

## Original Article



# Comparison of pharmacokinetics and safety characteristics between two olopatadine hydrochloride 5 mg tablet formulations in healthy Korean subjects

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## ABSTRACT

Histamine acts by binding to four histamine receptors (H1 to H4), of which the H1 is known to participate in dilate blood vessels, bronchoconstriction, and pruritus. Olopatadine hydrochloride blocks the release of histamine from mast cells and it inhibits H1 receptor activation. Olopatadine hydrochloride is anti-allergic agent that is effectively used. The object of this study had conducted to compare the pharmacokinetics (PKs) and safety characteristics between olopatadine hydrochloride 5 mg (test formulation) and olopatadine hydrochloride 5 mg (reference formulation; Alerac<sup>®</sup>) in Korean subjects. This study had conducted an open-label, randomized, fasting condition, single-dose, 2-treatment, 2-period, 2-way crossover. Subjects received single-dosing of reference formulation or test formulation in each period and blood samples were collected over 24 hours after administration for PK analysis. A wash-out period of 7 days was placed between the doses. Plasma concentration of olopatadine were determined using liquid chromatography-tandem spectrometry mass (LC-MS/MS). A total of 32 subjects were enrolled and 28 subjects completed. There were not clinical significantly different in the safety between two treatment groups for 32 subjects who administered the study drug more than once. The geometric mean ratio of test formulation to reference formulation and its 90% confidence intervals for The peak plasma concentration ( $C_{max}$ ) and the areas under the plasma concentration–time curve from 0 to the last concentration ( $AUC_{last}$ ) were 1.0845 (1.0107–1.1637) and 1.0220 (1.0005–1.0439), respectively. Therefore, the test formulation was bioequivalent in PK characteristics and was equally safe as the reference formulation.

**Trial Registration:** Clinical Research Information Service Identifier: [KCT0005943](https://www.cris.kci.go.kr/clinical/registertable.do?registNo=KCT0005943)

**Keywords:** Olopatadine Hydrochloride; Bioequivalence; Pharmacokinetics

#### Trial Registration

Clinical Research Information Service  
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#### Conflict of Interest

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## INTRODUCTION

Histamine is a substance synthesized from histidine or released from mast cells. Histamine is released as a defense reaction of the body to external stimuli, and when histamine is released excessively, allergic reactions such as runny nose, pruritus, and urticaria occur. Histamine acts by binding to four histamine receptors (H1 to H4), of which the H1 is known to participate in increase vascular permeability, dilate blood vessels, bronchoconstriction, and pruritus caused by skin nerve stimulation [1-3].

Olopatadine hydrochloride is a selective histamine H1-receptor antagonist. Olopatadine hydrochloride inhibit the effects of histamine on capillaries, bronchial smooth muscles, and gastrointestinal smooth muscles, and inhibit histamine-induced pain and itching in the mucous membrane. Olopatadine hydrochloride is anti-allergic agent that is effectively used for allergic rhinitis and chronic urticarial [4,5]. In the previous studies, olopatadine hydrochloride reached the peak plasma concentration of  $48.11 \pm 15.58$  ng/mL at  $0.71 \pm 0.26$  hour, and half-life was  $4.88 \pm 1.14$  hours [6]. The time to reach the peak blood concentration is within 1 hour, so we can expect a quick treatment effect.

Olopatadine hydrochloride is approved by the Korean Ministry of Food and Drug Safety to take a 5 mg twice a day for adults. Therefore, Huons Co., Ltd. (Seongnam, Korea) aimed to develop a generic drug containing olopatadine hydrochloride 5 mg and collect the pharmacokinetic (PK) and safety characteristics of olopatadine hydrochloride in Korean subjects. We compared the PK and safety characteristics between olopatadine hydrochloride 5 mg (test formulation) and olopatadine hydrochloride 5 mg (reference formulation; Alerac<sup>®</sup>) in healthy Korean subjects.

## METHODS

### Subjects

This study had recruited for healthy Korean volunteers aged 19 years and over who weigh 55 kg or more and within  $\pm 20\%$  of percent change from ideal body weight (IBW). All volunteers were written informed consent through a consent form approved before all processes. The consent form was prepared in accordance with regulatory guidelines [7,8]. Volunteers who were judged to be in health based on the results of the screening test: medical history, pre-study interview, physical examination, vital signs, laboratory tests, and 12-lead electrocardiogram (ECG) were enrolled in this study. Those who were unable to comply with the restrictions of this study or who were unable to refrain from drinking and smoking 48 hours prior to study drug administration of each period were excluded.

### Study design

This study had an open-label, randomized, fasting condition, single-dose, 2-treatment, 2-period, 2-way crossover design.

The intra-subject variability of the primary endpoints ( $AUC_{last}$ ,  $C_{max}$ ) of PK of olopatadine was reported as reported as about 12.62%, 20.45%, respectively [9]. When test/reference geometric mean ratio was assumed 0.95 and consider 80%–125% bioequivalence range between treatment groups with 90% statistical power at the 0.05 level of significance, the

minimal sample size of subject was 26. The planned sample size of subject is 32 considering the dropout rate of about 20%. Volunteers judged appropriate through the screening visit were randomized to sequence A or sequence B at a 1:1 ratio with SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). The test formulation was test drug (Olopatadine hydrochloride 5 mg) manufactured by Huons Co., Ltd. and the reference formulation was “Allerac® 5 mg” (olopatadine hydrochloride 5 mg) manufactured by Kyowa Kirin Korea Co., Ltd. Subjects who randomized to sequence A were administered 1 tablet of reference formulation in period 1, 1 tablets of test formulation in period 2. Subjects who randomized to sequence B were administered 1 tablet of test formulation in period 1, 1 tablets of reference formulation in period 2. A wash-out period of 7 days was placed between study drug administrations of each period. The wash-out period of 7 days is more than 5 times of half-life of olopatadine [6].

During each period, the subjects were administered one tablet of reference formulation or one tablet of test formulation once daily with 150 mL of water after fasting for at least 10 hours. Blood sampling time for all subjects were: 0 (pre-dosing), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after dosing.

The study protocol was prepared in accordance with The International Council for Harmonisation of Technical Requirements for pharmaceuticals for Human Use (ICH) guidelines [10] and Korean Good Clinical Practice (KGCP) [11]. The study protocol was approved by the Institutional Review Board of the Chungnam National University Hospital, and then was conducted (approval date: 2019.1018). This study had registered with Clinical Research Information System (registration number: KCT0005943).

### Determination of plasma concentration

Blood samples were collected into EDTA K2 tubes. Collected blood samples were centrifuged at 3,000 rpm for 10 minutes at  $\leq 4^{\circ}\text{C}$  and plasma stored below  $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$  until analysis.

After pretreatment of 100  $\mu\text{L}$  of human plasma by the deproteination using acetonitrile (0.1% formic acid), the plasma olopatadine concentrations were determined by positive ion electrospray (ESI+) and multiple reaction monitoring (MRM) using validated liquid chromatograph-tandem mass spectrometer (LC-MS/MS). The ion transitions was  $m/z$  338.1 to 165.1 and  $m/z$  341.1 to 165.1 for olopatadine and olopatadine- $d_3$ , respectively. The used column was ZORBAX Eclipse Plus C18 (4.6  $\times$  100 mm, 3.5  $\mu\text{m}$ ). SCIEX Analyst (ver. 1.6.3) was used for detection. The mobile phase for olopatadine was 10 mM ammonium formate (0.1% formic acid) and acetonitrile (0.1% formic acid) in a 50:50 (v/v). The flow rate was 0.5 mL/min.

The determination method of plasma concentration was verified according to the guidelines [12,13]. Calibration standard responses, using linear regression (weighting factor 1/concentration<sup>2</sup>), were linear for olopatadine over the range of 0.5–250.0 ng/mL. The lower limit of quantification (LLOQ) was 0.5 ng/mL for olopatadine. The used internal standard was olopatadine- $d_3$ . It was validated using samples for calibration curve (0.5 [lower limits of quantification], 1, 5, 10, 50, 100 and 250 [upper limits of quantification] ng/mL) and quality control samples (1.5 ng/mL [low], 90 ng/mL [medium], 200 ng/mL [high]). The results were as follows: Intraday accuracy: 91.2%–103.3%; precision: 1.3%–6.0%; interday accuracy: 95.5%–101.7%; and precision: 1.7%–3.4%.

### PKs analysis

The PK parameters were calculated by non-compartmental methods based on the actual sampling times and using the Phoenix WinNonlin® software version 8.1 (Certara Inc., Princeton, NJ, USA).

The peak plasma concentration ( $C_{max}$ ) and the time to  $C_{max}$  values ( $T_{max}$ ) were directly determined from the plasma concentration-time curves. The areas under the plasma concentration–time curve from 0 to the last concentration ( $AUC_{last}$ ) was calculated using a linear trapezoidal method. The area under the plasma concentration versus time curve from time 0 to infinity ( $AUC_{inf}$ ) was calculated using the following equation:  $AUC_{last} + C_{last}/$  terminal elimination constant ( $\lambda_z$ );  $\lambda_z$  was estimated from the log-linear terminal part of the concentration-time curve and the  $C_{last}$  was the last measurable concentration. The terminal elimination half-life ( $t_{1/2}$ ) was calculated the  $\ln(2)/\lambda_z$ .

### Safety assessment

Safety was assessed based on adverse events (AEs), concomitant medications, physical examination, vital signs, laboratory tests, and ECG. All AEs were coded with system organ classes and preferred terms by Medical Dictionary for Regulatory Authorities version 21.1. concomitant medications were coded by Anatomical Therapeutic Chemical Classification System. The laboratory tests were performed before administration at each period and 7 ( $\pm$  2) days after the last administration, and the results before administration and after administration were compared.

### Statistical analysis

The statistical analysis was performed by using SAS software Version 9.4 (SAS Institute, Inc., Cary, NC, USA). All PK parameters were summarized by the treatment group using descriptive statistics. For the comparison of the PK characteristics between 2 formulations, the log-transformed data of primary PK parameters ( $AUC_{last}$  and  $C_{max}$ ) were analyzed using a mixed model. Sequence, period, and formulation were used as fixed effects while a participant nested within the sequence was used as a random effect. The geometric mean ratio (GMR) and its 90% confidence interval (CI) of test formulation to reference formulation were estimated for the primary PK parameters. The two formulations were considered bioequivalent if the 90% CI of the GMR of primary PK parameters is within the acceptance interval of 0.8–1.25.

## RESULTS

### Subjects and demographic characteristics

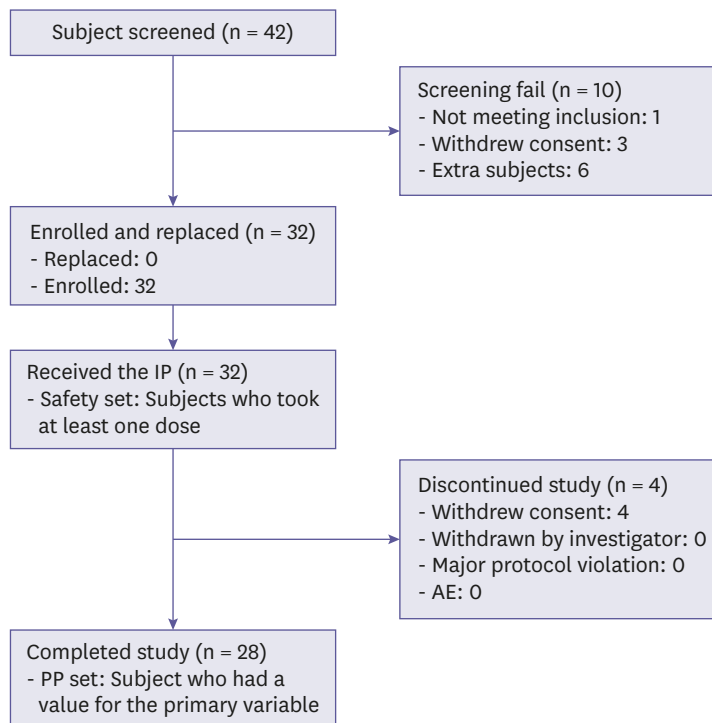
A total of 45 subjects who had signed the informed consent underwent screening test. And 32 subjects aged  $24.72 \pm 3.52$  years (21–34 years) with weight of  $69.43 \pm 8.11$  kg and height of  $173.58 \pm 5.89$  cm were enrolled. There was no significant difference in the mean age, height, weight between the two sequence groups (**Table 1**). The 32 subjects those who administered the study drug more than once were included in safety assessment. Four subjects withdrew their consent after administration of the study drug in period 1, and a total of 28 subjects completed the study. As a result, 28 subjects included in these pharmacokinetic assessment (**Fig. 1**).

**Table 1.** Demographic characteristics of the subjects enrolled

Characteristics	Sequence A (n = 16)	Sequence B (n = 16)	Total (n = 32)	p
Age (yr)	24.94 ± 4.39	24.50 ± 2.50	24.72 ± 3.52	0.7321*
Sex				-
Male	16	16	32	
Female	0	0		
Weight (kg)	70.71 ± 7.63	68.15 ± 8.61	69.43 ± 8.11	0.9743*
Height (cm)	173.55 ± 7.27	173.62 ± 4.34	173.58 ± 5.89	0.9743*

Values are presented as mean ± standard deviation.

\*t-test.



**Figure 1.** Disposition of the study participants.

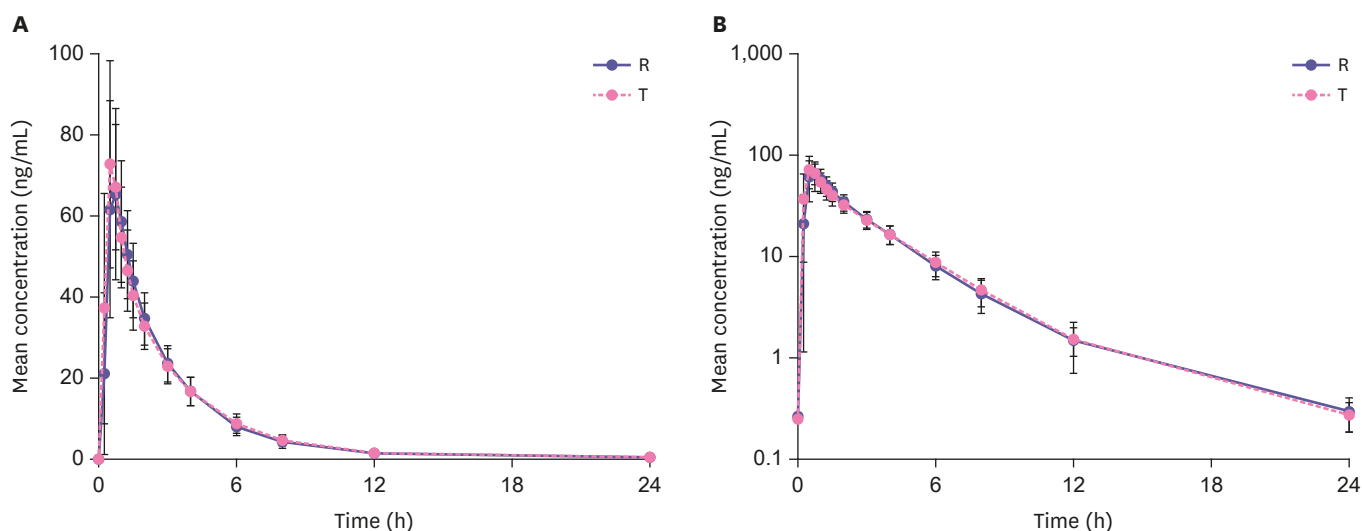
IP = investigational products; AE = adverse events; PP = per protocol.

### PK analysis

Reference formulation reached the peak plasma concentration at  $0.74 \pm 0.29$  hour, and  $t_{1/2}$  was  $3.44 \pm 0.75$  hours, and test formulation reached the peak plasma concentration at  $0.56 \pm 0.18$  hour, and  $t_{1/2}$  was  $3.39 \pm 0.51$  hours. The mean plasma concentration-time profiles after administrated olopatadine hydrochloride 5 mg was shown in **Fig. 2**. The PK parameters for the reference formulation and test formulation are shown in **Table 2**. The GMRs (90% CI) of the  $C_{max}$  and  $AUC_{last}$  were 1.0845 (1.0107–1.1637) and 1.0220 (1.0005–1.0439), respectively. The 90% CIs of GMR for primary PK parameters were within the range of 0.8–1.25, which is the criterion for bioequivalence (**Table 3**).

### Safety

A total of 3 subjects reported 3 cases of AE. One AE cases were reported in 1 subject after taking the test formulation and 2 AE cases were reported in 2 subjects after received the reference formulation (**Table 4**). All AEs were mild and resolved without any intervention. There were no AE leading to withdrawal or death and no serious AE. There were no clinically



**Figure 2.** Mean plasma concentration–time curves of olopatadine using (A) linear and (B) log-linear scales. Reference formulation: olopatadine hydrochloride 5 mg (Alerac®, Kyowa-Kirin Corp., Ltd., Tokyo, Japan), Test formulation: olopatadine hydrochloride 5 mg, Huons Corp., Ltd. (Seongnam, Korea).

**Table 2.** Summary of PK parameters

PK parameter	Test formulation (n = 28)	Reference formulation (n = 28)
Olopatadine hydrochloride 5 mg		
$C_{max}$ (ng/mL)	79.66 ± 21.96 (27.57)	72.69 ± 17.97 (24.72)
$AUC_{last}$ (ng·h/mL)	202.21 ± 199.59 (98.70)	198.23 ± 35.22 (17.77)
$AUC_{inf}$ (ng·h/mL)	203.50 ± 33.87 (16.64)	199.64 ± 35.55 (17.80)
$T_{max}$ (hr)	0.50 [0.25–1.25]	0.75 [0.50–1.50]
$t_{1/2}$ (hr)	3.39 ± 0.51 (15.04)	3.44 ± 0.75 (21.80)

Values are presented as the mean ± standard deviation (CV%) or median [minimum–maximum]. PK, pharmacokinetic;  $C_{max}$ , peak plasma concentration;  $AUC_{last}$ , areas under the plasma concentration–time curve from 0 to the last concentration;  $AUC_{inf}$ , areas under the plasma concentration–time curve from 0 to infinity;  $T_{max}$ , time to  $C_{max}$ ;  $t_{1/2}$ , terminal half-life; CV, coefficient of variation.

**Table 3.** Bioequivalence assessment of PK parameters

PK parameter	Geometric least squares mean ratio (test formulation/reference formulation)		Intra subject CV
	Point estimate	90% confidence interval	
Olopatadine hydrochloride 5 mg			
$C_{max}$	1.0845	1.0107–1.1637	15.47
$AUC_{last}$	1.0220	1.0005–1.0439	4.66

PK, pharmacokinetic; CV, coefficient of variation;  $C_{max}$ , peak plasma concentration;  $AUC_{last}$ , areas under the plasma concentration–time curve from 0 to the last concentration.

significant changes in the physical examination, vital signs, laboratory tests, and ECG result of after administration.

## DISCUSSION

This study object was to compare the PK and safety characteristics between two formulations containing olopatadine hydrochloride 5 mg in Korean subjects.

In two formulations, the GMR (90% CI) of the  $C_{max}$  and  $AUC_{last}$  were 1.0845 (1.0107–1.1637) and 1.0220 (1.0005–1.0439), respectively. The 90% CIs for GMR of primary PK parameters ( $C_{max}$  and  $AUC_{last}$ ) satisfied acceptable bioequivalence criteria, compared with reference

**Table 4.** Summary of adverse events

System organ class	Preferred term	Test (n = 30)			Reference (n = 30)			Total (n = 60)		
		n	%	#	n	%	#	n	%	#
Infections and infestations		1	3.3	1				1	1.7	1
	Nasopharyngitis	1	3.3	1				1	1.7	1
Investigations		1	3.3	1	1	3.3	1	2	3.3	2
	Alanine aminotransferase increased	1	3.3	1				1	1.7	1
	White blood cells urine positive				1	3.3	1	1	1.7	1

n, number of subjects with adverse events; %, percentage of subjects among n; #, number of adverse events.

formulation. Therefore, we confirmed that the test formulation had bioequivalent PK characteristics to the reference formulation.

$T_{max}$  of test formulation was 0.5 hour and reference formulation was 0.75 hour. The half-life of test formulation was 3.39 hours and reference formulation was 3.44 hour. From results of this study, we confirmed that the study design for sampling times and wash-out period met the guideline [14].

The intra-subject variability of  $C_{max}$  and  $AUC_{last}$  were 15.47% and 4.66%, respectively. If the results were used and the sample size was calculated the same as before, the minimum sample size was calculated as 16. Therefore, there were 16 or more subjects to completed this study, and the number of subjects was adequate for comparing the pharmacokinetics between the test formulation and the reference formulation. Also, this intra-subject variability is less than that of previous studies, and will be a reference that can prove bioequivalence with less exposure in next bioequivalence tests [15].

In conclusion, we confirmed that the PK characteristics for 2 formulations were within the bioequivalence range (0.8–1.25) and was equally safe as the reference formulation. Therefore, it has been demonstrated that test formulation can be used on an equal basis with the reference formulation as anti-allergic agents.

## REFERENCES

1. Assanasen P, Naclerio RM. Antiallergic anti-inflammatory effects of H1-antihistamines in humans. *Clin Allergy Immunol* 2002;17:101-139.  
[PUBMED](#)
2. Shimamura T, Shiroishi M, Weyand S, Tsujimoto H, Winter G, Katritch V, et al. Structure of the human histamine H1 receptor complex with doxepin. *Nature* 2011;475:65-70.  
[PUBMED](#) | [CROSSREF](#)
3. Thangam EB, Jemima EA, Singh H, Baig MS, Khan M, Mathias CB, et al. The role of histamine and histamine receptors in mast cell-mediated allergy and inflammation: the hunt for new therapeutic targets. *Front Immunol* 2018;9:1873.  
[PUBMED](#) | [CROSSREF](#)
4. Ohmori K, Hayashi K, Kaise T, Ohshima E, Kobayashi S, Yamazaki T, et al. Pharmacological, pharmacokinetic and clinical properties of olopatadine hydrochloride, a new antiallergic drug. *Jpn J Pharmacol* 2002;88:379-397.  
[PUBMED](#) | [CROSSREF](#)
5. Ohmori K, Hasegawa K, Tamura T, Miyake K, Matsubara M, Masaki S, et al. Properties of olopatadine hydrochloride, a new antiallergic/antihistaminic drug. *Arzneimittelforschung* 2004;54:809-829.  
[PUBMED](#) | [CROSSREF](#)
6. Chu NN, Chen WL, Xu HR, Li XN. Pharmacokinetics of orally administered single- and multiple-dose olopatadine in healthy Chinese subjects: an open-label study. *Clin Drug Investig* 2009;29:451-457.  
[PUBMED](#) | [CROSSREF](#)



7. Ministry of Food and Drug Safety. Guidelines for preparation of consent form for clinical trial subjects. Cheongju: Ministry of Food and Drug Safety; 2019.
8. Personal Information Protection Commission. Personal Information Protection Act, Updated 2017. Seoul: Personal Information Protection Commission; 2017.
9. Choi SW, Ryu JH, Park JS, Lee MJ, Yim SV, Lee KT. Development and validation for the determination of olopatadine in human plasma by liquid chromatography–tandem mass spectrometry: application to a bioequivalence study of Ilhwa Allotadine tablet (olopatadine HCl 5 mg). *J Pharm Investig* 2015;45:285-292.  
**CROSSREF**
10. Branch SK. Guidelines from the international conference on harmonisation. *J Pharm Biomed Anal* 2005;38:798-805.  
**PUBMED | CROSSREF**
11. Ministry of Food and Drug Safety. Korean good clinical practice. Cheongju: Ministry of Food and Drug Safety; 2019.
12. Ministry of Food and Drug Safety. Guideline on bioanalytical method validation. Cheongju: Ministry of Food and Drug Safety; 2013.
13. U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER); Center for Veterinary Medicine (CVM). Bioanalytical method validation guidance for industry. White Oak, MD: Food and Drug Administration; 2018.
14. Ministry of Food and Drug Safety. Guidance document for bioequivalence studies updated in 2019. Cheongju: Ministry of Food and Drug Safety; 2019.
15. Ring A, Lang B, Kazaroho C, Labes D, Schall R, Schütz H. Sample size determination in bioequivalence studies using statistical assurance. *Br J Clin Pharmacol* 2019;85:2369-2377.  
**PUBMED | CROSSREF**