

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. 3

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	A Single-Dose, Partial Replicate, Bioequivalence Study of Two Formulations of Sacubitril/Valsartan 97 mg/103 mg Film-Coated Tablets under Fasting Conditions Protocol Number: 2023-5528 Version: 1.0 Date: 17.10.2023
6. Phase of clinical trial	Bioequivalence Study
7. Period of clinical trial	from 30.11.2023 till 14.12.2023
8. Countries, where clinical trial has been conducted	Canada
9. Number of trial subjects	planned:84 actual: 80
10. Objective and secondary endpoints of clinical trial	The primary objective of this study was to evaluate the bioequivalence of sacubitril and valsartan between the Test Product (Treatment A) versus the Reference Product (Treatment B) after a single-dose in healthy subjects under fasting conditions. The secondary objective of this study was to evaluate the safety and tolerability of the study treatments.
11. Clinical trial design	Open-label, single-dose, randomized, three-period, two-treatment, three-sequence, crossover, partial replicate, bioequivalence study, designed to compare the bioavailability of sacubitril and valsartan between the Test

	Product to the Reference Product (Entresto®) in healthy, non-smoking, male and female subjects under fasting conditions.
12. Main inclusion criteria.	Subjects enrolled in the study met all of the following inclusion criteria assessed at screening: 1) Healthy, non-smoking, male and female subjects, 18 years of age to 65 years of age. 2) BMI ≥ 18.5 to ≤ 30 kg/m² 3) Females may be of childbearing or non-childbearing potential: • Childbearing potential: - o Physically capable of becoming pregnant. • Non-childbearing potential: - o Surgically sterile (i.e., both ovaries removed, uterus removed, or bilateral tubal ligation); and/or - o Postmenopausal (no menstrual period for at least 12 consecutive months without any other medical cause and follicle-stimulating hormone [FSH] and luteinizing hormone [LH] values consistent with being postmenopausal). 4) Willing to use acceptable, effective methods of contraception. 5) Able to tolerate venipuncture. 6) Be informed of the nature of the study and give written consent prior to any study procedure.
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 fasting 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 fasting conditions
15. Concomitant therapy	The Investigator may request the administration of concomitant drug or non-drug treatment for subjects. If drug therapy other than the permitted medication is required during the study, the decision whether to continue or discontinue the subject's participation in the study will be made by the Investigator/PK Scientists and/or the Sponsor. The Sponsor needs to be informed as soon as possible in any case in all such occurrences. Clinic staff may also administer non-drug treatment(s) that do not deviate from the procedures outlined in the protocol (e.g., ice pack, allowing the subject to lie down). All treatment(s) provided will be documented.
16. Criteria for evaluation efficacy	AUC_t • The 90% CI of the relative mean AUC_t of the Test to Reference Product should be between 80.00–125.00% and C_{max} • If the within-subject variability for C_{max} of the Reference Product was ≤30%, the 90% CI of the relative mean C_{max} of the Test to Reference Product should be between 80.00–125.00%. • If the within-subject variability for C_{max} of the Reference Product was >30%: 1. The 90% CI of the relative mean C_{max} of the Test to Reference Product should be within the bioequivalence range determined as follows: o Upper limit = $\exp(+k \cdot sWR)$ o Lower limit = $\exp(-k \cdot sWR)$ where $k=0.760$ and sWR is the

	within-subject-within-reference standard deviation estimated in the study for the C_{max} parameter to a maximum range of 69.84–143.19%. 2. The ratio of geometric means of the Test to Reference Product should be within 80.00–125.00%
17. Criteria for evaluation safety	An assessment of safety was based primarily on the incidence, frequency, and severity of adverse events (AEs). Adverse events were tabulated by treatment and subject number for all subjects in the safety dataset.
18. Statistical methods	Analysis of variance (ANOVA) (PROC GLM) was performed on log-transformed plasma sacubitril and valsartan AUC _t , AUC _{inf} , and C _{max} . Based on log-transformed data, ratios of the geometric means for treatments and the corresponding 90% confidence intervals (CIs) were calculated for AUC _t , AUC _{inf} , and C _{max} .
19. Demographic indices of studied population (sex, age, race, etc.)	There were 50 males and 34 females. Of these 50 were White, 16 Asian, 17 Black and 1 Multiracial. Participants were aged between 18 and 65 years.
20. Efficacy results	The 90% CIs of the relative mean AUC _t , of the Test to Reference Product were between 80.00–125.00% for both sacubitril and valsartan. The calculated intra-subject-within-reference variability for sacubitril and valsartan C _{max} was less than 30% (sacubitril, 29.86%; valsartan, 28.81), therefore, the standard bioequivalence range was applied. The 90% CI of the relative mean C _{max} of the Test to Reference Product was within the 80.00–125.00% range and the ratio of geometric means of the Test to Reference Product was within 80.00–125.00%.
21. Safety results	During the study, adverse events were reported in a proportion of subjects, most of which were assessed as related to the investigational medicinal product. The adverse events were predominantly mild in intensity, with a smaller proportion being moderate. The most frequently reported adverse event was headache. The majority of adverse events resolved by the end of the study; however, for one event, outcome information was not available due to the subject being lost to follow-up. No serious adverse events were reported during the study, and none of the adverse events compromised subject safety or had a clinically significant impact on the integrity of the study results.

22. Conclusion (summary)	The Test Product, as Treatment A, exhibited equivalent rate and extent of sacubitril and valsartan absorption compared to the Reference Product obtained from the EU market, as Treatment B, after a single, oral dose in healthy, non-smoking, male and female subjects under fasting conditions. Bioequivalence of the Test and Reference Product can be concluded. Both treatments (A and B) appear to be safe after a single, oral dose under fasting conditions in the healthy, male and female subjects who participated in this study. No new safety concerns with respect to the Test or Reference Product were raised during the conduct of the study.
Applicant (registration certificate holder)	 (signature) Janja Recelj (full name)