Medicines Evaluation Board

Public Assessment Report

Scientific discussion

Lumivaxon 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets (sacubitril sodium and valsartan disodium)

NL/H/6440/001-003/DC

Date: 8 July 2026

This module reflects the scientific discussion for the approval of Lumivaxon 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated-tablets. The procedure was finalised on 30 September 2025. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Lumivaxon 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated-tablets, from axunio Pharma GmbH.

The product is indicated for:

- Adult heart failure
  Lumivaxon is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.
- Paediatric heart failure
  Lumivaxon is indicated in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated-tablets, which has been registered by Novartis Europharm Limited in the EEA via a centralised procedure (EU/1/15/1058).

The concerned member states (CMS) involved in this procedure were Denmark, Germany, Finland and Norway.

II. QUALITY ASPECTS

II.1 Introduction

Lumivaxon is a film-coated tablet, containing two active substances in a fixed combination: sacubitril (as sacubitril sodium) and valsartan (as valsartan disodium). The three strengths are distinguishable by colour, size and debossing, as follows:

24 mg/26 mg strength
Violet white, ovaloid, biconvex film-coated tablets debossed with ‘C 50’ on the upper side and plain on the lower side, with approximate dimensions of 7.8 x 4.0 mm. Each film-coated tablet contains sacubitril sodium equivalent to 24.3 mg sacubitril and valsartan disodium equivalent to 25.7 mg valsartan.

49 mg/ 51 mg strength
Pale yellow, ovaloid, biconvex film-coated tablets debossed with ‘C 100’ on the upper side and plain on the lower side, with approximate dimensions of 12.0 x 5.0 mm. Each

film-coated tablet contains sacubitril sodium equivalent to 48.6 mg sacubitril and valsartan disodium equivalent to 51.4 mg valsartan.

97 mg/ 103 mg strength
Light pink, ovaloid, biconvex film-coated tablets debossed with ‘C 200’ on the upper side and plain on the lower side, with approximate dimensions of 15.1 x 6.0 mm. Each film-coated tablet contains sacubitril sodium equivalent to 97.2 mg sacubitril and valsartan disodium equivalent to 102.8 mg valsartan.

The excipients are:
Tablet core - colloidal hydrated silica (E551), microcrystalline cellulose (102) (E460), low-substituted hydroxypropyl cellulose (E463), crospovidone (type A) (E1202), mannitol (E421), magnesium stearate (E470b) and talc (E553b)
Film-coating - substitution type 2910 hypromellose (50 mPas for the 24 mg/26 mg and 49 mg/51 mg strengths and 3 mPas for the 97 mg/103 mg strength) (E464), titanium dioxide (E171), macrogol (3350)(E1521), iron oxide red (E172), iron oxide black (24 mg/26 mg and 97 mg/103 mg strengths) (E172), iron oxide yellow (49 mg/51 mg strength) and talc (97 mg/103 mg strength).

The three tablet strengths of the fixed combination are dose proportional for both active substances.

The film-coated tablets are packed in oriented polyamide – aluminium - polyvinyl chloride/aluminium (OPA-Alu-PVC/Alu) blisters.

II.2 Drug Substance

The drug substances are sacubitril sodium and valsartan disodium, both are established drug substances that are not described in the European Pharmacopoeia (Ph.Eur.).

Sacubitril sodium is an almost white to yellow powder, freely soluble in water. It has two chiral centres and can exist in four isomers. The active substance shows polymorphism; crystal form B is used.

Valsartan disodium is a white or almost white powder, freely soluble in water. The active substance shows polymorphism and the amorphous form is consistently produced.

The Active Substance Master File (ASMF) procedure is used for both active substances using two suppliers for each drug substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Adequate specifications for both active substances have been adopted for starting materials, solvents and reagents. Both active substances have been adequately characterised and the manufacturing process is described in sufficient detail.

Sacubitril sodium by manufacturer I

The manufacturing process comprises three chemical transformation steps followed by salt formation. The process starts with one starting material. Two catalysts are used in the first step of the synthesis. Two intermediates are isolated in the process. No class 1 organic solvents are used in the process.

Sacubitril sodium by manufacturer II

The manufacturing process comprises a three step process with two intermediates. The manufacturing is finalised by salt formation and crystallisation.

Valsartan disodium by manufacturer I

The manufacturing process comprises of five chemical transformation steps, followed by salt formation and purification. The process starts with one starting material, the second starting material is introduced in the second reaction (alkylation), the third starting material in the third reaction step (acylation). No class 1 organic solvents or heavy metal catalysts are used in the process.

Valsartan disodium by manufacturer II

The manufacturing process comprises of three steps, with two intermediates, followed by hydrolysis and salt formation.

Quality control of drug substance

Sacubitril sodium

The active substance specification for sacubitril sodium has been established in-house by the MAH and is based on the specification of both manufacturers. The specification is considered adequate to control the quality and is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for two batches by manufacturer I and three batches by manufacturer II.

Valsartan disodium

The active substance specification for valsartan disodium has been established in-house by the MAH and is based on the specification of both manufacturers. The specification is acceptable in view of the route of synthesis and the various European guidelines. The specification is considered adequate to control the quality and is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches by manufacturer I and three batches by manufacturer II.

Stability of drug substance

Sacubitril sodium

Stability data on sacubitril sodium have been provided for six production scaled batches in manufacturer I and for three production scaled batches in manufacturer II, both in accordance with applicable European guidelines. Based on the data submitted,

a retest period could be granted of 48 and 36 months respectively, when stored under the stated conditions.

Valsartan disodium
Stability data on valsartan disodium have been provided for three production scaled batches in both manufacturer sites, both in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 48 months for manufacturer I and 24 months in manufacturer II, when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The main development studies performed were the characterisation of the reference products, establishment of a Quality Target Product Profile and deriving of Critical Quality Attributes thereof, pilot bioequivalence studies, formulation optimisation studies and manufacturing process development. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are dry granulation followed by extragranular blending and lubrication, compression, coating and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches per strength at 10% of the maximum commercial batch size in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients, except for the in-house coating mixtures comply with Ph.Eur. requirements. These specifications are acceptable. The in-house specifications for the coating mixtures are also acceptable. The colourants comply with the EU Regulation No. 231/2012 on food additives.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, water content, dissolution, related substances, assay, uniformity of dosage units, microbiological quality and one specific nitrosamine. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three batches stored at 25°C/ 60% RH (36 months) and 40°C/75% RH (6 months) in accordance with the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 36 months, with label storage condition '*This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.*'

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for magnesium stearate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lumivaxon has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

For the environmental risk assessment, the MAH has submitted the following study results:

Summary of main study results for sacubitril: Phase I

Substance (INN/Invented Name):	LBQ657 (active metabolite of sacubitril)		
CAS-number (if available):	149709-44-4		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Kow	OECD 107	log Dow 2.9 at pH 2.0 for fully neutral species	Potential PBT: **N**
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	log Kow	2.9	Not B
Persistence	Ready biodegradability	Not readily biodegradable	
	$DegT_{50,system}$	23 d at 12°C 23 d at 12°C	not P
Toxicity	NOEC algae	≥ 100 mg/L	not T based on aquatic toxicity data
	NOEC crustacea	46 mg/L	
	NOEC fish	≥ 10 mg/L	
	CMR	Not investigated	Potentially T
PBT/vPvB statement:	LBQ657 is considered to be **not PBT**, **nor vPvB**		

Phase I			
Parameter	Value	Unit	Conclusion
PEC_{sw} (default F_{PEN})	0.972	µg/L	≥ 0.01 threshold: **Y**
Other concerns (e.g. chemical class)	Not investigated		

Summary of main study results for sacubitril: Phase II

Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Result**			**Remarks**
Adsorption-Desorption Sludge 1	OECD 106	$K_{OC, SLUDGE\ 1}$ = 22.6 L/kg$_{OC}$			
Sludge 2		$K_{OC, SLUDGE\ 2}$ = 45.0 L/kg$_{OC}$			
Soil 1 (non-sterilized)		$K_{OC, SOIL\ 1}$ = 367 L/kg$_{OC}$			
Soil 2 (sterilized)		$K_{OC, SOIL\ 2}$ = 39.2 L/kg$_{OC}$			
Soil 3 (sterilized)		$K_{OC, SOIL\ 3}$ = 40.6 L/kg$_{OC}$			
Ready Biodegradability Test	OECD 301B	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DissT_{50, water}$ = 6.0 / 6.5 d $DegrT_{50, system}$ = 11 / 11 d shifting to sediment = 36% / 56% at day 14, increasing thereafter			Values determined at 20°C
Phase II Aquatic effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Raphidocelis subcapitata*	OECD 201	NOEC	≥ 100	mg/L	Growth rate
Daphnia sp. Reproduction Test/ *Daphnia magna*	OECD 211	NOEC	46	mg/L	Reproduction and growth
Fish, Early-Life-Stage Toxicity Test */Fathead minnow (P. promelas)*	OECD 210	NOEC	≥ 10	mg/L	Survival, growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC EC_{10}	≥ 1000 756	mg/L	Respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/*Chironomus riparius*	OECD 218	NOEC	≥ 1867	mg/kg$_{dw}$	Emergence, development; normalised to 10% o.c.
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**		**Conclusion**
STP	0.0972 µg/L	75,600 µg/L	0.0000012857		No risk
Surface water	0.972 µg/L	1000 µg/L	0.000972		No risk
Groundwater	0.243 µg/L	100 µg/L	0.00243		No risk
Sediment	0.03917 mg/kg$_{dw}$	18.67 mg/kg$_{dw}$	0.002098		No risk
Soil	0.0001033 mg/kg$_{ww}$	Not available			
Secondary Poisoning	Assessment of secondary poisoning is **not** triggered.				

Summary of main study results: Phase I

Substance (INN/Invented Name):	Valsartan		
CAS-number (if available):	137862-53-4		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Kow	OECD117	log *D* = 2.8 at pH 2.5 log *D* = 1.2 at pH 7.0*	Potential PBT: **N**
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	log Kow	log *D* = 2.8 at pH 2.5 log *D* = 1.2 at pH 7.0*	Not B
Persistence	Ready biodegradability	Not readily biodegradable	
	DT_{50} Values are derived from the OECD 308 or OECD 307 study below and have been recalculated to 12°C	DT_{50} total system = 25.6 – 34.3 days DT_{50} sediment = 5.5 – 7.5 days	not P
Toxicity	NOEC or CMR	CMR	T
PBT/vPvB statement:	Valsartan is considered to be **not PBT**, **nor vPvB**		

Phase I			
Parameter	Value	Unit	Conclusion
$PEC_{sw,\ default}$ (*default* F_{PEN})	1.028	µg/L	≥ 0.01 threshold: **Y**
Other concerns (e.g. chemical class)			N

* Same ionised species throughout the environmentally relevant pH range 5 to 9. Fraction of neutral form increases at lower pHs, up to around 90% neutral form at pH 2.5.

Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Result**	**Remarks**
Adsorption-Desorption	OECD 106		
Sludge 1 = Tilburg		$K_{oc,\ sludge\ 1}$ = 41 L/kg$_{oc}$	
Sludge 2 = St Oendenrode		$K_{oc,\ sludge\ 2}$ = 52 L/kg$_{oc}$	
Sludge 3 = 's-Hertogenbosch		$K_{oc,\ sludge\ 3}$ = 58 L/kg$_{oc}$	
Ready Biodegradability Test	OECD 301B	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = sandy loam Sediment 2 = silt loam	OECD 308	$DT_{50,\ water}$ = 13.6 /9.4 d $DT_{50,\ sediment}$ = 3.5 / 2.6 d $DT_{50,\ whole\ system}$ = 16.1 / 12.0 d shifting to sediment = 20 / 27% CO_2 = 29 / 17 % NER = 45 / 50 % Transformation products >10% = Y, TP1 = 0.2 / 3.2 %, TP5 = n.d. / 0.1 %,	DT_{50}s at 20°C 1 / 2 at day 14 at test end at test end at test end at test end

Phase II Aquatic effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Raphidocelis subcapitata*	OECD 201	NOEC	≥100,000	µg/L	growth rate
Daphnia magna, Reproduction Test	OECD 211	NOEC	5,600	µg/L	survival and reproduction
Fish, Early Life Stage Toxicity Test/*Fathead minnow*	OECD 210	NOEC	≥10,000	µg/L	survival and growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	750,000	µg/L	respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/*Chironomus riparius*	OECD 218	NOEC	≥400	mg/kg$_{dw}$	survival and emergence

Risk characterisation				
Compartment	**PEC**	**PNEC**	**RQ**	**Conclusion**
STP	0.1028 µg/L	75,000 µg/L	0.00000137	No risk
Surface water	1.028 µg/L	560 µg/L	0.0018357	No risk
Groundwater	0.257 µg/L	56 µg/L	0.004589	No risk
Sediment	0.0097 mg/kg$_{dw}$	4 mg/kg$_{dw}$	0.0024158	No risk
Soil	0.0001977 *mg/kg$_{ww}$*	Not available		
Secondary Poisoning	Assessment of secondary poisoning is **not** triggered.			

Considering the above data from Phase I and Phase II, LBQ657 (active metabolite of sacubitril) and valsartan are not expected to pose a risk to the environment.

Considering the above data of the definitive hazard assessment, LBQ657 (active metabolite of sacubitril) and valsartan are not PBT or vPvB substances.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Entresto which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sacubitril sodium and valsartan disodium are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides two bioequivalence studies on two strengths, which are discussed below. In addition, a biowaiver is requested for the third strength.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies. In one bioequivalence study (ARL/19/245) the pharmacokinetic profile of the test product Lumivaxon 97 mg/103 mg film-coated-tablets (axunio Pharma GmbH, Germany) was compared with the pharmacokinetic profile of the reference product Entresto 97 mg/103 mg film-coated-tablets (Novartis Europharm Limited, Ireland). In the second bioequivalence study (C1B03669) the pharmacokinetic profile of the test product Lumivaxon 24 mg/26 mg film-coated-tablets (axunio Pharma GmbH, Germany) was compared with the pharmacokinetic profile of the reference product Entresto 24 mg/26 mg film-coated-tablets (Novartis Europharm Limited, Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the three different strengths is the same,
c. the composition of the three strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data for both analytes, sacubitril and valsartan, should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

For the 24 mg/26 mg strength, the requirements b and c are fulfilled. The similarity of *in vitro* dissolution data could (requirement d) not been demonstrated. For the 97/103 mg strength, similarity of dissolution between test and reference product was demonstrated in pH 4.5 but not in pH 6.8 and pH 1.0. For the 24/26 mg strength, similarity of dissolution between test and reference product was demonstrated in pH 4.5 and pH6.8 but not in pH 1.0. However, since bioequivalence has been demonstrated *in vivo* for both strengths, these results prevail and test and reference products are considered bioequivalent. A biowaiver of strength is therefore not required for the 24 mg/26 mg tablet strength.

For the 49 mg/51 mg strength a bracketing approach between the lowest and highest strength is being used. Comparative dissolution profiles in 3 pH's are provided for the 49 mg/51 mg strength in support of a biowaiver of strength. Furthermore, the MAH demonstrated that the dissolution is similar between the 97 mg/103 mg strength and the 49 mg/51 mg strength in pH conditions 6.8 and 4.5, for both analytes sacubitril and valsartan, under the conditions as described in the EMA Bioequivalence guideline. In addition, the 49 mg/51 mg strength dissolution is in between the dissolution of the 97 mg/103 mg and 24 mg/26 mg tablet strength for the paddle apparatus at 0.1N and similar to the 24 mg/26 mg strength for the basket apparatus at 0.1N. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

In conclusion, the bracketing approach is acceptable and a biowaiver for the 49 mg/51 mg strength can be granted.

Bioequivalence studies

Design study ARL/19/245: Lumivaxon 97 mg/103 mg film-coated-tablets

A single-dose, open label, randomised, three-period, two-treatment, three-sequence, partial replicate, crossover, pivotal bioequivalence study was carried out under fasted conditions in 90 healthy male subjects, aged 23-43 years. Each subject received a single dose (97 mg sacubitril/103 mg valsartan) of one of the two sacubitril/valsartan formulations. The tablet was orally administered with 240 mL water after an overnight fast of 10 hours. There were three dosing periods, separated by a washout period of eight days.

Blood samples were collected pre-dose and at 0.08, 0.17, 0.25, 0.33, 0.5, 0.67, 1, 1.33, 1.5, 1.67, 2, 2.33, 2.5, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 14, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Sacubitril and valsartan may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of sacubitril and valsartan. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
A total of 54 subjects were enrolled in the study. Three subjects dropped out in Period II as those subjects did not report to the study centre on check in. All 54 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sacubitril, 97 mg under fasted conditions.

Treatment N=54	**AUC_{0-t} (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	3202.3 ± 711.6	2560.4 ± 970.3	0.5 (0.33 - 4.50)
Reference	3267.4 ± 756.6	2510.0 ± 987.4	0.67 (0.25 – 5.00)
***Ratio (90% CI)**	98.10 (95.64 - 100.61)	98.38 (90.31 - 107.16)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of valsartan, 103 mg under fasted conditions.

Treatment N=54	**AUC_{0-t} (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	38553.2 ± 12807.4	5482.3 ± 1496.0	1.67 (1.33 - 4.50)
Reference	35208.8 ± 12484.4	5104.5 ± 1629.6	1.67 (1.0 - 4.50)

***Ratio (90% CI)**	110.68 (102.60 - 119.39)	109.88 (100.62 - 119.98)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Design study C1B03669: Lumivaxon 24 mg/26 mg film-coated-tablets
A single-dose, open label, randomised, three-period, two-treatment, three-sequence, partially replicate, crossover balanced bioequivalence study was carried out under fasted conditions in 90 healthy male subjects, aged 19-45 years. Each subject received a single dose (24 mg sacubitril/26 mg valsartan) of one of the two sacubitril/valsartan formulations. The tablet was orally administered with 240 mL water after a fast of at least 10 hours. There were three dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.08, 0.17, 0.25, 0.33, 0.5, 0.67, 1, 1.33, 1.5, 1.67, 2, 2.33, 2.5, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 14, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
A total of 90 subjects were enrolled in the study. Three subjects were discontinued only for Period II as they did not report to the study centre at check-in. Four subjects were discontinued only for Period III for various reasons (one did not report to facility, two had a positive alcohol test and one withdrawn consent). Three subjects only completed Period ! of the study. As all subjects completed at least one test and one or two reference administrations, all 90 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sacubitril, 24 mg under fasted conditions.

Treatment N=90	**AUC_{0-t} (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	569.15 ± 174.87	581.16 ± 340.92	0.73 (0.25 - 2.67)
Reference	585.93 ± 167.82	598.71 ± 316.91	0.84 (0.25 - 4.00)
***Ratio (90% CI)**	94.56 (89.71 - 99.66)	91.56 (81.52 - 102.84)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of valsartan, 26 mg under fasted conditions.

Treatment N=90	**AUC_{0-t} (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	8325.00 ± 3441.05	1333.75 ± 462.97	1.58 (1.00 - 3.50)
Reference	8111.63 ± 3013.34	1280.52 ± 431.47	1.79 (0.67 - 4.52)
***Ratio (90% CI)**	100.29% (93.77%-107.26%)	102.65% (95.35%-110.50%)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 80.00 – 125.00%. Based on the two submitted bioequivalence studies Lumivaxon 24 mg/26 mg and 97 mg/103 mg are considered bioequivalent with Entresto 24 mg/26 mg and 97 mg/103 mg respectively.

The results of the studies ARL/19/245 and C1B03669, with the 97 mg/103 mg and 24 mg/26 mg formulations respectively, can be extrapolated to the intermediate 49 mg/ 51 mg strengths, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The MEB has been assured that the two bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Lumivaxon. At the time of approval, the most recent version of the RMP was version 1.2 dated 25 July 2025.

Table 5. Summary table of safety concerns as approved in RMP

Important identified risks	Embryo-fetal toxicity/lethality
Important potential risks	Neonatal/infantile toxicity through exposure from breast milk Cognitive impairment
Missing information	Long term use of LCZ696 in HF patients

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Entresto. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets (procedure number EMEA/H/C/004062/0000), for the content and to Capecitabin Tiefenbacher 500 mg film-coated tablets (BE/H/0196/01-02/DC (RMS change to FR/H/0589/001-002/DC)) for the layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lumivaxon 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated-tablets have a proven chemical-pharmaceutical quality and are generic forms of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated-tablets. Entresto is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data

submitted, considered that essential similarity has been demonstrated for Lumivaxon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 September 2025.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N.A.	N.A.	N.A.	N.A.	N.A.	N.A.