Quantification of dexchlorpheniramine and betamethasone in human plasma by the uplc-ms/ms method and its application in a bioequivalence study containing the two drugs in combination, administered as a single dose in healthy volunteers

Quantificação de dexclorfeniramina e betametasona em plasma humano pelo método clue-em/em e sua aplicação em um estudo de bioequivalência contendo os dois fármacos em associação, administrados em dose única em voluntários sadios

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ABSTRACT

This study was carried out in order to compare the relative bioavailability of two different formulations containing 2.00 mg of dexchlorpheniramine maleate + 0.25 mg of
bethametasona, test formulation (Dexmine®) and reference formulation (Celestamine®) in healthy volunteers of both sexes under fasting conditions. The study was conducted in a single dose, randomized, open-label, crossover 2 x 2. The tolerability was evaluated by the monitoring of adverse events and vital signs, results of clinical and laboratory tests. Plasma concentrations were quantified by validated bioanalytical method employed the ultra-performance liquid chromatography triple quadrupole tandem mass spectrometry, using as the internal standard brompheniramine. Non-compartmental model was applied to determine different pharmacokinetic parameters and these were calculated from the plasma concentrations obtained from the volunteer samples. Bioequivalence between test and reference formulation were demonstrated as the calculated 90% confidence interval for the corresponding ratios of log transformed pharmacokinetic parameters ($C_{\text{max}}$, $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\infty}$) fell within the 80–125% range, the predetermined criterion for therapeutic equivalence. It can be concluded that the two formulations were bioequivalent in terms of rate and absorption extent and thus interchangeable.

**Keywords:** Dexchlorpheniramine, Bethametasona, Bioequivalence, UPLC-MS/MS

**RESUMO**

Este estudo foi realizado para comparar a biodisponibilidade relativa de duas formulações distintas contendo 2,00 mg de maleato de dextrofeniramina + 0,25 mg de betametasona, formulação de teste (Dexmine®) e formulação de referência (Celestamine®) em voluntários saudáveis, de ambos os sexos em condições de jejum. O estudo foi realizado em dose única, randomizado, aberto, crossover 2 x 2. A tolerabilidade foi avaliada pelo monitoramento de eventos adversos e sinais vitais, resultados de exames clínicos e laboratoriais. As concentrações plasmáticas foram quantificadas por método bioanalítico validado usando a cromatografia líquida de ultra eficiência acoplada a espectrometria de massa triplo quadrupolo, utilizando a bronfeniramina como padrão interno. O modelo não compartimental foi utilizado para determinar os diferentes parâmetros farmacocinéticos e estes foram calculados a partir das concentrações plasmáticas obtidas das amostras de voluntários. A bioequivalência entre a formulação teste e a de referência foi demonstrada como o intervalo de confiança de 90% calculado para as razões correspondentes de parâmetros farmacocinéticos log transformados ($C_{\text{max}}$, $\text{AUC}_{0-t}$ e $\text{AUC}_{0-\infty}$) dentro do intervalo 80–125%, o critério predeterminado para equivalência terapêutica. Pode-se concluir que as duas formulações foram bioequivalentes em termos de taxa e extensão de absorção e, portanto, intercambiáveis.

**Palavras Chaves:** Dexchlorfeniramina; Bethametasona; Bioequivalência; CLUE-EM/EM

**1 INTRODUCTION**

Pharmaceutical forms contemplating the combination of dexchlorpheniramine maleate / betamethasone are indicated in the prevention and alleviation of allergic manifestations. The purpose of such a combination is to decrease the symptoms caused by allergic reactions through the antihistamine action of dexchlorpheniramine maleate and the anti-inflammatory and antiallergic effect of betamethasone. The mixture use of
these compounds allows the use of smaller doses of corticosteroids, with results similar to those obtained with higher doses of corticoid alone (Yasuda et al., 2002; Vester & Volkerts, 2004; Raju et al., 2007; Moreno et al., 2010).

Dexchlorpheniramine maleate (3S)-3-(4-chlorophenyl)-N, N-dimethyl-3-(pyridin-2-yl) propan-1-amine (Z)-butanedioate is a potent antihistamine used for the treatment of several allergies and skin irritation and betamethasone 9 α-fluoro-16 s-methyl-11 s, 17 α 21-trihydroxy-1, 4-pregna diene- 3, 20-dione is a synthetic glucocorticoid that suppress the activity of endogenous mediators of inflammation including prostaglandins, kinins, and histamine (Fereja et al., 2015).

Dexchlorpheniramine maleate is the dextrorotatory isomer of chlorpheniramine that demonstrates stereoselectivity in the pharmacological response: (S) - (+) enantiomer. The dexchlorpheniramine maleate is an alkylamine, a first generation histamine antagonist with anti-allergic activity that competitively blocks peripheral H1 receptors, thus preventing the actions of histamine (Yasuda et al., 2002; Vester & Volkerts, 2004; Raju et al., 2007; Moreno et al., 2010), H1 antagonists are well absorbed in the gastrointestinal tract and after oral administration of dexchlorpheniramine the peak plasma concentration is reached within 2 to 3 hours. Its oral bioavailability is around 25 to 50% and its binding to plasma proteins is 69 to 72%. It undergoes considerable first-pass metabolism. The half-life ranged from 20 to 24 hours and the unchanged drug and its metabolites were primarily excreted in the urine, with 19% of the dose appearing in 24 hours and a total of 34% in 48 hours (Alcántara, et al., 2000; Alabazi, 2012).

Betamethasone is a fluorinated corticosteroid, synthetically derived from hydrocortisone and suppresses inflammation on a wide range of diseases including allergies (Pereira, 2005; Alcántara, et al., 2000). It is well absorbed orally after its administration and the plasma concentrations of betamethasone reach plasma peak in 2 hours, gradually decreasing the concentrations during 24 hours. Natural and synthetic glucocorticoids, including betamethasone, are metabolized in the liver and 64% of the administered dose of betamethasone binds to plasma proteins. Its plasma half-life was calculated between 3 and 5 days and its biological half-life ranges from 36 to 54 hours (Celestone®, 2015).

Although both drugs have been available for more than 50 years and are taken by millions of people, their pharmacokinetics have been incompletely characterized. In addition to the divergent data among the authors, there is almost no information on the pharmacokinetics of these compounds. Wandalsen, 2017 reported that the association of
dextrochlorpheniramine and betamethasone accounts for 34.79% of sales of products available in this segment in Brazil in 2015.

In Brazil, relative bioavailability tests are required for the registration of similar medicinal product and generic which use the bioequivalence criterion. Based on that conclusion, one may subsequently claim that the therapeutic quality of these formulations is essentially the same. The latter means that both the beneficial and adverse side effects are essentially the same and hence the formulations are interchangeable.

The aim of this study was to compare the pharmacokinetics profiles of two tablet formulations of 2 mg dexchlorpheniramine maleate + 0.25 mg betamethasone under fasting conditions in healthy volunteers of both sexes, following single dosing in order to prove bioequivalence between both preparations.

2 MATERIAL AND METHODS
2.1 CLINICAL PROTOCOL

The study included healthy volunteers of both sexes, aged over 18 and body mass index (BMI) between 18.0 and 30.0 kg/m². Volunteers were equality distributed among groups and the same number of men and women were used. All subjects were in good health condition confirmed by normal medical history, physical examination, vital signs measurement, anthropometric data, 12-lead electrocardiogram (ECG) and laboratory tests (hematology, biochemistry, urine 1, serology), as well as pregnancy testing for women.

Subjects were excluded if participation in any clinical study within six months prior to the study initiation, pregnancy or lactation, significant loss or blood donation in quantities higher than 450 mL, and alcohol and/or drug abuse also prevented the individual’s participation in the study. Those reactions of hypersensitivity to drugs, clinically significant case history or presence of renal, pulmonary, neurological, psychiatric, hematological, cardiological, endocrine, immunological and diseases neoplasms, those with intake of foods or beverages containing xanthines for 48 h prior to dosing, those with regular intake of any medication in the previous 14 days prior to dosing.

Prior to the study, the volunteers were informed about the nature, purpose, risks, and discomforts that could arise from their participation, and about their right to withdraw at any time. Subjects documented their willingness to participate by signing the informed consent form. The clinical trial protocol and information given to study subjects were
approved by the Ethical Committee of the Faculty of Medical Sciences, State University of Campinas, Brazil (approval number: 1216/2011 and CAAE: 1115014600011). The study was performed in accordance to the Declaration of Helsinki (revised version of Seoul 2008) and the provisions of Good Clinical Practice. All study stage were carried out by Claudia Marques Research and Development Institute (ICMP&D), Pouso Alegre, Brazil.

2.2 STUDY DESIGN

The study was conducted in single dose, two-period, two-sequence, fasting, open-label, crossover randomized design with a 2 week washout period between the doses. The oral administration of one tablet of each product (test and reference) was initiated, regarding the list of randomization, at 07:00 am, after a fasting period of 9 hours with 200 mL of water. No food was allowed for four hours after the dose intake. Subjects received standardized meals at 4 hours (lunch), 8 hours (snack) and 10 hours (supper) after the drug intake in each treatment. The volunteers did not alcoholic beverage, coffee, drinks containing xanthines, or foods outside the prescribed diet during the study. No fluid intake was allowed from 1 h before until 1 h after drug administration.

*Tolerability*

Tolerability was evaluated by monitoring adverse events. The subjects were under constant supervision after first administration of the drug and during confinement, blood pressure, pulse and body temperature were monitored at predefined times. Additionally, all volunteers were asked to report immediately any adverse event. The vital signs, physical examination, laboratory tests (except serology) and ECG were also performed at the end of the study.

*Sample collection and processing*

The definition of the number of collections and the interval from obtaining the blood samples to constructing the concentration curves versus time were based on the pharmacokinetic profile of the drugs: dextchlorpheniramine maleate and betamethasone. Blood samples (~ 7.5 mL) were collected to heparinized tubes according to time schedule before and 0.33, 0.66, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.66, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 14.00, 24.00, 48.00, 72.00, 96.00, 120.00 hours after dosing. Plasma was immediately separated by centrifugation at 3500 rpm for 10 minutes at 4ºC and transferred to polypropylene tubes and stored frozen at -20ºC until assayed.

*Bioanalytical methods*
Plasma dexchlorpheniramine and betamethasone were quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS) method developed and validated. The apparatus used were a Waters Acquity UPLC System (Waters Corporation, MA, USA) coupled to a Mass Spectrometer Xevo TQS Detector (Waters Corporation, MA, USA) analyzer using the MassLynx™ software (Waters Corporation, MA, USA) in version 4.1. Chromatographic separation was performed using a Acquity UPLC BEH C8 1.7 µm column (2.1 x 50 mm, Waters) and VanGuard BEH C18 1.7 µm guard column (2.1 x 5.0 mm) heated at 30°C. The mobile phase consisted of ethyl acetate solution (2 mM)/acetonitrile (60:40, v/v) was delivered at a flow rate of 0.30 mL/min. Brompheniramine was used as internal standard (IS). Each 500 µL plasma sample spiked with 25 µL of IS solution (5000 ng/mL). Then 50 µL ammonium hydroxide (10 %) was added to alkalized the spiked sample before the following extracting process. After extracted by 1,00 mL methyl-tert-butyl-ether, dichloromethane and ethyl acetate (3:3:4, v/v/v) and then centrifuged, the 800 µL of supernatant were evaporated under compressed air until dry. The residue was dissolved in 200 µL ultrapure water and acetonitrile (60:40, v/v) and injected 5.0 µL.

Mass spectra were obtained using a tandem quadrupole equipped with a electrospray source (ESI) using a crossflow counter electrode was run in positive mode (ES+), and set up in multiple reaction monitoring (MRM), monitoring the transitions 275.22 > 230.00, 393.36 > 373.27 and 319.04 > 274.10 for dexchlorpheniramine, betamethasone and brompheniramine, respectively. The detailed MS parameters are show in Table 1. The total run time was 2.00 minutes and the retention time for dexchlorpheniramine (1.09 minutes), betamethasone (1.00 minute) and IS (1.16 minutes).

**Method validation**

Bioanalysis was performed under the Good Laboratory Practice and the bioanalytical process validated according to ANVISA, therefore taking into consideration the study linearity, precision and accuracy intra-assay and interassay, selectivity, lower limit of quantitation (LLOQ), recovery, matrix effect, ionic suppression and stability under different conditions.

Linearity was determined to assess the performance of the method. A linear least-squares regression with a weighting index of 1/x² was performed on the peak areas of dexchlorpheniramine / IS and betamethasone / IS to analytes concentration ratios for the eight plasma standards in duplicate to generate a calibration curves. In addition, a blank
and zero plasma samples were analyzed to confirm the absence to interference. The calibration curves were evaluated by correlation coefficient, slope and intercept. The quality control plasma samples were prepared accomplished daily by spiking drug-free with know amounts of analytes (Dexchlorpheniramine: 100 pg/mL LLOQ, 300 pg/mL, 4100 pg/mL and 8200 pg/mL; Betamethasone: 50 pg/mL LLOQ, 150 pg/mL, 4000 pg/mL and 8000 pg/mL).

Intra and inter-assay precision and accuracy were determined by repeated analysis of quality control plasma samples on the same day and on different days. Percentage coefficient of variation (CV%) was used as the measure of precision and accuracy. The accept criterion for the variation coefficient was no more than 20% deviation at LLOQ and no more than 15% deviation for standards above the LLOQ.

The recoveries of substances at the concentration range of curve were evaluated by comparison of the peak areas obtained after extration of know amount of dexchlorpheniramine, betamethasone and IS from plasma with those obtained from same amounts of unextracted drug.

Stabilities of the analytes in plasma were subjected to short-term incubation at room time, minimum 3 freeze/thaw cycles, post processing autosampler. Long-term stability was determined by comparing the results of analysis of plasma samples from quality controls maintained at storage temperature (-20 °C) for a time interval longer than that between the collection of the first biological volunteer sample in the clinical stage of the study and the analysis of the latter in the analytical stage, with the results of samples analyzed immediately after the preparation (freshly prepared samples).

**Pharmacokinetic and statistical analysis**

All pharmacokinetic and statistical analyses were performed using Phoenix WinNonlin™ 5.3 software version (Pharsigh Corporation, NC, USA). The pharmacokinetic parameters were determined after the quantification of plasma concentrations performed in the analytical stage and the non-compartmental model application. The peak plasma concentration (C_{max}) and the corresponding peak time (T_{max}) were obtained directly from individual plasma concentration–time profiles. The area under the curve (AUC_{0-t}) was calculated by the trapezoidal rule and the total AUC_{0-inf} was calculated according to the following equation:

\[ AUC_{0-inf} = AUC_{0-t} + C_t / K_{el} \]

where, \( C_t \) is the drug concentration last time and \( K_{el} \) is the elimination rate constant.
The pharmacokinetic parameters employed in the relative bioavailability / bioequivalence analysis were $C_{\text{max}}$ and AUC. For each of the parameters, the values obtained for the two products were subjected to analysis of variance (ANOVA) to assess the effect of treatment (formulation), periods, sequences and subjects parameters. The effects were tested at the 5% level of significance.

The traditional criterion of average bioequivalence was used, thus, a 90% confidence interval (CI) was constructed for the difference of log-transformed data averages of test drugs and reference, for $C_{\text{max}}$, AUC$_{0-4}$ and AUC$_{0-\infty}$ parameters. The antilogarithm of the obtained CI constituted the 90% CI for geometric averages ratio of these parameters: The two formulations were considered to be bioequivalent if the 90% CI for $C_{\text{max}}$ and AUC was located within 80% to 125%, according ANVISA.

3 RESULTS
3.1 SUBJECTS AND TOLERABILITY

The study was completed with 29 volunteers (15 men and 14 women), with 19 to 47 years old (mean ± SD; 30.00 ± 8.00) and body mass index (BMI) between 18.71 and 28.96 kg / m$^2$ (mean ± SD; 24.91 ± 2.44), which are part of the statistical analyses. Two volunteers dropped out of the study after the first period due to personal reasons. The volunteer 05 was withdrawn from the study during the first hospitalization period, due to an episode of vomiting before twice the Tmax, and was discharged from the study at 4:00 p.m. The most common adverse event reported by 6 volunteers was headache. Both formulations were well tolerated, no serious adverse events were reported or observed during the study. No clinical and laboratory abnormalities were found at the conclusion of the study.

Method validation and analysis of plasma samples

This liquid-liquid extraction performed due to relatively high plasma concentrations expected. The compounds were in positive eletrospray showing a more intense and stable signal for both analytes.

Calibrations curves acceptable linear relationships were found in the range of dexchlorpheniramine 100 pg/mL to 10000 pg/mL and betamethasone 50 pg/mL to 10000 pg/mL concentrations. The linear regression equations were $y = 0.00038 x + 0.00202$ and $y = 0.00014 x + 0.00083$ with the correlation coefficients ($r^2$) of 0.999 and 0.998 of dexchlorpheniramine and betamethasone, respectively. Calculations were performed according to the calibration curve constructed for dexchlorpheniramine and
betamethasone, analyzed in the MassLynx data system, using the calibration standards. These functions are calculated by the ratio between the peak areas of the analytes dexchlorpheniramine and betamethasone and brompheniramine (IS). Blank plasma samples plus standard internal were not select in constructing the calibration curves. The analytical method was sensitive, specific, precise and accurate. The chromatograms showed that three peaks were completely resolved from one another and also from plasma components. **Figura 1**

The limits of quantification were found as the lowest concentration on the calibration curves for which acceptable precision of 2.6%/4.0% and accuracy of 107.9%/113.6% of dexchlorpheniramine and betamethasone. Precision, measured as percent relative standard deviation (RSD%), were between 1.1–3.9% (dexchlorpheniramine) and 1.6–4.5% (betamethasone), intra-assay and between 0.5–2.0% (dexchlorpheniramine) and 0.6–5.3% (betamethasone), inter-assay. The recoveries of dexchlorpheniramine, betamethasone and brompheniramine from plasma were 95.7%, 88.7% and 89.9%, respectively. Stabilities of the analytes in plasma were subjected to short-term (8h) incubation at room time, four freeze/thaw cycles, post processing autosampler (9h) and storage for 3 months (-20°C).

**Pharmacokinetic and statistical analysis**

The mean plasma concentration-time profiles of the two formulations after single-dosing of dexchlorpheniramine (2.00 mg) and betamethasone (0.25 mg) are show in **Figure 2**. **Table 2**, shows the pharmacokinetic parameters of dexchlorpheniramine and betamethasone in 29 healthy volunteers after single dose. The 90% confidencial interval (CI) for the ratio on the log-transformed scale for primary variables (C\text{max} and AUC) laid between the predefined range of 80% - 125%. Results are presented in **Table 3**. No period, no formulation, and not sequence effects were found in the ANOVA analysis for the primary pharmacokinetics parameters. The Wilcoxon-Mann-Whitney test performed on un-transformed data of Tmax did not detect a statiscally significant difference between means.

**4 DISCUSSION**

Clinical studies of bioequivalence are the accepted gold standard to guarantee the efficacy of similar or generic medications. Their rationale is the monitoring of pharmacokinetic parameters after the administration of tested new reparation compared with the reference formulation of the drug studied. The ultimate target of such studies is
to evaluate the therapeutic interchangeability of tested formulations. Together with the pharmaceutical quality data of the new formulation, the search output of the bioequivalence study is one of the main parts of the registration file submitted to national regulatory authorities. Both formulations were well tolerated and all volunteers completed the study without any incidence of serious adverse events.

In this study, we used the liquid chromatography coupled to mass spectrometry to quantify dexchlorpheniramine and betamethasone in plasma by a single method of analysis. Various methods have been reported for the determination of betamethasone or dexchlorpheniramine alone or in combination with other drugs (Pereira et al., 2005; Raju et al., 2007; Zou, 2008; Moreno et al., 2010) but no method report for the simultaneous determination in plasma of this combination of drugs. The method validation results indicated that the specificity, precision, accuracy, recovery and stability of the present method were comparable to those previously reported methods for the determination of dexchlorpheniramine and betamethasone, bisedes the advantage of dosing both compounds simultaneously and rapidly, yet it is simple and can be used for pharmacokinetic or bioequivalence studies.

The aim of the present investigation was to demonstrate comparable bioavailability of two different tablet formulations. For AUC$_{0-t}$ and AUC$_{0-\infty}$ as well as C$_{\text{max}}$ the bioequivalence criteria were completely fulfilled. All other pharmacokinetic parameters were well comparable between both preparations. Thus, no relevant differences were found for T$_{\text{max}}$ and T$_{1/2}$.

The results of the present study showed that the 90 % confidence intervals of the test/reference AUC ratio and C$_{\text{max}}$ ratio were within the acceptance range for bioequivalence (80%-125%). The drugs dexchlorpheniramine and betamethasone were evaluated in both formulations according to the results obtained. The test formulation is statistically bioequivalent to the reference formulation in terms of rate and extent of absorption and therefore interchangeable.

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ANNEXES

Figura 1

a)

b)
Representative chromatograms of a) blank control plasma normal and b) plasma containing 100 pg/mL dexchlorpheniramine, 50 pg/mL bethametasone and 5000 pg/mL brompheniramine.

Figura 2

Profile of mean plasma concentrations of dexchlorpheniramine (DPN) and bethametasone (BMT) versus time, for one dose of the test and reference (REF) formulations.
Table 1. MS parameters on positive electrospray and selected reaction monitoring for the detection of dexchlorpheniramine (DPN), betamethasone (BMT) and brompheniramine (BPN).

| MS parameter                      | Setting value                       |
|-----------------------------------|-------------------------------------|
| Capillary (kV)                    | 3.50                                |
| Cone (V)                          | DPN / BMT / BPN: 24.0               |
| Source temperature (°C)           | 150                                 |
| Desolvation temperature (°C)      | 600                                 |
| Cone gas flow (L/h)               | 150                                 |
| Desolvation gas (mL/min)          | 1200                                |
| Collision gas (mL/min)            | 0.15                                |
| Low and high-mass resolution      | LM 1.2.6                            |
|                                  | HM 1.15.1                           |
| Ion energy 1                      | 1.0                                 |
| Entrance                          | DPN: 36.00                          |
|                                  | BMT: 6.00                           |
|                                  | BPN: 15.00                          |
| Collision energy (eV)             | DPN: 36.00                          |
|                                  | BMT: 6.00                           |
|                                  | BPN: 15.00                          |
| Exit                              | 1.0                                 |
| Low and high-mass resolution 2    | LM 2.2.8                            |
|                                  | HM 2.15.2                           |
| Ion energy 2                      | 0.6                                 |
| Multiplier                        | 516.00                              |
| Dwell (s)                         | DPN: 0.085                          |
|                                  | BMT: 0.050                          |
|                                  | BPN: 0.025                          |

Table 2. Pharmacokinetic parameters of dexchlorpheniramine and betamethasone after single-dosing in 29 healthy volunteers.

| PK parameter          | Dexchlorpheniramine | Betamethasone |
|-----------------------|---------------------|----------------|
|                       | Reference           | Test           | Reference           | Test           |
| Cmax (pg/mL)          | 4358.56 ± 1504.11   | 4265.85 ± 1363.41 | 2234.40 ± 574.27    | 2309.38 ± 531.64 |
| AUC_{0-1} (h*pg/mL)   | 97084.84 ± 32219.93 | 97631.27 ± 34659.01 | 25431.40 ± 6058.93  | 24392.98 ± 6137.76 |
| AUC_{0-inf} (h*pg/mL) | 104751.56 ± 37767.56 | 109428.08 ± 52634.88 | 27748.41 ± 6684.42  | 26619.17 ± 6644.90 |
| T_{max} (h)           | 2.62 ± 0.96         | 2.85 ± 1.39     | 2.02 ± 0.90         | 1.82 ± 0.83     |
| T \frac{1}{2} (h)     | 22.20 ± 8.46        | 24.03 ± 10.31   | 10.06 ± 3.47        | 10.43 ± 4.92    |

Table 3. Bioequivalence evaluation of two formulations of dexchlorpheniramine and betamethasone tablets after single-dosing in 29 healthy volunteers.
| PK parameter | Dexchlorpheniramine | Betamethasone |
|--------------|---------------------|---------------|
|              | Ratio (%) 90% IC (%) | Ratio (%) 90% IC (%) |
| C<sub>max</sub> | 98.53 93.10 - 104.28 | 103.60 95.90 - 111.92 |
| AUC<sub>0-t</sub> | 100.21 95.66 - 104.98 | 95.33 86.92 - 104.57 |
| AUC<sub>0-inf</sub> | 101.92 96.62 - 107.51 | 95.54 87.44 - 104.39 |