

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. 2

1. Name of medicinal product (registration certificate №, if available)	VALKUBIT 24 mg/26 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 24 mg/26 mg Formulations in Healthy Volunteers under Fasting Conditions Protocol Number: CAV-105-23 Version: final Date: 12.04.2023
6. Phase of clinical trial	Bioequivalence Study
7. Period of clinical trial	from 15.05.2023 till 25.05.2023
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 is to compare the rate and extent of absorption of sacubitril and valsartan from Test as Treatment A versus Reference as Treatment B, administered to healthy male and non-pregnant female volunteers in a single-dose, randomized, 2-way cross-over study under fasting conditions. The secondary objective of this study was to evaluate the safety and tolerability of the study treatments.
11. Clinical trial design	This study was planned in healthy male and non-pregnant female volunteers under fasting conditions and designed as a single-dose,

	randomized, 2-way cross-over study with an at least 7 days wash-out period between the two periods. A total of 44 healthy male and non-pregnant female non-smokers were planned to be included in this study.
12. Main inclusion criteria	Healthy male and non-pregnant female subjects aged between ≥ 18 to ≤ 55. 1. Body mass index (weight/height²) in the range 18.5 to 30 kg/m². 2. 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. 3. 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) 4. Able to communicate and co-operate with the investigator and his staff. 5. Capable of consent.
13. Investigational medicinal product, mode of administration and strength	Sacubitril/Valsartan 24 mg/26 mg film-coated tablets Batch No.: R45581

	Batch Size: 200.000 tablets (Manufacturer: Krka, d. d., Novo mesto, Slovenia, EU) Strength: 24.3 mg sacubitril (as sacubitril sodium salt)/25.7 mg valsartan (as valsartan sodium salt) Mode of Administration: Oral under fasting conditions
14. Reference product, dose, mode of administration and strength	Entresto® 24 mg/26 mg film-coated tablets (sacubitril/valsartan) Batch No.: MG7623 (Marketing Authorization Holder: Novartis Europharm Limited, Ireland, EU; Manufacturer: LEK Pharmaceuticals d. d., Slovenia, EU) Strength: 24.3 mg sacubitril and 25.7 mg valsartan (as sacubitril valsartan sodium salt complex) Mode of Administration: Oral under fasting 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 K_{el} 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, haematology, 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, haematology 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 55 years.
20. Efficacy results	The 90% confidence intervals of the ratio (Test (Treatment A)/Reference (Treatment B)) of least-squares means derived from analyses on the ln-transformed PK parameters AUC _t and C _{max} for sacubitril and valsartan in plasma are within the 80.00–125.00 % acceptance range.
21. Safety results	During the study, a limited number of post-dose adverse events were reported among subjects in the safety population, with events observed in both treatment groups. The most frequently reported adverse event was headache. The reported adverse events were assessed as mild to moderate in intensity and were considered probably related to the study medication. All 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 conduct of the study.
22. Conclusion (summary)	Based on these results, Test as Treatment A and Reference obtained from EU market as Treatment B are bioequivalent after single dose administration under fasting conditions. Both treatments appear to be safe and generally well tolerated by all subjects. Upon conclusion of the clinical portion of the study, the results from all the subjects who completed end of study procedures, including laboratory tests and vital signs measurement confirmed the absence of significant changes in the subject's state of health. No new safety concerns related to administered formulations were raised during the conduct of this study.
Applicant (registration certificate holder)	 (signature)

Janja Recelj (full name)
