concentration
- $C_{avg\ 0\text{-}4}$: Average glucose concentration in the period 0–4 h
- $C_{avg\ 0\text{-}12}$: Average glucose concentration in the period 0–12 h
- $AUC_{0\text{-}4}$: Area under the glucose concentration–time curve from 0 to 4 h
- $AUC_{0\text{-}12}$: Area under the glucose concentration–time curve from 0 to 12 h

- C_{min}: Insulin minimum concentration
- $C_{avg\ 0\text{-}4}$: Average insulin concentration in the period 0–4 h
- $C_{avg\ 0\text{-}12}$: Average insulin concentration in the period 0–12 h
- $AUC_{0\text{-}4}$: Area under the insulin concentration–time curve from 0 to 4 h
- $AUC_{0\text{-}12}$: Area under the insulin concentration–time curve from 0 to 12 h

To compare the PD effects of gliclazide, the areas under the glucose and insulin concentration–time curve from 0 to 4, and 0 to 12 h after the administration of gliclazide will be calculated using the linear trapezoidal rule. The minimum glucose and insulin concentration will be determined by observation of the concentration–time data, and mean concentrations from 0 to 4 h and from 0 to 12 h will be calculated by dividing the area under the glucose/insulin concentration–time curve by the corresponding time interval.

Safety assessment and precaution measures

The volunteers will undergo a detailed physical, ECG, and laboratory examination upon inclusion in the drug interaction study. The subjects will be contacted within 14 days of study completion in order to confirm the adequate post-study status.

If any clinical reasons arise that could endanger health status of the subjects by taking blood samples, the blood samples will not be drawn. Considering that bruising, bleeding, infection or pain may occur at the site of venepuncture and cannulation, these procedures will be performed by experienced medical staff to minimise the risk of excessive bleeding or bruising, and a topical anaesthetic may be used, if required, to reduce the pain.

Since this combination of drugs can potentially induce risk of hypoglycaemia, administration of the two drugs will be carried out in the hospital where the subjects will be hospitalised for 24 h and will be continuously under direct medical supervision. In order to avoid the risk of hypoglycaemia, subjects will receive 8 meals (breakfast, lunch, dinner and 5 snacks). In case of any symptom suggestive of hypoglycaemia (nervousness, sweating, intense hunger, trembling, weakness, palpitations), the blood glucose level will be measured using a glucometer and one of the standard measures of raising blood sugar will be applied, such as administration of 20% oral glucose solution, glucose solution for intravenous use, or glucagon for intramuscular use.

In addition, systolic and diastolic blood pressure and heart rate will be measured in the supine position after a 5-minute rest, before drug intake and during the PK profiles at 2, 4, 12 and 24 hours after gliclazide administration.

Power analysis

For identification of clinically relevant drug-drug interaction, we will use the bioequivalence approach. The main outcome to be evaluated is the exposure to gliclazide, expressed as $AUC_{0\text{–}t}$. Sample size calculation was performed using SAS Proc Power procedure for equivalence test in 2x2 crossover design.[25] For an equivalence range of 80–125%, the within-subject coefficient of variation for the AUC values for gliclazide of 7.8% based on previous PK studies,[26,27] and expected test/reference geometric

mean ratios between 87–115%, 14 volunteers (7 individuals per sequence) are required to show the lack of interaction with 85% power. To account for potential drop-outs due to non-compliance or loss of follow up (assuming a drop-rate of 10%), a total of 16 subjects, CYP2C19 EM/UM metabolisers, will be randomised. To achieve this number, minimally 40 volunteers will be initially recruited.

Statistical analysis
The geometric mean will be calculated for each PK and PD parameter. Logarithmic transformation will be used for PK variables, except t_{max}, before the analysis. The ratios of the geometric means with 90% confidence intervals (CI) will be assessed by linear mixed models between the two treatment assignments: gliclazide and omeprazole coadministration to that of gliclazide and placebo. The statistical analyses will be performed using the SAS 9.3 software (SAS Institute Inc., Cary, NC).

Original scientific contribution and clinical significance of the research
This research will establish whether omeprazole can alter PK/PD of gliclazide, and thus increase the risk of serious hypoglycaemia with this recommended SU drug.

This study can unravel new, previously unrecognized drug-drug and drug-drug-gene interactions. If clinically relevant alterations in gliclazide PK/PD parameters are established, our findings can lead to changes in clinical practice with the aim of preventing serious, potentially life-threatening hypoglycaemia induced by gliclazide treatment.

Confidentiality and data protection
All clinical, laboratory and genetic data will be processed in a manner designed to protect the identity of the participants, in accordance with the rules of personal data protection and the guidelines of the Good Clinical Practice. Participants' privacy will be respected in all published and other public written data that will result from this study.

Withdrawal from the study
Participants are free to withdraw from the study at any time, without obligation to explain their decision.

Insurance
In accordance with the guidelines of Good Clinical Practice, the subjects will be insured under the terms of insurance for Clinical Trials.

Compensation of costs
The costs of participants arising from their participation in the screening visit will be reimbursed in the amount of 50.00 BAM upon completion, and the costs of participants arising from their participation in the drug interaction study will be reimbursed in the amount of 400.00 BAM upon completion of the study. The funds will be paid to the participants' bank account.

Adverse events

Definitions
An *adverse event* (AE) is any untoward medical event affecting a clinical trial participant. Each initial AE will be considered for severity, causality or expectedness and may be reclassified as a serious event or reaction based on prevailing circumstances.
An *adverse reaction* (AR) is where it is suspected that an AE has been caused by a reaction to a trial drug.

A *serious adverse event* (SAE), *serious adverse reaction* (SAR) or *suspected unexpected serious adverse reaction* (SUSAR) is any AE, AR or UAR that at any dose:

- results in death or is life threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect.

Recording and reporting adverse events and serious adverse events
The principal investigator should report any SAE that is both related to the research procedures and is unexpected, to the Ethics Committees which approved the study, and to the Faculty of Pharmacy University of Sarajevo, within 24 hours of the becoming aware of the event.

An adverse event log will be maintained in the CRF. The principal investigator on this study is medically qualified and will assess all adverse events for expectedness, seriousness and causality and will follow up to resolution or to within 30 days of the end of the study. The seriousness of the adverse event will be graded according to the *Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Publish Date: November 27, 2017*
(https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

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