Amsterdam, 25 July 2024
EMA/CHMP/469993/2024
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Epixram

International non-proprietary name: levetiracetam

Procedure No. EMEA/H/C/006186/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AAS	Atomic Absorption Spectrometry
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
Cmax.ss	Peak plasma concentration at steady state
CMS	Concerned Member State
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EP	European Pharmacopoeia
FT-IR	Fourier Transform infrared spectroscopy
GC	Gas chromatography
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICP-OES	Inductively coupled plasma – optical emission spectroscopy
IPC	In-process control
IR	Infrared
IU	International Units
LDPE	Low Density Polyethylene
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MEK	Methyl ethyl ketone
MO	Major objection
MS	Mass Spectrometry
MTBE	Methyl *tert*-Butyl Ether
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OC	Other concern
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PP	Polypropylene

PVC	Poly vinyl chloride
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a ASMF
RPM	Reference Medicinal Product
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
TEA	Triethylamine
TTC	Threshold of Toxicological Concern
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRD	X-Ray Diffraction

*** This is a general list of abbreviations. Not all abbreviations will be used.**

1. Rapporteur recommendation

Based on the review of the data on quality and PK the generic/hybrid application for Epixram (levetiracetam):

as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

as adjunctive therapy:
- in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 12 years of age with epilepsy.
- in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality:

Limited data on discriminatory power of dissolution method.

Clinical

The bridge between the test product and the reference product has not been established, a therapeutic equivalence study should be conducted by the applicant.

1.1. Questions to be posed to additional experts

N/A

1.2. Proposal for inspection

1.2.1. GMP inspection(s)

N/A

1.2.2. GCP inspection(s)

N/A

1.3. Similarity with authorised orphan medicinal products

N/A

1.4. Derogation(s) from market exclusivity

N/A

2. Executive summary

2.1. Problem statement

Epilepsy is a chronic neurologic condition characterised by recurrent episodes of seizures (Thijs et al., 2019). Epileptic seizures consist of hyper synchronous, paroxysmal discharges of a group of hyper excitable neurons which arise as a result of a sudden imbalance between neuronal excitation and inhibition. This abnormal burst of action potentials starts in a discrete region of cortex or hippocampus and then spreads to other cortical areas and subcortical structures (Carcak and Ozkara, 2017). Epilepsy is defined as two unprovoked seizures occurring more than 24 h apart; a single unprovoked seizure if recurrence risk is high (i.e., >60% over the next 10 years); or a diagnosis of an epilepsy syndrome (Fisher et al., 2017).

The principal mechanisms assumed to lead to seizure activity include increased excitation by hyperactivity of glutamatergic transmission and functional disturbances of the ligand or voltage-gated sodium and Ca2+ channels or decreased inhibition which is linked mainly with loss of GABA mediated neurotransmission and extracellular potassium currents (Carcak and Ozkara, 2017). The causes of epilepsy can be structural, genetic, infectious, metabolic, immune and unknown. Although many underlying disease mechanisms can lead to epilepsy, the underlying cause remains unknown in about 50% of cases globally (Thijs et al., 2019).

Epidemiological data have shown that epilepsy affects around 50 million people worldwide. Globally, an estimated 5 million people are diagnosed with epilepsy annually (WHO Epilepsy, 2019). There is significant discrepancy in the prevalence and incidence of epilepsy in high- versus low-income countries, with approximately 80% of the epileptic patients worldwide living in low- and middle-income countries (Singh and Sander, 2020). Epilepsy does not affect all ages equally but has a bimodal distribution, with one peak at 5-9 years (due to genetic or developmental causes) and a second at approximately 80 years of age (due to accumulated injury to the brain) (Falco-Walter, 2020).

In 2017, the International League Against Epilepsy (ILAE) updated the classification and terminology of seizures and epilepsy. According to ILAE, classification is made at 3 levels: seizure onset, epilepsy type and syndrome (Fisher et al., 2017; Scheffer et al., 2017). Onset of a seizure is defined first, as focal, generalised, unknown or unclassifiable. After determining onset type, it is necessary to distinguish whether consciousness is impaired. The options for this designation include aware or impaired awareness. The final designation determines whether a focal or generalised seizure has a motor component (Fisher et al., 2017). Once a seizure has been classified, if an individual has been determined to have epilepsy (as defined above), epilepsy should be classified as focal, generalised, combination of focal and generalised, or unknown. In the third level, a specific syndrome diagnosis can be made. Underlying aetiology should be investigated along each step (Scheffer et al., 2017).

Pharmacological therapy is the most common approach to control seizures. It is indicated to be initiated after the occurrence of two unprovoked seizures or following the first seizure if there is a risk of recurrence. Beyond pharmacological therapy, surgical treatment (resection, destruction or disconnection of epileptic focus) and neurostimulation techniques can be used for severe cases of drug-resistant focal epilepsy. The goal of treatment is complete abolition of seizures without side effects, a goal presently achieved in approximately 50% of patients with the current range of antiepileptic drugs available. Many factors influence the choice of an antiepileptic drug for the individual patient. These include epilepsy characteristics, namely focal or generalised, and patient characteristics, such as gender, childbearing potential, age of onset, comorbid conditions and other medications. Drug characteristics such as spectrum of activity, efficacy, need for titration and side effects, including teratogenic potential in women, are equally important. Globally, cost is an important determining factor, as often treatment may be needed for several years, if not indefinitely *(Ali, 2018)*.

2.2. About the product

The medicinal product object of this application is levetiracetam (Epixram) a modified-release formulation of levetiracetam as prolonged-release granules for once daily dosing at the strengths of 1000, 1500, 2000 and 3000 mg. The new formulation has been developed with the aim to be equivalent to the same daily doses of marketed levetiracetam immediate release (IR) tablets (Keppra) administered twice daily (reference product; Marketing Authorisation Holder [MAH]: UCB Pharma SA, Belgium).

Levetiracetam belongs to the pharmacotherapeutic group of antiepileptics, other antiepileptics, ATC code: N03AX14.

Levetiracetam is a pyrrolidone derivative, particularly, the *S*-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide, chemically unrelated to existing antiepileptic active substances. Its main mechanism of action is through binding to the synaptic vesicle protein 2A (SV2A) *(Lynch et al., 2004)*. It also reverses the inhibition of neuronal gamma-aminobutyric acid (GABA)- and glycine-gated currents induced by zinc and beta-carbolines *(Rigo et al., 2002)* and affects intraneuronal calcium ion (Ca^{2+}) levels by inhibiting *N*-type Ca^{2+} channels *(Niespodziany et al., 2001; Lukyanetz et al., 2002)*.

However, the mechanism of action of levetiracetam still remains to be fully elucidated. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.

Keppra (levetiracetam) is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

Keppra (levetiracetam) is indicated as adjunctive therapy:

- in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy.
- in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

Levetiracetam 1000, 1500, 2000 and 3000 mg prolonged release (PR) granules is a new formulation developed by Neuraxpharm Pharmaceuticals S.L. In the US, levetiracetam was first approved by the Food and Drug Administration (FDA) in 1999 as an immediate-release (IR) tablet (Keppra IR). An extended-release (XR) tablet, Keppra XR, was approved by the FDA later in 2008. Currently, a prolonged release oral formulation of levetiracetam is not approved for the EU innovator product.

Levetiracetam 1000, 1500, 2000 and 3000 mg PR granules will follow the approved Keppra indications, with a differentiation in the targeted age groups:

- (i) as monotherapy in the treatment of partial onset seizures (POS) with or without secondary generalisation in adults and adolescents aged ≥16 years with newly diagnosed epilepsy
- (ii) as adjunctive therapy in the treatment of
    - a) POS with or without secondary generalisation in adults and adolescents aged ≥12 years with epilepsy
    - b) myoclonic seizures in adults and adolescents aged ≥12 years with juvenile myoclonic epilepsy

c) primary generalised tonic-clonic seizures in adults and adolescents ≥12 years with idiopathic generalised epilepsy.

2.3. The development programme/compliance with CHMP guidance/scientific advice

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev.1) and Guideline on the pharmacokinetic and clinical evaluation of modified-release dosage forms (EMA/CHMP/EWP/280/96 Rev.1.

The applicant had initially discussed the clinical development strategy in the following occasions with the Swedish agency and the European Medicines Agency (EMA):

- Scientific advice (SA) to Läkemedelsverket (Swedish Medical Products Agency), receiving meeting minutes after the meeting on 21 April 2021.
- EMA Initial Qualification Procedure (EMA/SA/0000079358), receiving a qualification method letter in the above from the CHMP in 15 December 2022.
- EMA Initial SA Procedure (EMA/SA/0000109253), receiving an SA letter on the above from the CHMP on 15 December 2022.

The scientific advice pertained to the following clinical aspects:

- the proposed overall clinical (PK) study programme; adequacy of a Real-World Evidence study to support comparative PK and non-inferiority of effectiveness between Keppra twice daily and Keppra XR once daily to support the future marketing authorization application

It was stated in the FAL that since in the pivotal study comparative bioavailability has not been shown for peak plasma concentration at steady state (Cmax.ss), with lower and upper boundary of 90% CI crossing outside of the 80-125% interval, and exposure response relationship is not well characterised for levetiracetam, a therapeutic equivalence study comparing the efficacy and safety of the test and reference products will be needed to establish a bridge between the EU reference product and the test product to allow reference to the reference product's pre-clinical and clinical data. However, a therapeutic equivalence study was not submitted by the applicant.

Moreover, as per EMA/SA/0000079358, based on the current state of literature, PBPK models currently cannot be considered reliable for the prediction of CSF drug concentration specifically for transporter substrates, when no in vivo CSF data is available for parameter optimization/model verification.

Furthermore, it was agreed that the model cannot be considered to support safety claims and that other sources of data would be required for the evaluation of safety.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Manufacturer's authorisation and valid GMP certificates for all manufacturing sites are available in EudraGMP database.

A QP declaration, based on audit performed in 2023, issued on behalf of Neuraxpharm Pharmaceuticals, S.L. (MAH) for an active substance manufacturing site has been provided.

GLP

N/A

GCP

The applicant provided a statement that clinical trials carried out outside the European Union met the ethical requirements of Directive 2001/20/EC.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

- Article 10(3) of Directive 2001/83/EC, as amended– relating to applications for hybrid medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Keppra, 250 mg, 500mg, 750 mg, 1000mg, Film-coated tablet
- Marketing authorisation holder: UCB Pharma SA
- Date of authorisation: 2000-09-29
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number:

250 mg

- EU/1/00/146/001
- EU/1/00/146/002
- EU/1/00/146/003
- EU/1/00/146/004
- EU/1/00/146/005
- EU/1/00/146/029
- EU/1/00/146/034

500mg

- EU/1/00/146/006
- EU/1/00/146/007
- EU/1/00/146/008
- EU/1/00/146/009
- EU/1/00/146/010
- EU/1/00/146/011
- EU/1/00/146/012
- EU/1/00/146/013

750 mg

- EU/1/00/146/014
- EU/1/00/146/015

- EU/1/00/146/016
- EU/1/00/146/017
- EU/1/00/146/018
- EU/1/00/146/019
- EU/1/00/146/028
- EU/1/00/146/036

1000mg

- EU/1/00/146/020
- EU/1/00/146/021
- EU/1/00/146/022
- EU/1/00/146/023
- EU/1/00/146/024
- EU/1/00/146/025
- EU/1/00/146/026
- EU/1/00/146/037

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Keppra, 250 mg, 500mg, 750 mg, 1000mg, Film-coated tablet
- Marketing authorisation holder: UCB Pharma SA
- Date of authorisation: 2000-09-29
- Marketing authorisation granted by:

□ Union

- Marketing authorisation number:

250 mg

EU/1/00/146/001

EU/1/00/146/002

EU/1/00/146/003

EU/1/00/146/004

EU/1/00/146/005

EU/1/00/146/029

EU/1/00/146/034

500mg

- EU/1/00/146/006

- EU/1/00/146/007
- EU/1/00/146/008
- EU/1/00/146/009
- EU/1/00/146/010
- EU/1/00/146/011
- EU/1/00/146/012
- EU/1/00/146/013

750 mg

- EU/1/00/146/014
- EU/1/00/146/015
- EU/1/00/146/016
- EU/1/00/146/017
- EU/1/00/146/018
- EU/1/00/146/019
- EU/1/00/146/028
- EU/1/00/146/036

1000mg

- EU/1/00/146/020
- EU/1/00/146/021
- EU/1/00/146/022
- EU/1/00/146/023
- EU/1/00/146/024
- EU/1/00/146/025
- EU/1/00/146/026
- EU/1/00/146/037

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: Keppra 500mg Film-coated tablet
- Marketing authorisation holder: UCB Pharma SA
- Date of authorisation: 2000-09-29

- Marketing authorisation granted by:

□ Union

Marketing authorisation number(s):

500mg

- EU/1/00/146/006
- EU/1/00/146/007
- EU/1/00/146/008
- EU/1/00/146/009
- EU/1/00/146/010
- EU/1/00/146/011
- EU/1/00/146/012
- EU/1/00/146/013

- Bioavailability study number(s): **LVM-BEMD-09-LLV/20, LVM-BESD-12-LLV/22**

2.5.2. Orphan designation

Not applicable (N/A).

2.5.3. Similarity with orphan medicinal products

N/A

2.5.4. Derogation(s) from orphan market exclusivity

N/A

2.5.5. Information on paediatric requirements

N/A

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as prolonged-release granules containing 1000 mg, 1500 mg, 2000 mg or 3000 mg of Levetiracetam as active substance.

Other ingredients are: Core: Cellulose, microcrystalline, Copovidone, Talc, Magnesium stearate; Coating: Ethylcellulose, Triglycerides, medium-chain, Oleic acid, Ammonium hydroxide, Hypromellose.

The product is available in sachets made of PET 12 µm / ALU 9 µm / PE 50 µm reel or PATZ 47435 / PET 12 / ALU 9 / PE 50 dull, but only one kind of sachet (PET/Alu/PE) is mentioned in SmPC and in the Application Form.

3.1.2. Active substance

3.1.2.1. General information

The active substance levetiracetam is described in the Ph. Eur. The manufacturer of levetiracetam used in this application has been granted an EDQM Certificate of Suitability

3.1.2.2. Manufacture, process controls and characterisation

One site is involved in the manufacture of the active substance.

The relevant information has been assessed by the EDQM before issuing the certificate of suitability.

3.1.2.3. Specification

The active substance specification is in accordance with the current Ph. Eur. monograph no. 2535 and the CEP requirements.

The analytical procedures adopted by the finished product manufacturer are those described in the European Pharmacopoeia monograph of levetiracetam, with the exception of the method for the determination of ethyl carbamate and residual solvent content (acetone), where in-house analytical methods are used.

The in-house analytical methods used have been adequately described and sufficiently validated in accordance with the ICH guidelines.

Batch analysis data of three batches of the active substance has been provided. The results are within the specifications and consistent from batch to batch.

3.1.2.4. Stability

The stability results assessed during CEP procedure indicate that the active substance is sufficiently stable. The stability results justify the proposed retest period.

3.1.3. Finished medicinal product

3.1.3.1. Description of the product and pharmaceutical development

The finished product levetiracetam prolonged-release granules was developed in four strengths of 1000 mg, 1500 mg, 2000 mg and 3000 mg.

The active substance levetiracetam is a white or almost white powder and belongs to BCS Class 1. It is very soluble in water, soluble in acetonitrile and practically insoluble in heptane. Levetiracetam does not exhibit polymorphism.

The finished product has been developed as extended-release product with similar characteristics to Keppra XR tablets.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except for Surelease. There are no novel excipients used in the finished product formulation, however Surelease is considered a co-processed excipient. The choice of excipients has been based on binary compatibility studies. Excipients used have been characterised and their grade has been defined however, the characterisation of Surelease still needs to be updated. (OC) he applied product can be used in children over 12 years however, compliance of the formulation with requirements for a paediatric and elderly population is still not sufficient (OC).

A clear summary of the manufacturing process development has been presented.

Information on dissolution development is still not fully sufficient. The discriminatory power of dissolution method cannot be considered as documented. (MO) Also, information on an influence of alcohol on dissolution is not fully clear – clarification is needed why tests with 5% ethanol were performed for 2 hours, and tests with 10% or 20% ethanol were performed for 1 hour. (OC)

The microbiological attributes proposed for the final product comply with Ph. Eur. 5.1.4: Non aqueous preparations for oral use.

3.1.3.2. Manufacture of the product and process controls

The manufacturing process consists of steps: weighing, blending, granulation solution preparation, granulation, drying, screening, blending, lubrication, compression, coating, and packaging. The process is considered to be a non-standard manufacturing process.

The batch formula for the intended commercial batch size is stated. A detailed narrative description of the full manufacturing process is provided, accompanied by a flow chart including in-process controls. Critical steps of the manufacturing process are adequately described.

The finished product manufacturing process has been satisfactorily validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

A validation report for the sachet-filling and packaging step for three production scale batches has also been presented. However, since there are two manufacturing sites responsible for primary and secondary packaging, the validation protocol for the filling and packaging step should be presented from the second declared manufacturing site or it should be confirmed that the presented packaging validation is also obligatory at the second manufacturing site (OC).

The transport arrangements of bulk product have been sufficiently described. The potential impact of short or longer excursions outside of the original storage conditions has been discussed and supported by accelerated and long-term stability data.

3.1.3.3. Product specifications

The updated specifications are acceptable. The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach. Batch analysis data on three batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

An updated risk evaluation concerning the presence of nitrosamine impurities in the finished product has been submitted considering suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). A justification for testing two specified nitrosamines is expected.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three batches of stick packs for strength 1000 mg, one batch of stick packs for strength 1500 mg, one batch of stick packs for strength 2000 mg, one batch of stick packs for strength 3000mg, and two batches of stick packs for strength 3000 mg for a different batch size. They indicate that the process is under control.

3.1.3.4. Stability of the product

Stability data from three batches of size 100 000 stick packs for strength 1000 mg, two batches of size 100 000 stick packs for strength 3000 mg and one batch of size 33 333 stick packs for strength 3000 mg, stored for up to 24 months under long term conditions (25ºC±2ºC / 60%RH±5%RH) and for up to 6 months under accelerated conditions (40ºC±2°C / 75%RH±5%RH) according to the ICH guidelines were provided. The batches were packed in the primary packaging proposed for marketing, i.e. PET / ALU / PE sachets.

Levetiracetam prolonged release granules 1500 mg and 2000 mg strengths packed in PET / ALU / PE sachets were not included in the stability studies, as according to the Note for Guidance on Bracketing and Matrixing designs for Stability Testing of Drug Substances and Drug Products (CPMP/ICH/4104/00) a reduced design (bracketing design) can be applied for the finished product.

Additionally, stability studies data covering 3 months at long term and accelerated conditions have been presented for three finished product batches of strengths 1000 mg, 1500 mg, 2000 mg, 3000 mg packed in PATZ 47435 / PET / ALU / PE sachets.

Samples are tested for appearance, colour, water, assay, dissolution, related substances and microbial contamination tests. The analytical procedures used are stability indicating.

Stability studies results presented comply with specifications. No significant changes have been observed.

Photostability studies performed in line with ICH Q1B demonstrated that finished product is photostable.

Based on available stability data, the proposed shelf-life of 36 months and storage conditions: "This medicinal product does not require any special storage conditions", as stated in the SmPC (section 6.3), are acceptable.

3.1.3.5. Post approval change management protocol(s)

Not applicable

3.1.3.6. Adventitious agents

No excipients derived from animal or human origin have been used.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The quality dossier for medicinal product Epixram cannot be recommended for approval at this stage of the procedure since 1 Major Objection remain unresolved. In addition, 12 other concerns identified in relation to the active substance and the finished product should be adequately resolved before a MA is granted.

The provided Module 3 dossier is well-structured and divided into active substance and finished product parts, followed by Appendixes and Regional Information.

The active substance dossier is based on a CEP and complete assessment was performed by EDQM. Module 3.2.S is clearly written, however, still requires further amendments / explanations.

The finished product dossier cannot be considered approvable, as many issues have been raised in relation to development, manufacturing and quality control of the finished product. A MO has been raised in relation to discriminatory power of dissolution method.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product is not acceptable at this stage, as one Major Objection and 12 of Other Concerns have been identified. From the quality point of view the dossier cannot be recommended for approval.

3.1.6. Recommendations for future quality development

Not applicable.

3.2. Non clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Pharmacodynamic, pharmacokinetic and toxicological properties of levetiracetam are well known. As Levetiracetam is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

3.2.1. Ecotoxicity/environmental risk assessment

The applicant submitted Environmental Risk Assessment was submitted.

PEC has been estimated considering the default values stated by the EMA guideline.

The $PEC_{SURFACEWATER}$ obtained is above the threshold stated by the EMA guideline (0.01 µg/L) suggesting that levetiracetam should enter in the Phase IIa to complete its Environmental Risk Assessment.

Assessment on Levetiracetam increase in environmental exposure and consumption data

Regardless of the levetiracetam $PEC_{SURFACEWATER}$ results in Phase I above the threshold of 0.01 µg/l and although no information of public domain from Phase IIA studies is available, an evaluation of the increase in levetiracetam environmental exposure has been performed.

According to EMA guideline, if the product application refers to Article 10 of Directive 2001/83/EC and the absence of increased environmental exposure can be justified, the ERA risk assessment should be stopped in Phase I. An increase in environmental exposure is generally expected when the patient population is increased as a consequence of 1) the addition of a new indication, 2) the inclusion of a new patient population or 3) an increase of the maximum recommended therapeutic dose; none of these assumptions are applicable in the case of Levetiracetam 1000 mg/ 1500 mg/ 2000 mg/ 3000 mg prolonged release granules as it is intended to be a hybrid medicinal product with the same dose,

therapeutic indication and treatment duration as a number of medicinal products already marketed in the Member States included in this procedure, being the maximum daily dose in most cases 3000 mg. Therefore, although strengths of Neuraxpharm Levetiracetam 1000 mg/ 1500 mg/2000 mg/ 3000 mg prolonged release granules are higher than those approved for the reference product, the maximum recommended daily dose is the same.

Another difference between Levetiracetam prolonged release granules and the reference product is in the target population for the indication "Partial onset seizures with or without secondary generalization in patients with epilepsy". Whereas Levetiracetam prolonged release granules is indicated in adults and adolescents aged ≥12 years, the reference product is indicated in adults, adolescents, children and infants from 1 month of age.

Therefore, Levetiracetam 1000 mg/ 1500 mg/ 2000 mg/ 3000 mg prolonged release granules is intended for substitution, in a mode similar to generic, of the already marketed medicinal products with the same pharmaceutical indication within a specific age range (adults and adolescents aged ≥12 years), and then no increase in environmental exposure is expected.

Levetiracetam is marketed in the Member States included in this procedure in several pharmaceutical forms mainly oral (tablets and oral solution) and solution for perfussion, which means that granules are only one source of the total levetiracetam environmental exposure.

Literature supports the absence of increase in environmental exposure after the marketing of compounds intended to partly substitute those already marketed. The penetration of a hybrid medicinal product onto a specific market may vary depending on several factors such as price, number and years in market of other generic/hybrid competitors and it is case-by-case specific. However, it is well accepted that generic medicinal products partly replace the active ingredient consumption for a specific therapeutic indication (Kaplan et al, 2013; Geitona et al, 2006; Dylst et al 2013, Dylst and Simoens, 2011). Then, a generic medicinal product does not generally lead to an increase of the treated population by itself and competes for the same market, which is consistent with the EMA Q&A document. The more generic compounds are available in a local market the less sales rate correspond to each generic or for the innovator (Ventimiglia and Kalali, 2010; Puig-Junoy, 2010).

The same criteria applicable to generic drugs can be applied to the hybrid medicinal product Levetiracetam (1000 mg/ 1500 mg/ 2000 mg/ 3000 mg prolonged release granules) in terms of ERA as the therapeutic indication and MRDD are the same as those for the products already marketed and intends to partly substitute the consumption in adults and adolescents aged ≥ 12 years, excluding children and infants from 1 month of age.

3.2.2. Discussion on non-clinical aspects

Epixram is considered approvable from a non-clinical point of view.

The non-clinical sections of the SmPC are acceptable.

3.2.3. Conclusion on non-clinical aspects

Epixram is approvable for a non-clinical point of view.

3.3. Clinical aspects

3.3.1. Exemption

Dissolution studies for the Levetiracetam prolonged-release granules were performed in four different pHs (1.2, 4.5, 6.0 and 6.8) for the four strengths 1000, 1500, 2000 and 3000 mg (rotational speed conditions: 100 rpm). Such tests were also performed for the reference product Keppra® tablets.

Comparative dissolution studies have been further performed between the different strengths of Levetiracetam 1000, 1500, 2000 and 3000 mg prolonged-release granules to support the strength biowaiver proposal, whereas the respective dissolution profiles of the reference product Keppra IR® 500 mg film-coated tablet were also determined.

The *in vitro* dissolution tests in support of biowaiver of strengths further demonstrated similarity at different pH values (pH 1.2, 4.5, 6.0 and 6.8) between the additional strengths and the strength used for bioequivalence testing.

The dissolution profiles of the reference product Keppra® IR 500 mg film coated tablet were also determined in 900 ml of pH 1.2 (HCl 0.1 N), pH 4.5, pH 6.0 and pH 6.8, using basket at 100 rpm.

The *Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1/ Corr**)* gives specific indications to evaluate the similarity of dissolution profiles. Following these indications, the dissolution similarity between levetiracetam prolonged-release granules 1000, 1500 and 2000 mg 3000 mg were assessed for the dissolution media HCl 0.1 N, acetate buffer pH 4.5 and phosphate buffer pH 6.0 and pH 6.8. In all media, the similarity was evaluated mathematically by calculating the similarity factor.

According to the results, it can be concluded that the dissolution profiles of the developed Levetiracetam prolonged-release granules' additional strengths of 1500, 2000 and 3000 mg are similar to the 1000 mg strength used in the bioequivalence study in all media tested, since the f2 statistic obtained is between 50 and 100 in pH 1.2 (HCl 0.1 N), acetate buffer pH 4.5, phosphate buffer pH 6.0 and phosphate buffer pH 6.8 media.

Taking all the above into consideration and based on the recommendations of the current EMA Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**, EMA 2010), all respective strength biowaiver criteria are fulfilled and bioequivalence testing using the 1000 mg strength of Levetiracetam prolonged-release granules at a dose of 3000 mg is considered acceptable. Then, the results of the BE assessment can be extrapolated to the additional strengths. The dissolution of Keppra® IR 500 mg film coated tablet, in all the evaluated pH was greater than 85 % in 15 min, hence f2 values were not calculated.

Assessor's comment

The applicant applies for the 1000 mg, 1500 mg, 2000mg and 3000mg strength of the prolonged-release granules. In support the applicant performed a dissolution study (pH 1.2, 4.5, 6.0 and 6.8 using a basket apparatus with 100 rpm to compare the 1000 mg, 1500 mg, 2000mg and 3000mg strengths.
Based on the study results it could be concluded that additional bioequivalence testing in vivo can be waived since levetiracetam prolonged-release granules' additional strengths of 1500, 2000 and 3000 mg can be considered similar to the 1000 mg strength used in the bioequivalence study in all media tested, as the calculated f2 was between 50 and 100 in pH 1.2 (HCl 0.1 N), acetate buffer pH 4.5, phosphate buffer pH 6.0 and phosphate buffer pH 6.8 media.

● Tabular overview of clinical studies

To support the MAA, the applicant submitted two bioequivalence studies, one dose-proportionality study and one RWE study. Moreover, PKPB model has been provided by the applicant.

Table 1: Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Drug Products; Dosage Regimen and Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	LVM-BEMD-09-LLV/20	5.3.1.2	The aim of the study was to demonstrate the steady state bioequivalence between the extended-release TEST formulation and a corresponding dose of the REFERENCE medicinal product, both administered under fasting conditions for 5 consecutive days. The bioequivalence assessment was based on plasma drug levels of levetiracetam. As a secondary objective, the safety and tolerability of both formulations was assessed.	Open label, two-period, two-way crossover, block randomized, multiple dose bioequivalence pivotal study on healthy volunteers with administration under fasting conditions.	Keppra 500 mg film-coated Administered orally, three tablets taken simultaneously twice daily, the first dose in the morning and the second one in the evening (12 hours after the morning dose), for a 3000 mg daily dose for five consecutive days with 240 ml of still bottled water at room temperature, under fasting conditions. Levetiracetam 1000 mg prolonged-release granules in sachets Administered orally, three sachets (for a 3000 mg daily dose) administered simultaneously once daily, for five consecutive days, in the morning with 240 ml of still bottled water at room temperature, under fasting conditions.	Planned: 42 subjects; Enrolled: 42; Analyzed (bio-assay): 42 subjects; Statistically analyzed: 40 subjects for whom steady-state status was confirmed , N=42) as supportive information	Healthy Subjects	Multiple Dose	Complete; Full Report
BE	LVM-BESD-10-LLV/21	5.3.1.2	The aim of the study was to demonstrate the dose proportionality between TEST1 formulation (3 x 1000 mg sachets, 3000 mg daily dose) and TEST2 formulation (1 x 1000 mg sachet, 1000 mg daily dose), both administered under fasting conditions. The dose proportionality assessment was based on plasma drug levels of levetiracetam. As a secondary objective, the safety and tolerability of the formulations were assessed.	An open label, two-period, two-way crossover, block randomized, single dose pivotal bioequivalence study on healthy adults male and female volunteers with administration under fasting conditions.	Levetiracetam 1000 mg prolonged-release granules in sachets Administered orally, 3 sachets taken simultaneously, once daily, with 240 ml of still bottled water at room temperature, under fasting conditions. Levetiracetam 1000 mg prolonged-release granules in sachets Administered orally, 1 sachet, once daily, with 240 ml of still bottled water at room temperature, under fasting conditions	32 subjects; enrolled: 32; analyzed (bio-assay): 31 subjects	Healthy Subjects	Single Dose	Complete; Full Report

BE	LVM-BESD-12-LLV/22	5.3.1.2	The aim of the study was to assess the bioequivalence and to determine the food effect between a TEST formulation of levetiracetam 3x1000 mg prolonged-release granules in sachets administered under fasting conditions (TFAST) and under fed conditions (TFED) and the levetiracetam IR REFERENCE formulation 500 mg oral tablet administered as three tablets at once in the morning and three tablets at once in the evening under fasting conditions (RFAST). The bioequivalence assessment/food effect was based on plasma drug levels of levetiracetam.	An open label, three-period, three-way crossover, block randomized, single dose bioequivalence study on healthy volunteers with administration under fasting and fed conditions.	Levetiracetam 1000 mg prolonged-release granules in sachets Administered orally, 3 sachets administered simultaneously, once daily, with 240 ml of still bottled water at room temperature, under fasting and fed conditions. Keppra 500 mg film-coated tablets Administered orally, 3 tablets taken simultaneously, twice daily for a 3000 mg total dose, with 240 ml of still bottled water at room temperature, under fasting conditions.	36 subjects; enrolled: 36; analyzed (bio-assay): 33 subjects	Healthy Subjects	Single Dose	Complete; Full Report
			As a secondary objective, the safety and tolerability of the formulations were assessed.						
RWE	LESVILEVE/22/RWE-4	5.3.3.5	The primary objective was to compare the proportion of subjects who were seizure-free for at least 24 weeks while receiving a stable dose of medication between new users of oral levetiracetam XR and new users of oral levetiracetam IR in the clinical practice.	This was a non-interventional, retrospective, cohort study in new users of levetiracetam IR or XR using a large national private claim registry linked to EMR information from the US.	levetiracetam XR and levetiracetam IR	The final sample size evaluable for the primary endpoint was 428 for levetiracetam XR and 442 for levetiracetam IR, with a response rate in the control group of 34.6%, which provided a statistical power of 52% at an alpha (α) error of 0.025.	Diagnosis of Patients	N.A	Complete; Full Report

PBPK	N.A	5.3.5.2	Application of a PBPK model platform to predict levetiracetam concentrations in the CNS after the administration of the modified release formulation (test PR) compared to the immediate release formulation (Keppra® IR) with different posology	PBPK model	- Levetiracetam 1000 mg prolonged-release granules (test PR) once daily vs the reference product Keppra® IR 500 mg twice daily - Levetiracetam 3000 mg prolonged-release granules (test PR) once daily vs reference product Keppra® IR 1500 mg twice daily	N.A	N.A	N.A	Complete; Full Report

N.A: Not Applicable

Type of study	Study Identifier	Objectives of the Study	Study design	Drug products: dosage, regimens and route of administration	Number of subjects	Healthy subjects or patients	Duration of treatment	Study status/type of report
BE	LVM-BEMD-14-LLV/23	The aim of the study was to demonstrate the steady state bioequivalence between the TEST prolonged-release granules in sachets formulation and a corresponding dose of REFERENCE film-coated extended-release tablets, both administered under fasting conditions for 5 consecutive days. The bioequivalence assessment was based on plasma drug levels of levetiracetam. As a secondary objective, the safety and tolerability of both formulations	Open label, two-period, two-way crossover, block randomized, multiple dose bioequivalence study on healthy volunteers with administration under fasting conditions.	*Reference product:* KEPPRA XR 750 mg film-coated extended-release tablets of UCB, Inc. Smyrna, GA 30080, United States. *Test product:* Levetiracetam 1000 mg prolonged-release granules in sachets manufactured by Laboratorios Lesvi S.L., Spain.	Enrolled: 30; Analyzed (bio-assay): 30 subjects; Statistically analyzed: 25 subjects for whom steady-state status was confirmed.	HV	Multiple dose	Complete, full report

		was assessed.						

3.3.2. Clinical pharmacology

3.3.2.1. Pharmacokinetics

Study LVM-BEMD-09-LLV/20: Open label, two-period, two-way crossover, block-randomized, multiple dose bioequivalence study of Levetiracetam 1000 mg prolonged release granules in sachetes, 3000mg or 2000mg once per day (test formulation) vs. equal daily dose of the reference product (Keppra 500mg immediate release film-coated tablets) twice per day in healthy male and female volunteers, under fasting conditions.

- **Study design**

Open label, two-period, two-way crossover, block randomized, multiple dose bioequivalence pivotal study on healthy volunteers with administration under fasting conditions.
Hospitalization of subjects from the evening of Day -1 until 36 hours after the 5th morning dose (until the evening of Day 6) on each study period.

Blinding
This was an open labeled but laboratory-blinded study. The randomization table was not made available to the personnel in charge of the determination of levetiracetam plasma levels until samples analyses was finalized.

The study medication, 5 consecutive once daily doses of TEST formulation, Levetiracetam 1000 mg prolonged-release granules in sachets, taken as 3000 mg dose in the morning (T) or 5 consecutive treatment days with REFERENCE formulation, Keppra 500 mg immediate release film-coated tablets, administered twice daily as 1500 mg (3 tablets) on each treatment day, in fasting conditions: the first dose in the morning and the second one in the evening (12 hours after the morning dose) (R) was administered in Days 1 to 5, under fasting conditions by the Clinical Investigator.
The study products were administered orally a total volume of 240 mL of still bottled water at room temperature. The subjects kept a standing position during treatment intake.
After each administration, the Investigator or her designee performed a mouth and hands check in order to ensure that each dose has been taken entirely.

Selection of doses in the study: The selection of the study dosage (3000 mg/day levetiracetam) was done according to the recommended doses normally administered to patients (relating to the therapeutic range) stated in the SmPC. The strength tested in the bioequivalence study was in agreement to the regulatory authority requirements and allows obtaining measurable plasma concentrations after administration through the bioanalytical method.

The subjects were separated in dosing groups:
Dosing group 1 (sentinel group): was comprised of 4 subjects and was treated with daily doses of 3000 mg levetiracetam, for 5 consecutive days in each study period.
Dosing group 2: as the initial 4 subjects from the sentinel group have tolerated well the daily treatment with 3000 mg levetiracetam for 5 consecutive days, dosing group 2 was comprised of 8 subjects and the daily dose remained unchanged (3000 mg/day). There were 5 consecutive dosing days per study period.
Dosing groups 3 and 4: an additional number of 18 subjects were included in dosing group 3 and 12 subjects in dosing group 4 and the daily dose remained 3000 mg/day

Blood samples: Blood samples were collected at the following times (the theoretical collection times expressed in hours are relative to first dose administration on Day 1): 0 (pre-dose for the 1st morning daily dose), 47.917 (47h 55min, pre-dose for the 3rd morning daily dose), 71.917 (71h 55min, pre-dose for the 4th morning daily dose), 95.917 (95h 55min, pre-dose for the 5th morning daily dose) and at 96.5 (96h 30min), 97.0, 98.0, 99.0, 100.0, 101.0, 102.0, 103.0, 104.0, 105.0, 106.0, 107.0, 108.0, 108.5 (108h 30min), 109.0, 110.0, 111.0, 112.0, 116.0 and 120.0 hours after the 1st dose (24 samples of 5 mL/ study period). Also, an additional reserve blank sample of 20 mL was drawn pre-dose only on Period I.

Wash-out period: 10 days.
Analytical method: HPLC validated method, with MS/MS detection technique for levetiracetam.

Safety: Adverse events, clinical and laboratory screening and follow up examinations, vital signs, ECG, physical examination, drugs of abuse and breath alcohol test.

Duration of treatment: Five consecutive administration days per study period, with one daily dosing for the Test product and two daily dosing when the Reference product is administered: the first dose in the morning and the second one in the evening (12 hours after the morning dose).

Criteria for evaluation:
Pharmacokinetics: AUC(0-т), Cmax.ss, Cmin.ss, (primary) and Cav.ss, Tmax.ss and PTF (additional).
Safety: Adverse events, clinical and laboratory screening and follow up examinations, vital signs, ECG, physical examination, drugs of abuse and breath alcohol test, COVID-19 test.

Protocol deviations
No protocol deviation was registered in the present study.

- **Test and reference products**

TEST formulation (T)
Name of the product: Levetiracetam 1000 mg prolonged-release granules in sachets
Pharmaceutical form: Prolonged-release granules in sachets
Strength: 1000 mg/sachet
Mode of administration: Oral, 3 sachets taken simultaneously, once daily for a 3000 mg daily dose
Manufacturer: Laboratorios Lesvi, S.L.
Country of manufacturer: Spain, EU

Reference formulation (R)
Name of the product: Keppra 500 mg film-coated tablets
Pharmaceutical form: Film-coated tablets (Immediate release)
Strength: 500 mg
Mode of administration: Oral; 3 tablets taken simultaneously, twice daily for a 3000 mg daily dose
MAH: UCB Pharma SA, Belgium
Country of purchase: Spain

- **Population(s) studied**

Inclusion criteria (applicable at screening)
1. Healthy Caucasian1 male and female volunteers of at least 18 years of age but not older than 55 years.
2. Subject with the Body Mass Index within 20.0 and 29.0 kg/m2.
3. Normal haematology, clinical chemistry and urinalysis (some deviations outside the normal limits may be acceptable if judged so by the Investigator, except for haematology that must not have value under the lower normal limit).
4. Absence of renal and hepatic impairment.
5. Absence of cardiovascular diseases.

6. Non-smokers or ex-smokers that gave up smoking for at least two years prior to the study (Day 1 of Period I).
7. The subject agrees to abstain from alcohol and from beverages or food containing methylxanthines (coffee, tea, cola, energy drinks, chocolate etc.) and chewing-gum for 48 hours prior to the first study drug administration and during each study period (until 36 h after the 5th morning dose).
8. The subject has not consumed and agrees to continue to abstain from St John's Wort, vitamins and herbal remedies for two weeks prior to the first study drug administration and during the study (until 36 h after the 5th morning dose of Period II).
9. The subject has not consumed and agrees to continue to abstain from beverages or food containing orange, grapefruit or pomelo for two weeks prior to the first study drug administration and during the study (until 36 h after the 5th morning dose of Period II).
10. Ability to understand the full nature and purpose of the study, including possible risks and side effects; ability to cooperate with the Clinical Investigator and to comply with the requirements of the entire study.
11. Informed written consent given voluntarily before the initiation of the study screening.
12. No relevant abnormal findings at physical examination.
13. For female subjects only: non-lactating status.
14. For female subjects only: negative pregnancy test.

15. For female subjects of child-bearing potential* only: subject agrees to use effective nonhormonal method of contraception (condoms, intra-uterine device, sponge, diaphragm or a combination of these) or abstinence starting from screening and until follow-up examination.

16. Based on the opinion of the Clinical Investigator, subject is medically fit for participation in the study.

Exclusion criteria (applicable at screening)
1. History of hypersensitivity to the test drug or to drugs belonging to the same pharmacological and chemical class or to the inactive ingredients.
2. Subject intends to be hospitalized within 3 months after last study drug administration.
3. Participation in a clinical study with an investigational product in the preceding three months or in a clinical study with a generic product in the preceding two months.
4. Hospitalization for any reason within eight weeks prior to the study initiation.
5. Donation of 450 ml or more of blood, within eight weeks prior to the study initiation.
6. Intake of any prescription or non-prescription drugs during the two weeks preceding the study or throughout the study.
7. Depot injection or an implant of any drug within 3 months prior to the first dosing.
8. History or presence of any relevant medical condition including cancer, significant disease of the renal, hepatic, gastrointestinal, respiratory, cardiovascular, endocrine or locomotor systems, and any metabolic, hematological (see also exclusion criteria 9 to 10) or neurological disorder.
9. History or actual presence of coagulation disorders such as thromboembolic diseases (e.g. thrombophlebitis, pulmonary embolism or coagulation factors deficiency), cerebrovascular diseases, angina pectoris, myocardial infarction or coronary arterial disease, porphyria.

Number of subjects:
Planned: 42 subjects; Enrolled: 42; Analyzed (bio-assay): 42 subjects; Statistically analyzed: 40 subjects for whom steady-state status was confirmed.
All the 42 dosed volunteers completed the study and all underwent the follow-up examination.
A separate analysis was performed for subjects that could be considered evaluable according to the provisions of the Study Protocol (the entire population, N=42) as supportive information.

Data sets analyzed
For the bioequivalence assessment, levetiracetam pharmacokinetic data coming from 40 subjects for whom steady-state status was confirmed out of 42 subjects enrolled in the study were statistically analysed. The descriptive statistics of demographic characteristics for the 42 subjects that were

enrolled in the study has been performed. Screening and follow-up safety data were analyzed on 42 complete datasets.

Demographic and other baseline characteristics

N = 42	*AGE (years)*	*WEIGHT (kg)*	*HEIGHT (cm)*	*BMI (kg/m^2)*
Mean	31.98	70.45	169.86	24.39
Median	29.00	69.00	169.50	24.30
SD	9.01	10.08	8.16	2.75
CV	28.16	14.31	4.81	11.27
Min.	18	55	151	20.1
Max.	53	98	187	28.9

- **Analytical methods**

Development of an HPLC-MS/MS method to determine levetiracetam in plasma samples was performed and the report submitted as LVA-BE-LCMSMS-01/09.
The analytical method was used in the following studies: LVM-BEMD-09-LLV/20; LVM-BESD-10-LLV/21; LVM-BESD-12-LLV/22.

Assessor's comments
The objective of the analysis presented in report LVA-BE-LCMSMS-01/09 was to validate the HPLC-MS/MS method for determining levetiracetam levels in plasma samples using heparin as an anticoagulant.
The LLOQ for levetiracetam was established at 200 ng/mL with a mean accuracy of 108.280%. The precision and accuracy across all QC concentrations were acceptable (between-run accuracy: 99.362-102.619%; between-run precision: 2.629-5.243%; within-run accuracy: 97.582-100.616%; within-run precision: 1.687-5.374%). The method's selectivity, extraction recovery, and dilution integrity (1/4) were all assessed and found acceptable.
Stability conditions for levetiracetam storage were approved up to 6 hours at room temperature, up to 1 week at – 5 ºC, up to 7 weeks below – 20 ºC and up to 1 week at – 70 ºC, in plasma extracts up to 24 hours when kept at 10 ºC. Further, internal standard was found to be stable up to 16 hours when kept at room temperature and stock solutions of the analyte and internal standard were found to be stable for 6 hours at room temperature and up to one month. Levetiracetam was found to be stable after 3 freeze-thaw cycles.
Partial validation has been performed to 1) show levetiracetam stability in spiked plasma samples over an extended period (up to 4 months) and to evaluate the levetiracetam bio-conversion, 2) express selectivity in presence of possible co-medication, (acetylsalicylic acid, paracetamol and caffeine), and exclude carryover effect, 3) express selectivity in presence of possible co-medication (metamizole, ibuprofen, salicylic acid) and exclude matrix effect, 4) to show the effect of plasma hemolysis on levetiracetam detection, 5) to approve long-term stability of levetiracetam at -20ºC after 12 months. No carry-over effect was present. No bioconversion of levetiracetam was seen. Hemolysis of the plasma and co-medication did not influenced levetiracetam analysis. No matrix and carryover effects were identified.

All parameters recommended for analytical method validation were addressed (EMEA/CHMP/EWP/192217/2009) and met the acceptance criteria. Validation seems to be acceptable.
According to the validation procedure described above, three bioanalytical assessments were performed:

1) determination of LEV in plasma samples supporting clinical study No. LVM-BEMD-09-LLV/20;
2) determination of LEV in plasma samples supporting clinical study No. LVM-BESD-10-LLV/21;
3) determination of LEV in plasma samples supporting clinical study No. LVM-BESD-12-LLV/22.

1) Analytical report for LEV determination in plasma samples supporting clinical study No. LVM-BEMD-09-LLV/20
In total, 2016 human plasma samples with heparin as an anticoagulant were analyzed for levetiracetam using HPLC with MS/MS detection. Samples were stored for a period not exceeding 12 months. These storage conditions are within the validated parameters (validated for up to 12 months of storage).
In a total of 42 runs, the samples from the study subjects were analyzed, and within each sequence, QC sets (a multiple of 2 for each sequence) were included. Three supplementary analytical runs have been used for 71 samples re-assay and for systematic samples re-assay (ISR).
Incurred sample reproducibility was performed for 168 samples. The results were found to be repeatable for 100% of samples as repeated samples had relative differences not exceeding 20% compared to the first evaluation. ISR was acceptable.
The accuracy and precisions for calibration standards and QC samples were acceptable. The levetiracetam concentrations were within calibration range of the curve. Bioanalysis is acceptable.

2) Analytical report for LEV determination in plasma samples supporting clinical study No. LVM-BESD-10-LLV/21.
In total, 1195 human plasma samples with heparin as an anticoagulant were analyzed for levetiracetam using HPLC with MS/MS detection. Samples were stored for a period not exceeding 12 months. These storage conditions are within the validated parameters (validated for up to 12 months of storage).
In a total of 31 runs, the samples from the study subjects were analyzed, and within each sequence, QC sets (a multiple of 2 for each sequence) were included. Three supplementary analytical runs have been used for drop-out subject 12 samples assay, for 2 samples re-assay and for systematic samples re-assay (ISR).
Incurred sample reproducibility was performed for 124 samples. The result were found to be repeatable for 99.194% of samples as repeated samples had relative differences not exceeding 20% compared to the first evaluation. ISR was acceptable.
The accuracy and precisions for calibration standards and QC samples were acceptable. The levetiracetam concentration were within calibration range of the curve. Bioanalysis is acceptable.

3) Analytical report for LEV determination in plasma samples supporting clinical study No. LVM-BESD-12-LLV/22.
In total, 2414 human plasma samples with heparin as an anticoagulant were analyzed for levetiracetam using HPLC with MS/MS detection. Samples were stored for a period not exceeding 12 months. These storage conditions are within the validated parameters (validated for up to 12 months of storage).
Total 33 runs were analyzed levetiracetam in human plasma. Three runs were reanalyzed and two were ISR.
In a total of 33 runs, the samples from the study subjects were analyzed, and within each sequence, QC sets (a multiple of 2 for each sequence) were included. Five supplementary analytical runs have been used for drop-out subjects (1, 9 and 15) samples assay (72 samples), for samples re-assay (50 samples) and for systematic samples re-assay (ISR).
Incurred sample reproducibility was performed for 202 samples. The result were found to be repeatable for 91.584% of samples as repeated samples had relative differences not exceeding 20% compared to the first evaluation. ISR was acceptable.
The accuracy and precisions for calibration standards and QC samples were acceptable. The levetiracetam concentration were within calibration range of the curve. Bioanalysis is acceptable.

- **Pharmacokinetic variables**

The following pharmacokinetic parameters were calculated for levetiracetam:

(AUC0-tau)ss - AUC during the dosing interval

Cmax.ss - Peak drug concentration within the 24-h dosing interval, at steady state.

Obtained directly from the data, without interpolation

Cmin.ss - Minimum drug concentration within the 24-h dosing interval, at steady state (95.917h pre-dose sample excluded). Obtained directly from the data, without interpolation.

Cav.ss - Average plasma concentration during the 24-h dosing interval

Tmax.ss - Time of the maximum measured plasma concentration during the 24-h dosing interval, at steady state. Obtained directly from the data, without interpolation.

PTF - Peak Trough Fluctuations over the dosing interval.

PTF% = 100* Cmax.ss – Cmin.ss / Cav.ss

All calculations were performed using SAS (Ver. 9.4) software.

- **Statistical methods**

All evaluable subjects had to be assessed in the pharmacokinetic data analysis.

All statistical calculations were performed using SAS version 9.4 software. Descriptive statistics was done for all pharmacokinetic parameters (arithmetic mean, harmonic mean, geometric mean, SEM, standard deviation, coefficient of variation, median, range and number of measures).

Bioequivalence comparison: The bioavailability comparison was carried out on the following levetiracetam primary pharmacokinetic parameters: AUC(0-τ); Cmax,ss and Cmin,ss

Comparison of primary pharmacokinetic parameters used for bioequivalence assessment: For the primary parameters considered for bioequivalence assessment (AUC(0-τ); Cmax,ss and Cmin,ss) a 90% confidence interval for the geometric mean ratio (TEST/REFERENCE) was calculated.

Evaluation of period, subject within sequence, sequence and formulation influence on primary pharmacokinetics parameters:

Analysis of variance (ANOVA) model was performed for ln-transformed data on the main pharmacokinetic parameters (AUC(0-τ); Cmax,ss and Cmin,ss) using sequence, period, subject within sequence and treatment as fixed effects. The level of significance was set at 0.05.

Y = μ + Sequence + Subject (Sequence) + Formulation + Period

Determination of Sample Size

A total number of 42 (if the 3000 mg daily dosing regimen was maintained for all dosing groups) healthy male and female volunteers was planned to be enrolled in the study. The number of 42 subjects has been estimated considering the following:

a) the significance level (alpha) of 0.05

b) an a priori test power of 80%

c) an intra-individual coefficient of variation for the primary PK parameters of up to 20%;

d) the expected geometric mean ratio TEST/REFERENCE for the primary PK parameters between 0.90 - 1.10;

e) the bioequivalence acceptance range of 80.00 – 125.00% for the 90% CIs of the of the geometric mean ratio TEST/REFERENCE for the primary PK parameters;

e) a potential drop-out/ withdrawal rate of up to 15%.

- ***Results***

Reference product

N = 40	$AUC_{0\text{-tau ss}}$ (ng/mL * Hours)	$C_{max.ss}$ (ng/mL)	$C_{min.ss}$ (ng/mL)	$C_{av\ ss}$ (ng/mL)	Ptf (%)	$T_{max.ss}$* (h)
Mean	796525.528	58546.711	16794.101	33188.564	127.288	5.038
GMean	785912.105	57752.769	16421.571	32746.338	124.672	2.002
SD	134429.931	9775.777	3684.850	5601.247	26.039	5.784
CV	16.877	16.697	21.941	16.877	20.457	114.817

* Median = 1.000 h

Test product

N = 40	$AUC_{0\text{-tau ss}}$ (ng/mL * Hours)	$C_{max.ss}$ (ng/mL)	$C_{min.ss}$ (ng/mL)	$C_{av\ ss}$ (ng/mL)	Ptf (%)	$T_{max.ss}$* (h)
Mean	722950.291	40919.224	17321.902	30122.929	80.466	7.338
GMean	704717.102	39998.727	16176.119	29363.213	78.067	6.855
SD	166594.186	8907.494	6128.198	6941.424	20.829	2.863
CV	23.044	21.768	35.378	23.044	25.886	39.020

* Median = 6.000 h

The intra-subject variability coefficients registered for the primary pharmacokinetic parameters of levetiracetam (for the subjects with steady-state status confirmed, N=40) were:

PK parameter	Intra-subject CV %
$C_{max.ss}$	15.623
$C_{min.ss}$	24.287
$(AUC_{0\text{-tau}})_{ss}$	10.808

Statistical analysis

Evaluation of the period, sequence, subject within sequence and treatment influence on primary pharmacokinetics parameters

Source of error	Significance level	Probability (p)		
		$AUC_{0\text{-tau ss}}$	$C_{max.ss}$	$C_{min.ss}$
SEQUENCE	0.05000	0.75958	0.68676	0.56351
SUBJECT(SEQUENCE)	0.05000	0.00000*	0.01076*	0.00211*
PERIOD	0.05000	0.47309	0.23259	0.99792
TREATMENT	0.05000	0.00006*	0.00000*	0.77998

* = $p<0.05$ = significant

The ANOVA model implemented by GLM procedure in SAS for checking the sequence and period effect, showed no statistically significant influence on the primary pharmacokinetic parameters. Statistically significant treatment effect was identified for AUC0-tau ss and for Cmaxss. Statistically significant subject within sequence fixed effects were identified for all primary parameters. It is noteworthy to

mention that subject effects are frequently observed due to inter-individual variations, without affecting the validity of the study.

Bioequivalence assessment
The summary results obtained for the different statistical tests used to compare the lntransformed data for (AUC0-tau)ss, Cmax,ss and Cmin,ss obtained for TEST and REFERENCE products are presented.

I. Bioequivalence assessment - including only the subjects for whom steady-state status was confirmed (N= 40):

TEST vs. REFERENCE

Test name	Parameter	Geo Mean Ratio (TEST/Reference)	90% Confidence Interval		Acceptance range		Intra-subject CV (%)
			Lower 90% CL	Upper 90% CL	Lower limit (%)	Upper limit (%)	
Classic 90% CI	$AUC_{0\text{-}tau}$	89.669	86.099	93.387	80.00	125.00	10.808
Classic 90% CI	$C_{max.ss}$	69.259	65.320	73.434	80.00	125.00	15.623
Classic 90% CI	$C_{min,ss}$	98.505	90.005	107.809	80.00	125.00	24.287

If the lower and upper CL (Confidence Interval limits) lie within accepted regulatory criteria, then we may conclude for bioequivalence.

The 90% confidence intervals of the ratio T/R for (AUC0-tau)ss and Cmin,ss were inside the accepted bioequivalence range of 80.00-125.00% and for Cmax.ss was not inside the accepted bioequivalence range of 80.00-125.00% thus permitting to conclude bioequivalence with respect to extent of absorption but not with respect to the rate of absorption.

Out of the 42 subjects completing the study and considered evaluable according to the provisions of the Study Protocol, there were 2 subjects (subjects no. 07 and 28) for which steady state could not be statistically confirmed. They were included in the data set for statistical analysis with their evaluable PK profiles for both study treatments. An analysis, with this subjects excluded, has been conducted and the 90 % confidence intervals for levetiracetam can be found in the table above. Full analysis is available as supportive information.

II. Supportive information - bioequivalence assessment for all subjects (N= 42)

The 90% confidence intervals for levetiracetam mean treatment T/R ratios were:

TEST vs. REFERENCE

Test name	Parameter	Geo Mean Ratio (TEST/Reference)	90% Confidence Interval		Acceptance range		Intra-subject CV (%)
			Lower 90% CL	Upper 90% CL	Lower limit (%)	Upper limit (%)	
Classic 90% CI	$AUC_{0\text{-}tau}$	90.174	86.706	93.781	80.00	125.00	10.704
Classic 90% CI	$C_{max.ss}$	70.092	66.181	74.234	80.00	125.00	15.722
Classic 90% CI	$C_{min,ss}$	99.700	91.389	108.766	80.00	125.00	24.022

If the lower and upper CL (Confidence Interval limits) lie within accepted regulatory criteria, then we may conclude for bioequivalence.

Evaluation of additional pharmacokinetic parameters

Tmax ss values were compared separately for TEST vs. REFERENCE using a non-parametric test (Wilcoxon Signed-Rank Test). The statistical test used did not identify any statistically significant difference between the formulations mentioned in regard to Tmax ss.

Parameter	Statistic Method	Significance level	Probability (p)
$T_{max\ ss}$	Wilcoxon Signed Rank test	0.0500	0.0514 Not significant

In total 40 patients were included in the PK analysis. Two patients, in whom steady state status was not confirmed were not included in the statistical analysis.

The 90% CI of the relative mean plasma levetiracetam AUCt and Cmin ss of test to reference products were between 80.00 and 125.00%. The 90% CI of plasma Levetiracetam Cmax of test to reference products were outside 80.00 and 125.00% (65.32% – 73.43%).
In the supplementary analysis, which include all the subjects (42), BE criteria for Cmax were also not met.

- ***Safety data***

Extent of exposure
42 subjects received 3000 mg daily doses of TEST formulation (Levetiracetam 1000 mg prolonged-release granules in sachets, taken as 3000 mg) for 5 consecutive days and 3000 mg of REFERENCE formulation (Keppra 500 mg immediate release film-coated tablets, administered twice daily, 3 tablets at once, on each treatment day: the first dose in the morning and the second one in the evening (12 hours after the morning dose) for 5 consecutive treatment days, in two different occasions separated by wash-out period of 10 days between last treatment administration of study period I and first treatment administration of study period II, under fasting conditions.
The study drug administration was performed in 4 dosing groups:
- dosing group 1 (sentinel group): comprised of 4 subjects
- dosing group 2: comprised of 8 subjects
- dosing group 3: comprised of 18 subjects and
- dosing group 4: comprised of 12 subjects.

Adverse events
In total 13 adverse events were reported during the study. All AE were considered related to study treatment. All AE, except for one (somnolence) were considered mild. The incidence of the AEs was comparable after administration of the Reference and the Test product (46% vs 54%). No serious adverse events occurred in the present study. No deaths occurred in the present study.
There were no new safety signals identified in the study. The subjects that encountered the adverse event completely recovered before the end of the study.

Table 2: Display of adverse events by SOC (System Organ Classes)

a. Study treatment: REFERENCE N = 42 observations

Adverse Events	Mild		Moderate		Severe		Total		Total
	Related	NR	Related*	NR#	Related	NR	Related	NR	R (Related) + NR (Non-related)
SOC: Nervous system disorders									
Somnolence **MedDRA code:** 10041349	1 (2.38%) **Subj. No. 03						**1 (2.38%)**		**1 (2.38%)**
Dizziness **MedDRA code:** 10013573	3 (7.14%) **Subj. No. 05, 14, 30						**3 (7.14%)**		**3 (7.14%)**
Headache **MedDRA code:** 10019211	2 (4.76%) **Subj. No. 11, 16						**2 (4.76%)**		**2 (4.76%)**

*Related = plausible relationship with drug administration; #NR = non plausible relationship with drug administration
** Subject identification number.

b. Study treatment: TEST N = 42 observations

Adverse Events	Mild		Moderate		Severe		Total		Total
	Related	NR	Related*	NR#	Related	NR	Related	NR	R (Related) + NR (Non-related)
SOC: Nervous system disorders									
Somnolence **MedDRA code:** 10041349			1 (2.38%) **Subj. No. 04				**1 (2.38%)**		**1 (2.38%)**
Dizziness **MedDRA code:** 10013573	4 (9.52%) **Subj. No. 07, 08, 19, 25						**4 (9.52%)**		**4 (9.52%)**
Headache **MedDRA code:** 10019211	1 (2.38%) **Subj. No. 15						**1 (2.38%)**		**1 (2.38%)**
Drowsiness **MedDRA code:** 10013649	1 (2.38%) **Subj. No. 29						**1 (2.38%)**		**1 (2.38%)**

*Related = plausible relationship with drug administration; #NR = non plausible relationship with drug administration
** Subject identification number.

Study LVM-BESD-10-LLV/21: Open label, two-period, two-way crossover, block-randomized single dose, dose proportionality study of Levetiracetam 1000 mg prolonged release granules in sachets, as 3000mg (3x1000 mg sachets) once per day (TEST 1 Formulation) vs. 10000mg (1x 1000mg sachet) once per day (TEST 2 Formulation) in healthy male and female volunteers, under fasting conditions.

Objectives:
The aim of the study was to demonstrate the dose proportionality between TEST1 formulation (3 x 1000 mg sachets, 3000 mg daily dose) and TEST2 formulation (1 x 1000 mg sachet, 1000 mg daily dose), both administered under fasting conditions.

The dose proportionality assessment was based on plasma drug levels of levetiracetam. As a secondary objective, the safety and tolerability of the formulations were assessed.

Methods

- **Study design**

An open label, two-period, two-way crossover, block randomized, single dose pivotal bioequivalence study on healthy adults male and female volunteers with administration under fasting conditions. Hospitalization of subjects from the evening of Day -1 (day before the dosing day) until 36 hours post administration on each study period.

Blinding
This was an open labelled but laboratory-blinded study. The randomization table was not made available to the personnel in charge of the determination of levetiracetam plasma levels.

Products administered:
On each study period the subjects received, as foreseen by the randomized table, either one dose of TEST1 formulation (Levetiracetam 1000 mg prolonged-release granules in sachets, 3 sachets taken simultaneously as 3000 mg overall dose in the morning, in fasting conditions) OR one dose of TEST2 formulation (Levetiracetam 1000 mg prolonged-release granules in sachets, 1 sachet taken as 1000 mg overall dose in the morning, in fasting conditions). The study products were administered orally with 240 ml of still bottled water at room temperature.

Blood samples were collected: before dose (0.0h) and at 0.5, 1.0, 1.50, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 14.0, 16.0, 24.0, 36.0 and 48.0 post dose after each administration (19 samples/ study period).

Wash-out period: 7 days.
Analytical method: HPLC validated method, with MS/MS detection technique for levetiracetam
Relevant pharmacokinetic parameters: dose-adjusted AUC0-t, Cmax and AUC0-∞, Tmax, dose-adjusted AUC%extra (residual area), t1/2, MRT, Kel

Safety: Adverse events, clinical and laboratory screening and follow up examinations, vital signs, ECG, physical examination, pregnancy test, drugs of abuse, breath alcohol test and COVID-19 test.

Determination of Sample Size
A total number of 32 healthy male and female volunteers were planned to be enrolled in the study.
The number of subjects enrolled has been considered adequate for the purposes of a comparative bioavailability study. In order to assure the dosing of 32 volunteers, 2 alternate volunteers had to remain at the study Center in the first period until the IMPs administration was finished. No alternate had to be enrolled and they left the study center after completion of dosing of Period I for both groups.

- **Test and reference products**

Test1 formulation (T1)
Name of the product: Levetiracetam 1000 mg Prolonged-release granules in sachets
Pharmaceutical form: Prolonged-release granules in sachets
Strength: 1000 mg
Mode of administration: Oral; 3 sachets taken simultaneously, once daily
Manufacturer: Laboratorios Lesvi, S.L.
Country of manufacturer: Spain

Test2 formulation (T2)

Name of the product: Levetiracetam 1000 mg Prolonged-release granules in sachets
Pharmaceutical form: Prolonged-release granules in sachets
Strength: 1000 mg
Mode of administration: Oral; 1 sachet, once daily
Manufacturer: Laboratorios Lesvi, S.L.
Country of manufacturer: Spain

- **Population(s) studied**

Number of subjects planned: 32 subjects; enrolled: 32; analyzed (bio-assay): 31 subjects.

Main inclusion criteria
1. Healthy Caucasian1 male and female volunteers of at least 18 years of age but not older than 55 years.
2. Subject with the Body Mass Index within 20.0 and 29.0 kg/m2.
3. Normal haematology, clinical chemistry and urinalysis (some deviations outside the normal limits may be acceptable if judged so by the Investigator, except for haematology that must not have value under the lower normal limit).
4. Absence of renal and hepatic impairment.
5. Absence of cardiovascular diseases.
6. Non-smokers or ex-smokers that gave up smoking for at least two years prior to the study (Day 1 of Period I).

Main Exclusion Criteria (applicable at screening)
1. History of hypersensitivity to the test drug or to drugs belonging to the same pharmacological and chemical class or to the inactive ingredients.
2. Subject intends to be hospitalized within 3 months after last study drug administration.
3. Participation in a clinical study with an investigational product in the preceding three months or in a clinical study with a generic product in the preceding two months.
4. Hospitalization for any reason within eight weeks prior to the study initiation.
5. Donation of 450 ml or more of blood, within eight weeks prior to the study initiation.
6. Intake of any prescription or non-prescription drugs during the two weeks preceding the study or throughout the study.
7. Depot injection or an implant of any drug within 3 months prior to the first dosing.
8. History or presence of any relevant medical condition including cancer, significant disease of the renal, hepatic, gastrointestinal, respiratory, cardiovascular, endocrine or locomotor systems, and any metabolic, hematological (see also exclusion criteria 9 to 10) or neurological disorder.
9. History or actual presence of coagulation disorders such as thromboembolic diseases (e.g. thrombophlebitis, pulmonary embolism or coagulation factors deficiency), cerebrovascular diseases, angina pectoris, myocardial infarction or coronary arterial disease, porphyria.

Disposition of Subjects
In the present study, 64 adult healthy male and female volunteers were screened.
Out of the 64 volunteers screened, a total number of 32 were enrolled (17 females and 15 males, a minimum representation of 31.25% (10 subjects) of each sex being necessary to be achieved.) and additionally, 2 overnight alternates (2 females) were present at the study center as one subject in each group from Day-1 and until the study drug administration of Period I was done. They were kept at the study center until dosing of Period I. 31 subjects out of 32 enrolled volunteers completed the study and underwent the follow-up examination (one subject was a drop-out after the first study drug administration and was lost to follow-up).

Study beginning*	19 February 2022
First volunteer Informed Consent Form signature	21 February 2022
PERIOD I *(dosing Day)*	Subjects 01 to 16: 11 March 2022 Subjects 17 to 32: 15 March 2022
Wash-out	7 days
PERIOD II *(dosing Day)*	Subjects 01 to 16#: 18 March 2022 Subjects 17 to 32: 22 March 2022
FOLLOW-UP	Subjects 01 to 16#: 25 March 2022## Subjects 17 to 32: 28 March 2022

** The study beginning is defined as the date when the volunteers received information about the study and the "Volunteer Information Leaflet and Informed Consent Form"in local language was presented and explained to them and afterwards given to take at home for careful consideration and consultation*
 # Except for subject no. 12 who was a drop-out and was lost to follow-up
On 11.04.2022 subjects with the study nos. 08, 09, and 10, and on 12.04.2022 subjects with the study nos. 14 and 16, returned at the clinical center for repetition of some clinical laboratory parameters (for details see Table 14.3.4.1, at the end of the text).

One subject was considered a drop-out in the present study: Subject No. 12 was a drop-out since 12 March 2022 due to personal reason and was lost to follow-up.

Data Sets Analyzed

For the bioequivalence assessment, Levetiracetam pharmacokinetic data coming from 31 subjects out of 32 subjects enrolled in the study (subject study numbers 01-11 and 13-32) were statistically analysed (only 31 subjects completed the clinical part of the study). The descriptive statistics of demographic characteristics for the 32 subjects that were enrolled in Period I of the study has been performed. Screening and follow-up safety data were analyzed on 31 complete datasets.

Demographic and Other Baseline Characteristics

All volunteers were Caucasians. From the 32 subjects who were dosed in Period I, 15 were males and 17 were females (all included in the safety evaluation). From the 31 subjects that completed all study periods and were included in the statistical analysis for bioequivalence comparison, 14 were males and 17 were females.

N = 32	*AGE (years)*	*WEIGHT (kg)*	*HEIGHT (cm)*	*BMI (Kg/m^2)*
MEAN	**32.34**	**69.31**	**169.47**	**24.15**
SD	**10.44**	**8.59**	**8.56**	**2.76**
Minimum	**18**	**49**	**152**	**20.0**
Maximum	**55**	**83**	**190**	**28.7**

- **Analytical methods**

Please see description of the Study LVM-BESD-10-LLV/20.

- **Pharmacokinetic variables**

The following pharmacokinetic parameters were calculated for levetiracetam based on dose adjusted plasma concentrations:

AUC0-t - area under the plasma concentration time curve from administration to last observed concentration over LLOQ, calculated by linear trapezoidal rule

Cmax - peak drug concentration, obtained directly from the data – without interpolation

Tmax - time of the peak drug concentration, obtained directly from the data, without interpolation

AUC0-∞ (AUC from time 0 to infinite) - area under the curve integrated from the plasma concentrations extrapolating the terminal elimination period

AUC%extra (residual area) - the ratio (AUC0-∞ – AUC0-t)/ AUC0-∞ * 100 will be calculated using the previous data

t1/2 - plasma half-life, calculated as 0.693/kel, where kel = elimination rate constant

MRT (mean residence time) - calculated as AUMC0-∞/ AUC0-∞ where AUMC0-∞ = area under the 1st moment curve

Kel - elimination rate constant

- **Statistical methods**

Pharmacokinetic data:
-for dose-adjusted Cmax and AUC0-t: dose proportionality assessment will be done by means of an ANOVA (model: treatments, sequence, subject within sequence and periods of administration) and calculating the 90% confidence intervals of the geometric mean ratio TEST1/TEST2 (equivalent to two one-sided t-test procedure) for lntransformed data. The same procedure was applied also for the additional (not considered for dose proportionality assessment) parameter dose-adjusted AUC0-∞. The acceptance criteria for the 90% confidence intervals of the geometric mean ratios TEST1/TEST2 were set to 80.00%-125.00% for dose-adjusted AUC0-t and Cmax for levetiracetam.
- for Tmax, Wilcoxon Signed-Rank Test.
- Descriptive statistics were also done for all pharmacokinetic parameters: arithmetic mean, harmonic mean, geometric mean, SEM, standard deviation, coefficient of variation, median, range and number of measures.
- for clinical laboratory parameters at screening and follow-up: descriptive statistics (arithmetic mean, standard deviation, coefficient of variation, median, range and number of measures).
- for the vital signs measured at screening, in the admission days, in the dosing days before administration and at follow-up: descriptive statistics (arithmetic mean, standard deviation, coefficient of variation, median, range and number of measures).

All statistical calculations were performed using SAS version 9.4 software.

Evaluation of additional pharmacokinetic parameters:
Tmax data for Levetiracetam T1 vs. T2 have been compared using a non-parametric statistical method: Wilcoxon Signed-Rank Test. The limit of statistical significance was set at 0.05. The test was applied to untransformed data.
Descriptive statistic was also done (arithmetic mean, harmonic mean, geometric mean, standard error, standard deviation, coefficient of variation, median, range and number of measures).
For the remaining additional parameters AUC%extra (residual area), t1/2, MRT and Kel a simple descriptive statistic was performed (arithmetic mean, harmonic mean, geometric mean, standard error, standard deviation, coefficient of variation, median, range and number of measures).
Descriptive statistics was done for all pharmacokinetic parameters (arithmetic mean, harmonic mean, geometric mean, SEM, standard deviation, median, range).

- **Protocol Deviations**

Some minor protocol deviations occurred in this study:
• Subject with study number 16 (screening number 28) had lower value than the lower limit for hemoglobin at screening examination.

• Subject No. 12, who was a drop-out from 12 March 2022 due to personal reason and received study treatment only in period I, was lost to follow-up.
• Deviation from the theoretical sampling times outside the tolerance interval foreseen in the protocol

Subj. No.	Study period	Blood sampling time	Deviation outside tolerance window*
27	I	8 h	+ 3 minutes
28	I	8 h	+ 3 minutes

Since the actual sampling times were used for the calculation of pharmacokinetic parameters, this deviation from theoretical sampling time is irrelevant from a PK perspective. Protocol deviations did not affect the Study results.

- ***Results***

Pharmacokinetic parameters

The mean pharmacokinetic characteristics of Levetiracetam after treatment with TEST1 and TEST2 products were as follows:

TEST1 treatment

N=31	C_{max} *(ng/mL)*	AUC_{0-t} *(ng/mL* Hours)*	T_{max} *(Hours)*[#]	AUC_{0-inf} *(ng/mL* Hours)*	AUCextra *%*	T_{half} *(Hours)*	MRT *(Hours)*	K_{el} *(1/Hours)*
Mean	31219.282	679511.275	9.323	710580.085	4.120	8.822	18.578	0.083
GMean	30865.892	668586.811	8.912	697704.553	3.236	8.586	18.357	0.081
SD	4771.578	119669.735	2.761	132186.476	3.186	2.250	2.982	0.017
CV	15.284	17.611	29.621	18.603	77.341	25.500	16.052	20.888

[#] Median value: 9.000h

TEST2 treatment

N=31	C_{max} *(ng/mL)*	AUC_{0-t} *(ng/mL* Hours)*	T_{max} *(Hours)*[#]	AUC_{0-inf} *(ng/mL* Hours)*	AUCextra*%*	T_{half} *(Hours)*	MRT *(Hours)*	K_{el} *(1/Hours)*
Mean	31143.340	652564.853	8.842	681223.859	4.067	8.738	18.189	0.083
GMean	30881.896	639702.646	8.390	667233.907	3.335	8.515	17.941	0.081
SD	4030.380	124473.060	2.898	132948.756	3.291	2.251	3.185	0.017
CV	12.941	19.074	32.777	19.516	80.923	25.761	17.512	20.025

[#] Median value: 8.000 h

The intra-subject variability coefficients registered for Levetiracetam, were 13.429% for AUC0-t and 8.205% for Cmax.

Statistical analysis

Evaluation of the period, sequence, subject within sequence and treatment influence on primary pharmacokinetics parameters

The ANOVA model implemented by GLM procedure in SAS for checking the sequence, period or treatment effects, showed no statistically significant influence on the primary pharmacokinetic parameters. Statistically significant subject within sequence effects were identified for both AUC0-t and Cmax. It is noteworthy to mention that subject effects are frequently observed due to inter-individual variations, without affecting the validity of the study.

Dose proportionality assessment
The summary results obtained for the different statistical tests used to compare the lntransformed data for AUC0-t and Cmax obtained for TEST1 and TEST2 products are presented below.

TEST1 vs. TEST2

Test name	Parameter	Geo Mean Ratio (Test1/Test2)	90% Confidence Interval		Acceptance range		Intra-subject CV (%)
			Lower 90% CL	Upper 90% CL	Lower limit (%)	Upper limit (%)	
Classic 90% CI	AUC_{0-t}	104.36	98.51	110.56	80.00	125.00	13.429
Classic 90% CI	C_{max}	99.92	96.44	103.51	80.00	125.00	8.205

If the lower and upper CL (Confidence Interval limits) lie within accepted regulatory criteria then we may conclude for bioequivalence.

The 90% confidence intervals of the ratio T1/T2 for Cmax and for AUC0-t were completely inside the accepted bioequivalence range of 80.00-125.00%, thus permitting to conclude bioequivalence with respect to both extent of absorption and rate of absorption thus meeting the dose proportionality criteria.

Evaluations of additional pharmacokinetic parameters
Tmax values have been compared separately for TEST1 vs. TEST2 using a non-parametric test (Wilcoxon Signed-Rank Test). The statistical test used identified no statistically significant difference between the formulations mentioned in regard to Tmax.

The statistical analysis did not show statistically significant differences between both treatment administered. It can be agreed that the dose proportionality criteria were met.
The 90% confidence intervals of the ratios T1/T2, for AUC0-t and Cmax were inside the accepted bioequivalence criteria of 80.00-125.00%, therefore it can be agreed that equivalence with respect to extent of absorption between the Test2 and the Test1 formulation was shown.

- ***Safety data***

Extent of Exposure
31 subjects received one dose of Levetiracetam 3x1000 mg prolonged-release granules in sachets – TEST1 formulation and 32 subjects received one dose of Levetiracetam 1x1000 mg prolonged-release granules in sachets – TEST2 formulation in two different occasions separated by washout periods of 7 days between two treatments, under fasting conditions.

Adverse Events
Six mild and moderate adverse events occurred in five subjects in the present study. No serious adverse events were reported in the study. All subjects that encountered an adverse event completely recovered before the end of the study.

Table 3: Display of adverse events by SOC (System Organ Classes) and according to MedDRA version 21.1

a. Study treatment: TEST1 N = 31 observations

Adverse Events	Mild		Moderate		Severe		Total		Total
	Related	NR	Related*	NR#	Related	NR	Related	NR	R (Related) + NR (Non-related)
SOC: Nervous system disorders									
Somnolence **MedDRA code:** 10041349	1 (3.23%) **Subj. No. 28		1 (3.23%) **Subj. No. 24				**2 (6.45%)**		**2 (6.45%)**
Dizziness **MedDRA code:** 10013573	1 (3.23%)						**1 (3.23%)**		**1 (3.23%)**

b. Study treatment: TEST2 N = 32 observations

Adverse Events	Mild		Moderate		Severe		Total		Total
	Related	NR	Related*	NR#	Related	NR	Related	NR	R (Related) + NR (Non-related)
SOC: Nervous system disorders									
Headache **MedDRA code:** 10019211			1 (3.125%) **Subj. No. 19				**1 (3.125%)**		**1 (3.125%)**
Somnolence **MedDRA code:** 10041349	1 (3.125%) **Subj. No. 19						**1 (3.125%)**		**1 (3.125%)**
Dizziness **MedDRA code:** 10013573	1 (3.125%) **Subj. No. 32						**1 (3.125%)**		**1 (3.125%)**

*Related = plausible relationship with drug administration; #NR = non plausible relationship with drug administration
** Subject identification number.

Study LVM-BESD-12-LLV/22: Open label, three-period, crossover, block randomized, single dose study to assess bioequivalence and food effect of Levetiracetam 3x1000 mg prolonged-release granules in sachets o.d. administered in fasting and fed conditions vs equal dose of the reference product (Keppra 500mg x 3 Immediate release film-coated tablets) b.i.d. administered in fasting conditions to healthy male and female volunteers.

Objectives:

The aim of the study was to assess the bioequivalence and to determine the food effect between a TEST formulation of levetiracetam 3x1000 mg prolonged-release granules in sachets administered under fasting conditions (TFAST) and under fed conditions (TFED) and the levetiracetam IR REFERENCE formulation 500 mg oral tablet administered as three tablets at once in the morning and three tablets at once in the evening under fasting conditions (RFAST).
The bioequivalence assessment/food effect was based on plasma drug levels of levetiracetam.
As a secondary objective, the safety and tolerability of the formulations were assessed.

Methods

- **Study design**

An open label, three-period, three-way crossover, block randomized, single dose bioequivalence study on healthy volunteers with administration under fasting and fed conditions.

Hospitalization of subjects from the evening of Day -1 (day before the dosing day) until 24 hours post administration on each study period.

Blinding
This was an open label but laboratory-blinded study. The randomization table was not made available to the personnel in charge of the determination of levetiracetam plasma levels.

Products administered:
On each study period the subjects received, as foreseen by the randomized table, either one dose of TESTFAST formulation (Levetiracetam 1000 mg prolonged-release granules in sachets, 3 sachets taken simultaneously as 3000 mg overall dose in the morning, in fasting conditions) OR one dose of TESTFED formulation (Levetiracetam 1000 mg prolonged-release granules in sachets, 3 sachets taken as 3000 mg overall dose in the morning, in fed conditions) OR REFERENCEFAST formulation (Keppra 500 mg immediate release film-coated tablets, 3 tablets taken simultaneously (1500 mg) in the morning and 3 tablets taken simultaneously (1500 mg) in the evening, in fasting conditions).

Blood samples were collected:
- when Test (TFED and TFAST) was administered before dose (0.0 h) and at 0.5, 1.0, 1.50, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 14.0, 16.0, 24.0, 36.0 and 48.0 post dose after each administration (19 samples/ study period).
- when Reference was administered before dose (0.0h) and at 0.083, 0.167, 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 5.0, 7.0, 9.0, 12.0 (after morning administration), 12.083, 12.167, 12.33, 12.67, 13.0, 13.33, 13.67, 14.0, 14.5, 15.0, 16.0, 17.0, 19.0, 21.0, 24.0, 36.0 and 48.0 post dose (after evening administration) (33 samples/ study period).

Wash-out period: 10 days.

Analytical method: HPLC validated method, with MS/MS detection technique for levetiracetam

Relevant pharmacokinetic parameters: AUC0-t, Cmax, AUC0-∞, Tmax, AUC%extra (residual area), t1/2, MRT, Kel

Safety: Adverse events, clinical and laboratory screening and follow up examinations, vital signs, ECG, physical examination, pregnancy test, drugs of abuse, breath alcohol test and COVID-19 test.

- **Test and reference products**

Test formulation

Name of the product: Levetiracetam 1000 mg Prolonged-release granules in sachets
Pharmaceutical form: prolonged-release granules in sachets
Strength: 1000 mg
Mode of administration: Oral; 3 sachets administered simultaneously, once daily, for a 3000 mg total dose, under fed conditions (TFED) or under fasting conditions (TFAST)
Manufacturer: Laboratorios Lesvi, S.L.
Country of manufacturer: Spain

Reference formulation
Name of the product: Keppra 500 mg film-coated tablets
Pharmaceutical form: Film-coated tablets (Immediate release)
Strength: 500 mg
Mode of administration: Oral; 3 tablets taken simultaneously, twice daily for a 3000 mg total dose under fasting conditions (RFAST)
Marketing Authorization Holder: UCB Pharma SA, Belgium
Country of purchase: Spain

- **Population(s) studied**

Number of subjects planned: 36 subjects; enrolled: 36; analyzed (bio-assay): 33 subjects

Selected Inclusion criteria
1. Healthy Caucasian male and female volunteers of at least 18 years of age but not older than 55 years
2. Subject with the Body Mass Index within 20.0 and 29.0 kg/m2
3. Normal haematology, clinical chemistry and urinalysis (some deviations outside the normal limits may be acceptable if judged so by the Investigator, except for haematology that must not have value under the lower normal limit)

Selected Exclusion Criteria
1. History of hypersensitivity to the test drug or to drugs belonging to the same pharmacological and chemical class or to the inactive ingredients.
2. Subject intends to be hospitalized within 3 months after last study drug administration
3. Participation in a clinical study with an investigational product in the preceding three months or in a clinical study with a generic product in the preceding two months.
4. Hospitalization for any reason within eight weeks prior to the study initiation.

Disposition of Subjects
Out of the 58 volunteers screened, a total number of 36 were enrolled (18 females and 18 males, a minimum representation of 33.33% (12 subjects) of each sex was achieved) and additionally, 2 overnight alternates (2 females) were present at the study centre in the second group from Day-1 and until the study drug administration of Period I was done. They leave the study centre after first study drug administration in Period I, without any treatment dosed.

Study beginning*	16 May 2022
First volunteer Informed Consent Form signature and screening procedures	Started on 20 May 2022
PERIOD I *(dosing Day)*	Subjects 01 to 18: 01 June 2022 Subjects 19 to 36: 03 June 2022
Wash-out	10 days
PERIOD II *(dosing Day)*	Subjects 01 to 18[1,2]: 11 June 2022 Subjects 19 to 36 and Subject no. 02: 13 June 2022
Wash-out	10 days
PERIOD III *(dosing Day)*	Subjects 01 to 18[1,2,3]: 21 June 2022 Subjects 19 to 36 and Subject no. 02: 23 June 2022
FOLLOW-UP	28 June 2022[#]: Subjects 01 to 36, except subject no. 09 29 June 2022: Subject no. 09

Data Sets Analyzed
For the bioequivalence assessment, Levetiracetam pharmacokinetic data coming from 33 subjects out of 36 subjects enrolled in the study were statistically analysed (only 33 subjects completed the clinical part of the study). The descriptive statistics of demographic characteristics for the 36 subjects that were enrolled in the study has been performed. Screening and follow-up safety data were analyzed on 36 complete datasets.

Demographic and Other Baseline Characteristics
All volunteers were Caucasians. From the 36 subjects who were dosed in Period I, 18 were males and 18 were females (all included in the safety evaluation). From the 33 subjects that completed all study

periods and were included in the statistical analysis for bioequivalence comparison, 17 were males and 16 were females.

N = 36	*AGE (years)*	*WEIGHT (kg)*	*HEIGHT (cm)*	*BMI (Kg/m^2)*
MEAN	34.03	68.00	168.36	23.93
SD	10.40	9.89	7.71	2.64
Minimum	18	50	153	20.1
Maximum	52	87	180	28.7

In total 36 subjects were included in the study, but 33 were included in the statistical analysis. The mean BMI was 23.93, the mean age 34.03 years. There are no concerns regarding demographic characteristics of the study population.

- **Analytical methods**

Please see description in Study LVM-BESD-10-LLV/20.

- **Pharmacokinetic variables**

The following pharmacokinetic parameters were calculated for levetiracetam based on dose adjusted plasma concentrations:

AUC0-t - area under the plasma concentration time curve from administration to last observed concentration over LLOQ, calculated by linear trapezoidal rule

Cmax - peak drug concentration, obtained directly from the data – without interpolation

Tmax - time of the peak drug concentration, obtained directly from the data, without interpolation

AUC0-∞ (AUC from time 0 to infinite) - area under the curve integrated from the plasma concentrations extrapolating the terminal elimination period

AUC%extra (residual area) - the ratio (AUC0-∞ – AUC0-t)/ AUC0-∞ * 100 will be calculated using the previous data

t1/2 - plasma half-life, calculated as 0.693/kel, where kel = elimination rate constant

MRT (mean residence time) - calculated as AUMC0-∞/ AUC0-∞ where AUMC0-∞ = area under the 1st moment curve

Kel - elimination rate constant

- **Statistical methods**

Pharmacokinetic data:
- for AUC0-t: bioequivalence assessment was done by means of an ANOVA (model: treatments, sequence, subject within sequence and periods of administration) and calculating the 96.7% confidence intervals of the geometric mean ratio TFAST / RFAST and TFED / TFAST (equivalent to two one-sided t-test procedure) for ln-transformed data. The same procedure was applied also for the additional (not considered for bioequivalence assessment) parameters Cmax and AUC0-∞. The acceptance criteria for the 96.7% confidence intervals of the geometric mean ratios TFAST / RFAST and TFED / TFAST were set to 80.00%-125.00% for AUC0-t for levetiracetam.

- for Tmax: Wilcoxon Signed-Rank Test.
- Descriptive statistics were also done for all pharmacokinetic parameters: arithmetic mean, harmonic mean, geometric mean, SEM, standard deviation, coefficient of variation, median, range and number of measures.
- for clinical laboratory parameters at screening and follow-up: descriptive statistics (arithmetic mean, standard deviation, coefficient of variation, median, range and number of measures).
- for the vital signs measured at screening, in the admission days, in the dosing days before administration and at follow-up: descriptive statistics (arithmetic mean, standard deviation, coefficient of variation, median, range and number of measures).

Determination of Sample Size

A total number of 36 healthy male and female volunteers were planned to be enrolled in the study. The following were taken into consideration:
a) the significance level (alpha) of 0.01667 (Bonferroni corrected for multiplicity)
b) an a priori test power of 80 %
c) intra-subject coefficients of variation of 15% for the primary pharmacokinetic metric AUC0-t
d) expected geometric mean TEST/REFERENCE ratios of the primary pharmacokinetic metric of 90%
e) the acceptance range of 80.00-125.00% for the 96.7% confidence interval of the geometric least square means ratios TEST/REFERENCE for the primary pharmacokinetic metrics
f) a potential dropout/withdrawal rate of 10%.
In order to assure the dosing of 36 volunteers, 2 alternate volunteers had to remain at the study Center in the first period until the IMPs administration was finished. No alternate had to be enrolled and they left the study center after completion of dosing of Period I for both group.

Protocol Deviations

Some minor protocol deviations occurred in this study:
• Subject No. 02, received the study treatment in period II and period III with the second group and had a longer wash-out period between period I and period II of 12 days instead of 10 days.
• Deviations from the theoretical sampling times outside the tolerance interval foreseen in the protocol:

Subj. No.	Study period	Blood sampling time	Deviation outside tolerance window*
02	II	0.67 h	+ 5 minutes
06	II	1 h	+ 2 minutes
25	I	48 h	+ 5h 3 min
29	II	48 h	+ 2h 58 min

- ***Since the actual sampling times were used for the calculation of pharmacokinetic parameters, this deviation from theoretical sampling time is irrelevant from a PK perspective. The deviations were caused by the volunteers late arrival due to personal reasonsResults***

Pharmacokinetic parameters

The mean pharmacokinetic characteristics of Levetiracetam after treatment with TESTFAST, TFED and REFERENCE products were as follows:

$TEST_{FAST}$ treatment (T1)

N=33	AUC_{0-t} *(ng/mL Hours)*	C_{max} *(ng/mL)*	T_{max} *(Hours)*[#]	AUC_{0-inf} *(ng/mL Hours)*	AUCextra *%*	T_{half} *(Hours)*	MRT *(Hours)*	K_{el} *(1/Hours)*
Mean	777762.891	34551.047	9.364	811750.064	3.986	8.414	18.848	0.086
GMean	757129.411	33650.891	8.952	788822.791	3.358	8.254	18.701	0.084
SD	183132.811	8064.620	2.859	197639.570	2.463	1.742	2.407	0.016
CV	23.546	23.341	30.537	24.347	61.797	20.698	12.770	18.868

[#] Median value: 9000

TESTFED treatment (T2)

N=33	AUC_{0-t} *(ng/mL Hours)*	C_{max} *(ng/mL)*	T_{max} *(Hours)*[#]	AUC_{0-inf} *(ng/mL Hours)*	AUCextra%	T_{half} *(Hours)*	MRT *(Hours)*	K_{el} *(1/Hours)*
Mean	698652.057	30263.275	10.909	739779.389	5.192	9.248	20.777	0.081
GMean	681906.175	29401.904	10.559	719611.165	4.378	8.867	20.610	0.078
SD	156366.270	7589.846	2.821	175887.174	3.028	3.403	2.676	0.018
CV	22.381	25.079	25.863	23.776	58.318	36.795	12.881	22.673

[#] Median value: 10.000

T1 vs. R

The intra-subject variability coefficient registered for Levetiracetam, was 8.738% for AUC0-t.

REFERENCE treatment

N=33	AUC_{0-t} *(ng/mL* Hours)*	C_{max} *(ng/mL)*	T_{max} *(Hours)*[#]	AUC_{0-inf} *(ng/mL* Hours)*	AUCextra%	T_{half} *(Hours)*	MRT *(Hours)*	K_{el} *(1/Hours)*
Mean	871677.890	56259.100	10.264	892453.636	2.256	7.323	16.653	0.097
GMean	853649.000	55186.406	6.190	873402.862	1.985	7.247	16.610	0.096
SD	180083.684	11193.732	5.593	186796.306	1.056	1.061	1.215	0.015
CV	20.659	19.897	54.491	20.931	46.806	14.493	7.299	15.378

[#] Median value: 13.000

T1 vs. T2

The intra-subject variability coefficient registered for Levetiracetam, was 11.259% for AUC0-t.

Statistical analysis

Evaluation of the period, sequence, subject within sequence and treatment influence on primary pharmacokinetics parameters.

The results obtained from the ANOVA comparisons of the main Levetiracetam pharmacokinetic data considered for bioequivalence assessment for TESTFAST vs. REFERENCE, are presented in the next table and in detail in tables.

T1 vs. R

Source of error	Significance level	Probability (p)
		AUC_{0-t}
SEQUENCE	1.00000E-01	8.92889E-01 Not significant
SUBJECT(SEQUENCE)	5.00000E-02	2.05887E-10*
PERIOD	5.00000E-02	2.49161E-01 Not significant
TREATMENT	5.00000E-02	7.00057E-06*

* = p<0.05 = significant

The ANOVA model implemented by GLM procedure in SAS for checking the sequence and period effects, showed no statistically significant influence on the primary pharmacokinetic parameter. Statistically significant treatment and subject within sequence effects were identified.
The results obtained from the ANOVA comparisons of the main Levetiracetam pharmacokinetic data considered for bioequivalence assessment for TESTFAST vs. TESTFED, are presented in the table below.

T1 vs. T2

Source of error	Significance level	Probability (p)
		AUC_{0-t}
SEQUENCE	1.00000E-01	7.13910E-01 Not significant
SUBJECT(SEQUENCE)	5.00000E-02	1.13993E-07*
PERIOD	5.00000E-02	6.81893E-01 Not significant
TREATMENT	5.00000E-02	7.31827E-04*

* = p<0.05 = significant

The ANOVA model implemented by GLM procedure in SAS for checking the sequence and period effects, showed no statistically significant influence on the primary pharmacokinetic parameter. Statistically significant treatment and subject within sequence effects were identified for AUC0-t.

Bioequivalence assessment
The summary results obtained for the different statistical tests used to compare the lntransformed data for AUC0-t obtained for TESTFAST and REFERENCE products are presented below.

TESTFAST vs. REFERENCE

Test name	Parameter	Geo Mean Ratio (T_{FAST}/R)	96.7% Confidence Interval		Acceptance range		Intra-subject CV (%)
			Lower 96.7% CL	Upper 96.7% CL	Lower limit (%)	Upper limit (%)	
Classic 96.7% CI	AUC_{0-t}	88.966	84.78	93.36	80.00	125.00	8.738

If the lower and upper CL (Confidence Interval limits) lie within accepted regulatory criteria then we may conclude for bioequivalence.

The 96.7% confidence intervals of the ratio TFAST/R for AUC0-t were completely inside the accepted bioequivalence range of 80.00-125.00%, thus permitting to conclude bioequivalence with respect to extent of absorption.
The summary results obtained for the different statistical tests used to compare the lntransformed data for AUC0-t obtained for TESTFAST and TESTFED products are presented below.

TESTFAST vs. TESTFED (T1 vs. T2)

Test name	Parameter	Geo Mean Ratio (T_{FAST}/T_{FED})	96.7% Confidence Interval		Acceptance range		Intra-subject CV (%)
			Lower 96.7% CL	Upper 96.7% CL	Lower limit (%)	Upper limit (%)	
Classic 96.7% CI	AUC_{0-t}	90.12	84.72	95.87	80.00	125.00	11.259

If the lower and upper CL (Confidence Interval limits) lie within accepted regulatory criteria then we may conclude for bioequivalence.

The 96.7% confidence intervals of the ratio TFAST/TFED for AUC0-t were completely inside the accepted bioequivalence range of 80.00-125.00%, thus permitting to conclude bioequivalence.

Evaluations of additional pharmacokinetic parameters
For Cmax and AUC0-inf same statistical tests as for AUC0-t were done.
The results obtained from the ANOVA comparison for Cmax and AUC0-inf, for TESTFAST vs. REFERENCE, are shortly presented in the table.

T1 vs. R comparison

Source of error	Significance level	Probability (p)	
		C_{max}	AUC_{0-inf}
SEQUENCE	1.00000E-01	7.99687E-01 Not significant	8.79595E-01 Not significant
SUBJECT (SEQUENCE)	5.00000E-02	7.09717E-08*	6.03612E-10*
PERIOD	5.00000E-02	4.49218E-01 Not significant	2.83624E-01 Not significant
TREATMENT	5.00000E-02	2.50189E-18*	1.63513E-04*

* = $p<0.05$ = significant

The summary results obtained for the different statistical tests used to compare the lntransformed data for Cmax and AUC0-inf obtained for TESTFAST and REFERENCE products are presented below.

TESTFAST vs. REFERENCE

Test name	Parameter	Geo Mean Ratio (T_{FAST}/R)	96.7% Confidence Interval		Acceptance range		Intra-subject CV (%)
			Lower 96.7% CL	Upper 96.7% CL	Lower limit (%)	Upper limit (%)	
Classic 96.7% CI	C_{max}	60.978	57.55	64.62	80.00	125.00	10.520
Classic 96.7% CI	AUC_{0-inf}	90.596	86.07	95.36	80.00	125.00	9.302

The results obtained from the ANOVA comparison for Cmax and AUC0-inf, for TESTFAST vs. TESTFED, are shortly presented in the table.

T1 vs. T2 comparison

Source of error	Significance level	Probability (p)	
		C_{max}	$AUC_{0\text{-inf}}$
SEQUENCE	1.00000E-01	8.68033E-01 Not significant	7.10802E-01 Not significant

Source of error	Significance level	Probability (p)	
		C_{max}	$AUC_{0\text{-inf}}$
SUBJECT (SEQUENCE)	5.00000E-02	1.69649E-06*	1.75133E-07*
PERIOD	5.00000E-02	2.60850E-01 Not significant	7.29586E-01 Not significant
TREATMENT	5.00000E-02	2.46383E-04*	4.22587E-03*

* = p<0.05 = significant

The summary results obtained for the different statistical tests used to compare the lntransformed data for Cmax and AUC0-inf obtained for TESTFAST and TESTFED products are presented below.

TESTFAST vs. TESTFED

Test name	Parameter	Geo Mean Ratio (T_{FAST}/T_{FED})	96.7% Confidence Interval		Acceptance range		Intra-subject CV (%)
			Lower 96.7% CL	Upper 96.7% CL	Lower limit (%)	Upper limit (%)	
Classic 96.7% CI	C_{max}	87.521	81.47	94.02	80.00	125.00	13.062
Classic 96.7% CI	$AUC_{0\text{-inf}}$	91.265	85.44	97.49	80.00	125.00	12.024

Tmax values have been compared separately for TESTFAST vs. REFERENCE and TESTFED vs. TFAST using a non-parametric test (Wilcoxon Signed-Rank Test). The statistical test used identified no statistically significant difference between the formulations mentioned in regard to Tmax for TFAST vs. R but a statistically significant difference between the formulations for TFED vs. TFAST.

Parameter	Statistic Method	Treatment	Significance level	Probability (p)
T_{max}	Wilcoxon Signed Rank test	T_{FAST} vs. R	5.00000 E-02	3.89400 E-01 Not significant
		T_{FED} vs. T_{FAST}	5.00000 E-02	4.70000 E-03*

* = p<0.05 = significant

The aim of the study was to evaluate the bioequivalence and to determine the food effect between a TEST formulation of levetiracetam 3x1000 mg prolonged-release granules in sachets administered under fasting conditions (TFAST) and under fed conditions (TFED) and the levetiracetam IR REFERENCE formulation 500 mg oral tablet administered as three tablets at once in the morning and three tablets at once in the evening under fasting conditions (RFAST). Only AUC0-t was considered a primary PK parameter. However, Cmax should also be considered a primary PK parameter.
The 96.7% confidence intervals of the ratios TFAST/R, for AUC0-t were inside the bioequivalence range of 80.00-125.00%. However, for Cmax the bioequivalence criteria were not met (The 96.7% confidence intervals 57.55 and 64.62). Therefore, the BE between the Tfast and the Reference product cannot be concluded.

The 96.7% confidence intervals of the ratios TFAST/TFED, for AUC0-t, Cmax and AUC 0-inf were inside the bioequivalence range of 80.00-125.00%.

- ***Safety data***

Extent of Exposure

33 subjects received one dose of Levetiracetam 3x1000 mg prolonged-release granules in sachets – TESTFAST formulation under fasting conditions, one dose of Levetiracetam 3x1000 mg prolonged-release granules in sachets – TESTFED formulation and one dose of Keppra 3x500 mg IR film-coated tablets taken at once in the morning under fasting conditions and one dose of Keppra 3x500 mg IR film-coated tablets taken at once in the evening (12 hours after the morning dose) in three different occasions separated by washout periods of 10 days between two consecutive treatments.
Subject no. 01 who was drop-out took only REFERENCE and TESTFED formulations.
Subject no. 09 who was drop-out took only TESTFAST formulation. Subject no. 15 who was drop-out took only TESTFED formulation.

Adverse Events
In total 42 adverse events in 24 subjects were reported during the study. All AE were considered related to study treatment. There were no severe AE observed. The incidence of the AEs was comparable after administration of the Reference and the Test product under fasting conditions (38.09% vs 35.71%). The incidence of AE was lower after administration of the Test product under fed conditions (26.19%). No deaths occurred in the present study.

There were no new safety signals identified in the Study.

Table 4: Display of adverse events by SOC (System Organ Classes)

Study treatment: TESTFAST N = 34 observations

Adverse Events	Mild		Moderate		Severe		Total		Total
	Related	NR	Related*	NR#	Related	NR	Related	NR	R (Related) + NR (Non-related)
SOC: Nervous system disorders									
Somnolence **MedDRA code:** 10041349	9 (26.47%) **Subj. No. 03, 08, 10, 11,16, 20, 21, 26, 31						**9 (26.47%)**		**9 (26.47%)**
Dizziness **MedDRA code:** 10013573	2 (5.88%) **Subj. No. 02, 24						**2 (5.88%)**		**2 (5.88%)**
Headache **MedDRA code:** 10019211	1 (2.94%) **Subj. No. 18		1 (2.94%) **Subj. No. 09				**2 (5.88%)**		**2 (5.88%)**
SOC: Gastrointestinal disorders									
Nausea **MedDRA code:** 10028813			1 (2.94%) **Subj. No. 09				**1 (2.94%)**		**1 (2.94%)**
Vomiting **MedDRA code:** 10047700			1 (2.94%) **Subj. No. 09				**1 (2.94%)**		**1 (2.94%)**

*Related = plausible relationship with drug administration; #NR = non plausible relationship with drug administration
** Subject identification number.

Study treatment: TESTFED N = 35 observations

Adverse Events	Mild		Moderate		Severe		Total		Total
	Related	NR	Related*	NR#	Related	NR	Related	NR	R (Related) + NR (Non-related)
SOC: Nervous system disorders									
Somnolence **MedDRA code:** 10041349	10 (28.57%) **Subj. No. 01, 02, 08, 11, 13,		1 (2.86%)				**11 (31.43%)**		**11 (31.43%)**

Adverse Events	Mild		Moderate		Severe		Total		Total
	Related	NR	Related*	NR#	Related	NR	Related	NR	R (Related) + NR (Non-related)
	18, 20, 24, 30, 34		**Subj. No. 25						

*Related = plausible relationship with drug administration; #NR = non plausible relationship with drug administration
** Subject identification number.

c. Study treatment: REFERENCE N = 34 observations

Adverse Events	Mild		Moderate		Severe		Total		Total
	Related	NR	Related*	NR#	Related	NR	Related	NR	R (Related) + NR (Non-related)
SOC: Nervous system disorders									
Somnolence **MedDRA code:** 10041349	5 (14.7%) **Subj. No. 03, 07, 12, 24, 29		6 (17.65%) **Subj. No. 04, 05, 13, 16, 26, 30				**11 (32.35%)**		**11 (32.35%)**
Dizziness **MedDRA code:** 10013573	5 (14.7%) **Subj. No. 01, 02, 06, 18, 20						**5 (14.7%)**		**5 (14.7%)**

*Related = plausible relationship with drug administration; #NR = non plausible relationship with drug administration
** Subject identification number.

Study LESVILEVE/23/BQ-2

Study title: Open label, two-period, two-way, crossover, block-randomized multiple dose bioequivalence study of Levetiracetam 1000 mg prolonged-release granules in sachets (TEST FORMULATION) vs. the US reference product (KEPPRA XR 750 mg film-coated extended-release tablets), both administered as 3000 mg once daily dose to healthy male and female volunteers, under fasting conditions.

Independent Ethics Committees and Medicine Agency approvals
The trial protocol with appendices and all the other documents required by the Ethics Committee and/or the Medicine Agency was submitted for the approval to the Ethics Committee (National Ethics Committee for Drugs Clinical Trials) and to the Medicine Agency.
The study protocol and the Principal Investigator were approved: National Ethics Committee for Drugs Clinical Trials approved the study and the use of the documentation provided on 29 March 2023 and approval was issued on 30 March 2023. The Medicine Agency approved the study on 24 March 2023 and the approval was issued on 28 March 2023. The Order of the Ministry of Health of the Republic of Moldova was given to perform the study by O.M. No. Rg.04-000073 from 31 March 2023.

Methods

- **Study design**

Open label, two-period, two-way crossover, block randomized, multiple dose bioequivalence study on healthy volunteers with administration under fasting conditions.
Hospitalization of subjects from the evening of Day -1 until 36 hours after the 5th dose (until the evening of Day 6) on each study period.

Products administered (T and R): On each study period the subjects received, as foreseen by the randomized table, either 5 consecutive once daily doses of TEST formulation (Levetiracetam 1000 mg prolonged-release granules in sachets, taken as 3000 mg dose in the morning, in fasting conditions) or 5 consecutive treatment days with REFERENCE formulation (Keppra 750 mg extended-release tablets, taken as 3000 mg dose in the morning, in fasting conditions).

Blood samples: Blood samples were collected at the following times (the theoretical collection times expressed in hours are relative to first dose administration on Day 1): 0 (pre-dose for the 1st daily dose), 47.917 (47h 55min, pre-dose for the 3rd daily dose), 71.917 (71h 55min, pre-dose for the 4th daily dose), 95.917 (95h 55min, pre-dose for the 5th daily dose) and at 96.5 (96h 30min), 97.0, 98.0, 99.0, 100.0, 101.0, 102.0, 103.0, 104.0, 105.0, 106.0, 107.0, 108.0, 109.0, 110.0, 111.0, 112.0, 116.0, 120.0, 132.0 and 144.0 hours after the 1st dose (25 samples of 5 mL/ study period). Also, an additional reserve blank sample of 20 mL was drawn pre-dose only on Period I.

Wash-out period: 11 days.

Safety: Adverse events, clinical and laboratory screening and follow up examinations, vital signs, ECG, physical examination, drugs of abuse and breath alcohol test.

- **Test and reference products**

Test product:
Levetiracetam 1000 mg prolonged-release granules in sachets manufactured by Laboratorios Lesvi S.L., Spain. Batch No. GAL20127C, Re-test date: 06/2023, Batch size: 100.000 stick packs. Administered orally, three sachets administered simultaneously once daily (for a 3000 mg daily dose), for five consecutive days, in the morning with 240 ml of still bottled water at room temperature, under fasting conditions.

Reference product:
KEPPRA XR 750 mg film-coated extended-release tablets of UCB, Inc. Smyrna, GA 30080, United States,
Batch No. 916155, Expiry date: 05/2025, Country of purchase: United States. Administered orally, four tablets taken simultaneously once daily (for a 3000 mg daily dose), for five consecutive days with 240 ml of still bottled water at room temperature, under fasting conditions.

Duration of treatment: Five consecutive administration days per study period, with one daily dosing for the Test and Reference product.

- **Population(s) studied**

Healthy Caucasian male and female volunteers, aged at least 18 years but not older than 55 years, body mass index within 20.0-29.0 kg/m2

- **Analytical methods**

Development of an HPLC-MS/MS method to determine levetiracetam in plasma samples was performed and the report submitted as LVM-BE-LCMSMS-01/23 as a support of LVM-BEMD-14-LLV/23 study.

The LLOQ for levetiracetam was established at 200 ng/mL with a mean precision 4.340 and accuracy 100.777%. The precision and accuracy across CAL concentrations were: between-run accuracy: 99.059-108.155%; between-run precision: 2.629- 3.798, (besides CAL3 with precision 28.182%); within-run accuracy: 97.814-101.295%; within-run precision: 0.871-1.359%). The method's selectivity, extraction recovery, and dilution integrity (1/4) were all assessed and found acceptable. Hemolysis of the plasma did not influenced levetiracetam analysis. No matrix and carryover effects were identified. Partial validation has been performed to show that levetiracetam is stable after storing for 2.5 months below -20 °C. All parameters recommended for analytical method validation were addressed (EMEA/CHMP/EWP/192217/2009) and met the acceptance criteria. Validation seems to be acceptable.

Analytical report for LEV determination in plasma samples supporting clinical study No. LVM-BEMD-14-LLV/23 (LESVILEVE/23/BQ-2).

In total, 1476 human plasma samples with heparin as an anticoagulant were analyzed for levetiracetam using HPLC with MS/MS detection. Samples were collected from 11.05.2023 - 01.06.2023 and analyzed from 09.06.2023 - 20.06.2023. Thus, it can be concluded, that storage conditions are within the validated parameters. Total 29 runs were analyzed levetiracetam in human plasma. Incurred sample reproducibility was performed for 145 samples. The result were found to be repeatable for 98.621% of samples as repeated samples had relative differences not exceeding 20% compared to the first evaluation. ISR was acceptable. The accuracy and precisions for calibration standards and QC samples were acceptable. The levetiracetam concentration were within calibration range of the curve. Bioanalysis is acceptable.

- **Pharmacokinetic Variables**

Pharmacokinetics: AUC(0-tau).ss, Cmax.ss, Ctau.ss, Cmin.ss (primary) and Tmax.ss and PTF (additional). The primary analysis was performed on all evaluable subjects that were dosed in both administration periods and completed the study, irrespective the steady-state evaluation criteria.

- **Statistical methods**

For levetiracetam pharmacokinetic data the following procedures were used:
- for AUC(0-tau).ss, Cmax.ss, Ctau.ss, Cmin.ss: the analysis of variance (ANOVA) model was used having sequence, period, subject within sequence and treatment as fixed effects for ln transformed data. The model was applied in order to build the classic (shortest) 90% confidence intervals for the least square geometric mean ratios. The acceptance criteria for the 90% confidence intervals of the geometric mean ratios TEST/REFERENCE were set to 80.00%-125.00% for AUC(0-tau).ss, Cmax.ss, Ctau.ss, Cmin.ss for levetiracetam.
- for Tmax.ss, Wilcoxon Signed-Rank Test.
- for PTF only descriptive statistic by treatment
- Descriptive statistics were also done for all pharmacokinetic parameters: arithmetic mean, harmonic mean, geometric mean, SEM, standard deviation, coefficient of variation, median, range and number of measures.
- for clinical laboratory parameters at screening and follow-up: descriptive statistics (arithmetic mean, standard deviation, coefficient of variation, median, range and number of measures).
- for the vital signs measured at screening, in the admission days, in the dosing days before administration and at follow-up: descriptive statistics (arithmetic mean, standard deviation, coefficient of variation, median, range and number of measures).

Determination of Sample Size
A total number of 30 healthy male and female volunteers were enrolled in the study. The number of 30 subjects has been estimated considering the following:
a) the significance level (alpha) of 0.05

b) an a priori test power of 80%
c) an intra-individual coefficient of variation for the primary PK metrics of up to 24%;
d) the expected geometric mean ratio TEST/REFERENCE for the primary PK metrics between 0.95 - 1.05;
e) the bioequivalence acceptance range of 80.00 – 125.00% for the 90% CIs of the of the geometric mean ratio TEST/REFERENCE for the primary PK metrics;
f) a potential drop-out/ withdrawal rate of up to 15%.

Results

Disposition of Subjects

Out of the 44 volunteers screened, a total number of 30 were enrolled. Out of the 30 dosed volunteers, 29 volunteers completed the study but all 30 enrolled subjects underwent the follow-up examination. 25 subjects (for whom steady-state status was confirmed) were included in a statistical analysis. A separate analysis was performed for subjects that could be considered evaluable according to the provisions of the Study Protocol (the entire population, N=29) as supportive information. One subject was drop-out since 27 April 2023 due to personal reason and was excluded from statistical analysis.

Pharmacokinetic Results

The mean pharmacokinetic characteristics of levetiracetam after treatment with REFERENCE and TEST products were as follows:

REFERENCE treatment

N = 25	$AUC_{0\text{-tau ss}}$ (ng/mL * Hours)	$C_{max.ss}$ (ng/mL)	$C_{tau.ss}$ (ng/mL)	$C_{min.ss}$ (ng/mL)	PTF (%)	$T_{max.ss}$ * (h)
Mean	769323.029	49072.575	16768.645	16357.087	105.281	4.147
GMean	757202.758	48667.564	15871.257	15502.286	102.393	3.858
SD	140993.628	6613.821	5713.547	5549.138	25.122	2.037
CV	18.327	13.478	34.073	33.925	23.862	49.113

* Median = 3.967 h

TEST treatment

N = 25	$AUC_{0\text{-tau ss}}$ (ng/mL * Hours)	$C_{max.ss}$ (ng/mL)	$C_{tau.ss}$ (ng/mL)	$C_{min.ss}$ (ng/mL)	PTF (%)	$T_{max.ss}$* (h)
Mean	751271.514	41416.323	21857.280	17087.302	80.256	8.906
GMean	736772.619	40873.792	20982.004	15991.938	78.196	8.649
SD	153237.508	6975.225	5892.002	6166.153	18.982	2.123
CV	20.397	16.842	26.957	36.086	23.652	23.840

* Median = 9.000 h

Statistical analysis
Evaluation of the period, sequence, subject within sequence and treatment effects of the primary pharmacokinetics parameters

Source of error	Significance level	Probability (p)			
		$AUC_{0\text{-tau ss}}$	$C_{max.ss}$	$C_{tau.ss}$	$C_{min.ss}$
SEQUENCE	0.10000	0.76573	0.60790	0.80710	0.98192
SUBJECT(SEQUENCE)	0.05000	0.00000*	0.00010*	0.00000*	0.00003*
PERIOD	0.05000	0.27506	0.06662	0.36356	0.67029
TREATMENT	0.05000	0.18878	0.00000*	0.00000*	0.59345

The ANOVA model implemented by GLM procedure in SAS for checking the sequence and period effect, showed no statistically significant influence on the primary pharmacokinetic parameters. Statistically significant treatment effect was identified for Cmax.ss and for Ctau.ss.
Statistically significant subject within sequence fixed effects were identified for all primary parameters. It is noteworthy to mention that subject effects are frequently observed due to interindividual variations, without affecting the validity of the study. The treatment effects are further evaluated by the size of the confidence intervals.

BIOEQUIVALENCE COMPARISON (based on primary PK parameters)

TEST vs. REFERENCE

Test name	Parameter	Geo Mean Ratio (TEST/Reference)	90% Confidence Interval		Acceptance range		Intra-subject CV (%)
			Lower 90% CL	Upper 90% CL	Lower limit (%)	Upper limit (%)	
Classic 90% CI	$AUC_{0\text{-tau}}$	97.21	93.79	100.75	80.00	125.00	7.388
Classic 90% CI	$C_{max.ss}$	83.83	80.47	87.34	80.00	125.00	8.458
Classic 90% CI	$C_{tau.ss}$	132.01	123.49	141.12	80.00	125.00	13.814
Classic 90% CI	$C_{min,ss}$	103.06	93.68	113.38	80.00	125.00	19.857

If the lower and upper CL (Confidence Interval limits) lie within accepted regulatory criteria, then we may conclude for bioequivalence.

The 90% confidence intervals of the ratio T/R for (AUC0-tau)ss, Cmax.ss and Cmin,ss were within the accepted bioequivalence range of 80.00-125.00%. However, the confidence interval for Ctau,ss was not within the accepted bioequivalence range of 80.00-125.00% therefore bioequivalence cannot be concluded with respect to concentration at the end of dosing interval.

One possible reason for the Ctau,ss exceeding the limits may be explained by the shift in the reported time Tmax,ss which was higher for the TEST product with about 5 hours (median). This may be noticed on the plateau region of the TEST mean curve where relatively steady mean concentrations were reported between 4-12 hours (around Cmax at steady state) whereas the mean concentrations in the REFERENCE have started to decrease significantly following 5 hours since the last dose administration. In such a case, even though the elimination half-life were similar, the concentrations at the end of dosage interval will remain higher for the TEST product affecting the size of the Ctau,ss ratios.

Out of the 29 subjects completing the study and considered evaluable according to the provisions of the Study Protocol, there were 4 subjects (subjects no. 06, 08, 13 and 14) for which steady state could not be statistically confirmed.

They were included in the data set for statistical analysis with their evaluable
PK profiles for both study treatments. An analysis, with these subjects excluded, has been conducted and the 90 % confidence intervals for levetiracetam can be found in the table above. Full analysis (N=29) is available as supportive information.

II. Supportive information - bioequivalence assessment for all subjects (N= 29)

The 90% confidence intervals for levetiracetam mean treatment T/R ratios were

TEST vs. REFERENCE

Test name	Parameter	Geo Mean Ratio (TEST/Reference) %	90% Confidence Interval		Acceptance range		Intra-subject CV (%)
			Lower 90% CL	Upper 90% CL	Lower limit (%)	Upper limit (%)	
Classic 90% CI	$AUC_{0\text{-}tau}$	96.72	93.31	100.24	80.00	125.00	8.018
Classic 90% CI	$C_{max.ss}$	83.21	80.25	86.28	80.00	125.00	8.111
Classic 90% CI	$C_{tau.ss}$	130.76	122.95	139.08	80.00	125.00	13.836
Classic 90% CI	$C_{min,ss}$	102.42	93.44	112.26	80.00	125.00	20.718

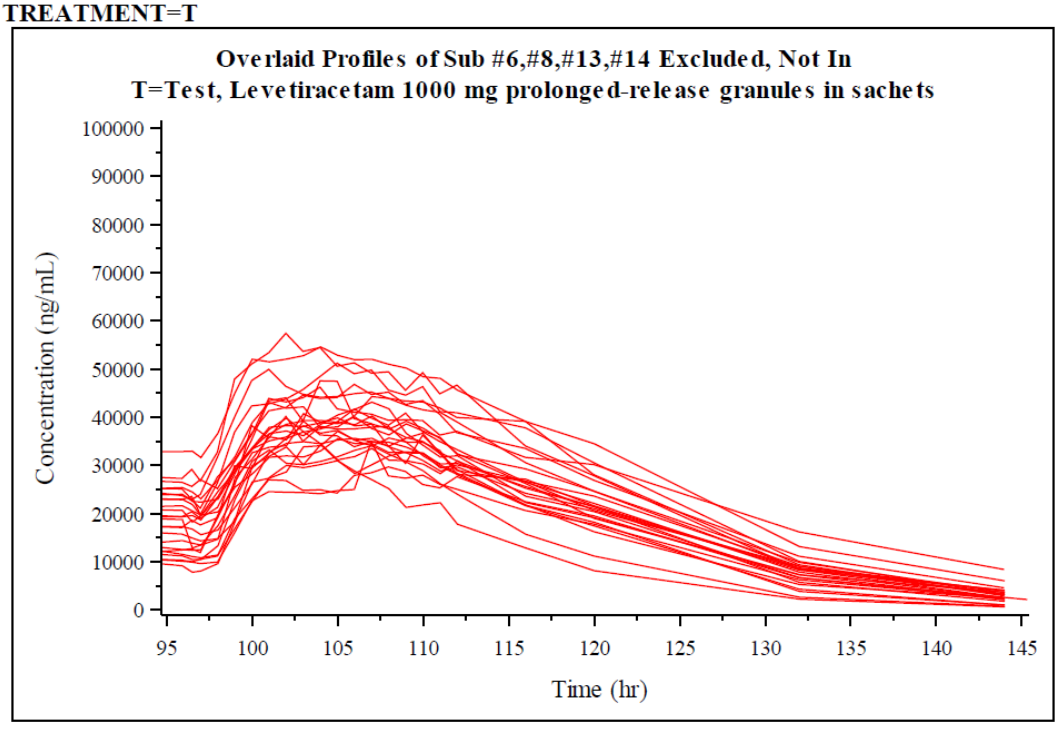
If the lower and upper CL (Confidence Interval limits) lie within accepted regulatory criteria, then we may conclude for bioequivalence.

ADDITIONAL parameters:

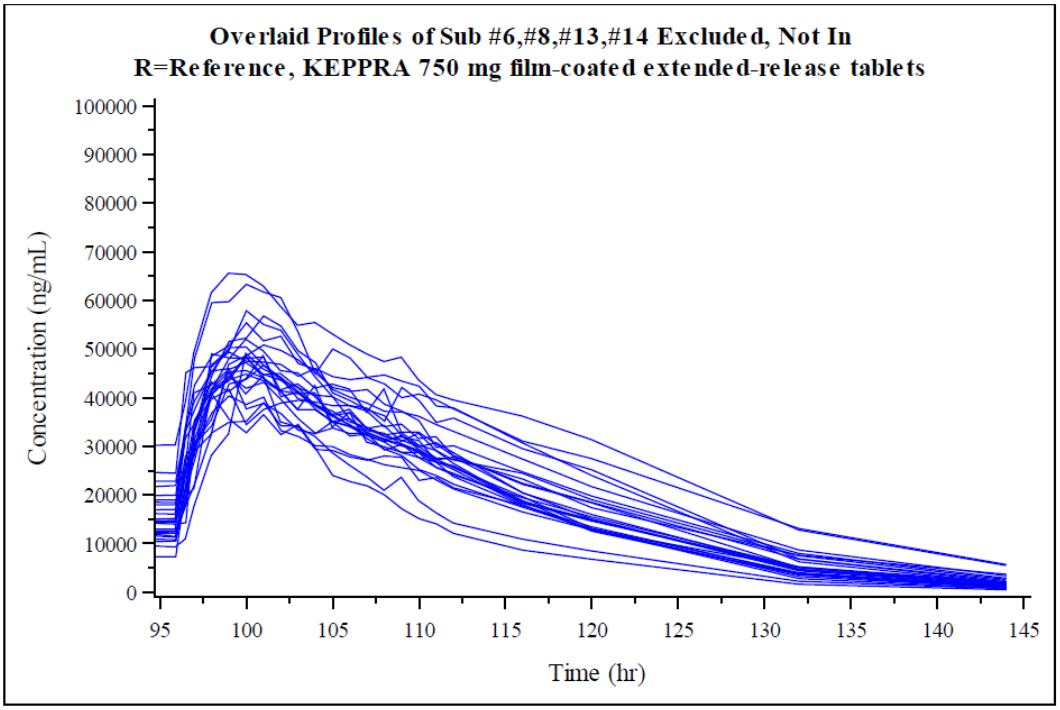
Parameter	Statistic Method	Significance level	Probability (p)
T_{max}	Wilcoxon Signed Rank test	0.0500	<.0001

Levetiracetam Concentration by Treatment for all Subjects in Steady-state

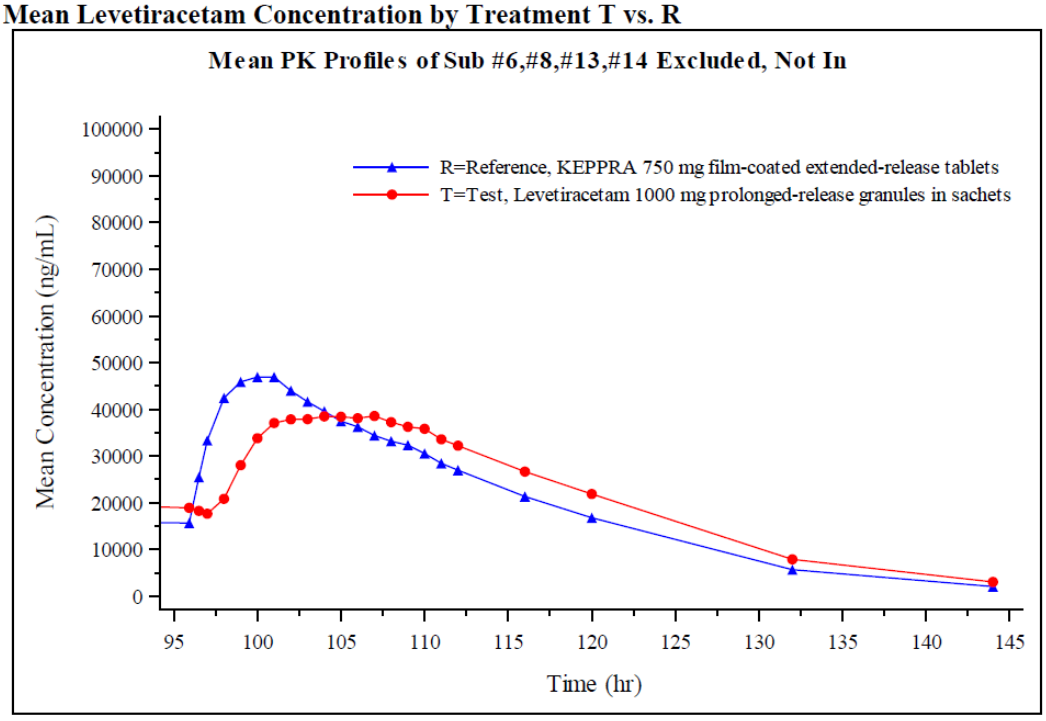
TREATMENT=T

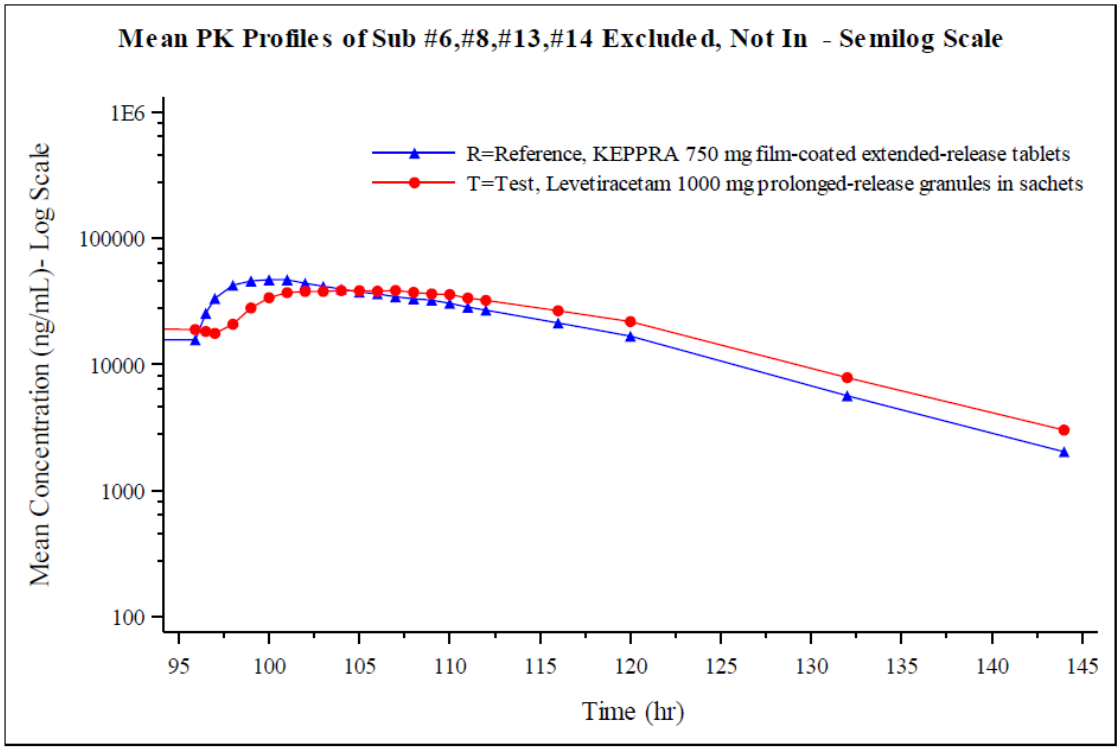


TREATMENT=R



Mean Levetiracetam Concentration by Treatment T vs. R





- ***Safety data***

Five adverse events of mild intensity occurred in three subjects in the present study after administration of the Reference Product.

Listing of Adverse Events by Subject

Subject no.	Study treatment	Adverse event	Date/time of onset	Duration	Seriousness	Intensity	Frequency	Action taken	Outcome	Relationship to test drug
16	REFERENCE	Haemoglobin decreased **MedDRA code:** 10018884	05 June 2023	Unknown	Not serious	Mild	-	Subject was re-called for additional measurements[1]	Unknown	No reasonable possibility
29	REFERENCE	Dizziness **MedDRA code:** 10013573	12 May 2023 11:29	33 min	Not serious	Mild	Intermittent	None	Complete recovery	Reasonable possibility
		Dizziness **MedDRA code:** 10013573	14 May 2023 8:53	11 min	Not serious	Mild	Intermittent	None	Complete recovery	Reasonable possibility
		Nausea **MedDRA code:** 10028813	14 May 2023 8:55	2 min	Not serious	Mild	Intermittent	None	Complete recovery	Reasonable possibility
30	REFERENCE	Dizziness **MedDRA code:** 10013573	12 May 2023 11:45	20 min	Not serious	Mild	Intermittent	None	Complete recovery	Reasonable possibility

These were not serious adverse events. One adverse event reported was related to a clinical laboratory parameter found outside normal range at the follow-up examination in one subject who declined to return for additional measurements of this parameter. Lacking further information, the clinical significance of this value could not be assessed and also, the outcome and the duration were classified as "Unknown".

Population PK

To assess the interchangeability between the reference IR and test PR formulation, PK parameters of levetiracetam as PR granules versus equal daily dose of the reference product (Keppra® IR film-coated tablets) were estimated based on data from the LVM-BEMD-09-LLV/20 study and using the industry standard *(FDA Guidance for Industry, Population Pharmacokinetics, 1999)* and validated Nonlinear Mixed Effects Modeling software package NONMEM® (version 7.3, Icon Plc, Dublin, Ireland). Data

exploration, statistical testing external to NONMEM® and graphics were performed using S-Plus® (TIBCO Spotfile S+ v.8.2, MA, USA). An iterative process of model and data selection was used involving:

1. Exploratory data analysis
2. Fit the data to different compartmental models
3. Select the model that best describes the observations
4. Goodness of fit diagnostics

Immediate release levetiracetam tablets (Keppra®) fit to a one compartment model with a single first-order constant of absorption. The multiphasic absorption process for the PR formulation was described by two sequential absorption processes, i.e., a zero-order input followed by a first-order input. The final selection between alternative models was based on the inspection of residual plots and goodness of fit plots and a visual predictive check to ensure adequate model performance to predict the data.

Simulations of switching patients from the IR to the PR formulation (N=200) at low and high daily dose scenarios were performed using the population PK model in humans (Figure 1 and Figure 2 below).

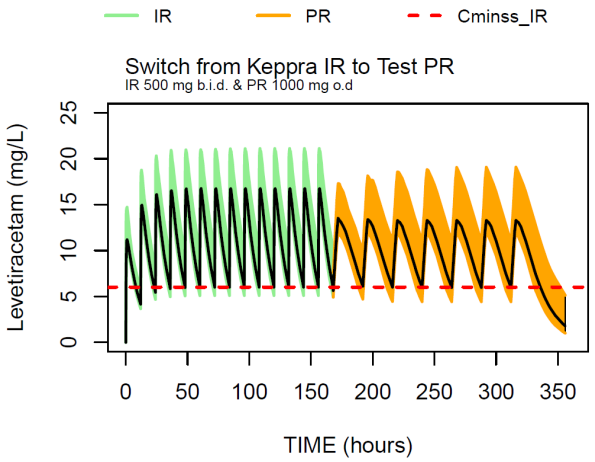


Figure 1: Simulation of mean levetiracetam concentration-time profile after switching from levetiracetam IR (Keppra®, Reference) to Levetiracetam PR granules (Test) at low doses (500 mg BID vs 1000 mg once daily [OD], respectively) based on data from the LVM-BEMD-09-LLV/20 study (n=200)

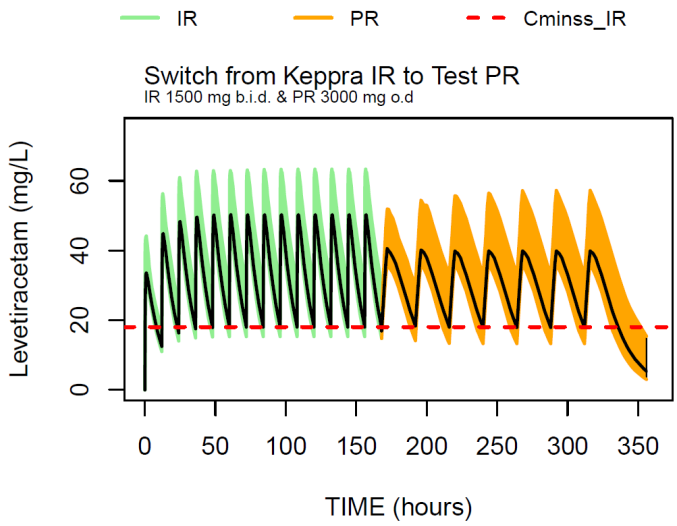


Figure 2. Simulation of mean levetiracetam concentration-time profile after switching from levetiracetam IR (Keppra®, Reference) to Levetiracetam PR granules (Test) at high doses (1500 mg BID vs 3000 mg OD, respectively) based on data from the LVM-BEMD-09-LLV/20 study (N=200)

Mean estimated PK parameters $C_{min,ss}$ and AUC_{tau} at steady state were comparable after switching patients from the IR to PR both at the low (500 mg bid of Levetiracetam IR vs. 1000 mg Levetiracetam PR) and high doses assessed (1500 mg bid of Levetiracetam IR vs. 3000 mg Levetiracetam PR).

Table 5: Simulated plasma exposure metrics for levetiracetam after switching from the reference product (Keppra® IR) at a dose of 500 mg bid to 1000 mg od of the test product (Levetiracetam PR granules)

PK metrics	IR Median (2.5th- 97.5%CI)	PR Median (2.5th- 97.5%CI)
AUC_{tau} (mg*h/L)	267.5 (199.6 -367.3)	239.8 (157.3 -360.4)
$C_{min,ss}$ (mg/L)	6.01 (3.43- 10.12)	5.96 (2.61- 10.95)
$C_{max,ss}$ (mg/L)	17.22 (13.40-21.26)	13.47 (9.45-19.09)

Table 6: Simulated plasma exposure metrics for levetiracetam after switching from the reference product (Keppra® IR) at a dose of 1500 mg bid to 3000 mg od of the test product (Levetiracetam PR granules)

PK metrics (median)	IR Median (2.5th- 97.5%CI)	PR Median (2.5th- 97.5%CI)
AUC_{tau} (mg*h/L)	802.50 (598.7 -1102)	719.5 (471.9 -1081.1)
$C_{min,ss}$ (mg/L)	18.03 (10.29- 30.37)	17.90 (7.84- 32.86)
$C_{max,ss}$ (mg/L)	51.65 (40.21-63.77)	40.41 (28.36-57.26)

In contrast, $C_{max,ss}$ was lower after switching patients from the IR to PR both at the low (500 mg bid of Levetiracetam IR vs. 1000 mg Levetiracetam PR) and high doses evaluated (1500 mg bid of Levetiracetam IR vs. 3000 mg Levetiracetam PR). However, peak plasma concentration, C_{max}, is not considered to be the main driver for the antiepileptic efficacy of levetiracetam and is more likely related to the appearance of adverse effects. On the contrary, a relatively controlled C_{min} under therapeutic ranges should ensure non-inferiority in seizure control.

PBPK analysis to estimate concentrations at site of action

The objective of the PBPK model developed was to predict levetiracetam concentrations at the site of action (CNS) after administration of Levetiracetam PR granules in comparison to different doses of the IR formulation (Keppra®). The methodology used in the analysis followed the guidelines recommended by the FDA and EMA for the format and content for a sponsor or applicant to submit PBPK analyses and exposure-response relationships *(EMA 2018 (EMA/CHMP/458101/2016; FDA 2003; FDA, 2018)*.

The compared formulations and dosing scenarios within this PBPK study were as follows:

- Levetiracetam 1000 mg PR granules (Test PR) once daily versus the reference product Keppra® 500 mg twice daily.
- Levetiracetam 3000 mg PR granules (Test PR) once daily versus Keppra® 1500 mg twice daily.

The development of the PBPK model for levetiracetam was based on the PBPK model published by *Verscheijden et al. (2019)*, as this latter model allows predicting the passage of the blood brain barrier (BBB) in humans as well as the CNS concentrations. The model from Verscheijden and colleagues has been validated for a variety of drugs, including paracetamol, ibuprofen, flurbiprofen, naproxen and meropenem, and its code is readily available in the public domain.

The availability of levetiracetam concentration data in the CNS from brain microdialysis studies in rats facilitated the application of the PBPK model to the specific case of predicting CNS levetiracetam concentrations in humans. To that purpose, the first step was to translate the model to the rat species with the aim of predicting the BBB permeability and to then scale up this value to humans. The model capacity to predict the BBB permeability from rats to humans was verified via qualification of a platform model before the specific application to levetiracetam, using acetaminophen, oxycodone, lacosamide and diazepam as model drugs for passive transportation through the BBB. After that, the

model for levetiracetam was developed and applied according to the three stages briefly described below.

Stage 1

This stage consisted in the application of the PBPK platform model to the rat species using data from a microdialysis study in this species from *Tong and Patsalos (2001)* in order to obtain a value for the permeability surface area product and for BBB permeability. In this study, plasma and extracellular fluid (ECF) data are available after the administration of levetiracetam at doses of 40 and 80 mg/kg. The dose of 40 mg/kg was used initially to optimise the value of the permeability. For that, after developing the model for the plasma data, the value of the BBB permeability obtained for the 40 mg/kg was input into the model and used to predict the ECF or cerebrospinal fluid (CSF) concentrations.

PK data obtained following the 80 mg/kg dose from the study of *Tong and Patsalos (2001)* was used for model verification together with CSF and serum concentration data in rats after administration of three different levetiracetam dose levels (20, 40 and 80 mg/kg) from another published report *(Doheny et al., 1999)*.

Stage 2

In this stage, the PBPK platform model was applied to the human data. The passage of the BBB was scaled using the surface area of the human BBB. Plasma concentrations from the multiple dose bioequivalence study LVM-BEMD-09-LLV/20 were used to develop the model. The ratios plasma:brain ECF (P:ECF) and plasma:CSF (P:CSF) of levetiracetam concentrations in humans were then verified using a paper from the literature *(Rambeck et al., 2006)*, which collected CNS samples in human patients with intractable epilepsy. The model was then applied to predict the CNS concentrations after levetiracetam IR and PR administration following the doing scenarios described below.

The PBPK model was used to investigate the parameters sensitivity and identify those parameters that could have a higher impact on levetiracetam CNS exposure. For Keppra® IR, the permeability surface area product was the driver for the passage to the BBB as it was the rate limiting process. While, in the case of the prolonged release granules formulation (Test PR), the passage to the BBB is highly dependent on the release rate from the formulation and thus, on the absorption rate, as it was the slower process.

Stage 3

In this stage, the model was applied to evaluate potential formulation differences by comparing the percentage of virtual subjects maintaining steady state levels below the minimum ECF concentrations ($C_{min,ss}$) of the reference product (Keppra®) at different dose levels. ECF concentrations of 1.7 µg/ml were defined as the $C_{min,ss}$ for the lower posology (i.e., 500 mg twice daily IR versus 1000 mg once daily for the PR) at steady state and 5.2 µg/ml as the $C_{min,ss}$ for the higher posology (i.e., 1500 mg twice daily IR vs. 3000 mg once daily for the PR) according to steady state PK data from the proprietary multiple-dose BE study.

Simulations were performed using the PBPK model in 200 virtual patients at the equivalent dosing regimens of 500 mg twice daily for the reference IR versus 1000 mg once daily for the test PR formulation as well as 1500 mg twice daily for the IR vs 3000 once daily for the PR formulation. The proportion of patients below the reference ECF concentrations $C_{min,ss}$ were then calculated at steady state for the three formulations after the two proposed equivalent dosing regimens.

Results of the application of the PBPK model

For the rat model, all predicted AUC and C_{max} values lied within the 1.25-fold range of their respective observed counterparts. Therefore, the rat model provides a consistent representation of levetiracetam systemic and CNS exposure following administration in rats and thus can be applied to properly predict brain ECF and CSF concentrations over time.

In humans, the PBPK model appropriately predicted the mean plasma concentrations for Keppra® IR (reference formulation) and also captured the variability in the data very well as can be seen in Table 7. Across the population being investigated, the simulations represented the data adequately with prediction errors in the PK metrics (AUC, C_{max} and C_{min}) of 1%, 18.5% and 4%, respectively, for the reference product.

Table 7: Plasma exposure metrics for reference product (Keppra® IR)

PK Parameters	Mean Predicted (n=200)	Mean Observed (n=40)	Ratio (Pred/Obs)
IR – Reference Product			
$AUC_{(96\text{-}120h)}$ (mg×h/L)	796.60	804.559	0.99
$C_{max,ss}$ (mg/L)	62.09	52.37	1.18
$C_{min,ss}$ (mg/L)	18.89	19.68	0.96
$C_{avg,ss}$ (mg/L)	33.19	36.03	0.92

In addition, the model appropriately predicted the mean plasma concentrations for the PR formulation (Test formulation) and captures the variability in the data very well. Across the population being investigated, the simulations represented the data adequately with prediction errors in the PK metrics (AUC, C_{max} and C_{min}) of 4%, 6% and 0.25%, respectively, for the test product.

Table 8: Plasma exposure metrics for the test product (PR granules)

PK Parameters	Mean Predicted (n=200)	Mean Observed (n=40)	Ratio (Pred/Obs)
PR granules – Test Product			
$AUC_{(96\text{-}120h)}$ (mg×h/L)	764.29	736.03	1.04
$C_{max,ss}$ (mg/L)	41.47	39.1	1.06
$C_{min,ss}$ (mg/L)	20.64	20.69	1
$C_{avg,ss}$ (mg/L)	31.84	29.89	1.07

The developed PBPK model predicted comparable daily CSF and ECF levels from the steady state plasma concentration profiles for the two products supporting exposure similarity at the site of action (CNS) between the two formulations despite of a different release rate. Furthermore, the PBPK model-based approach reveals that the differences in daily plasma profile shapes associated to the PR formulation do not translate to lower concentrations at the site of action at the end of the dosing interval. Therefore, a higher risk of breakthrough seizures associated with transitional periods of low concentrations can be excluded.

Table 9: Comparison of ECF simulated exposures at steady state between Keppra® IR and test PR

Products	$AUC_{(96\text{-}120h)}$ (mg*h/L)	C_{maxss} (mg/L)	C_{minss} (mg/L)	C_{avgss} (mg/L)
Reference Keppra® IR	192.43	10.4	5.17	8.01
Test PR	184.51	9.82	5.38	7.68
Diff (%)	-4.12	-5.58	4.06	-4.12

All the simulated exposure metrics at steady state in the ECF showed a relative difference (%diff) lower than 5.6%.

The prediction of ECF and CSF concentrations were verified with data from patients with either complex partial seizures or secondarily generalized seizures published by *Rambeck et al. (2006)*. During the neurosurgical intervention, a microdialysis study was performed and samples were taken from serum,

CSF and ECF. Due to limited information related with the dosing regimen of these subjects only the reported values of the plasma:brain extracellular fluid (P:ECF) and plasma cerebrospinal fluid (P:CSF) were considered for the verification of the PBPK model predictions in the CNS. Considering that levetiracetam crosses the BBB via passive transport, no non-linearity issues are expected due to differences in the drug posology between studies. The mean reported values of P:CSF and P:ECF ratios were 1.14 and 4.37, respectively *(Rambeck et al., 2006)*. The model predicted values are reported in the table below.

Table 10: Model Predicted Ratio of Plasma, CSF and ECF

	Plasma	**CSF**	**ECF**	**Ratio Plasma:CSF**	**Ratio Plasma:ECF**
AUC (mg×h/L)	796.60	760.75	192.43	1.05	4.14

The percentage of subjects falling below the reference concentration of C_{minss} = 1.7 mg/L after administration of 500 mg b.i.d of Keppra® IR and 1000 mg o.d. of test PR in a 24-h interval at steady state was 60% for Keppra® IR and 48% for the Test PR. The same proportion of subjects falling below the reference concentration of $C_{min,ss}$ = 5.2 mg/L is observed after administration of 1500 mg b.i.d of Keppra® IR and 3000 mg o.d. of test PR in line with the linear pharmacokinetic of levetiracetam in the CNS due to the lack of active processes involved in the transport of levetiracetam through the BBB.

Based on the simulations, similar efficacy profile is expected between the reference (Keppra® IR) and the test PR. The results of the PBPK model show that differences in plasma concentration profile shape do not impact the effectiveness of levetiracetam. The predictions of brain concentrations provide further evidence on the exposure resemblance at the CNS level between the test and reference formulations. Therefore, as the profile shapes and concentrations at the site of action are similar, equivalence in terms of efficacy is supported between levetiracetam IR (Keppra®) to Levetiracetam PR.

Study LESVILEVE/22/RWE-4

The RWE LESVILEVE/22/RWE-4 study was designed as a non-interventional, retrospective, cohort study in new users of Levetiracetam IR or XR using a large national private claim registry linked to EMR information from the US. The overall research question of this study was whether effectiveness and safety outcomes associated with the use of oral prolonged release formulations of levetiracetam were not inferior compared to oral levetiracetam IR among epileptic subjects with POS, with or without secondary generalisation, using real-world data from claims and EMR in the US.

The primary objective of this study was to compare the proportion of subjects who were seizure-free for at least 24 weeks while receiving a stable dose of medication between new users of oral levetiracetam XR and new users of oral levetiracetam IR in the clinical practice.

The secondary objectives were:

- To compare the subject retention, calculated as the proportion of subjects without treatment discontinuation after 48 weeks (key secondary objective).
- To compare the percentage of subjects who were seizure-free for at least 16 and 48 weeks while receiving a stable dose of medication.
- To compare the time to first seizure, defined as first seizure occurring after treatment initiation within 48 weeks.
- To compare the time to treatment failure, calculated as the number of days on treatment until switch to/or addition of other antiepileptic drugs (AEDs).
- To compare the incidence of major epilepsy-related events, defined as the utilisation of ambulance, emergency department or inpatient hospital routes of care with a primary diagnosis of epilepsy for the recorded event.
- To describe the incidence of AEs of special interest (AESIs).
- To compare all-cause healthcare resource utilisation (HCRU) during the follow-up period.

These objectives were investigated by comparing subjects initiating treatment with oral levetiracetam XR to subjects initiating treatment with oral levetiracetam IR in the clinical practice.

Study population

The study population included subjects from 12 years of age with at least one diagnosis code for epilepsy who initiated oral Levetiracetam XR or oral Levetiracetam IR during the study period between September 2015 and April 2022. Main exclusion criteria were missing or ambiguous data on age or gender or having at least one diagnosis code for a generalised seizure type and no codes for a partial (focal) seizure type during the entire study period for the subject (i.e., from 1 year before the index date until last data available in the data source).

Effectiveness outcomes

The primary effectiveness outcome of the study was the proportion of subjects free from seizures for at least 24 weeks while receiving a stable dose of medication. It was assessed within the first 24 weeks of continuous treatment at a stable dose (i.e., initial weeks of potential dose tapering/adaptation were not taken into account).

The study secondary effectiveness outcomes were:

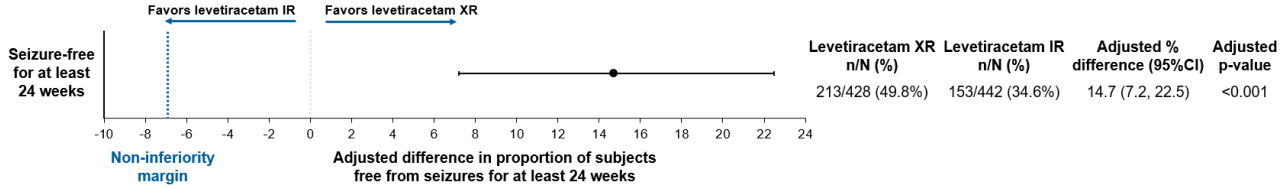
- Proportion of subjects without treatment discontinuation after 48 weeks (key secondary outcome).
- Proportion of subjects free from seizures for at least 16 and 48 weeks while receiving a stable dose of medication.
- Time to first seizure, calculated as days from the index date to the first seizure occurring after treatment initiation within 48 weeks.
- Time to treatment failure (i.e., number of days on treatment until switch to/or addition of other AEDs).
- Reasons for treatment discontinuation, in subjects where this information was directly available or could be reasonably inferred (e.g., using medical notes or coincidence between major events and treatment end date), were also described as percentage of subjects who dropped off treatment for safety/tolerance reasons, lack of efficacy, need for another AED, change in the formulation of levetiracetam (i.e., switch from IR to XR or *vice versa*), change in titration or other/unknown reasons.
- Incidence rate of major epilepsy-related events, defined as the utilisation of ambulance, emergency department or inpatient hospital routes of care with a primary diagnosis of epilepsy for the recorded event.
- Secondary safety outcomes included incidence rate of AESIs (allergic reaction, hyponatraemia, psychiatric AEs, including suicidality, cognition-related AEs, hepatic toxicity, cardiac rhythm and conduction disorders, hypertension).

A total of 20,000 subjects from the reviewed databases were diagnosed with epilepsy and had at least one filled prescription of oral levetiracetam XR or oral levetiracetam IR between the 1st of September 2015 and the 30th of April 2022 and were assessed for eligibility. After applying selection criteria and performing the propensity score matching, the groups for the comparison of levetiracetam XR with levetiracetam IR were reduced to 1,172 subjects in each cohort. From them, 6 subjects did not contribute to the outcome analysis due to not having follow-up time. Thus, the final number of subjects evaluable for outcomes analyses were 1,171 and 1,167 for the levetiracetam IR and levetiracetam XR cohorts, respectively. Switchers from Levetiracetam IR to Levetiracetam XR were considered in sensitivity analyses as expected to be one representative population according to clinical practice.

For the assessment of the primary efficacy endpoint, a total of 428 and 442 subjects in the Levetiracetam XR and Levetiracetam IR cohorts, respectively, were evaluable (i.e., they had at least 24 weeks of follow-up while receiving a stable dose of medication or they had less than 24 weeks of follow-up but at least one seizure occurring while receiving a stable dose of medication). The proportion of subjects free from seizures for at least 24 weeks while receiving stable dose of medication was higher for subjects who received Levetiracetam XR (49.8%) than levetiracetam IR (34.6%) (adjusted odds ratio: 1.84; 95%CI: 1.36, 2.52). The non-inferiority margin was set to -6.9%, corresponding to the 20% of the rate in the control group (i.e., rate of the levetiracetam IR cohort,

34.6%). The lower bound of the 95%CI of the adj. percentage difference in the proportion of subjects free from seizures for at least 24 week was above this non-inferiority margin (i.e., 7.2% was above -6.9%), meeting the criterion for non-inferiority of levetiracetam XR compared with levetiracetam IR (Figure 3).

Consequently, the results of this main analysis confirmed the non-inferiority of Levetiracetam XR in comparison to Levetiracetam IR with regards to seizure freedom for 24 weeks while receiving a stable dose of medication.



CI, confidence interval; IR, immediate-release; XR, extended-release.

Figure 3. Adjusted difference between Levetiracetam XR and Levetiracetam IR in the Proportion of Subjects Free from Seizures for at Least 24 Weeks

The assessment of the other outcomes of this study showed the non-inferiority of Levetiracetam XR once daily in comparison to Levetiracetam IR twice daily with regards to seizure freedom after 16, 24 and 48 weeks of receiving stable dose of medication, as well as with regards to treatment maintenance. In addition, there were no statistically significant differences in time to treatment failure (defined as addition or dose increase in other AEDs) between subjects treated with levetiracetam XR and levetiracetam IR (adjusted hazard ratio: 0.99; 95%CI: 0.80, 1.23). However, when focusing on exposure to levetiracetam and subject retention at 48 weeks, results confirm that subjects on levetiracetam XR remained under treatment for a longer time than those with levetiracetam IR. On the other hand, Levetiracetam XR showed a safety profile in line with Levetiracetam IR. The incidence rate and the proportion of subjects experiencing at least one psychiatric AE (including suicidality), cognition related-AE, cardiac rhythm/conduction disorder and hypertension were statistically significant lower in subjects being treated with Levetiracetam XR than in subjects receiving Levetiracetam IR. Incidence rates for allergic reactions, hyponatremia and hepatic toxicity were similar between Levetiracetam XR and Levetiracetam IR cohorts, with no statistically significant differences in the risk of experiencing at least one event.

The results obtained in the comparison of levetiracetam XR versus levetiracetam IR use for the primary and secondary effectiveness outcomes confirmed the non-inferiority of levetiracetam XR compared with levetiracetam IR and are in line with data from literature where levetiracetam XR has been shown to provide, at equal daily doses, very similar safety and tolerability profiles as adjunctive treatment in patients with partial epilepsy and comparable efficacy in reducing the frequency of POS when used as add-on therapy in adult patients with uncontrolled epilepsy in a 12-week treatment, double-blind, double-dummy randomised, paralleled, multicentre trial *(Wu et al., 2018)*. In this study, the median POS frequency per week was 0.3 (95% CI: 1.3-4.8) in the levetiracetam XR and 0.3 (95% CI: 0.1-4.3) in the levetiracetam IR group, with both groups having the same responder rate (58.6%), and a higher rate of seizure freedom over the treatment period noted in the XR group (27.6% versus 13.8%, respectively). Similar efficacy and safety conclusions had been observed in conversion studies to XR formulations of AEDs with similar mechanism of action *(Ramey et al., 2014)*, as well as highlighted in recently published guidelines to clinicians *(Gidal et al., 2021)*.

In the present study, levetiracetam XR use was associated with a statistically significant higher proportion of subjects who were seizure-free for at least 24 weeks than levetiracetam IR (49.8% versus 34.6%; adjusted odds ratio: 1.84; 95%CI: 1.36, 2.52). At weeks 16 and 48, statistically significant results regarding seizure freedom were also observed in favour or levetiracetam XR. Moreover, levetiracetam XR was associated with a statistically significant delay in the occurrence of the first seizure after treatment initiation. An improvement in seizure control has already been observed

with the use of other XR medications compared with their respective IR formulations, such as lamotrigine (*Ramey et al., 2014*) and topiramate (*Chung 2015; O'Neal et al., 2018*). The use of modified release formulations with a longer half-life that allow a once-daily regimen has several advantages over IR formulations with shorter half-life that require multiple dosing. The XR formulations present a simplified dosing regimen, a reduced medication burden and a decreased peak-to-trough fluctuation in serum drug concentration, thereby increasing adherence and enhancing overall seizure control with an improved overall safety profile (*Gidal et al., 2021*).
Regarding safety results, the four most frequent AESIs in our study population, including psychiatric AEs, cognition-related AEs, cardiac rhythm and conduction disorders and hypertension had a statistically significant lower incidence in the Levetiracetam XR cohort than in the levetiracetam IR cohort. Incidence rates for allergic reactions, hyponatremia and hepatic toxicity were similar between Levetiracetam XR and Levetiracetam IR cohorts, with no statistically significant differences in the risk of experiencing at least one event. These results are in line with better tolerability profiles observed with other long-acting AED *(Leppik and Hoving, 2013; Miller et al., 2004; Uthman 2014)*.
However, the results of the conducted analysis are not considered relevant for demonstration of the bridge between the test product and the reference product, since no results of studies conducted with the test product were included in the analysis. Moreover, in the light of the results of Study LVM-BEMD-14-LLV/23, the results of the real-word evidence study LESVILEVE/22/RWE-4, aimed to compare the proportion of subjects who were seizure-free for at least 24 weeks while receiving a stable dose of medication between new users of oral levetiracetam XR and new users of oral levetiracetam IR in the clinical practice in the US appear not relevant for the current MAA. Since the Test product was not shown to be bioequivalent to the US comparator, extrapolation of the efficacy and safety data from the US comparator is not possible.

3.3.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

3.3.3. Discussion on clinical pharmacology

To support this MAA, the applicant initially submitted results of three PK studies, PBPK model and non-interventional RWE study. In addition, to address the MO raised at Day 120, the applicant provided results of the study LVM-BEMD-14-LLV/23.

Two PK studies (Study LVM-BEMD-09-LLV20 and Study LVM-BESD-12-LLV/22) were aimed to assess bioequivalence of the test prolonged-release granules in sachets formulation versus the reference product Keppra immediate release film-coated tablets.
Study LESVILEVE/21/BQ-1 (LVM-BEMD-09-LLV/20) was an open-label, two-period, two-way crossover, multiple-dose BE study of levetiracetam 1000 mg XR granules in sachets, administered at the dose of 3000 mg once per day (test formulation) versus equal daily dose of the reference product (Keppra 500 mg IR film-coated tablets) administered twice daily in healthy male and female volunteers, under fasting conditions. The overall design of the study is supported.

The wash out period of 10 days appears acceptable, taking into account that the Test product T1/2 is 7±1 hours. The selection of the primary PK parameters (AUC(0-τ), Cmax.ss, Cmin.ss, and secondary PK parameters (Cav.ss, Tmax.ss and PTF) is supported.

The 90% CI of the relative mean plasma levetiracetam AUCt and Cmin ss of test to reference products were between 80.00 and 125.00%.

However, the 90% CI of plasma Levetiracetam Cmax of test to reference products were outside 80.00 and 125.00% (65.32% – 73.43%) **(part of the MO).**

Study LESVILEVE/22/BQ-1 (LVM-BESD-12-LLV/22) was an open-label, three-period, crossover, randomised, single-dose study to assess bioequivalence and food effect of Levetiracetam 3×1000 mg XR granules in sachets once daily administered in fasting and fed conditions versus equal dose of the Reference product (Keppra 500 mg × 3 IR film-coated tablets) twice daily administered in fasting conditions to healthy male and female volunteers. In line with the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms EMA/CHMP/EWP/280/96 Rev1, if there is no clinically relevant food effect on the immediate-release formulation, a 2-way cross-over study comparing the modified release formulation in fasted and fed states could be sufficient (given that other studies compare the modified release and the immediate release formulations under fasting conditions).

Only AUC0-t was considered a primary PK parameter, which is not considered appropriate. In line with Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms EMA/CHMP/EWP/280/96 Rev1, Cmax should be included for the assessment of food effects**.** However, the confidence interval is presented for Cmax and the results are within the conventional acceptance range.

The 96.7% confidence intervals of the ratios TFAST/R, for AUC0-t were inside the bioequivalence range of 80.00-125.00%. However, for Cmax the bioequivalence criteria were not met (The 96.7% confidence intervals 57.55 and 64.62). Therefore, the BE between the Tfast and the Reference product cannot be concluded **(part of the MO).** The 96.7% confidence intervals of the ratios TFAST/TFED, for AUC0-t, Cmax and AUC 0-inf were inside the bioequivalence range of 80.00-125.00%.

Study LESVILEVE/21/BQ-6 (LVM-BESD-10-LLV/21) was an open-label, two-period, two-way, crossover, randomised, single-dose, dose-proportionality study of Levetiracetam 1000 mg prolonged-release granules in sachets, as 3,000 mg (3×1000 mg sachets) once per day (test-1 formulation) versus 1000 mg (1×1000 mg sachet) once per day (test-2 formulation) in healthy male and female volunteers, under fasting conditions. The overall design of the study is supported. the time points for blood samples collection are considered acceptable. The wash out period of 10 days appears acceptable, taking into account that the Test product T1/2 is 7±1 hours. The selection of the PK parameters is appropriate.

The statistical analysis did not show statistically significant differences between both treatment administered. The 90% confidence intervals of the ratios T1/T2, for AUC0-t and Cmax were inside the accepted bioequivalence criteria of 80.00-125.00%, therefore it can be agreed that equivalence with respect to extent of absorption between the Test2 and the Test1 formulation was shown. It can be agreed that the dose proportionality criteria were met.

Study LVM-BEMD-14-LLV/23 was an open label, two-period, two-way crossover, block randomized, multiple dose bioequivalence study LVM-BEMD-14-LLV/23 in healthy volunteers with administration under fasting conditions aimed to demonstrate the steady state bioequivalence between the TEST prolonged-release granules in sachets formulation and a corresponding dose of REFERENCE film-coated extended-release tablets, both administered under fasting conditions for 5 consecutive days. As a comparator in the Study, KEPPRA XR 750 mg film-coated extended-release tablets of UCB (Country of purchase: United States) was used. Since there is no approved levetiracetam-containing modified release formulation in the EU that could be used as a comparator and since the study is a supportive study, the use of the US comparator can be considered acceptable. The overall design of the study is supported. The wash out period of 11 days appears acceptable, taking into account that the Test product T1/2 is 7±1 hours. The selection of the primary PK parameters (AUC(0-τ), Cmax.ss, Cmin.ss, is supported. The 90% CI of the relative mean plasma levetiracetam AUCt, Cmax.ss, and Cmin ss of test to reference products were between 80.00 and 125.00%.

However, with respect to concentration at the end of dosing interval after the last administered dose, Ctau.ss, the TEST/REFERENCE geometric mean ratio was not within the acceptance criteria of 80.00-125.00% after multiple dosing.

Since Cτau,ss (concentration at the end of the dosing interval at steady state) is a primary PK parameter it cannot be agreed that the BE between the Test product and the US comparator was shown.

To predict cerebrospinal fluid (CSF) and extracellular fluid (ECF) levetiracetam levels following administration of levetiracetam prolonged-release granules in comparison with Keppra IR, the applicant developed PBPK model. The results from Studies LVM-BESD-10-LLV/21 and LVM-BESD-12-LLV/22 were used for the external verification of the model.

It is noted that the model has structural limitations because it does not include the brain mass compartmentalisation (it does not separate intracellular and extracellular space). The brain mass has been modelled as a single compartment (as acknowledged by Verscheijden et al). In fact, ECF does not belong to the brain mass, and is modelled as an independent compartment. This structure is not physiologically correct.

Moreover, since data on concentrations of levetiracetam in the CSF was taken from Rambeck at al (2006), which included only 3 patients treated with levetiracetam, predictions based on the model cannot be considered informative and the predictive power of the model is uncertain. The assumptions that lower proportion of subjects treated with the test PR product will achieve Cminss concentrations compared to subjects treated with the reference product should therefore be treated with caution. However, given the limitations of the model and specificity of the target indication, predictions based on the model are not considered adequate to replace the therapeutic equivalence study **(part of the MO).**

No efficacy/safety studies have been conducted by the applicant. Instead, the applicant performed the real-word evidence study LESVILEVE/22/RWE-4, aimed to compare the proportion of subjects who were seizure-free for at least 24 weeks while receiving a stable dose of medication between new users of oral levetiracetam XR and new users of oral levetiracetam IR in the clinical practice. The study was non-interventional, retrospective, cohort study in new users of Levetiracetam IR or XR using a large national private claim registry from the US.

In total 428 and 442 subjects in the Levetiracetam XR and Levetiracetam IR cohorts, respectively, were included in the analysis.

The proportion of subjects free from seizures for at least 24 weeks while receiving stable dose of medication was higher for subjects who received Levetiracetam XR (49.8%) than levetiracetam IR (34.6%). Non-inferiority of levetiracetam XR compared with levetiracetam IR was shown.
However, the submitted RWD study evaluating non-inferiority between Keppra XR and Keppra IR is at best supportive but cannot be considered a replacement for a therapeutic equivalence study. Bias cannot be excluded as the study is non-randomized and lacks assay sensitivity. Moreover, it is questioned whether the appropriate patient population was included in the study. A large proportion of patients in both cohorts (around 30%) used concomitant anti-seizure medication (ASM) of which the impact on Keppra efficacy cannot be excluded. In addition, not every patient was ASM treatment naïve, between 30-40% of patients in the cohorts had at least one prior ASM. It is known that the chance of having drug resistant seizures increases with each previous ASM used, and it cannot be excluded that this could have impacted the results on the primary endpoint seizure freedom.
Moreover, the results of the conducted analysis are not considered relevant for demonstration of the bridge between the test product and the reference product, since no data from patients treated with the test product were included in the analysis. Furthermore, since in the Study LVM-BEMD-14-LLV/23 the concentration at the end of dosing interval at steady state Ctau,ss ratio T/R, was not within the bioequivalence range of 80.00-125.00%, the bioequivalence cannot be concluded to be shown for the Test product and the US comparator **(part of the MO).**

Moreover, in line with the information provided in the Clinical Overview and results of the study LVM-BEMD-14-LLV/23, Tmax of Keppra XR and Levetiracetam PR differed by approximately 5 h, while the maximum Tmax was equal for both products. However, the minimum Tmax of Keppra XR and

Levetiracetam PR differs by approximately 3h. It should be noted that in the completed study LESVILEVE/23/BQ-2 the concentration at the end of the dosing interval, Ctau (i.e. Ctrough), the TEST/REFERENCE geometric mean ratio was not within the acceptance criteria of 80.00-125.00%. There were no severe AE observed in the conducted PK studies. The incidence of the AEs was generally comparable after administration of the Reference and the Test product.

In Study LVM-BESD-12-LLV/22, the incidence of AE was lower after administration of the Test product under fed conditions (26.19%) compared to fasted conditions (35.71%). There were no new safety signals identified in the conducted PK studies.

3.3.4. Clinical efficacy

N/A

3.3.5. Clinical safety

N/A

3.3.6. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

3.3.7. Discussion on clinical safety

N/A

3.3.8. Conclusions on clinical aspects

Due to following reasons, Epixram is not considered bioequivalent with Keppra:

For a hybrid application with a new pharmaceutical form with a prolonged release profile and change in strength, as a principle, comparative clinical efficacy and safety data are needed in addition to PK data. The waiver of the therapeutic equivalence study is not possible even if the assessment of concentration-effect relationship indicates that there is a well-defined relationship between plasma concentration(s) of the active substance /active metabolite(s) and clinical response because the three possibilities to waive the therapeutic equivalence studies given in section 5.2.1. of the Guideline on the Pharmacokinetic and Clinical Evaluation of Modified Release Dosage Forms are not applicable since:

- The shape of the profiles are not mimicked, which is a requirement for the first scenario.
- Bioequivalence between the reference and the test product has not been shown in terms of Cmax,ss for the second scenario
- It cannot be excluded that differences in the PK between the reference and the test products will not influence the safety and efficacy for the third scenario.

The results of the RWE study are not considered relevant for demonstration of the bridge between the test product and the reference product, since no data from patients treated with the test product were included in the study. Furthermore, the results of Study LVM-BEMD-14-LLV/23 showed that the TEST/REFERENCE Ctau.ss, geometric mean ratio was not within the acceptance criteria of 80.00-125.00% after multiple dosing.

The submitted RWD study evaluating non-inferiority between Keppra XR and Keppra IR is at best supportive but cannot be considered a replacement for a therapeutic equivalence study. Bias cannot be excluded as the study is non-randomized and lacks assay sensitivity. Moreover, it is questioned whether the appropriate patient population was included in the study. A large proportion of patients in both cohorts (around 30%) used concomitant anti-seizure medication (ASM) of which the impact on Keppra efficacy cannot be excluded. In addition, not every patient was ASM treatment naïve, between 30-40% of patients in the cohorts had at least one prior ASM. It is known that the chance of having drug resistant seizures increases with each previous ASM used, and it cannot be excluded that this could have impacted the results on the primary endpoint seizure freedom.

In the light of the results of Study LVM-BEMD-14-LLV/23, the results of the real-word evidence study LESVILEVE/22/RWE-4, aimed to compare the proportion of subjects who were seizure-free for at least 24 weeks while receiving a stable dose of medication between new users of oral levetiracetam XR and new users of oral levetiracetam IR in the clinical practice in the US appear not relevant for the current MAA. Predictions based on the PBPK model are not considered adequate to replace the therapeutic equivalence study.
In conclusion the therapeutic equivalence study cannot be waived and the applied product is not approvable.

3.4. Risk management plan

3.4.1. Safety specification

3.4.1.1. Summary of safety concerns

The Safety Specification (Part II, SVIII) from RMP version 0.2, dated 21 May 2024 is assessed below:

Summary of the safety concerns

Table SVIII.1: Summary of Safety Concerns for patients aged 12 years and older

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Long term effects on learning, intelligence, growth, endocrine function, puberty, and childbearing potential in children with epilepsy or in children exposed in utero

3.4.2. Discussion on safety specification

Having considered the data in the safety specification, it is agreed that the safety concerns listed by the applicant are appropriate.

3.4.3. Conclusions on the safety specification

Having considered the data in the safety specification, it is agreed that the safety concerns listed by the applicant are appropriate.

3.4.4. Pharmacovigilance plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

3.4.5. Risk minimisation measures

The safety information in the proposed product information (PI) is aligned to the reference medicinal product.

PRAC rapporteur's updated conclusions on RMMs

The PRAC Rapporteur, having considered the data submitted, was of the opinion that the proposed risk minimisation measures (alignment on the product information of the reference product) are in line with the regulatory requirements for hybrid applications under the Art. 10(3) of Directive 2001/83/EC and sufficient to minimise the risks of the product in the proposed indications.

3.4.6. Conclusion on the RMP

The RMP is acceptable.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.5.2. Periodic Safety Update Reports submission requirements

4. Benefit/risk assessment

This application concerns a hybrid version of Levetiracetam, film-coated tablets. The reference product Keppra is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

Keppra is also indicated as adjunctive therapy • in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy. • in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy. • in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature has been provided.

The PK studies form the pivotal basis for this MAA.

Two PK studies (Study LVM-BEMD-09-LLV20 and Study LVM-BESD-12-LLV/22) were aimed to assess bioequivalence of the test prolonged-release granules in sachets formulation versus the reference product Keppra immediate release film-coated tablets.

Study LESVILEVE/21/BQ-1 (LVM-BEMD-09-LLV/20) was an open-label, two-period, two-way crossover, multiple-dose BE study of levetiracetam 1000 mg XR granules in sachets, administered at the dose of 3000 mg once per day (test formulation) versus equal daily dose of the reference product (Keppra 500

mg IR film-coated tablets) administered twice daily in healthy male and female volunteers, under fasting conditions. The overall design of the study is supported.

The wash out period of 10 days appears acceptable, taking into account that the Test product T1/2 is 7±1 hours. The selection of the primary PK parameters (AUC(0-τ), Cmax.ss, Cmin.ss, and secondary PK parameters (Cav.ss, Tmax.ss and PTF) is supported.

The 90% CI of the relative mean plasma levetiracetam AUCt and Cmin ss of test to reference products were between 80.00 and 125.00%.

However, the 90% CI of plasma Levetiracetam Cmax of test to reference products were outside 80.00 and 125.00% (65.32% – 73.43%)**.**

Study LESVILEVE/22/BQ-1 (LVM-BESD-12-LLV/22) was an open-label, three-period, crossover, randomised, single-dose study to assess bioequivalence and food effect of Levetiracetam 3×1000 mg XR granules in sachets once daily administered in fasting and fed conditions versus equal dose of the Reference product (Keppra 500 mg × 3 IR film-coated tablets) twice daily administered in fasting conditions to healthy male and female volunteers. However, in line with the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms EMA/CHMP/EWP/280/96 Rev1, if there is no clinically relevant food effect on the immediate-release formulation, a 2-way cross-over study comparing the modified release formulation in fasted and fed states could be sufficient (given that other studies compare the modified release and the immediate release formulations under fasting conditions).

Only AUC0-t was considered a primary PK parameter, which is not considered appropriate. In line with Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms EMA/CHMP/EWP/280/96 Rev1, Cmax should be included for the assessment of food effects**.** However, the confidence interval was provided for Cmax and AUC 0-inf, the results were within the conventional acceptance range.

The 96.7% confidence intervals of the ratios TFAST/R, for AUC0-t were inside the bioequivalence range of 80.00-125.00%. However, for Cmax the bioequivalence criteria were not met (The 96.7% confidence intervals 57.55 and 64.62). Therefore, the BE between the Tfast and the Reference product cannot be concluded**.** The 96.7% confidence intervals of the ratios TFAST/TFED, for AUC0-t, Cmax and AUC 0-inf were inside the bioequivalence range of 80.00-125.00%.

The applicant conducted multiple dose bioequivalence study LESVILEVE/23/BQ-2) of the proposed product Levetiracetam PR 1000 mg (Test) versus Keppra XR 750 mg (approved in the US).

Study LVM-BEMD-14-LLV/23 was an open label, two-period, two-way crossover, block randomized, multiple dose bioequivalence study LVM-BEMD-14-LLV/23 in healthy volunteers with administration under fasting conditions aimed to demonstrate the steady state bioequivalence between the TEST prolonged-release granules in sachets formulation and a corresponding dose of REFERENCE film-coated extended-release tablets, both administered under fasting conditions for 5 consecutive days. As a comparator in the Study, KEPPRA XR 750 mg film-coated extended-release tablets of UCB (Country of purchase: United States) was used. Since there is no approved levetiracetam-containing modified release formulation in the EU that could be used as a comparator and since the study is a supportive study, the use of the US comparator can be considered acceptable. The overall design of the study is considered acceptable.

The wash out period of 11 days appears acceptable, taking into account that the Test product T1/2 is 7±1 hours. The selection of the primary PK parameters (AUC(0-τ), Cmax.ss, Cmin.ss, is supported.

The 90% CI of the relative mean plasma levetiracetam AUCt, Cmax.ss, and Cmin ss of test to reference products were between 80.00 and 125.00%.

However, with respect to concentration at the end of dosing interval after the last administered dose, Ctau.ss, the TEST/REFERENCE geometric mean ratio was not within the acceptance criteria of 80.00-125.00% after multiple dosing.

Since Cτau,ss (concentration at the end of the dosing interval at steady state) is a primary PK parameter it cannot be agreed that the BE between the Test product and the US comparator was shown.

Study LESVILEVE/21/BQ-6 (LVM-BESD-10-LLV/21) was an open-label, two-period, two-way, crossover, randomised, single-dose, dose-proportionality study of Levetiracetam 1000 mg prolonged-release granules in sachets, as 3,000 mg (3×1000 mg sachets) once per day (test-1 formulation) versus 1000 mg (1×1000 mg sachet) once per day (test-2 formulation) in healthy male and female volunteers, under fasting conditions. The overall design of the study is supported. the time points for blood samples collection are considered acceptable. The wash out period of 10 days appears acceptable, taking into account that the Test product T1/2 is 7±1 hours. The selection of the PK parameters is appropriate.

The statistical analysis did not show statistically significant differences between both treatment administered. The 90% confidence intervals of the ratios T1/T2, for AUC0-t and Cmax were inside the accepted bioequivalence criteria of 80.00-125.00%, therefore it can be agreed that equivalence with respect to extent of absorption between the Test2 and the Test1 formulation was shown. It can be agreed that the dose proportionality criteria were met.

To predict cerebrospinal fluid (CSF) and extracellular fluid (ECF) levetiracetam levels following administration of levetiracetam prolonged-release granules in comparison with Keppra IR, the applicant developed PBPK model.

Moreover, since data on concentrations of levetiracetam in the CSF was taken from Rambeck at al (2006), which included only 3 patients treated with levetiracetam, predictions based on the model cannot be considered informative. The assumptions that lower proportion of subjects treated with the test PR product will achieve Cminss concentrations compared to subjects treated with the reference product should therefore be treated with caution. However, given the limitations of the model and specificity of the target indication, predictions based on the model are not considered adequate to replace the therapeutic equivalence study**.**

The applicant performed a RWE study LESVILEVE/22/RWE-4, aimed to compare the proportion of subjects who were seizure-free for at least 24 weeks while receiving a stable dose of medication between new users of oral levetiracetam XR and new users of oral levetiracetam IR in the clinical practice. The study was non-interventional, retrospective, cohort study in new users of Levetiracetam IR or XR using a large national private claim registry from the US.

In total 428 and 442 subjects in the Levetiracetam XR and Levetiracetam IR cohorts, respectively, were included in the analysis.

The proportion of subjects free from seizures for at least 24 weeks while receiving stable dose of medication was higher for subjects who received Levetiracetam XR (49.8%) than levetiracetam IR (34.6%). Non-inferiority of levetiracetam XR compared with levetiracetam IR was shown.
The submitted RWD study evaluating non-inferiority between Keppra XR and Keppra IR is at best supportive but cannot be considered a replacement for a therapeutic equivalence study. Bias cannot be excluded as the study is non-randomized and lacks assay sensitivity. Moreover, it is questioned whether the appropriate patient population was included in the study. A large proportion of patients in both cohorts (around 30%) used concomitant anti-seizure medication (ASM) of which the impact on Keppra efficacy cannot be excluded. In addition, not every patient was ASM treatment naïve, between 30-40% of patients in the cohorts had at least one prior ASM. It is known that the chance of having drug resistant seizures increases with each previous ASM used, and it cannot be excluded that this could have impacted the results on the primary endpoint seizure freedom.

However, the results of the conducted analysis are not considered relevant for demonstration of the bridge between the test product and the reference product, since no results of studies conducted with the test product were included in the analysis.

Furthermore, the results of Study LVM-BEMD-14-LLV/23 showed that the TEST/REFERENCE Ctau.ss, geometric mean ratio was not within the acceptance criteria of 80.00-125.00% after multiple dosing. In the light of the results of Study LVM-BEMD-14-LLV/23, the results of the real-word evidence study LESVILEVE/22/RWE-4, aimed to compare the proportion of subjects who were seizure-free for at least 24 weeks while receiving a stable dose of medication between new users of oral levetiracetam XR and new users of oral levetiracetam IR in the clinical practice in the US appear not relevant for the current MAA. Predictions based on the PBPK model are not considered adequate to replace the therapeutic equivalence study**.**

From the quality point of view products cannot be recommended for approval.

A benefit/risk ratio comparable to the reference product therefore cannot be concluded.

The application contains inadequate quality and clinical data and the bioequivalence has not been shown.

4.1. Conclusions

The overall benefit /risk balance of Epixram is considered negative, given the major objection raised in the list of questions.