2. SYNOPSIS

Name of Sponsor/Company McNeil AB ***Name of Finished Product:*** Naproxen Sodium 275 mg tablet ***Name of Active Ingredient:*** naproxen sodium	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

Title of Study:

An open-label, randomized, single-dose, two-treatment, crossover bioequivalence study comparing a novel Naproxen Sodium 275 mg film-coated tablet (Bilim Ilac Sanayii Ve Ticaret A.S., Turkey) and Nalgesin® (naproxen sodium) 275 mg film-coated tablet (JSC "KRKA, d.d., Novo mesto", Slovenia), in healthy adult volunteers

Investigators:

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Study Centers:

Scientific and Research Centre "Eco-safety" Limited Liability Company (site # M84-RU10001), 65, Yuriya Gagarina prospect, 196143, Saint-Petersburg Russian Federation

Publication (reference):

None

Study Period:

Date of first enrollment: 28 November 2018

Date of last completed: 29 December 2018

Phase of Development:
Bioequivalence study

Objectives:

Primary Objective:

- To assess bioequivalence between Naproxen Sodium 275 mg tablet and Nalgesin® 275 mg tablet, with respect to single-dose pharmacokinetics of naproxen (i.e. the maximum observed naproxen concentration (C_{max}) and the area under the naproxen concentration-vs.-time curve until the last measurable concentration (AUC_t)).

Secondary Objectives:

- To describe the naproxen pharmacokinetics of the investigational products (IPs) with respect to the area under the naproxen concentration-vs.-time curve until infinity (AUC_{inf}), the extrapolated part of AUC_{inf} (AUC_{extrap}), the time at which C_{max} is observed (t_{max}), the elimination rate constant (λ_z),

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and the elimination half-life ($t_{1/2}$).

- To compare data on reported and observed adverse events (AEs).

Methodology:

The study had an open-label, randomized, two-way crossover design. Twenty-eight (28) healthy male and female subjects were included. Single-doses of naproxen sodium 275 mg tablet and Nalgesin® 275 mg tablet were given to all healthy adult subjects under fasting conditions on separate treatment visits separated by 7-days washout period. The total duration of subject participation in the study was 26 days from the screening visit to the end of study.

Overall, 28 subjects were randomized to one of two dosing sequences, AB or BA, 14 subjects per sequence (A – test treatment – Naproxen sodium 275 mg film-coated tablets (Bilim), B – reference treatment – Nalgesin® 275 mg film-coated tablets (KRKA)). During each study period, blood samples (6 mL + 0.5 mL of discarded blood) for pharmacokinetic analysis were collected at 15, 30, 45 minutes, and at 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 12, 16, 24, 48 and 72 hours after drug administration in appropriately labeled EDTA-tubes). Single K_2EDTA frozen human plasma samples tubes were sent to [redacted] for pharmacokinetic evaluation. The determination of naproxen was accomplished using an ultra-high-performance liquid chromatography method with tandem mass spectrometric detection. The lower limit of quantification (LLOQ) for naproxen was 0.250 µg/mL.

Number of Subjects (planned and analyzed):

Planned number of subjects – 28.

A total of 28 subjects were randomized, all of them completed the study and were included in the Full Analysis Set (FAS) and the Safety Analysis Set (SAS). Also all of 28 subjects had evaluable C_{max} and AUC_t and were therefore included in the bioequivalence assessment.

Diagnosis and Main Criteria for Inclusion:

Healthy males and females between the ages of 18 and 45 years, inclusive. Non- or ex-tobacco users (completely stopped smoking or using any form of tobacco or nicotine-containing product for at least 12 months before 1st dose of the study drug in this study). BMI between 18.5 and 30.0 kg/m^2, inclusive, and a total body weight >50 kg. For females

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– postmenopausal state (absence of menstrual discharge for at least two years and a follicle stimulating hormone serum level exceeding 30 IU/L) or premenopausal/perimenopausal state with an effective means of contraception during the study and 30 days thereafter, single male partner who has had a vasectomy, or abstinence from heterosexual intercourse, during the study and 30 days thereafter; for males – absence of pregnant spouse or partner at screening and willingness to protect potential spouse or partner from becoming pregnant during the study and 30 days thereafter. A personally signed and dated informed consent document, willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Test Product, Dose and Mode of Administration, Batch Number:

Naproxen Sodium 275 mg tablet for oral administration (Bilim Ilac Sanayii Ve Ticaret A.S., Turkey), [redacted]

Duration of Treatment:

Subjects received a single dose of each IP with 200 mL of water at ambient temperature on treatment days at the investigational site in the morning following an overnight fast (of at least 10 hours). The subjects were instructed to swallow the medication whole while sitting in an upright position, and not to chew or break the tablets.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Nalgesin® (naproxen sodium) 275 mg tablet for oral administration (JSC "KRKA, d.d., Novo mesto", Slovenia), [redacted]

Criteria for Evaluation:

Pharmacokinetic Evaluation:

The following pharmacokinetic parameters were determined by means of non-compartmental analysis for each subject and treatment:

C_{max}	maximal observed plasma concentration
t_{max}	time from start of treatment to occurrence of C_{max}
AUC_t	area under the plasma concentration-vs.-time curve from start of drug administration until the time of the last measurable plasma concentration
AUC_{inf}	area under the plasma concentration-vs.-time curve from start of drug

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	administration extrapolated to infinity
AUC_{extrap}	extrapolated part of AUC_{inf}
λ_z	elimination rate constant
$t_{1/2}$	elimination half-life (= $\ln 2/\lambda_z$)

Safety:

The number and percentage of subjects experiencing AEs that are considered related to study treatment (i.e. have a possible, probable, or very likely relation to the IP) during the AE reporting period, were summarized by treatment, system organ class, preferred term (in accordance with MedDRA dictionary, version 20.0), and worst recorded severity. For every AE with onset after start of the first treatment administration, treatment status was determined by the last treatment administered before the AE.

Statistical Methods:

The FAS included all randomized subjects who have any valid pharmacokinetic endpoint values from at least one IP. Pharmacokinetic data from the FAS was summarized descriptively. However, only data from randomized subjects who have valid pharmacokinetic endpoint values from both the test and reference products was included in the statistical model. The SAS included all subjects who receive at least one dose of study treatment.

Individual plasma concentration data from each subject and treatment and the corresponding blood sampling times were the basic data for the pharmacokinetic analysis. For subject-level analyses, plasma concentrations below the LLOQ that occurred at times before t_{max} were set to zero, whereas concentrations below the LLOQ and observed after t_{max} were omitted.

For comparisons of the primary pharmacokinetic parameters with respect to naproxen, the parameter geometric mean ratio, $\Phi = \mu_{Test}/\mu_{Reference}$, was estimated. Bioequivalence between the naproxen sodium 275 mg tablet and Nalgesin® 275 mg tablet with respect to naproxen was concluded if the model-based 90% confidence intervals for the geometric mean ratios, $\Phi = \mu_{Test}/\mu_{Reference}$ of the primary pharmacokinetic parameters are entirely contained in the equivalence interval (0.8000, 1.2500). This was equivalent to rejecting the null hypothesis of non-equivalence at significance level alfa = 5% for each of the two primary pharmacokinetic parameters. To conclude bioequivalence, these criteria had

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to be fulfilled for both primary parameters C_{max} and AUC_t.

No imputation of missing data was performed. All statistical analyses were conducted at the end of the trial after data base closure. No interim statistical analysis was conducted.

Statistical comparisons of the test and the reference products with respect to C_{max} and AUC_t, respectively, was based on a linear model for log transformed (natural log) pharmacokinetic parameter data. Product was included as a fixed factor in the statistical model. For each parameter evaluation, the statistical model also included covariate adjustments for period and sequence and subject, nested within sequence as fixed effects. Carry-over effects were assumed ignorable. In each case an interval estimates with confidence level 90% for the treatment geometric mean ratio were calculated from the fitted model.

Descriptive statistics (e.g. mean, standard deviation, median, minimum and maximum for continuous variables; frequency and percentage for categorical variables) were presented for demographic and baseline characteristics. The extrapolated part of AUC_{inf} (AUC_{extrap}), the time to C_{max} (t_{max}), the estimated terminal elimination constant (λ_z) and the estimated terminal half-life ($t_{1/2}$) were summarized descriptively for each treatment. Measured plasma values were summarized by treatment and measurement time point. For continuous variables, statistical summaries included mean values, standard deviations, medians and maximum as well as minimum values. In addition, geometric mean values and coefficients of variation were calculated for C_{max}, AUC_t, and AUC_{inf}. For t_{max} the frequency distribution was tabulated by treatment.

SUMMARY – CONCLUSIONS

An open-label, randomized, two-way crossover study was performed at one investigational site in the Russian Federation from 28 November 2018 (first subject enrolled) to 29 December 2018 (last subject completed study). A total of 28 subjects were randomized to one of two dosing sequences, AB or BA, 14 subjects per sequence, where A – test treatment, Naproxen sodium 275 mg film-coated tablets (Bilim), B – reference treatment, Nalgesin® 275 mg film-coated tablets (KRKA).

All 28 subjects completed the study, were included in FAS and SAS and had evaluable pharmacokinetic parameters. None of the subjects had conditions or a medical history that the Principal Investigator considered potentially affecting the conduct of the study or representing a potential risk to the subject during study participation. None of the subjects received concomitant medications during the study.

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The mean (SD) age of the study population was 27.1 (6.07) years and 100% of subjects were white. Overall, 46.4% of subjects were male. The mean (SD) BMI was 23.4 (3.48) kg/m^2.

Pharmacokinetic Results:

The estimated geometric mean ratios between Naproxen Sodium and Nalgesin® and 90% CI for the geometric mean ratios of the primary PK parameters (C_{max}, AUC_t) were:

- 104.86% [99.86%, 110.12%] for C_{max};
- 97.19% [95.16%, 99.26%] for AUC_t.

These intervals were entirely contained within the interval 80.00% - 125.00%. Thus, this study demonstrated bioequivalence between test product Naproxen Sodium 275 mg film-coated tablets (Bilim) and reference product Nalgesin® 275 mg film-coated tablets (KRKA) with respect to naproxen single-dose pharmacokinetic parameters.

Other PK parameters (AUC_{inf}, AUC_{extrap}, λ_z and $t_{1/2}$) were similar between the treatments. However, the t_{max} appeared to occur slightly earlier with the test product vs. reference product (median t_{max} 0.75 vs. 1.25 hours, respectively).

Safety Results:

In this study 15 AEs were reported by 12 subjects: 6 AEs after single-dose administration of Naproxen Sodium 275 mf film-coated tablets (Bilim) and 9 AEs after Nalgesin® 275 mg film-coated tablets (KRKA) administration; all AEs were of mild severity. All AEs except for 1 case of headache after administration of test product were considered related to the IPs. Treatment-emergent AEs after administration of reference product included red blood cells sedimentation rate increase, alanine aminotransferase increase, leukopenia and anaemia that occurred in 2 subjects (7.1%) each, and 1 case (3.6%) of dyspepsia. Treatment-emergent AEs after test product administration were red blood cell sedimentation rate increase, aspartate aminotransferase increase, leukopenia, proteinuria and diarrhoea that occurred in 1 case (3.6%) each. No SAEs were reported in this study.

Both of the study products were well tolerated. Reported AEs were mild and consistent with the known safety profile of the active ingredient (naproxen sodium).

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Conclusions:

This study demonstrated the bioequivalence between the new product Naproxen Sodium 275 mg film-coated tablets (Bilim) and Nalgesin® 275 mg film-coated tablets (KRKA) with respect to single-dose pharmacokinetic parameters for naproxen. However, the t_{max} appeared to occur slightly earlier with the test product vs. reference product.

The study products were well tolerated, with only mild AEs. Reported AEs were consistent with the known safety profiles of the active ingredient (naproxen sodium).

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