Tamivil

Study Title:	Randomized, open-label, 2-way cross-over bioequivalence study comparing single dose of oseltamivir 75 mg (Oseltamivir Biofarm – tablets [Biofarm Sp. z o.o.] vs. Tamiflu – hard capsules [Roche]) under fasting conditions in healthy volunteers
Name of the test product:	Oseltamivir Biofarm 75 mg tablets (Biofarm Sp. z o.o.). Each tablet contains 75 mg of oseltamivir.
Name of the reference product:	Tamiflu 75 mg, capsule, hard (Roche). Each hard capsule contains 75 mg of oseltamivir.
Study design:	Single center, single dose, open-label (laboratory-blind), randomized, two-period, two-way cross-over bioequivalence study under fasting conditions in forty (40) healthy adult Subjects with a wash-out period 7-14 days between study products administration in Period 1 and Period 2. The duration of a wash-out period was determined after obtaining study approval and was the same for all Subjects (7-14 days).
Sponsor:	Biofarm Sp. z o.o. Wałbrzyska St.13, 60-198 Poznań, Poland
Protocol number:	OS/BP/08/14
EUDRACT No.:	2015-000721-36
Study code in Central Register of Clinical Trials:	UR.DBL.BLE.475.0194.2015
Independent Ethics Committee Study code:	KB/982/15
Clinical phase:	Bioequivalence study
GCP Statement:	The study was conducted in compliance with the approved Study Protocol No. OS/BP/08/14 version 1.0 of February 18th 2015, World Medical Association Declaration of Helsinki and its amendments [1], current Good Clinical Practice guidelines (Note for Guidance on Good Clinical Practice [2], Directive 2001/20/EC [3] and Directive 2005/28/EC [4]), Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).
Objectives and methodology:	The primary objective of the study was to evaluate the pharmacokinetic properties and investigate the bioequivalence of oseltamivir from the test product (Oseltamivir Biofarm - tablets, Biofarm Sp. z o.o.) compared to the reference product (Tamiflu 75 mg capsule, hard, Roche) containing the same amount (75 mg) of an active substance (oseltamivir), after single oral dose administration under fasting conditions. The secondary objective of the study was to evaluate the safety and tolerability of both study products. **Methodology:** The study was performed as a single center, single dose, open-label (laboratory-blind), randomized, two-period, two-way cross-over bioequivalence study under fasting conditions with a wash-out period of seven to fourteen (7-14) days between study products administration in Period 1 and Period 2. Blood for determination of plasma level of oseltamivir was collected up to twenty four (24) hours after study product administration, in eighteen (18) time points in each Period: pre-dose blood sample “0” was collected within 30 minutes before study product administration and then at the established time points 15 min, 30 min, 45 min, 1 h, 1 h 15 min, 1 h 30 min, 2 h, 2 h 30 min, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 16 h, 24 hours after study product administration.
Main criteria for inclusion/exclusion:	All Subjects had to meet the following criteria: 1. The Subject is healthy male or female. Healthy Subjects are defined as individuals who are free from clinically significant illness or disease as determined by their medical history, physical examination, laboratory and ECG tests. Medical history check will also include

	verification of data concerning special precautions for study drug use, as contraindicated by the reference product characteristics as well as history of diabetes and renal impairment. 2. If males: male Subjects who are willing to use an acceptable method of contraception from the first dosing until completion of the study (barrier methods with spermicide and sexual abstinence are allowed). 3. If females: female Subjects are eligible to enter and participate in the study if they are of: a. Non childbearing potential (i.e. physiologically incapable of becoming pregnant) including females who: have had a hysterectomy or a bilateral oophorectomy, or a bilateral tubal ligation, or are post-menopausal (a demonstration of total cessation of menses for ≥ 12 months on the day of screening). b. Childbearing potential and have a negative result of urine pregnancy test at screening and on the evening prior to the first dose administration and agree to use one of the following contraception methods: complete abstinence from sexual intercourses or double barrier method (condom or occlusive cap used with spermicidal foam) from at least 6 days prior to administration of the study product until completion of the study or use of intrauterine non-hormonal device within at least 4 weeks prior to the first study product administration until completion of the study. No hormonal contraceptives or hormone replacement therapy are permitted in this study. 4. The Subject is ≥ 18 and ≤ 55 years of age on the day of screening. 5. BMI ≥ 18.5 to ≤ 30.0 kg/m^2 (on the day of screening). 6. Caucasian race. 7. Signed and dated written informed consent of the Subject to participate in the clinical study prior to screening evaluations. 8. The Subject is willing to refrain from the use of illicit drugs and alcohol and to adhere to other protocol-stated restrictions while participating in the study. 9. The Subject is able to understand and comply with the protocol requirements and instructions and is likely to complete the study as planned. 10. Non-smoker and non-tobacco user for at least 3 months before the day of screening. A Subject who met at least one of the following criteria couldn't enter into the study: 1. A significant abnormality in the past and/or at screening that influences present general health condition and requires pharmacological treatment during the study. 2. Any confirmed allergic reaction to any drug including allergy to study products or multiple allergies, as clinically significant in the judgement of the Investigator. 3. Any current or past disease or condition (e.g. of the alimentary tract and/or liver and/or kidneys) that may influence the absorption and/or distribution and/or metabolism and/or elimination of the drugs as assessed by the Investigator, or would constitute a risk factor when taking the study drug. 4. Clinically significant in the judgement of Investigator events of haemorrhage and syncope in medical history. 5. History of drug addiction and/or alcohol abuse (alcohol consumption of more than 500 mL of beer/day or 200 mL of wine/day or 50 mL of liquor/day) during last year preceding the day of screening. 6. Hypersensitivity to oseltamivir and/or its derivatives and/or to any excipient of the study products. 7. Blood loss or donation exceeding 200 mL in the last 30 days before the day of screening. 8. Positive results of HBsAg and/or anti-HCV and/or anti-HIV-1+2 tests during screening procedures. 9. Blood pressure: systolic > 140 mmHg or < 90 mmHg, diastolic < 60 mmHg or > 90 mmHg during screening procedures and on the evening prior to the first dose administration. 10. Pregnant or breast-feeding females. 11. Positive urine pregnancy test on the day of screening or on the evening before the first study product administration. 12. Heart rate < 50 or > 100 bpm at screening and on the evening prior to the first dose administration. 13. Body temperature < 36.0°C or > 37.4°C at screening and on the evening prior to the first dose administration. 14. Clinically significant abnormal laboratory values at screening. 15. Clinically significant abnormalities in 12-lead ECG recording performed at screening. 16. Use of any over-the-counter medication (except for paracetamol at dose ≤ 1 g daily) including vitamins, lozenges, herbal and dietary supplements within 7 days before Day 0 in Period 1. 17. Use of any prescription drug within 14 days before Day 0 in Period 1.

18. Use of steroids or anabolic or hormonal therapy within 30 days before Day 0 in Period 1.
19. Special diet (e.g. low calories, vegetarian, etc.) during 4 weeks before the day of screening.
20. Any significant change in lifestyle: dietary or exercise habits during 4 weeks before the day of screening.
21. Consumption of products (e.g. food or drink) containing caffeine or other methylxanthines (i.e. coffee, tea, coke, chocolate, cocoa, energy drinks) within 48 hours prior to the first product administration.
22. Drinking grapefruit juice and/or other citrus juices and/or eating citrus products for 7 days prior to the first drug administration.
23. Alcohol consumption within 72 hours prior to the first product administration.
24. Positive urine test results for drugs of abuse on the day of screening (opiates, cannabinoids) or on the evening before the first study product administration (opiates, barbiturates, benzodiazepines, amphetamines, cocaine, cannabinoids).
25. Positive urine test result for cotinine on the day of screening or on the evening before the first study product administration (in 10%-20% of randomly selected volunteers).
26. Positive result of breath alcohol test on the day of screening or on the evening before the first study product administration.
27. Participation in other clinical trials where at least one dose of study product was administered within 30 days prior to the first dose administration.
28. For any reason the Subject is considered by the Investigator to be an unsuitable candidate to participate in the study.

Criteria for evaluation:

Pharmacokinetics:
Primary parameters: C_{max} and $AUC_{(0-t)}$ for oseltamivir. These primary pharmacokinetic (PK) parameters of oseltamivir were used for bioequivalence assessment.
Secondary parameters: $AUC_{(0-\infty)}$, T_{max}, K_{el}, AUC $_{\%Extrap\_Obs}$, and $T_{1/2}$ for oseltamivir.
Secondary PK parameters were evaluated to characterize the pharmacokinetic profile of the test and reference products, they were not used for bioequivalence assessment.

Safety and tolerability evaluation:
All Subjects exposed to the study at least once were part of the safety analysis. Clinical safety of the test and the reference product after a single dose administration in healthy Subjects was assessed taking into consideration medical history, physical examination, vital signs (heart rate (HR), blood pressure (BP), body temperature), 12-lead electrocardiogram (ECG), clinical laboratory tests (haematology, biochemistry, urinalysis, serology, and pregnancy urine tests – females only) and Adverse Events monitoring. Information on AEs was obtained by medical observations, laboratory test analysis and spontaneous Subjects' reporting after product administration and recorded by Investigators using CTCAE v. 4.03

Statistical analysis:
Descriptive statistics was performed for all 40 Subjects pharmacokinetic parameters including the arithmetic mean, geometric mean, standard deviation, coefficient of variation, median, range, minimum (min.) and maximum (max.).
Both test and reference products were assessed to be bioequivalent on the ground of analysis of variance (ANOVA) with factors for sequence, Subject within sequence, period and treatment. The decisive criterion was constituted by $AUC_{(0-t)}$ and C_{max} parameters for the parent compound (oseltamivir), whereas $AUC_{(0-\infty)}$ and the other variables were considered as the secondary pharmacokinetic parameters and constituted supportive data.
The conclusion on bioequivalence of the test product with the reference product was based on the results for ln-transformed C_{max} and $AUC_{(0-t)}$ of oseltamivir (primary pharmacokinetic study endpoints). If the 90% confidence intervals for the proportion of μ_T/μ_R (geometric means for the test and reference formulation) of primary pharmacokinetic parameters C_{max} and $AUC_{(0-t)}$ of oseltamivir were included entirely in the acceptance range of 80.00-125.00%, the test formulation (Oseltamivir Biofarm - tablets) was considered as bioequivalent to the reference formulation (Tamiflu 75 mg capsule, hard). All calculations were performed using SAS (version 9.4) software.

Number of Subjects (planned and analysed):

Number of Subjects:	Planned		Screened	Randomized and dosed	Completed	Statistically evaluated
	to be randomized and dosed	to complete the study				
	40	36	48	40	40	40

Study initiation date:	On July 6th 2015 the study initiation visit took place and on July 24th, 2015 the first Subject was screened.
Study completion date:	On August 30th 2015 the last Subject completed the study and on October 2nd 2015 the close-out visit took place.
Pharmacokinetic results:	The mean values of oseltamivir pharmacokinetic parameters for 40 Subjects who completed the whole study and were included in the summary of descriptive statistics were as follows:

REFERENCE PRODUCT – Tamiflu 75 mg capsule, hard

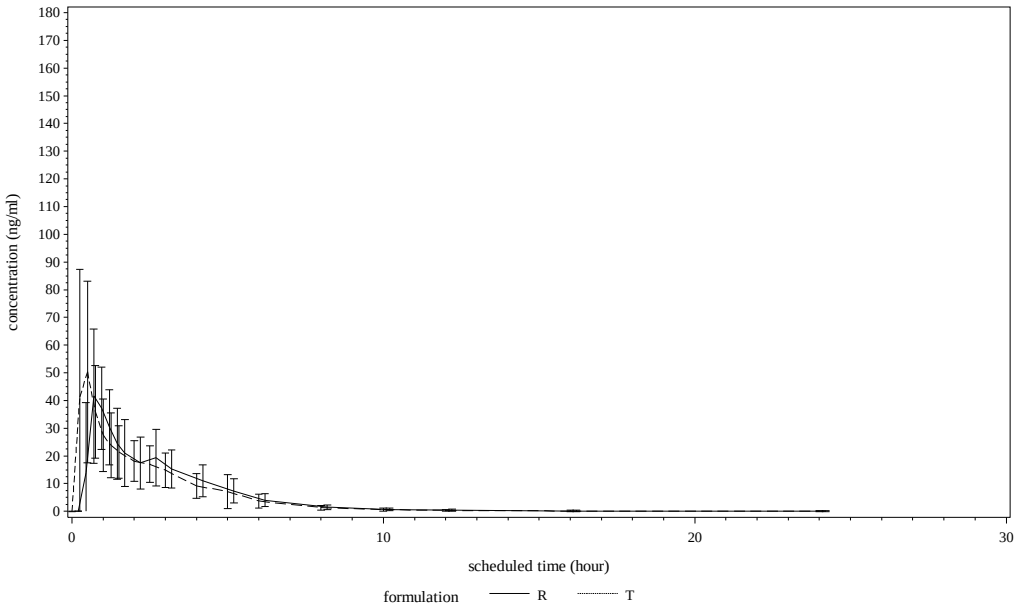
Parameter	$AUC_{0-t(last)}$ (ng*h/mL)	C_{max} (ng/mL)	$AUC_{(0-\infty)}$ (h*ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	MRT_{0-inf} (h)	$AUC_{\%Extrap\_Obs}$ (%)
N	40	40	40	40	40	40	40
Arithmetic mean	104.930	53.399	107.661	0.838	4.061	3.358	2.511
Geometric mean	100.690	49.462	103.307	0.701	2.826	3.112	1.900
SD	29.214	21.845	29.978	0.573	4.362	1.443	2.140

TEST PRODUCT – Oseltamivir Biofarm - tablets (75 mg)

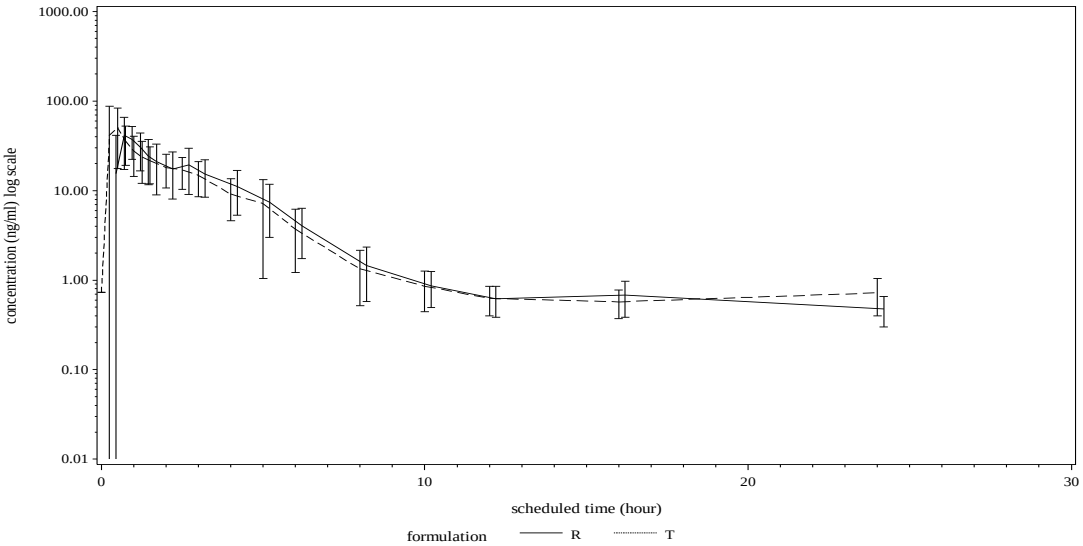
Parameter	$AUC_{0-t(last)}$ (ng*h/mL)	C_{max} (ng/mL)	$AUC_{(0-\infty)}$ (h*ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	MRT_{0-inf} (h)	$AUC_{\%Extrap\ Obs}$ (%)
N	40	40	40	40	40	40	40
Arithmetic mean	108.422	62.581	113.813	0.700	5.537	5.160	3.262
Geometric mean	102.599	50.639	106.633	0.532	2.572	2.924	1.712
SD	35.474	44.372	41.852	0.803	16.427	14.657	8.233

Mean oseltamivir plasma concentration vs. time curve (N = 40) following a single 75 mg oral dose of Oseltamivir Biofarm - tablets (Biofarm Sp. z o.o.) [test product, T] and single oral dose of Tamiflu 75 mg capsule, hard (Roche) [reference product, R] in linear- linear and log- linear scales are presented below:

A. linear / linear scale



B. log / linear scale



Bioequivalence comparison:

Statistical analysis summary

Pharmacokinetic parameters of oseltamivir after a single 75 mg dose

Parameter	T (geom. mean)	R (geom. mean)	T/R [%]	90% C.I. [%]
$AUC_{0\text{-}t(last)}$ [ng*h/mL]	102.599	100.690	1.0190	**0.9822-1.0571**
C_{max} [ng/mL]	50.639	49.462	1.0238	**0.8733-1.2001**
$AUC_{0\text{-}\infty}$ [ng*h/mL]	106.633	103.307	1.0322	**0.9843-1.0824**

T – test product (Oseltamivir Biofarm - tablets)
R – reference product (Tamiflu 75 mg capsule, hard)

Pharmacokinetic and statistical conclusion:

Based on the statistical results for the parent drug (oseltamivir) it can be concluded that the test product Oseltamivir Biofarm - tablets (Biofarm Sp. z o.o.) **is bioequivalent** with the reference product Tamiflu 75 mg capsule, hard (Roche).
The bioequivalence criteria with respect to the rate and extend of absorption of oseltamivir as per criteria set in the Study Protocol have been met: the 90% confidence interval for osletamivir $AUC_{(0\text{-}t)}$ and C_{max} T/R ratios are lying within the standard bioequivalence acceptance range of 80.00–125.00%. Such analysis was equivalent to two one-sided parametric t-tests according to Schuirmann.
The comparative statistics performed for the secondary pharmacokinetic parameters: $AUC_{(0\text{-}\infty)}$, T_{max}, AUC_%Extrap_Obs, $MRT_{0\text{-}inf}$, and $T_{1/2}$ for oseltamivir did not show significant differences between the test and the reference products **confirming the bioequivalence** of the two formulations.

Safety results:	During the study nine non-serious Adverse Events (AEs) were reported in five Subjects: three occurred after administration of test product and six after administration of the reference product. Out of the 40 Subjects who received products in Period 1, five experienced seven AEs (two classified as not related to the study product and five as possibly related to the study product). After product administration in Period 2, one Subject of 40 who continued the study experienced a total of two AEs (two classified as possibly related to the study product). Intensity of AEs were assessed as mild in eight cases and moderate in one case. All nine AEs were resolved. There were no deaths and serious adverse events (SAEs) during the conduct of the study.
Safety conclusion:	The clinical part of the study was completed without deaths, SAEs and suspected unexpected serious adverse reactions (SUSARs). During the study a total number of nine non-serious AEs were reported in five Subjects. Seven AEs were considered as possibly related to the study product, and two as not related. The intensity of these AEs was classified as mild in eight cases, and moderate in one case. Test product caused less AEs than the reference product (reference product - six AEs, test product – three AEs), although two of AEs reported after administration of the reference product were not related to the study product. Based on the clinical results of the study, it was clearly demonstrated that the test formulation of oseltamivir was tolerated in the same way as the reference drug. The safety profiles of both formulations are similar and do not differ from information described in the Investigator's Brochure.
Date of the Clinical Study Report:	November 25th 2015