Statistical Analysis Plan

Medical Statistics Core Facility
IDIBAPS (Institut d'investigacions Biomèdiques August Pi iSunyer)
[redacted]

Clinical Protocol	**TITLE:** Randomized, open-label, single-dose, two-sequence, two-period, crossover, comparative, oral bioequivalence study of Exib 120 mg etoricoxib film-coated tablets (PrJSC "Pharmaceutical firm "Darnitsa") and Arcoxia 120 mg etoricoxib film-coated tablets (Merck Sharp&Dohme B.V.) in healthy, adult volunteers under fasting conditions. **CLINICAL STUDY CODE:** 20ANE-3489C **Sponsor Study Code:** ETR01-E **EudraCT Number:** Not Applicable **Clinical Protocol Final Version:** Final 01, 23.DEC.20
Sponsor Global CRO	PrJSC "Pharmaceutical firm "Darnitsa", Ukraine Anapharm Europe, S.L.U., Spain
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Version and Date	Final 01, 25.FEB.21

2 SIGNATURES

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3 STUDY PERSONNEL

3.1 SPONSOR

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* PrJSC "Pharmaceutical firm "Darnitsa"
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4 STUDY OBJECTIVES

To evaluate and compare the bioavailability and therefore to assess the BE between a Test formulation of Exib 120 mg film-coated tablets (FCT) manufactured by PrJSC "Pharmaceutical firm "Darnitsa" (Ukraine) and a Reference formulation of Arcoxia®120 mg FCT manufactured by Merck Sharp&Dohme B.V. (The Netherlands) when administered orally at the same dose level to 28 healthy volunteers under fasting conditions, in a 2-way crossover design.

5 SCOPE OF ANALYSIS PLAN

This Statistical Analysis Plan (SAP) covers the bioequivalence assessment for study 20ANE-3489C, which will be performed by Medical Statistics Core Facility (MedStats) of IDIBAPS-Hospital Clínic. The SAP will follow the general regulatory recommendations given in the Guideline on the Investigation of Bioequivalence [1], as well as others specific guidance on methodological and statistical issues in bioequivalence studies [2].

6 SOFTWARE METHODS

The determination of pharmacokinetic (pk) parameters will be carried out using Phoenix® WinNonLin® v8.2 or an upgraded version [3] and the pharmacokinetic analysis will be performed with the SAS® System [4](Release 9.4 or an upgraded version).

All tables, figures and listings will be presented in WinWord (Version Microsoft Office 2007) documents.

7 STUDY DESIGN

This is an open-label, two-period, two-sequence, two-way crossover, randomised, single dose bioequivalence study in healthy male volunteers under fasting conditions. Treatment periods will be separated with a washout period of at least 14 days.

Each study subject will be randomly assigned (in accordance with the Randomization List) to receive one FCT of either Test or Reference medication on Day 1 of each study period.

The following measures will be implemented to reduce bias:

- Subjects will be sequentially assigned to receive either Test or Reference product in a random fashion.
- Eligibility of subjects will be based on the fulfillment of all study inclusion and exclusion criteria.
- The Clinical Unit (CU) staff will monitor and record subject's compliance and any non-compliance with the protocol requirements.

The Bioanalytical Laboratory staff will not have access to the study Randomization List.

8 JUSTIFICATION OF SAMPLE SIZE

Based on published data [5] [6] [7] [8], the highest intra-subject Coefficient of Variation (CV) following an oral single dose of etoricoxib 120 mg appears to be approximately 20% for C_{max}. Taking into account this value and assuming the a priori maximum difference of 5% between formulations, according to the approach of Zhang P [9] it is estimated that a sample size of 26 subjects in a two-period, two-sequence design should be sufficient to meet the bioequivalence (BE) range with a statistical a priori power of at least 90% with an alpha level protection of 0.05. Therefore, the inclusion of 28 subjects should be sufficient to also cover any potential drop-outs/withdrawals and variations around the estimated intra-subject CV.

To ensure that 28 volunteers are administered with the study medication, at least 2 standby subjects will remain at the CU until the last subject is dosed in the first study period.

9 RANDOMIZATION PROCEDURE

A number between 001 and 028 allocated to each subject after inclusion represents the randomization number (subject study number) of the subject. The numbers will be allocated to each volunteer according to the order of admission to the CU in Period 1.

The randomization list was generated using the software: proc Plan of SAS® System (Release 9.4 or an upgraded version), which assigns random numbers and treatments/periods to subjects.

The following table shows the generated volunteers randomization.

Subject	StudyId	Sequence	P1	P2
001	20ANE-3489C	TR	T	R
002	20ANE-3489C	RT	R	T
003	20ANE-3489C	TR	T	R
004	20ANE-3489C	RT	R	T
005	20ANE-3489C	TR	T	R
006	20ANE-3489C	RT	R	T
007	20ANE-3489C	TR	T	R
008	20ANE-3489C	RT	R	T
009	20ANE-3489C	RT	R	T
010	20ANE-3489C	TR	T	R
011	20ANE-3489C	RT	R	T
012	20ANE-3489C	TR	T	R
013	20ANE-3489C	TR	T	R
014	20ANE-3489C	RT	R	T
015	20ANE-3489C	TR	T	R
016	20ANE-3489C	RT	R	T
017	20ANE-3489C	TR	T	R
018	20ANE-3489C	RT	R	T
019	20ANE-3489C	TR	T	R
020	20ANE-3489C	RT	R	T
021	20ANE-3489C	TR	T	R
022	20ANE-3489C	RT	R	T
023	20ANE-3489C	RT	R	T
024	20ANE-3489C	TR	T	R
025	20ANE-3489C	RT	R	T
026	20ANE-3489C	TR	T	R
027	20ANE-3489C	RT	R	T
028	20ANE-3489C	TR	T	R

Treatment T:
Exib 120 mg film-coated tablets.
Manufactured by: PrJSC "Pharmaceutical firm "Darnitsa". Ukraine

Treatment R:
Arcoxia® 120 mg film-coated tablets.
Manufactured by: Merck Sharp&Dohme B.V., The Netherlands

10 TIME POINTS FOR PHARMACOKINETIC SAMPLES

The following table shows the pharmacokinetic samples schedule for each study period.

Sample No.	Sampling Time (h)
01	0.000 (Pre-dose)
02	0.083
03	0.167
04	0.250
05	0.333
06	0.500
07	0.750
08	1.000
09	1.250
10	1.500
11	2.000
12	3.000
13	4.000
14	6.000
15	8.000
16	12.000
17	24.000
18	36.000
19	48.000
20	72.000

11 STATISTICAL ANALYSIS

11.1 Pharmacokinetic population

Data from subjects who provide evaluable pk profiles for both Test and Reference products will be included in the pk and statistical analysis for bioequivalence determination. Subjects that are non-evaluable for a particular study period (or treatment in this case, as the study is a two-way crossover) are:

- Subjects with a pre-dose concentration greater than 5% of the C_{max} value for the subject in that period.

  (Note that if a pre-dose concentration of etoricoxib in Period 1 or 2 is detected but is equal to or less than 5% of the C_{max} value for the subject in that Period, the subject's data will be included in the pk and statistical analysis without adjustment).

- Subjects presenting no measurable concentrations or only very low plasma concentrations for the Reference product (i.e. $AUC_{0\text{-}72h}$ (or $AUC_{0\text{-}t}$ if applicable) is less than 5% of the Reference product geometric mean $AUC_{0\text{-}72h}$ (or $AUC_{0\text{-}t}$ if applicable), which should be calculated without inclusion of data from the outlying subject): These subjects will be excluded from the pk and statistical evaluation. However, an additional statistical evaluation including such subjects will be performed and presented in the Statistical Report.

- Subjects who experienced any circumstance(s) that could imply that the plasma concentration-time profile is unreliable (i.e. due to AEs, concomitant medications, violation of study restrictions, missing pk samples): In these cases, decisions on the non-inclusion of these subjects in the pk and statistical analysis will be made by the Sponsor prior to the start of the bioanalysis. In case of missing pk samples, subjects will be only excluded from both pk and statistical analysis when there are more than 2 consecutive missing samples along the concentration-time profile. However, a sensitive analysis (bioequivalence assessment) will be performed including these subjects.

Although not included in the statistical BE assessment, pk parameters of non-evaluable subjects as per criteria mentioned above will be calculated if enough data are available and will be presented separately.

Samples from drop-out/withdrawal subjects will be assayed; however, subjects who do not provide evaluable data for both Test and Reference products (according to the above mentioned criteria), will not be included in the statistical analyses for BE determination and will be presented separately. If there are enough data available, pk parameters will be calculated for these subjects and will be presented separately.

In cases where concentrations of etoricoxib cannot be determined due to bioanalytical or clinical reasons, these values will be set to missing (no value) for the pk analysis.

Below LLOQ (Lower Limit of Quantification) concentrations will be treated as zero for all statistical analyses.

Any decision for excluding data from the final data set will be provided with a detailed explanation and will be properly recorded and dated.

11.2 Pharmacokinetic Study Variables

Etoricoxib plasma concentrations achieved by administering a single dose of study medication (T or R) will be measured to determine the pharmacokinetic profile of the Test product in relation to the Reference product.

The pk parameters that will be estimated are listed below:

11.2.1 Primary Variables

The main PK parameters of interest for this study will be C_{max}, and AUC_{0-72h}.

C_{max}: Maximum observed plasma concentration, obtained directly from the data – without interpolation.

AUC_{0-72h}: Cumulative area under the plasma concentration time curve calculated from 0 to 72 hours, using the mixed model linear log trapezoidal rule. If there are concentrations below LLOQ (Lower Limit of Quantification) at 72 hours post-dose in at least one subject, then AUC_{0-t} will be calculated for all volunteers instead of AUC_{0-72h}.*

***AUC_{0-t}** (if applicable): Cumulative area under the plasma concentration time curve calculated from 0 to the last observed concentration above Lower Limit Of Quantification (LLOQ), using the mixed model linear log trapezoidal rule.

11.2.2 Secondary Variables

t_{max} will be provided for information purposes only.

t_{max}: Time of maximum observed plasma concentration; obtained directly from the data, without interpolation. If it occurs at more than one time point, t_{max} is defined as the first time point with this value.

*The following PK parameters will be calculated only in the event that not all subjects have quantifiable concentration levels at 72 hours post-dose (in addition to AUC_{0-t}, C_{max} and t_{max}). They will be provided for information purposes only:

$AUC_{0-\infty}$: Area under the plasma concentration time curve extrapolated to infinity.

Residual area (AUC%extra or Extrapolated %AUC): Extrapolated area calculated as follows: $(AUC_{0-\infty} - AUC_{0-t}) / AUC_{0-\infty} * 100$.

k_{el} (λ_z): Elimination rate constant.

$t_{1/2}$: Plasma half life, calculated as $0.693/k_{el}$.

11.3 Descriptive Statistics

The concentrations will be listed and described by formulation and theoretical time and the pharmacokinetic parameters will be listed and described by formulation.

The following descriptive statistics will be used: Mean, SD, Minimum, P25, Median, P75, Maximum, CV, 95% CI of Mean, Geometric Mean, SD (log), CV (Geometric Mean) and N.

Additionally the same listing and descriptive analyses will be performed separately for subjects not included in the statistical bioequivalence assessment (i.e. not included in the pharmacokinetic population, see section 11.1).

For C_{max} and AUC_{0-72h} (or C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, if applicable) individual ratios (T/R) will be presented as part of the descriptive analysis.

11.4 Pharmacokinetic Parameters Determination

The pharmacokinetic parameters will be estimated according to a non-compartmental approach with a log-linear terminal phase assumption using the drug concentration profiles and the actual sampling times with Phoenix WinNonLin v8.2 or an upgraded version [3].Values below the lower limit of quantification in the absorption phase and in the terminal phase will be set to zero. AUC_{0-72h} (or AUC_{0-t}, if applicable) will be calculated using the mixed model linear log trapezoidal rule.

Missing concentration will be treated as missing (no value) in pharmacokinetic parameters calculation.

The Global CRO will provide the Medical Statistics Core Facility (MedStats) of IDIBAPS-Hospital Clínic with the etoricoxib plasma concentrations and the actual sampling times.

Actual sampling times will be listed for each subject by period.

For AUC_{0-72h} (or AUC_{0-t}, if applicable) calculation, the linear trapezoidal rule will be used up to C_{max}, according to this formula:

$$AUC\Big|_{t_1}^{t_2} = \delta_t * \frac{C_1 + C_2}{2}$$

and the log trapezoidal rule from then to the last time measurement:

$$AUC\Big|_{t_1}^{t_2} = \delta_t * \frac{C_1 - C_2}{\ln\left(\frac{C_1}{C_2}\right)}$$

where $\delta_t=(t_2-t_1)$.

In case $AUC_{0-\infty}$ is calculated, it will be done by extrapolating to infinity AUC_{0-t}, by means of the following formula:

$AUC_{0-\infty}= AUC_{0-t} + C_n/\lambda_z$

where the C_n is the last concentration measured, and λ_z is the terminal rate constant obtained by the slope (λ_z = -1*estimated slope) of the log-linear regression analysis on data points assessed to be on the terminal log-linear phase.

The selection of the data points of the terminal log-linear phase will be obtained automatically by WinNonLin® (using at least three available above LLOQ concentration points occurring after C_{max}).

The extrapolation to infinity will be performed by regression with the last log-transformed data to estimate the terminal area by means of the line which maximized R'^2. The R'^2 is calculated by WinNonLin® according to this formula:

$$R'^2 = 1 - \frac{(1-R^2)(n-1)}{(n-2)}$$

Basically, this method weighted the R^2 by the number of points used in the regression model. After an initial automatic step performed by WinNonLin®, it will be checked that no R'^2 had been calculated using a time point $\leq t_{max}$. In this case, a manual adjustment will be performed to select the best R'^2 in concordance with the rule described.

The maximum plasma concentration (C_{max}) and the time of the peak concentration (t_{max}) will be directly derived from the plasma concentration-time curve.

In case $t_{1/2}$ (terminal half life) is calculated, it will be derived from the computed value of λ_z

and then

$$t_{1/2} = \ln(2) / \lambda z$$

11.5 Pharmacokinetics Statistical Methods

The level of significance will be set to the standard value of 5% (0.05) for all statistical tests.

11.5.1 Study of period, sequence and formulation effect

An analysis of variance (ANOVA) will be performed for the estimated values (ln-transformed values) of C_{max} and AUC_{0-72h} (or C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, when applicable) using the SAS® System[4] (Release 9.4 or an upgraded version) and the following model (with GLM method):

$$Y = \mu + \text{Sequence} + \text{Subject (Sequence)} + \text{Formulation} + \text{Period}$$

with all factors declared as fixed effects.

In the event that the study is conducted in two or more groups and those groups are dosed at the same Clinical Unit but greatly separated in time (1 month or more), the statistical model will be modified accordingly to incorporate the group effect. The fixed factors included in the modified model will be the study group, the treatment received, the period at which it was given, the sequence in which each treatment is received and the subject effect (nested within the group-by-sequence interaction).

In case of any significant effect by period or sequence, the magnitude of the effect will be calculated in terms of the ratio of both levels using geometric means.

11.5.2 Bioequivalence Assessment Criteria

The decision on bioequivalence will be based on C_{max} and AUC_{0-72h} using ln-transformed data.

The following margins are pre-defined for the acceptance of bioequivalence:

- Ln [C_{max}]	± 20% range [80.00% - 125.00%]
- Ln [AUC_{0-72h}]	± 20% range [80.00% - 125.00%]

In case of not all subjects have quantifiable concentration levels at 72 hours post-dose, the decision on bioequivalence will be based on C_{max} and AUC_{0-t} using ln-transformed data. The analysis of $Ln[AUC_{0-\infty}]$ will be considered only as additional information. The following margins are pre-defined for the acceptance of bioequivalence:

- Ln [C_{max}]	± 20% range [80.00% - 125.00%]
- Ln [AUC_{0-t}]	± 20% range [80.00% - 125.00%]

The variability estimated from the residual error of the ANOVA model detailed in section 11.5.1, will be used for the estimation of the 90% confidence interval.

The MSE (Mean Square Error) of the same ANOVA model will be used to calculate the Intra-subject coefficient of variation as follows: CV(%)=100 x $\sqrt{e^{MSE}-1}$ for ln-transformed data.

11.5.3 t_{max} treatment comparison

Test vs Reference t_{max} comparison will be performed, as an exploratory analysis, by means of the same ANOVA model shown in section 11.5.1 but with a previous rank-transformation of un-transformed data.

11.5.4 Graphic representation

The individual plasma concentration/time profiles (linear and semi-log scales) will be presented using the actual sampling times whereas the mean plasma concentration/time profiles (linear and semi-log scales) will be presented using the theoretical sampling times by treatment. Individual plasma concentrations per treatment will be presented as spaghetti plots.

12 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The Quality Control procedures for statistical analyses and Pharmacokinetic Statistical Report elaboration will be performed following the current Medical Statistics Core Facility (MedStats) SOPs.
Quality Assurance procedures on Pharmacokinetic Data management within Global CRO will follow the current related Global CRO SOPs.

13 STATISTICAL REPORT

A Pharmacokinetic Statistical Report will be generated for this study including the tables, listings and figures specified in section 14.

14 LIST OF TABLES, LISTINGS AND FIGURES TO BE INCLUDED IN THE PHARMACOKINETIC STATISTICAL REPORT

14.1 Tables

Table 1	Pk statistical analysis population.
Table 2.1	Bioequivalence Assessment Summary.
Table 2.2	Bioequivalence Assessment Summary. Additional information (if applicable).
Table 3.1	Summary of ANOVA effects.
Table 3.2	Summary of ANOVA effects. Additional information.
Table 4.1	Summary of Pharmacokinetic parameters analysis. Pharmacokinetic Population.
Table 4.2	Summary of Pharmacokinetic parameters analysis. Subjects not included in Pharmacokinetic population.
Table 5.1	Table theoretical time-actual time by period. Pharmacokinetic Population.

Table 5.2 Table theoretical time-actual time by period. Subjects not included in Pharmacokinetic population.
Table 6.1 Table time-concentration by treatment. Pharmacokinetic Population.
Table 6.2 Table time-concentration by treatment. Subjects not included in Pharmacokinetic population
Table 7 Table time-concentration for statistically significant effects (by sequence or by period).
Table 8.1 Table of pharmacokinetic parameters by treatment. Pharmacokinetic Population.
Table 8.2 Table of pharmacokinetic parameters by treatment. Subjects not included in Pharmacokinetic population.
Table 9 Table of pharmacokinetic parameters for the statistically significant effects (by sequence or by period).
Table 10 Table of C_{max} and AUC_{0-72h} (or C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, if applicable) individual ratios (T/R).

14.2 Figures

Figure 1 Individual time-concentration curves by subject.
Figure 2 Mean time-concentration curves by formulation.
Figure 3 Time-concentration curves and regression in semi-log scale by subject and formulation.
Figure 4 Mean Time-concentration curves in semi-log scale by formulation.
Figure 5 Spaghetti plot by formulation.

14.3 Listings

Listing 1 Bioequivalence assessment and ANOVA effects. Ln(C_{max}).
Listing 2 Bioequivalence assessment and ANOVA effects. Ln(AUC_{0-72h} or AUC_{0-t} if applicable).
Listing 3 Bioequivalence assessment and ANOVA effects. Ln($AUC_{0-\infty}$ if applicable).
Listing 4 Treatment comparison. t_{max}.
Listing 5 Pharmacokinetic Parameter Calculation Listings.

15 ORGINAL RANDOM LIST

See Appendix 1 for the signed original random list.

16 REFERENCES

1. CPMP/EWP/QWP/1401/98 Rev. 1 Corr**. Guideline on the investigation of Bioequivalence. London, 20 January 2020.
URL: https://www.ema.europa.eu/en/investigation-bioequivalence, last access: 23-Feb-2021.
2. EMA/618604/2008 Rev 13. Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party (PKWP).URL: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/clinical-pharmacology-pharmacokinetics-questions-answers, last access: 23-Feb-2021.
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4. SAS® version 9.4 software or upgraded version, SAS® Institute Inc., Cary, NC, URL: http://www.sas.com/, last access: 23-Feb-2021.
5. Etoricoxib Alter 30 mg, 60 mg, 90 mg and 120 mg Film-Coated Tablets (ES/H/0411/001-004/DC). Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). [Online].; January 2017. Access on 23-Feb-2021. Available at:https://cima.aemps.es/cima/pdfs/ipe/81826/IPE_81826.pdf.
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7. Tjandrawinata R.,et al. Pharmacokinetic equivalence study of nonsteroidal anti-inflammatory drug etoricoxib. Clinical Pharmacology: Advances and Applications. 2018;(10): p. 43-51.
8. Najib O.,et al. Bioequivalence Evaluation of Two Brands of Etoricoxib 120 mg Tablets (Etoricoxib-SAJA & ARCOXIA®) – in Healthy Human Volunteers. Modern Clinical Medicine Research. 2017; 1(1).
9. Zhang P. A simple formula for sample size calculation in equivalence studies. J Biopharm Stat. 2003; 13(3): p. 529-538.

17 TABLE TEMPLATES

Tables 1, 2.1, 2.2, 3.1 and 3.2 will be performed manually. The rest of tables, listings and figures will be generated automatically from the software and will not be edited.

Table 1. Pk statistical analysis population.

Subject	*Sequence*	*Period 1*	*Period 2*	*Included/Non-included in pharmacokinetic statistical population*	*Reason for pk statistical analysis exclusion*

Ref.: Arcoxia® 120 mg film-coated tablets (Merck Sharp&Dohme B.V., The Netherlands).
Test: Exib 120 mg film-coated tablets tablets (PrJSC "Pharmaceutical firm "Darnitsa". Ukraine).

Table 2.1. Bioequivalence Assessment Summary.

ln-transformed data*	**Geometric LSMEANS**		**Bioequivalence assessment**		**Intra-subject coefficient of variation (%)****
	Test	**Reference**	**T/R Ratio (%)**	**90%CI£ (%)**	
C_{max} (ng/mL)					
$AUC_{0\text{-}72h}$ (h*ng/mL) or $AUC_{0\text{-}t}$ (h*ng/mL) if applicable					

£: classic parametric CI.
*: Analysis of variance according to the first model of section 11.5.1

**: Intra-subject coefficient of variation= CV(%)= 100 x $\sqrt{e^{MSE}-1}$. MSE=Mean Square Error.
Source: listings 1 and 2.
Ref.: Arcoxia® 120 mg film-coated tablets (Merck Sharp&Dohme B.V., The Netherlands).
Test: Exib 120 mg film-coated tablets tablets (PrJSC "Pharmaceutical firm "Darnitsa". Ukraine).

Table 2.2. Bioequivalence Assessment Summary. Additional information (if applicable).

ln-transformed data*	**Geometric LSMEANS**		**Bioequivalence assessment**		**Intra-subject coefficient of variation (%)****
	Test	**Reference**	**T/R Ratio (%)**	**90%CI£ (%)**	
$AUC_{0\text{-}\infty}$ (h*ng/mL)					

£: classic parametric CI.
*: Analysis of variance according to the first model of section 11.5.1

**: Intra-subject coefficient of variation= CV(%)= 100 x $\sqrt{e^{MSE}-1}$. MSE=Mean Square Error.
Source: listing 3.
Ref.: Arcoxia® 120 mg film-coated tablets (Merck Sharp&Dohme B.V., The Netherlands).
Test: Exib 120 mg film-coated tablets tablets (PrJSC "Pharmaceutical firm "Darnitsa". Ukraine).

Table 3.1 Summary of ANOVA effects.

Parameters	p-values for the assessed effects		
	Sequence	Period	Formulation
C_{max} (ng/mL)			
AUC_{0-72h} (h*ng/mL) or AUC_{0-t} (h*ng/mL) if applicable			

Grey cells: statistically significance
Source: listings 1 and 2
Ref.: Arcoxia® 120 mg film-coated tablets (Merck Sharp&Dohme B.V., The Netherlands).
Test: Exib 120 mg film-coated tablets tablets (PrJSC "Pharmaceutical firm "Darnitsa". Ukraine).

Table 3.2. Summary of ANOVA effects. Additional information. (If applicable)

Parameter	p-values for the assessed effects		
	Sequence	Period	Formulation
$AUC_{0-\infty}$ (h*ng/mL) if applicable			

Grey cells: statistically significance
Source: listing 3
Ref.: Arcoxia® 120 mg film-coated tablets (Merck Sharp&Dohme B.V., The Netherlands).
Test: Exib 120 mg film-coated tablets tablets (PrJSC "Pharmaceutical firm "Darnitsa". Ukraine).

Tables 4.1 and 4.2. Summary of Pharmacokinetic parameters analysis.

Parameters	Test*	Reference*
C_{max} (ng/mL)		
AUC_{0-72h} (h*ng/mL) or AUC_{0-t} (h*ng/mL) if applicable		
$AUC_{0-\infty}$ (h*ng/mL) if applicable		
t_{max} (h) median (range)		
Extrapolated %AUC if applicable		
λ_z (h-1) if applicable		
$t_{1/2}$ (h) if applicable		

*: Median (Min-Max) for t_{max} and Mean (SD) for the other parameters
Ref.: Arcoxia® 120 mg film-coated tablets (Merck Sharp&Dohme B.V., The Netherlands).
Test: Exib 120 mg film-coated tablets tablets (PrJSC "Pharmaceutical firm "Darnitsa". Ukraine).

Tables 5.1 and 5.2. Table theoretical time-actual time by period.

Period =XXXX.
Actual Time (h)

			Theoretical_Time (h)																		
Subject	Seq	Treat	Baseline	0.083	0.167	0.250	0.333	0.500	0.750	1.000	1.250	1.500	2.000	3.000	4.000	6.000	8.000	12.000	24.000	36.000	48.000	72.000

Grey cells: difference between real time y actual time.
Ref.: Arcoxia® 120 mg film-coated tablets (Merck Sharp&Dohme B.V., The Netherlands).
Test: Exib 120 mg film-coated tablets tablets (PrJSC "Pharmaceutical firm "Darnitsa". Ukraine).

Tables 6.1 and 6.2. Table time-concentration by treatment.

Treat =XXXX. Concentration (ng/mL)

			Theoretical_Time (h)																			
Subject	Seq	Period	Baseline	0.083	0.167	0.250	0.333	0.500	0.750	1.000	1.250	1.500	2.000	3.000	4.000	6.000	8.000	12.000	24.000	36.000	48.000	72.000
N																						
NMiss																						
Mean																						
SD																						
Min																						
Median																						
Max																						
25%																						
50%																						
75%																						
CV%																						
Geometric Mean																						
Mean of Logs																						
SD of the Logs																						
CV% Geometric Mean																						
95% CI Lower Mean																						
95% CI Upper Mean																						

Grey cells: missing value

Table 7. Table time-concentration for statistically significant effects (by sequence or by period). By sequence

Seq=XXXX. Concentration (ng/mL)

			Theoretical_Time (h)																			
Subject	Treat	Period	Baseline	0.083	0.167	0.250	0.333	0.500	0.750	1.000	1.250	1.500	2.000	3.000	4.000	6.000	8.000	12.000	24.000	36.000	48.000	72.000
N																						
NMiss																						
Mean																						
SD																						
Min																						
Median																						
Max																						
25%																						
50%																						
75%																						
CV%																						
Geometric Mean																						
Mean of Logs																						
SD of the Logs																						
CV% Geometric Mean																						
95% CI Lower Mean																						
95% CI Upper Mean																						

Grey cells: missing value

Table 7. Table time-concentration for statistically significant effects (by sequence or by period). By period

Period=XXXX. Concentration (ng/mL)

			Theoretical_Time (h)																			
Subject	Treat	Seq	Baseline	0.083	0.167	0.250	0.333	0.500	0.750	1.000	1.250	1.500	2.000	3.000	4.000	6.000	8.000	12.000	24.000	36.000	48.000	72.000
N																						
NMiss																						
Mean																						
SD																						
Min																						
Median																						
Max																						
25%																						
50%																						
75%																						
CV%																						
Geometric Mean																						
Mean of Logs																						
SD of the Logs																						
CV% Geometric Mean																						
95% CI Lower Mean																						
95% CI Upper Mean																						

Grey cells: missing value

Tables 8.1 and 8.2. Table of pharmacokinetic parameters by treatment.

Treat = XXXX

			Parameter							
Subject	**Seq**	**Period**	**C_{max} (ng/mL)**	**$AUC_{0\text{-}72h}$ (h*ng/mL) or $AUC_{0\text{-}t}$ (h*ng/mL) if applicable**	**$AUC_{0\text{-}\infty}$ (h*ng/mL) if applicable**	**t_{max} (h)**	**Extrapolated %AUC if applicable**	**λ_z (h-1) if applicable**	**$t_{1/2}$ (h) if applicable**
N									
NMiss									
Mean									
SD									
Min									
Median									
Max									
25%									
50%									
75%									
CV%									
Geometric Mean									
Mean of Logs									
SD of the Logs									
CV% Geometric Mean									
95% CI Lower Mean									
95% CI Upper Mean									

Grey cells: missing value

Table 9. Table of pharmacokinetic parameters for the statistically significant effects (by sequence or by period). By sequence
Seq = XXXX

			Parameter		
Subject	Period	Treat	C_{max} (ng/mL)	AUC_{0-72h} (h*ng/mL) or AUC_{0-t} (h*ng/mL) if applicable	$AUC_{0-\infty}$ (h*ng/mL) if applicable
N					
NMiss					
Mean					
SD					
Min					
Median					
Max					
25%					
50%					
75%					
CV%					
Geometric Mean					
Mean of Logs					
SD of the Logs					
CV% Geometric Mean					
95% CI Lower Mean					
95% CI Upper Mean					

Table 9. Table of pharmacokinetic parameters for the statistically significant effects (by sequence or by period). By period

Period = XXXX

			Parameter		
Subject	**Seq**	**Treat**	C_{max} (ng/mL)	$AUC_{0\text{-}72h}$ (h*ng/mL) or $AUC_{0\text{-}t}$ (h*ng/mL) if applicable	$AUC_{0\text{-}\infty}$ (h*ng/mL) if applicable
N					
NMiss					
Mean					
SD					
Min					
Median					
Max					
25%					
50%					
75%					
CV%					
Geometric Mean					
Mean of Logs					
SD of the Logs					
CV% Geometric Mean					
95% CI Lower Mean					
95% CI Upper Mean					

Table 10. Table of C_{max} and AUC_{0-72h} (or C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, if applicable) individual ratios (T/R).

		Parameter		
Subject	Seq	Ratio Test/Ref. C_{max} (ng/mL)	Ratio Test/Ref. AUC_{0-72h} (h*ng/mL) or AUC_{0-t} (h*ng/mL) if applicable	Ratio Test/Ref. $AUC_{0-\infty}$ (h*ng/mL) if applicable
N				
NMiss				
Mean				
SD				
Min				
Median				
Max				
25%				
50%				
75%				
CV%				
Geometric Mean				
Mean of Logs				
SD of the Logs				
CV% Geometric Mean				
95% CI Lower Mean				
95% CI Upper Mean				

18 APPENDIX 1 – RANDOM LIST

RANDOM LIST CLINICAL STUDY CODE 20ANE-3489C

Subject	StudyId	Sequence	P1	P2
001	20ANE-3489C	TR	T	R
002	20ANE-3489C	RT	R	T
003	20ANE-3489C	TR	T	R
004	20ANE-3489C	RT	R	T
005	20ANE-3489C	TR	T	R
006	20ANE-3489C	RT	R	T
007	20ANE-3489C	TR	T	R
008	20ANE-3489C	RT	R	T
009	20ANE-3489C	RT	R	T
010	20ANE-3489C	TR	T	R
011	20ANE-3489C	RT	R	T
012	20ANE-3489C	TR	T	R
013	20ANE-3489C	TR	T	R
014	20ANE-3489C	RT	R	T
015	20ANE-3489C	TR	T	R
016	20ANE-3489C	RT	R	T
017	20ANE-3489C	TR	T	R
018	20ANE-3489C	RT	R	T
019	20ANE-3489C	TR	T	R
020	20ANE-3489C	RT	R	T
021	20ANE-3489C	TR	T	R
022	20ANE-3489C	RT	R	T
023	20ANE-3489C	RT	R	T
024	20ANE-3489C	TR	T	R
025	20ANE-3489C	RT	R	T
026	20ANE-3489C	TR	T	R
027	20ANE-3489C	RT	R	T
028	20ANE-3489C	TR	T	R

Treatment T:

Exib 120 mg film-coated tablets.
Manufactured by: PrJSC "Pharmaceutical firm "Darnitsa". Ukraine

Treatment R:

Arcoxia® 120 mg film-coated tablets.
Manufactured by: Merck Sharp&Dohme B.V., The Netherlands

The randomisation scheme has been created using a list of randomised numbers obtained by Proc Plan procedure of SAS software version 9.4.

Project Statistician: [redacted]

Date: [redacted]

Signature