

Annex 30
to the Procedure for Conducting Expert
Evaluation of Registration Materials
Pertinent to Medicinal Products
Submitted for the State Registration (Re-
Registration) and for Expert Evaluation
of Materials about Introduction of
Changes to Registration Materials
during the Validity Period of
Registration Certificate (item 4 section
IV)

Clinical study report No. 1

1. Name of medicinal product (registration certificate №, if available)	VALKUBIT 97 mg/103 mg film-coated tablet
2. Applicant	Krka, d.d., Novo mesto, Smarjeska cesta 6, 8501 Novo mesto, Slovenia
3. Manufacturer	Krka, d.d., Novo mesto, Smarjeska cesta 6, 8501 Novo mesto, Slovenia
4. Studies conducted:	X yes no if no, please justify
1) type of medicinal product, which has been or will be registered	Generic medicinal product
5. Title of clinical trial, code number of clinical trial	Comparative, Randomised, Single-Dose, Crossover Bioavailability Study of Sacubitril/Valsartan 97 mg/103 mg Formulations in Healthy Volunteers under Fed Conditions Protocol Number: CAV-104-23 Version: final Date: 12.04.2023
6. Phase of clinical trial	Bioequivalence Study
7. Period of clinical trial	from 12.05.2023 till 30.05.2023
8. Countries, where clinical trial has been conducted	Republic of North Macedonia
9. Number of trial subjects	planned: 44 actual: 43
10. Objective and secondary endpoints of clinical trial	The objective of this study was to compare the rate and extent of absorption of sacubitril and valsartan from Test (Treatment A) versus Reference (Treatment B), administered to healthy male and non-pregnant female

	volunteers in a single-dose, randomized, 2-way cross-over study under fed conditions. The secondary objective of this study was to evaluate the safety and tolerability of the study treatments.
11. Clinical trial design	Single-dose, randomised, 2 way cross-over study, under fed conditions, with 14 days wash-out period between two consecutive study treatment administrations.
12. Main inclusion criteria	The subjects with the following criteria were eligible for this trial: 1. Healthy male and non-pregnant female subjects aged between ≥ 18 to ≤ 55. 2. Body mass index (weight/height²) in the range 18.5 to 30 kg/m². 3. Non-smokers or ex-smokers, where an ex-smoker is defined as someone who did not use nicotine/tobacco-containing products in the last 6 months prior to screening. 4. A female volunteer must meet one of the following criteria: a) Participant is of childbearing potential and agrees to use one of the accepted contraceptive regimens from at least 28 days prior to the first administration of the study drug, during the study and for at least 30 days after the last dose of the study drug. An acceptable method of contraception includes one of the following: - Abstinence from heterosexual intercourse - Intrauterine device (without hormones) - Condom with spermicide or condom with intra-vaginally applied spermicide - or b) Participant is of non-childbearing potential, defined as surgically sterile (i.e. has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation) or in a menopausal state (at least 1 year without menses) 5. Able to communicate and co-operate with the investigator and his staff.

	6. Capable of consent.
13. Investigational medicinal product, mode of administration and strength	Sacubitril/Valsartan 97 mg/103 mg film-coated tablets Batch No.: R45582 Batch Size: 100.000 tablets (Manufacturer: Krka, d. d., Novo mesto, Slovenia, EU) Strength: 97.2 mg/102.8 mg (one combination tablet) Mode of Administration: Oral under fed conditions
14. Reference product, dose, mode of administration and strength	Entresto® 97 mg/103 mg film-coated tablets (sacubitril/valsartan) Batch No.: MH7013 (Marketing Authorization Holder: Novartis Europharm Limited, Ireland, EU; Manufacturer: LEK Pharmaceuticals d. d., Slovenia, EU) Dose: 97.2 mg/102.8 mg (one combination tablet) Mode of Administration: Oral under fed conditions
15. Concomitant therapy	Concomitant medication was not allowed during the study. Exceptions would have been allowed only if treatment for an acute condition had become medically necessary. In this case, the investigator had to record the medication administered to the subjects' CRF. The investigator had to decide whether the subject could continue with the study.
16. Criteria for evaluation efficacy	AUC_t, AUC_i, C_{max}, residual area (RAUC), T_{max}, T_{1/2} and Kel for sacubitril and valsartan were determined from individual plasma concentration / time profiles using a model-independent approach.
17. Criteria for evaluation safety	Clinical (including ECG) and laboratory analyses (biochemistry, hematology, urinalysis), vital signs measurement performed at screening, pre-dose measurement of vital signs, monitoring of pre-dose health events, on-study monitoring of adverse events, measurement of blood pressure and heart rate on study, as well as end-of-study clinical laboratory tests (biochemistry, hematology and urinalysis) and vital signs measurements.

	Urine drug screen, alcohol test and cotinine test were performed before dosing at Check-in (Day -1) of each period. Serum pregnancy tests (for female subjects only) were performed at screening, at Check-in of each period and at the end-of-study.
18. Statistical methods	Analysis of variance (ANOVA) was performed on the ln-transformed AUC_t, AUC_i and C_{max} parameters for sacubitril and valsartan. Consistent with the two one-sided tests for bioequivalence, 90% confidence intervals were calculated for the Test (Treatment A) to Reference (Treatment B) ratios of least-squares means for parameters AUC_t, AUC_i and C_{max} using ln-transformed data.
19. Demographic indices of studied population (sex, age, race, etc.)	There were 22 males and 22 females. All are Caucasian race. Participants were aged between 20 and 54 years.
20. Efficacy results	The 90% confidence intervals of the Test (Treatment A)/Reference (Treatment B) ratios of LS-Means derived from analyses of the ln-transformed PK parameters AUC_t and C_{max} for sacubitril and valsartan in plasma were within the 80.00-125.00% acceptance range.
21. Safety results	During the study, adverse events were reported in a limited number of subjects across both treatment groups. The reported events were mostly mild in intensity, with a small number assessed as moderate. Most adverse events were considered probably related to the study medication. All reported adverse events resolved completely by the end of the study. No severe or serious adverse events, deaths, or new safety concerns related to the administered formulations were identified during the study.
22. Conclusion (summary)	Based on these results, Sacubitril/Valsartan 97 mg/103 mg film-coated tablets (KRKA, d. d., Novo mesto) (Treatment A) and Reference Entresto® 97 mg/103 mg film-coated tablets (sacubitril/valsartan) (MAH: Novartis Europharm Limited, Ireland, EU) obtained from the EU market (Treatment B) are bioequivalent after single-dose administration under fed conditions.

Applicant (registration certificate holder)	 (signature) Janja Recelj (full name)
---	---