Amsterdam, 27 February 2020
EMA/666721/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Doxorubicin Hydrochloride Tillomed

International non-proprietary name: doxorubicin

Procedure No. EMEA/H/C/005194/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BE	Bioequivalence
CI	Confidence intervals
C_{max}	Maximum serum concentration
Cr	creatinine
CR	Complete response
CrCl	creatinine clearance
CRF	Case record form
CSR	Clinical study report
DOX	doxorubicin
EDQM	European Directory for the Quality of Medicines & HealthCare
GCP	Good clinical practice
Hb	haemoglobin
IIR	Integrated inspection report
INN	International nonproprietary name
IP	Investigative product
IV (i.v.)	Intravenous
KS	Kaposi's sarcoma
LSM	Least square means
MAA	Marketing Authorization Application
MM	Multiple myeloma
MO	Major objection
MPS	mononuclear phagocyte system
MR	minimal response
PD	Pharmacodynamic
PK	Pharmacokinetic
PLD	pegylated liposomal doxorubicin
PR	Partial response
QOL	quality of life
ROC	relapsed/recurrent ovarian cancer
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
$T_{1/2}$	Elimination half-life
TEARs	Treatment-emergent adverse reactions
TM	Trademark
t_{max}	Time to reach C_{max}
TTP	time to progression
Vss	volume of distribution at steady state
WBC	White blood cell

1. Recommendation

Based on the review of the data on quality, safety, efficacy, the application for Doxorubicin hydrochloride pegylated liposomal Tillomed:

- As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.
- For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.
- In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.
- For treatment of AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (<200 CD4 lymphocytes/mm^3) and extensive mucocutaneous or visceral disease.

  Doxorubicin hydrochloride pegylated liposomal Tillomed may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other anthracycline)

is not approvable since a "major objection" has been identified, which precludes a recommendation for marketing authorisation at the present time. The details of this major objection are provided in the List of Outstanding Issues (see section 5).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Outstanding Issues.

The major objection precluding a recommendation of marketing authorisation, pertains to the following principal deficiencies:

Due to the critical GCP findings related to the pivotal clinical study PCLPL-200-17, credibility of the PK results is questioned and thus, bioequivalence between test and reference product cannot be considered established.

Inspection issues

GMP inspection(s)

No GMP inspection is requested.

GCP inspection(s)

A request for GCP inspection was adopted for the clinical study PLCL 200 17. The inspection was conducted at one of the clinical sites (India) and at the bioanalytical lab (India)

New active substance status

N/A

Similarity with authorised orphan medicinal products

It is considered that Doxorubicin Hydrochloride Tillomed is not similar to Darzalex (daratumumab), Farydak (panobinostat), Imnovid (pomalidomide), Kyprolis (carfilzomib), Ninlaro (ixazomib citrate), Yondelis (trabectedin), Lartruvo (olaratumab), Mozobil (plerixafor), Zejula (niraparib) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The application is a hybrid application and refers to Adriamycin which contains doxorubicin hydrochloride 2 mg/mL solution for injection. Doxorubicin hydrochloride 2mg/ml solution for injection is authorised in the treatment of acute leukaemia, lymphomas, soft-tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours, in particular breast and lung carcinomas.

Adriamycin and Doxorubicin Hydrochloride Tillomed differ in terms of formulation as Adriamycin contains doxorubicin hydrochloride in a non-liposomal formulation while doxolipad contains doxorubicin hydrochloride in a pegylated liposomal formulation. As bioequivalence against the reference medicinal product was not feasible due to the differences in formulation, Caelyx, which contains doxorubicin hydrochloride in a pegylated liposomal formulation was considered as appropriate comparator to establish with respect to quality, non-clinical and clinical comparability. Doxorubicin Hydrochloride Tillomed is designed to have the same indications and posology as Caelyx®. According to the Summary of Product Characteristics (SmPC) of reference drug Caelyx® (SmPC of Caelyx, 2017), the approved posology for specific clinical indications is different in metastatic breast cancer, advanced ovarian cancer, progressive multiple myeloma and AIDS-related Kaposi's sarcoma. For breast and ovarian cancer, the dosing schedule is 50mg/m^2 once every 4 weeks. For the treatment of multiple myeloma, Caelyx® is administered at a dose of 30 mg/m^2 on day 4 of the bortezomib 3-week regimen and for AIDS-related Kaposi's sarcoma at a dose of 20 mg/m^2 every two-to-three weeks.

The applicant proposes the same indications and posology for their product as for Caelyx®.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Not applicable

2.1.3. Biologic features><Aetiology and pathogenesis

Not applicable

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Not applicable

2.1.5. Management

Not applicable

2.2. About the product

Pharmacological classification: Cytotoxic agents (anthracyclines and related substances), ATC Code L01DB01

Doxorubicin hydrochloride is a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius var. caesius*. The exact mechanism of the antitumour activity of doxorubicin is not known. It is generally believed that inhibition of DNA, RNA and protein synthesis is responsible for the majority of the cytotoxic effects. This is probably the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix thus preventing their unwinding for replication.

In the liposome formulation, doxorubicin hydrochloride is encapsulated in liposomes with surface-bound methoxypolyethylene glycol (MPEG). Pegylation protects liposomes from detection by the mononuclear phagocyte system (MPS), which increases blood circulation time.

Pegylated liposomal doxorubicin (PLD) is associated with less frequent neutropenia, alopecia and cardiotoxicity than conventional doxorubicin and has an improved pharmacokinetic profile including a slower plasma clearance and a reduced volume of distribution than conventional doxorubicin.

The extended circulation time enables the liposomes to better reach tissues with increased vascular permeability, such as tumours and specific skin areas.

Doxorubicin Hydrochloride Tillomed is indicated:

- As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.

- For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.

- In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.

- For treatment of AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (< 200 CD4 lymphocytes/mm3) and extensive mucocutaneous or visceral disease.

Doxorubicin Hydrochloride Tillomed may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other anthracycline).

Doxorubicin Hydrochloride Tillomed should only be administered under the supervision of a qualified oncologist specialised in the administration of cytotoxic agents.

2.3. The development programme/Compliance with CHMP Guidance/Scientific advice

The following relevant CHMP guidelines were followed.

- Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev 01, Corr
- Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product, EMA/CHMP/806058/2009/Rev. 02
- Pegylated liposomal doxorubicin hydrochloride concentrate for solution 2 mg/ml product-specific bioequivalence guidance, EMA/CHMP/800775/2017

No Scientific advice has been given by the EMA for this development.

National scientific advice was sought from the UK MHRA on 2018-01-16 (reference: 1731/Doxorubicin hydrochloride) to establish the quality, non-clinical and clinical data requirements for the development of this product, as per the current EU regulations and guidance. The MHRA agreed that published data supports linearity of the pharmacokinetics of liposomal doxorubicin in the dose range of 20-50 mg/m^2 and that bioequivalence studies performed with the 50 mg/m^2 dose are adequate to support a biowaiver for 20 mg/m^2 and 30 mg/m^2 doses.

General comments on compliance with GMP, GLP, GCP

GLP

The applicant states that the non-clinical single-dose PK study in mice has been conducted in compliance with GLP.

GMP

All the relevant GMP certificates are: (1) provided within Annexes, (2) valid (i.e. within the last 3 years) and (3) EUDRAGDMP DB traceable.

A QP declaration concerning GMP compliance of the AS manufacture is also provided in Annex 5.22.

GCP

The applicant stated that the clinical trial was conducted in accordance with the Principles of Good Clinical Practice.

A routine GCP inspection was carried out for Doxorubicin Hydrochloride Tillomed, at one investigator site and at the analytical laboratory where the blood samples were analysed. The inspection at the investigator site resulted in 2 critical and 9 major findings, the inspection at the analytical laboratory resulted in 2 critical and 7 major findings. Non-compliance that could affect the rights, safety and wellbeing of the patients or the credibility of the data was observed. The investigator site did not meet GCP requirements with regard to IMP handling, handling of the equipment and archiving of documents, hence there is concern that errors in dispensing could have jeopardized the validity of the pharmacokinetic data. The findings observed at the bioanalytical laboratory trigger serious concerns in relation to the plausibility and credibility of the reported PK concentrations, Therefore the inspectors recommended not using the reported data for the evaluation by the assessors.

Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:

Article 10(3) of Directive 2001/83/EC, as amended – "hybrid application" and Article 3(2)b of Regulation (EC) No 726/2004 – "Interest of patients".

The medicinal product under consideration, is a "hybrid version" of the reference medicinal product Adriamycin® 2 mg/mL Solution for Injection of Pfizer Aps Lautrupvang 8, 2750 Ballerup (authorised nationally in Denmark on 24th October 1979) and a "generic version" of the centrally authorised product Caelyx® 2mg/mL Concentrate for Solution for Infusion of Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse, Belgium. The latter is used for comparative physico-chemical, non-clinical and bioequivalence studies.

The applicant requests "essential similarity" of Doxorubicin Hydrochloride 2 mg/mL Concentrate for Solution for Infusion to Caelyx® 2 mg/mL Concentrate for Solution for Infusion of Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse, Belgium.

Product name

Following a number of reports of serious medication errors, some leading to death, and after consultation with EMA's safety committee (PRAC), the CHMP and CMDh agreed on actions to reduce the risk of mix-up between liposomal and non-liposomal formulations of the same active substance.

In the present application, CHMP requested that the product name should include a qualifier related to "pegylated liposomal" formulation. Furthermore, the EDQM standard term 'dispersion', which includes liposomes in its definition, should be used consistently throughout the product information (instead of "solution"). The applicant incorporated the respective qualifiers in the product name and amended the product information accordingly.

Orphan designation

Not Applicable

Similarity with orphan medicinal products

The application contained a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products. Assessment of these claims is appended.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The drug substance in this product is Doxorubicin hydrochloride. The "reference product" for the comparability exercise is Caelyx® from Janssen-Cilag.

The finished product is a liposomal formulation, provided as concentrate for solution for infusion containing 2 mg/ml of Doxorubicin Hydrochloride as active substance.

Other ingredients are sucrose, ammonium sulfate, MPEG 2000-DSPE sodium salt, cholesterol, HSPC (hydrogenated soya phosphatidylcholine), L-histidine, hydrochloric acid (pH adjustment), sodium hydroxide (pH adjustment) and water for injection.

The product is available in two packaging sizes: 10 mL or respectively 30 mL Type I, clear glass vial, stoppered with a 20 mm rubber stopper and sealed with a 20 mm MT flip off seal.

3.1.2. Active Substance

General Information

The quality of this active substance is covered by a CEP.

Active Substance (related to additional data provided by the applicant only)

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specification of Doxorubicin hydrochloride Ph.Eur. followed for testing by the drug product manufacturer is provided. Appearance, solubility, identification, pH, water content, optical rotation,

residue on ignition, chloride content, related substances, assay, residual solvents, bacterial endotoxins test and microbial enumeration tests & tests for specified microorganisms are tested. Limits are acceptable. Relevant information on control of the drug substance, respective analytical methods and verification of the analytical methods are provided.

Details of reference standard used by the drug product manufacturer is sufficiently documented.

Doxorubicin Hydrochloride is packed in amber glass bottles closed with screw caps inside a thermally welded polyester-aluminium-polyester-polypropylene (PAPP) bag and then inside an aluminium drum.

Stability

The stability of the drug substance is not covered by the provided CEP, therefore stability data on 60 months long term and 6 months accelerated conditions are provided. The retest period of 60 months for the drug substance is appropriate without storage condition.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Concerning pharmaceutical development, exhaustive information is provided. Starting with the drug substance, risk assessment is initially performed and updated and adapted throughout dossier section 3.2.P.2 based on respective study reports, which are provided. Reference to the Ph.Eur. monograph is made for the drug substance. All parameters mentioned in the respective monograph are considered in the development. Critical quality attributes are justified. Batch analyses from three batches of drug substance have been analysed. All initially high- and medium risk quality attributes are stated as adequately controlled. The applicant is stating that a control strategy for the drug substance is applied. Therefore, the conclusion after batch analyses was that the drug substance does not propose a critical risk. This argumentation cannot be fully supported as the risk does not change. However, although the risk remains the same (and is not reduced as indicated by the applicant), it is adequately controlled. The specification of the drug substance is adequately controlling the substance; hence no further control strategy has to be applied.

Used excipients are stated including their pharmaceutical function and the respective quantity thereof. Stability studies have shown that excipients are compatible with the drug substance and with each other.

The aim to achieve during formulation development is a generic drug product pharmaceutically equivalent to Caelyx. The initial process is described as hydration – size reduction by extrusion – ultrafiltration – drug loading and volume make up – filtration and filling. Therefore, an adequate control strategy based on risk assessment has been established. Risk assessment is based on literature and characterization studies. In the initial risk assessment, some parameters were regarded as high risk; justification for lowering the risk after characterization studies and/or adaption of the process is provided. This argumentation cannot be fully supported as the risk does not change. However, although the risk remains the same (and is not reduced as indicated by the applicant), it is adequately controlled. Two manufacturing process optimization studies have been performed – results thereof led to lowering the risk from the initial risk assessment. Process parameters have been identified and optimized which play a critical role for the adequate manufacture of the proposed drug product.

According to EMA/CHMP/CVMP/QWP/850374/2015, the proposed sterilisation method has to be justified. However, as it is obvious that liposomes are temperature-sensitive, higher temperatures would affect liposomes in their intactness and stability. Therefore, terminal sterilisation is not suitable for proposed drug product. No further questions on the proposed sterilisation method.

All manufacturing steps and used equipment are described. A risk assessment for compatibility study of bulk solution with different materials and stability studies at different pH, photostability study, thermal cycling study and bulk holding study at different stages of the manufacturing process) has been performed to identify the high risk steps that may affect the CQAs of the final drug product. With results of the compatibility study, the risk assessment of the formulation process has been updated and led to a prototype formulation, which is stable according to preliminary stability studies. Scale up was successfully performed. An exhibit batch has been manufactured which has been used for the pivotal BE study. All results comply with their respective limits. Test setup and equipment is regarded as acceptable as no variability within different batches is found. The proposed manufacturing process development is regarded as reasonable and justified.

According to EMA guidance EMA/CHMP/806058/2009/Rev.02, a range of relevant physicochemical properties of a liposomal product is regarded as critical to ensure its quality, therefore specific parameters need to be addressed. The applicant has considered all relevant parameters and studies have been performed sufficiently. The physicochemical characteristics of the proposed drug product are comparable to those of the reference product.

A risk assessment according to ICH Q3D has been performed. Elemental impurities are adequately controlled.

The intended packaging is mentioned. A leachable study has been performed with the equipment with the container closure system (glass vial and rubber stopper). All elements found are well within the limits defined by the guidance. Provided control strategy seems appropriate. Bacterial endotoxins, sterility and bioburden have been sufficiently investigated.

Compatibility of the proposed drug product with glass, metal, tubing, filter and rubber stopper has been shown. Moreover, compatibility with admixture diluent (5 % dextrose injection USP) for 24 hours and with material of IV administration set is shown. It is mentioned that no significant change was observed when stored in PVC and non-PVC bags.

Taken together data and information provided in pharmaceutical development section, the proposed drug product is regarded as pharmaceutically equivalent to Caelyx based on information provided in the dossier.

In view of recent discussions, an evaluation of the risk on presence of nitrosamine impurities in active substance (as well as in final drug product) has been submitted (see EMA/189634/2019). However, this has not been finalized and the applicant should provide the final risk assessment report including information from all product components.

Manufacture of the product and process controls

The name, address and responsibility of each manufacturer and each proposed production site involved in manufacturing and testing is stated. A batch formula is provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch and per ml basis, including a reference to quality standards. A flow diagram and a narrative description on the manufacturing process are depicted in the dossier.

All respective IPCs are mentioned including processing steps, testing parameters and acceptance criteria. Intermediates are clearly outlined in respective dossier section 3.2.P.3.4. Bioburden is tested as IPC on the unfiltered bulk solution with a limit of NMT 10 cfu/100 mL.

Process validation for three commercial scale batches for both packaging sizes is provided.

All critical process parameter ranges and observed parameters from each batch are provided. A schematic sampling plan indicating where, when and how samples were taken, is provided. Compliance of critical process parameters is demonstrated by means of batch data.

Data on filter validation are shown. E/L studies were performed accordingly including worst case scenario. Adsorption behaviour of the drug product with regard to filter material is discussed. All filter parameters are mentioned. The maximum holding time for bulk solution was validated. The maximum number of batches filtered, before the sterilisation filter is exchanged is indicated Sterilisation of the sterilisation filter, prior to its use is described Integrity of the sterilisation filter was demonstrated before and immediately after usage with a suitable method

Satisfactory retention capacity of the sterilisation filter has been demonstrated with regard to microbiological impurities.

Sucrose, ammonium sulfate, ethanol anhydrous, L-histidine, hydrochloric acid, sodium hydroxide, nitrogen and water for injection are compendial excipients,

For ammonium sulfate, this is regarded as acceptable as sufficient information including specification is provided. Histidine is monographed in the Ph.Eur and the quality of the used histidine complies with respective monograph (<01/2017:0911>). Full information on cholesterol is provided according to EMA/-CHMP/¬806058/¬2009/¬Rev.02 which is regarded as sufficient. Specification is appropriate as it is based on Ph.Eur. monograph and pesticides are controlled additionally by the manufacturer.

Stability testing showed that the substance is stable for 5 years if stored in the original container closure system and protected from light, when not exceeding 25°C.

All the excipients are well known and have been in use in the industry for a long time. Every batch of excipient received from the supplier is provided with a certificate of analysis confirming compliance to Ph.Eur. monograph (for compendial excipients). For excipients that are not monographed in European pharmacopoeia, the details of the specifications, test procedure, certificate of analysis and justification of specification is provided in respective section of the excipient information. No information on the admixture diluent dextrose is given. However, as this excipient is not part of the drug product and used in diluent mixture, information does not need to be indicated in the dossier. For the lipid excipients HSPC and MPEG 2000-DSPE, full documentation is provided.

The applicant has proposed additional information regarding an additional vial manufacturing line (line-2) As this is a non-standard process, full validation of the proposed manufacturing route at the additional vial manufacturing line (line-2) should be provided otherwise this process line is not acceptable (OC).

Product specification, analytical procedures, batch analysis

The specification contains all relevant parameters to sufficiently control the drug product for release and for shelf life. Identification for the drug substance and the lipid forming excipients are performed by HPLC. Contents of free, encapsulated and total doxorubicin and all relevant impurities originating from the drug substance and the lipids are controlled. In vitro release is controlled with a stability indicating method. Essential physical parameter particle size and zeta potential are listed and other parameters related to composition like sulfate and ammonium content as well as assay of sucrose and histidine are under control. Limits for assay and density in release and shelf-life specification are not acceptable yet as they are regarded as too wide. Therefore, mentioned limits should be tightened (OC). Taken together, the drug product specification is not acceptable yet.

Descriptions for all methods used to test the quality at release and at shelf life are provided. All analytical methods are validated according to ICH Q2. Former MO2 has been discussed adequately, therefore no open issues concerning analytical methods and validations thereof occur.

Data of several batches have been provided. All batches are from production size and are used as validation- as well as stability batches.

Potential degradation impurities are listed. Sufficient analytical data and comparison to the reference product is provided.

Provided information regarding reference standards is sufficient.

Stability of the product

Stability studies are started for three batches of each strength. Accelerated conditions (25°C ± 2°C/ 60 %RH ± 5 % RH) with 6 months data and long-term studies (2-8°C) for 24 months are provided leading to a proposed shelf-life of 24 months.

An obvious trend to lower values can be seen for the parameter assay. In correlation to this, an increase in impurities was observed. The content of free doxorubicin seems to decrease over time. All other parameters are stable and without any significant change. Justification on the storage restriction "do not freeze" is provided.

Post approval change management protocol(s)

Not applicable

Adventitious agents

Not applicable

GMO

Not applicable

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

Based on the review of the data on quality and the answers provided to the D180 LoOI, two concerns are still not sufficiently resolved. The release- and shelf-life specifications of the drug product are not regarded as acceptable and the assay limit should be tightened to actual batch data. The applicant should submit the validation report of the drug product manufacturing process (Line-2) or otherwise remove this additional manufacturing line from the description of the drug product manufacturing process.

The risk assessment on the potential presence of nitrosamine impurities should be revised to include relevant information from the active substance and excipients.

From a quality point of view the application could be approvable, provided that the open issues are adequately solved.

3.2. Non clinical aspects

3.2.1. Pharmacology

Doxorubicin belongs to the pharmaceutical class of anthracyclines and related substances and is used as a cytotoxic agent in oncologic indications. The exact mode of action is not known, however, it is assumed that the cytotoxic activity is exerted via inhibition of DNA, RNA and protein synthesis most probably by intercalation into DNA.

Formulation of doxorubicin in pegylated liposomes alters its pharmacokinetic properties: Circulation time in plasma is increased and compared with conventional doxorubicin tissue distribution is more targeted to tumour tissues, which is primarily attributed to increased vascular permeability within tumour tissue. It is therefore claimed that similar or lower doses of pegylated liposomal doxorubicin elicit lower toxicity but, at the same time, are equally or more efficient as conventional doxorubicin.

Doxorubicin Hydrochloride Tillomed was developed as a generic of a centrally authorized product for the same indications as the reference product. In line with this type of application, the applicant did not submit a full set of non-clinical studies, but supplied the majority of information as a summary of published literature. Thus, the pharmacodynamics section of the dossier is covered by bibliographic information exclusively. The "Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product" (EMA/CHMP/806058/2009/Rev. 02) recommends the conduct of non-clinical in vivo/in vitro studies on the pharmacodynamic response in support of the demonstration of similarity between test and reference product. No such studies have been submitted in the MAA dossier of Doxorubicin Hydrochloride Tillomed. However, a justification for the absence of these studies based on the quality and non-clinical tissue distribution studies has been provided with the D120 responses, which is regarded sufficient for this particular application. Similar pharmacodynamic performance can be concluded from the similarity between Doxorubicin Tillomed and Caelyx shown in the in vitro characterization studies as well as from the similar tissue distribution profiles in the comparative in vivo study

Essentially, the applicant reviewed in vitro and in vivo tumour model systems, in which pegylated liposomal doxorubicin has been proven to be efficacious and which are relevant for the intended indications. These model systems include multiple myeloma, breast cancer, osteosarcoma, ovarian cancer and lung carcinoma. It has been demonstrated in many of these models that the anti-tumour efficacy of liposomal doxorubicin exceeds that of conventional doxorubicin and is exerted at even lower doses. Moreover, published non-clinical studies point towards the property of liposomal doxorubicin to overcome multidrug resistance in cancer patients. An enhancing pharmacodynamic effect of doxorubicin has been observed when used in combination with other anti-cancer therapies.

Overall, the majority of non-clinical studies in various cancer models demonstrated a clearly longer survival of animals treated with pegylated liposomal doxorubicin as compared to conventional doxorubicin which is at the same time associated with less toxicity of the treatment.

Secondary pharmacology was also covered by a literature review, in which it was mentioned that pegylated liposomal doxorubicin (PLD) tends to be targeted to and to accumulate in arthritic joints in a rat rheumatoid arthritis model. Apart from that, it is known that PLD infusions can cause anaphylactic reactions. Moreover, literature references covering secondary pharmacodynamics and safety pharmacology have been provided.

Non-clinical studies on pharmacodynamic drug interactions are not available for liposomal doxorubicin. However, clinical data are available for the reference product indicating that the concomitant use of PLD with other chemotherapies potentially increases the toxicity of these therapies.

Overall, the literature review on the pharmacodynamic properties of pegylated liposomal doxorubicin is considered comprehensive and sufficient for the type of application.

3.2.2. Pharmacokinetics

Liposomal products are recognised to have formulation- and manufacturing-specific distribution characteristics after IV administration. To support the similarity claim of Doxorubicin Hydrochloride 2 mg/mL concentrate for solution for Infusion (Pegylated Liposomal Doxorubicin Hydrochloride) and the reference product Caelyx 2 mg/mL concentrate for solution for Infusion (pegylated liposomal Doxorubicin Hydrochloride), the applicant performed a GLP-compliant single dose in vivo PK study.

The study was conducted in male syngeneic fibrosarcoma bearing mice; two dose levels (2.4 mg/kg and 6.0 mg/kg) of two batches of the reference product and one batch of the test product were administered. The applicant's rationale for the selected dose levels for the in vivo tissue distribution study is based on the aim of achieving plasma levels relevant for/comparable to those of patients. Given that the human plasma AUC at a dose of 20 mg/m^2 is referred to as 1702.96, the mean plasma AUC achieved in the in vivo study of 2274 h▪µg/mL for the 2.4 mg/kg dose and 6417 h▪µg/mL for the 6 mg/kg dose are deemed sufficiently high.

Blood and samples of heart, liver, spleen, skin and tumour were collected at 0.5, 1, 4, 24, 48, 96, 168, 240 and 336 hours post-dose. Levels of free and encapsulated doxorubicin were determined in plasma only, whereas total doxorubicin and doxorubicinol were determined in all tissue samples.

The total number of animals treated per batch and time-point is considered sufficient for the purpose of the study; however, corresponding tissue samples of three mice per time-point were pooled prior to analysis, which is considered to reduce the variability of data and to conceal potentially existing differences.

The analytical methods for the estimation of free, encapsulated and total doxorubicin as well as doxorubicinol in mouse plasma and of doxorubicin and doxorubicinol in mouse tissues were validated according to the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009) and acceptance criteria are considered to be fulfilled.

Mean plasma AUC_{0-t} and T_{max} values for free doxorubicin were similar for all batches tested with the exemption of the reference batch G2 that generated significantly lower exposure at the 6 mg/kg dose level. Encapsulated doxorubicin was detected in plasma at similar levels in all experimental groups.

The mean AUC_{0-t} and T_{max} of total doxorubicin was comparable for both dose levels of the test formulation and the two reference batches in all tissues analysed except for tumour tissue, where the AUC was significantly lower for one of the two reference batches (G2) at both dose levels. Similarly, the mean AUC_{0-t} was comparable between all batches in all tissue except for tumour tissue. In line with the results for total doxorubicin, the levels of doxorubicinol were significantly lower in tumour tissue for one of the reference batches (G2), however, only at the 2.4 mg/kg dose level. Of note, the results of the PK analysis do not point towards accumulation of either of the tested batches in any tissues and, thus, do not raise any toxicological concern.

No data on metabolism or excretion have been generated from the conducted in vivo study.

No studies on pharmacokinetic drug interactions have been conducted. However, literature-derived information on a known pharmacokinetic drug interaction, i.e. increased AUC and decreased clearance of doxorubicin if co-administered with multidrug resistance modulators, were provided.

In summary, the scope of product specific data provided is limited to a single comparative tissue distribution study.

3.2.3. Toxicology

The present dossier for Doxorubicin Hydrochloride Tillomed is submitted as a hybrid application. Therefore, the majority of the information provided on the active substance is based on published scientific literature.

The applicant did not perform dedicated toxicity studies for Doxorubicin Tillomed, but observation for clinical safety signs was included in the performed pharmacokinetics study in humans, which did not reveal any adverse events. In general, it is agreed that toxicity studies may not be needed.

With regard to complement activation-related pseudoallergy (CARPA) the applicant argues that complement activation by liposomal doxorubicin is dependent on dose and dose rate. Therefore, an appropriate note for the administration of Doxorubicin Tillomed was included into the SmPC. Moreover, it was stated that quality attributes such as liposomal surface charge and liposome shape – influenced by the presence of a drug such as doxorubicin - importantly contribute to complement activation. Comparative analysis of these parameters with the reference product demonstrated high similarity and comparative variability between the batches of the same product with respect to surface charge and liposome shape. In general, non-clinical studies point towards a reduction of toxicities of liposomal formulations as compared with standard doxorubicin formulations. Most importantly, this applies to myelotoxicity, cardiotoxicity and nephrotoxicity. In addition, dermal lesions appear to be less severe after treatment with liposomal doxorubicin. These published non-clinical study results are in line with clinical observations (Rafiyath et al., 2012).

From the PK data provided, no signs of Doxorubicin Hydrochloride Tillomed accumulation in any organ investigated, consequently leading to toxicity, were observed.

The known genotoxic, clastogenic and carcinogenic properties of doxorubicin were also covered by bibliographic information and no specific studies were performed.

In terms of reproductive and developmental toxicity, a summary of literature on adverse findings on the male reproductive tract was provided; no specific studies were performed by the applicant.

As far as non-clinical topics are concerned, the SmPC wording corresponds to that of the reference product.

3.2.4. Ecotoxicity/environmental risk assessment

According to the EMA "Guideline on the Environmental risk assessment of Medicinal products for Human Use" (EMA/HMP/SWP/4447/00 corr. 2) "an environmental risk assessment (ERA) is required for all new marketing authorisation applications for a medicinal product through a centralised, mutual recognition, decentralised or national procedure". Therefore, the applicant followed the recommendations laid down in the Q & A on the Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/44609/2010 Rev.1) and provided sales data for the reference product Caelyx. These data do not point towards an increased consumption of the particular product. However, for the purpose of estimating the development of the consumption in the scope of an ERA, consumption data for the totality of products containing doxorubicin would be required.

Apart from the sales data the applicant provided the log K_{ow} value for doxorubicin and conducted a Phase I risk assessment and, triggered by the PEC value of 0.45 µg/L, a Phase II risk assessment. The ratio of PEC/PNEC was evaluated based on a published PNEC derived from a Daphnia magna test and resulted in a value below 1.

Based on the risk assessment provided Doxorubicin Tillomed is considered not to pose a risk to the environment.

3.2.5. Discussion on non-clinical aspects

In compliance with the requirements of a hybrid application, the majority of non-clinical information was provided in a bibliographical form.

A literature-based discussion on the proposed mode of action and the specific pharmacodynamic and pharmacokinetic properties of pegylated liposomal doxorubicin was provided. For this purpose a variety of in vivo tumour models in which pegylated liposomal doxorubicin proved to be efficacious were described. In view of the existing clinical experience with conventional and liposomal doxorubicin the applicant did not conduct in vivo pharmacology studies.

Formulation and manufacturing can influence the distribution characteristics of liposomal products. To investigate potential differences regarding the distribution characteristics between test and reference product, the applicant performed a comparative single-dose pharmacokinetics study, in accordance with the "Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product" (EMA/CHMP/806058/2009/Rev. 02). The study was conducted in male syngeneic fibrosarcoma bearing mice involving two batches of the reference product Caelyx and one batch of Doxorubicin Hydrochloride Tillomed 2 mg/mL concentrate for solution for infusion. Notwithstanding some weaknesses of the study, it can be concluded that tissue levels of test and reference product were largely comparable, and no observations triggering safety concerns were made.

The more recent product-specific guidance *"Pegylated liposomal doxorubicin hydrochloride concentrate for solution 2 mg/ml product-specific bioequivalence guidance"* (EMA/CHMP/800775/2017) recommends a stepwise approach to demonstrate bioequivalence. The decision on the extent of non-clinical studies needed in addition to the quality- and clinical data should be made on a case-to-case basis. For the present application, in principle, a single comparative non-clinical PK study could be considered sufficient in view of the totality of quality and in vitro data, provided that in vivo bioequivalence is shown in an adequate clinical study.

In terms of toxicology, it is acknowledged that standard doxorubicin and pegylated liposomal doxorubicin have been extensively studied and the applicant provided a comprehensive review on the published data. With regard to complement activation related pseudo-allergy (CARPA), a potential adverse event common to liposomal doxorubicins, no increased risk was concluded from the quality attributes of Doxorubicin Tillomed. In this context, a precautionary note was included into the SmPC.

3.2.6. Conclusion on non-clinical aspects

Overall, the applicant submitted a comprehensive, albeit largely bibliographical, data package on the pharmacology, pharmacokinetics and toxicology of Doxorubicin Hydrochloride Tillomed 2 mg/mL concentrate for solution for infusion. The provided in vivo data are considered supportive for the claimed similarity to the reference product.

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

Study/Sponsor	Design	Population	Reference Drug	Location	Subjects	Test Dosage
PCLPL-200-17/ Emcure Pharmaceuticals Ltd.	Multicentre, Open label, Randomized, Two-treatment, Two-period, Two-sequence, Single dose, Two-way crossover Bioequivalence study	Female patients with advanced ovarian cancer	Caelyx 2 mg/mL solution for infusion	India	67 patients were enrolled and 59 were considered for BE	50 mg/m²

The pivotal clinical study for this hybrid application was a bioequivalence study comparing the PK of Doxorubicin Hydrochloride Tillomed with Caelyx as reference product. No other clinical studies were performed.

3.3.1. Pharmacokinetics

The bioequivalence study compared the applicant's product Doxorubicin Hydrochloride 2 mg/mL concentrate for solution for infusion of Emcure Pharmaceuticals Ltd., India, with Caelyx® 2 mg/mL Concentrate for Solution for Infusion of Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse, Belgium.

The study was carried out by a CRO (India), project no. **PCLPL-200-17**.

The BE study was a multicentre, open label, randomized, two-treatment, two-period, two-sequence, single dose, two-way crossover study. The study population consisted of female patients with advanced ovarian cancer who had failed a first-line platinum-based chemotherapy regimen and/or were already receiving or scheduled to start therapy with liposomal doxorubicin hydrochloride.

Each subject received a single dose of doxorubicin hydrochloride liposome concentrate for solution for infusion (2 mg/mL) at a dose of 50 mg/m^2, obtained from 20 mg/10 mL vials of both Test and Reference product, according to the randomization scheme.

Drug products were administered as intravenous infusion via infusion pump over a 60 minutes (± 5 minutes) period, under yellow monochromatic light (or) sodium vapour lamp (or) low yellow light, and after a supervised overnight fasting of at least 10 hours. To subjects in whom health conditions prevented fasting, a standard (non-high-fat) diet was provided at least 2 hours prior to dosing.

The dose of doxorubicin hydrochloride liposome injection for individual subject was period specific and was calculated according to body surface area using appropriate formula (Du Bois method):

$$\text{Body Surface Area } (m^2) = 0.007184 \times \text{Weight}(kg)^{0.425} \times \text{Height}(cm)^{0.725}$$

For the majority of subjects, dosing differences between the two periods were between [-0.5 to 0.5 mg], with 33 subjects presenting no dosing differences.

As the recommended dosage interval of doxorubicin hydrochloride is every 4 weeks, two consecutive treatment cycles were used for the two treatment periods. The washout period was therefore 28 days.

A total of 25 blood samples (1 × 5 mL) were collected in each period. Blood samples were collected at pre-dose (0.00 within 02 hrs prior to dosing) and post dose at 00.17, 00.33, 00.50, 00.67, 00.83, 01.00, 01.08, 01.25, 01.50, 01.75, 02.00, 03.00, 04.00, 06.00, 08.00, 12.00, 24.00, 48.00, 96.00, 144.00, 192.00, 240.00, 288.00 and 336.00 hours. Blood sample collection at 01.00 hour was carried out immediately after the completion of infusion. Blood samples at 48.00, 96.00, 144.00, 192.00, 240.00, 288.00 and 336.0 hours blood draw were collected as ambulatory blood draw.

Pharmacokinetic (PK) parameters C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, $t_{1/2}$, k_{el}, AUC_{0-48hr}, $AUC_{48-336hr}$, $AUC_{\%\ Extrapolated}$, V_d and CL were calculated using plasma concentration *versus* time profile data for both the test and reference products obtained from individual subjects.

The following parameters were calculated for total doxorubicin, free doxorubicin and liposome encapsulated doxorubicin:

C_{max}	Maximum measured plasma concentration following each treatment.
AUC_{0-t}	The area under the plasma concentration versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method.
$AUC_{0-\infty}$	The area under the plasma concentration versus time curve from time zero to infinity. Where $AUC_{0-\infty} = AUC_{0-t} + C_t/k_{el}$, C_t is the last measurable concentration and kel is the terminal elimination rate constant.
T_{max}	Time to reach the maximum concentration of drug in plasma.
AUC_{0-48hr}	The area under the plasma concentration versus time curve from time zero to concentration at 48 h as calculated by linear trapezoidal method
$AUC_{48-336hr}$	The area under the plasma concentration versus time curve from time 48 h to concentration at 336 h as calculated by linear trapezoidal method
k_{el}	First order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration. This parameter was calculated by linear least squares regression analysis using at least last three or more non-zero plasma concentration values**.**
$t_{1/2}$	Terminal half-life as determined by quotient $0.693/k_{el}$
% $AUC_{extrapolation}$	$(1-(AUC_{0-t} / AUC_{0-\infty}))*100$
V_d	Clearance / k_{el}
CL	Dose / $AUC_{0-\infty}$

C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were assessed as primary parameters for free doxorubicin, encapsulated doxorubicin and total doxorubicin.

Furthermore, all PK parameters listed above were evaluated for the primary metabolite doxorubicinol.

PK parameters were calculated by non-compartmental methods for free doxorubicin, liposome encapsulated doxorubicin, total doxorubicin and doxorubicinol using Phoenix WinNonlin v 8.1. PK parameters AUC_{0-t}, AUC_{0-48h}, AUC_{0-336h} were calculated by the linear trapezoidal method. C_{max} and t_{max} were based on the actual data. The apparent first-order terminal elimination constant (k_{el}) was calculated from the semi-log plot of the plasma concentration versus time curve for each analyte. The parameter was calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (three or more non-zero plasma concentrations). Parameter AUC_{0-inf} was calculated as the sum of AUC_{0-t} plus the ratio of the last measurable plasma concentration to the k_{el}. The elimination $t_{1/2}$ was calculated as (ln 2)/k_{el}.

Sample size and randomization

The sample size was calculated from the published literature, based on an intra-subject CV of ~28%.

Parameters	**C_{max}**
T/R (%)	95% - 105%
Intra-Subject CV (%)	28
Significance Level (%)	5
Power (%)	80
Bioequivalence Limits (%)	80.00-125.00

The sample size calculation resulted in 28 patients per treatment group.

All subjects were randomized to two treatment sequences (TR and RT) as per the randomization schedule generated by the biostatistician prior to conduct of the study.

Handling of missing data

Any missing sample (MS) or non-reportable values (NRV) of the plasma concentration data were treated as 'missing values'. Such missing values were to be represented as MS and NRV in the plasma concentration tables. These missing values were not to be included in pharmacokinetic and statistical analysis. Patients were to be excluded if there were less than three quantifiable concentrations in any period. Concentration data of withdrawal/ drop-out patients were not to be considered for pharmacokinetics and statistical analysis.

According to the study protocol, patient data where the pre-dose concentration was ≤5 percent of C_{max} value were to be included in all pharmacokinetic measurements and calculations without any adjustments. Patients were to be excluded if there were less than three quantifiable concentrations in any period. Concentration data of withdrawal/ drop-out patients were not to be considered for pharmacokinetics and statistical analysis.

Statistical analysis

Statistical analysis for establishing bioequivalence was carried out using the software SAS Version 9.4. Least square mean differences (Test to Reference) of the test to reference formulation for the log-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Free doxorubicin, Liposome encapsulated doxorubicin and Total doxorubicin were estimated using SAS procedure.

ANOVA was performed on log transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Free doxorubicin, Liposome encapsulated doxorubicin and Total doxorubicin α (level of significance)

0.05 using SAS procedure. The analysis of variance model included terms Sequence, Subject (Sequence), Period and Treatment as fixed effects.

Analysis of variance also included calculation of least-square means, adjusted differences between formulation means and the standard error associated with these differences.

Analysis sets:

Statistical analysis were to be performed on pharmacokinetic data of Free doxorubicin, Liposome encapsulated doxorubicin, Total doxorubicin and Doxorubicinol using the SAS® package (SAS® Institute Inc., USA and Version 9.4 or higher). The data of all patients completing the study successfully were to be subjected to statistical analysis (PK analysis population).

Demographic and other baseline characteristics:

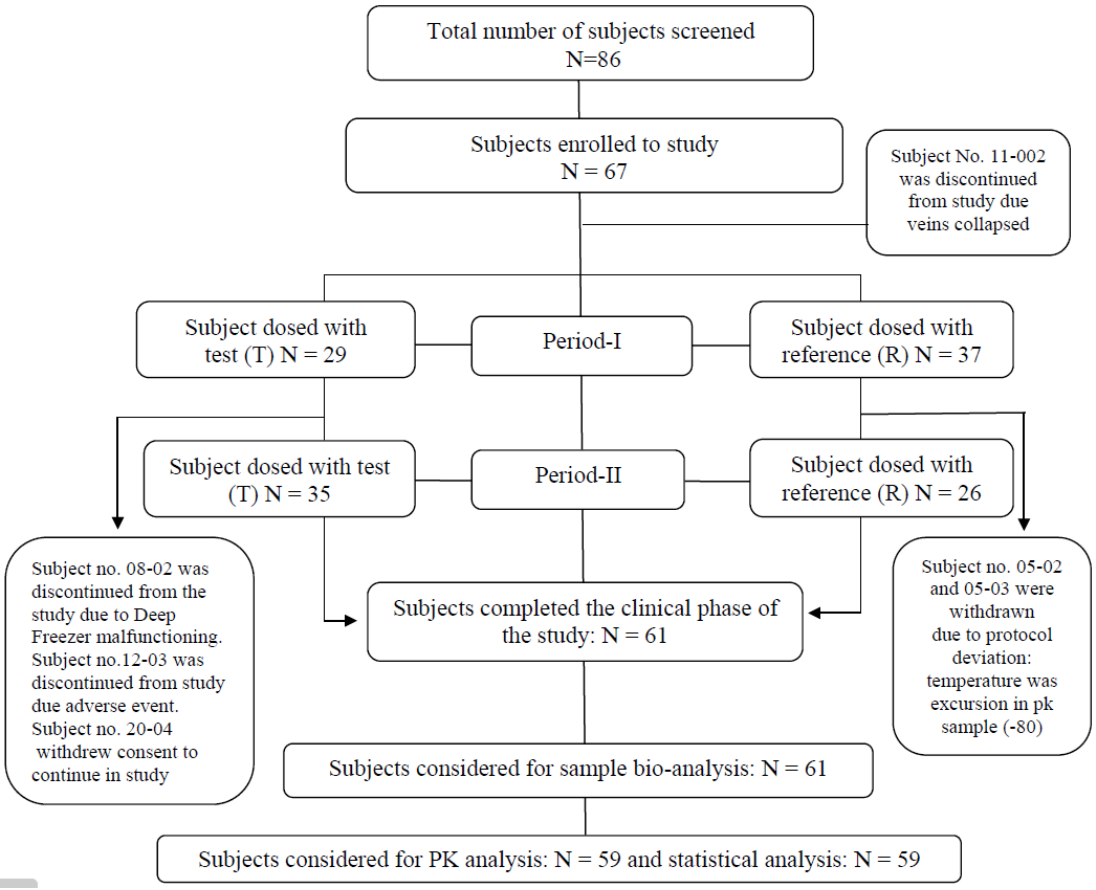
The study population in the clinical phase of the study was 67 female patients with ovarian cancer with a mean age 51.49 ± 9.08 years, mean height of 151.33 ± 5.46 cm, mean weight of 54.61 ± 10.12 kg and mean BMI of 23.81 ± 4.13 kg/m^2. The study population included in the PK and statistical analysis (n = 59) had similar parameters: mean age 51.72 ± 9.13 years, mean height of 151.48 ± 5.63 cm, mean weight of 54.57 ± 10.45 kg and mean BMI of 23.75 ± 4.26 kg/m^2.

According to the applicant, all the subjects admitted into the study fulfilled all the inclusion criteria and none of the exclusion criteria. All the subjects were of normal health based on general physical examination and laboratory test reports.

Disposition of subjects:

A total of 86 subjects were screened across 18 sites. Of these, 67 subjects were randomized in the study to have 56 evaluable subjects as per requirements of study protocol. Of 67 randomized subjects, 61 subjects completed the clinical phase of study, and 59 were considered for PK and statistical analysis.

The following flowchart describes the number of subjects who were screened, enrolled and completed the study:



The following table displays the list of discontinued subjects and reason for withdrawal.

Subject. No.	Period Completion status	Time of Exclusion	Reason for exclusion	Considered for Bio analysis	Considered for Pharmacokinetic and Statistical Analysis
05-01	Period-I and II completed	Clinical phase completed	Subject No. 05-01 was excluded from the bioanalysis as the storage condition for plasma samples at the clinical site was not maintained as per protocol requirements (-70±10°C).	No	No
05-02	Period I completed, Not dosed in period-II	Not dosed in period-II and withdrawn from study	Subject No. 05-02 was excluded from the bioanalysis as the storage condition for plasma samples at the clinical site was not maintained as per protocol requirements (-70±10°C).	No	No
05-03	Period I completed, Not dosed in period-II	Not dosed in period-II and withdrawn from study	Subject No. 05-03 was excluded from the bioanalysis as the storage condition for plasma samples at the clinical site was not maintained as per protocol requirements (-70±10°C).	No	No
08-01	Period-I and II completed	Clinical phase completed	Subject No. 08-01 was excluded from the bioanalysis as the storage condition for plasma samples at the clinical site was not maintained as per protocol requirements (-70±10°C).	No	No
08-02	Period I completed, Not dosed in period-	Not dosed in period-II and withdrawn from study	Subject No. 08-02 was excluded from the bioanalysis as the storage condition for plasma samples at the clinical site was not maintained as per protocol requirements (-70±10°C).	No	No

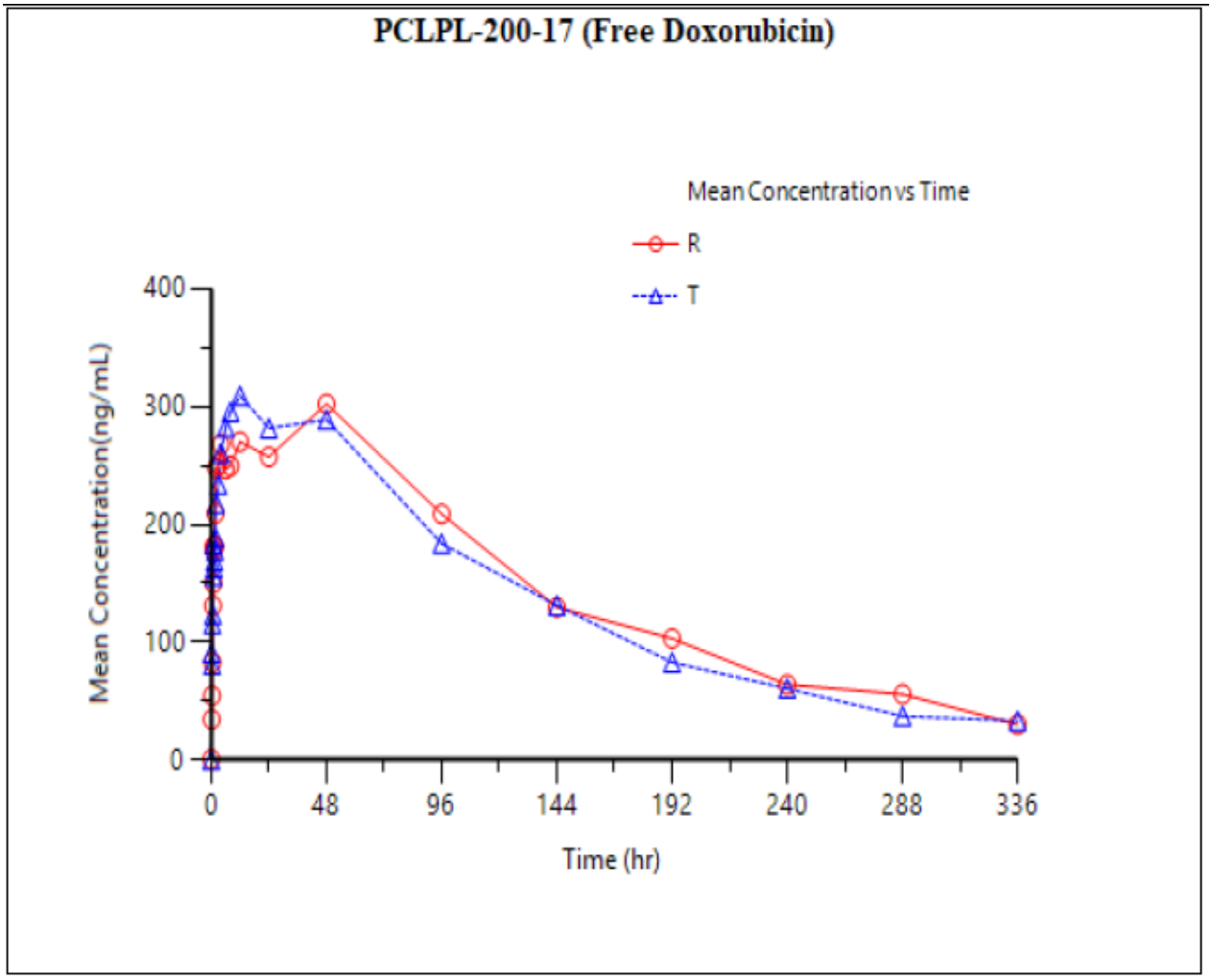
Subject. No.	Period Completion status	Time of Exclusion	Reason for exclusion	Considered for Bio analysis	Considered for Pharmacokinetic and Statistical Analysis
	II				
11-02	None	Period-I and II Not completed	Subject No. 11-02 was not dosed in period-I due to veins collapsed (difficulty in cannulation) and hence withdrawn from study.	No	No
12-03	None	Withdrawn after 0.17 hrs. blood sample collection in period I	Subject No. 12-03 was withdrawn from study after 0.17 hrs. blood sample collection in period-I, due to occurrence of Serious Adverse Event (SAE), All the collected samples of subject no. 12-03 were analysed, but data were not included in Pharmacokinetic and statistical analysis as subject has not completed the study.	Yes (Available samples analysed)	No
20-04	None	Discontinued in period I	Subject No. 20-04 withdraw consent to participate in study. Last blood sample collection was 192.00 hrs in period-I. All the collected samples of subject no. 20-04 were analysed, but data were not included in Pharmacokinetic and statistical analysis as subject has not completed the study.	Yes (Available samples analysed)	No

Protocol deviations:

Protocol deviations are listed in Appendix 16.2.2 of the study report. According to the study report, they "did not have any significant impact on the outcome of the study".

Results – Primary parameters:

Mean plasma concentration (ng/mL) of **Free Doxorubicin** vs. Time (h) plot for Test (T) and Reference (R) formulations:



% extrapolated AUC was more than 20% for the following subjects:

Treatment R: 01-03 (in Period II), 13-01(P-II), 20-03 (P-I)
Treatment T: 06-10 (P-I), 09-01 (P-II), 09-03 (P-II), 17-03 (P-II)

In one case, C_{max} was observed at the first measured time point: subject 10-01 in treatment T (P-II).

No pre-dose sample was >5% C_{max}.

Table No. 20A: ANOVA Summary Table - Free doxorubicin

Free doxorubicin			
Parameters	**ANOVA p-values***		
Effects	**Cmax**	**AUC0-t**	**AUC0-∞**
Sequence	0.9015	0.9299	0.8366
Period	0.9721	0.6820	0.5057
Formulation	0.9222	0.6543	0.6834

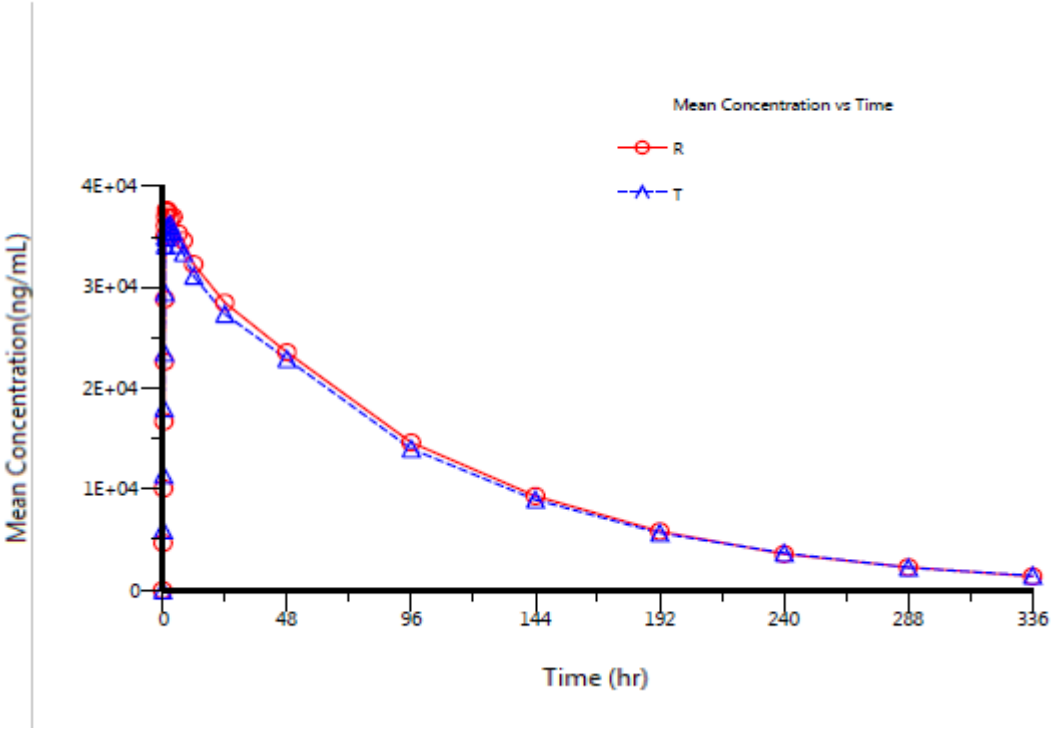
*** Effect was tested at 5% level of significance. **If p-value is < 0.05 it was considered significant**

In response to the D180 LoOI, the ANOVA of AUC0-∞ for free doxorubicin was repeated including data from only 54 subjects, for whom data are available for both products (test and reference). This did not

result in significant ANOVA p-values for the parameters listed above and did not change the overall notion of bioequivalence for this analyte.

Mean plasma concentration (ng/mL) of **Liposome encapsulated doxorubicin** vs. Time (h) plot for Test (T) and Reference (R) formulations:

PCLPL-200-17 (Liposome encapsulated doxorubicin)



% extrapolated AUC was more than 20% for the following subjects:

Treatment R: 23-02 (P-II) and 23-04 (P-I)
Treatment T: 10-01 (P-II), 23-03 (P-I), 23-04 (P-II)

No pre-dose sample was >5% C_{max}.

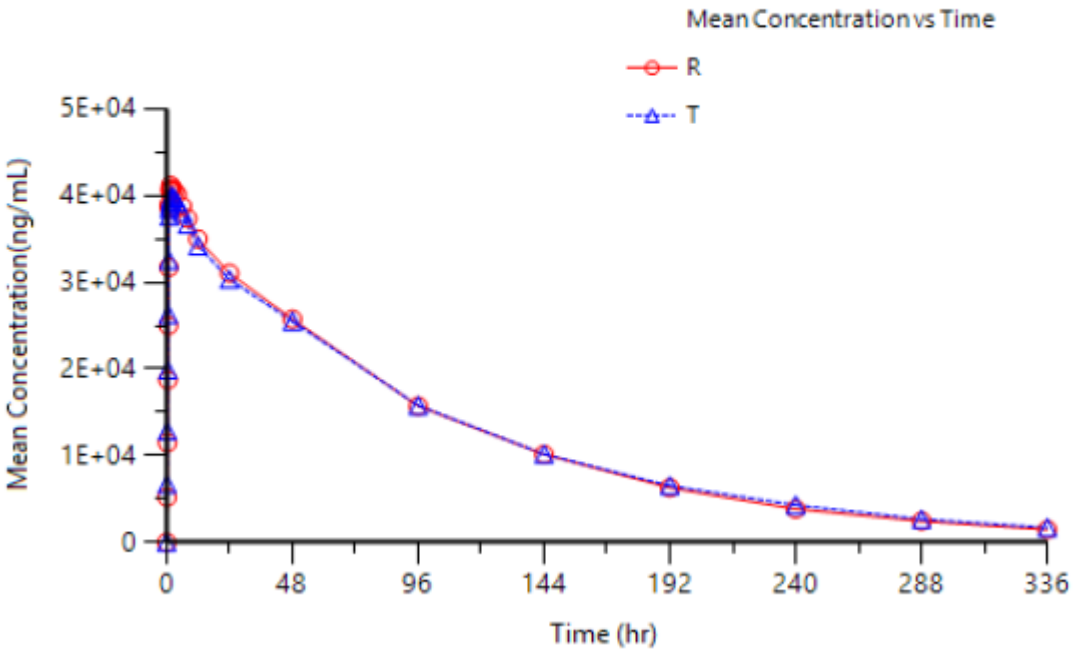
Table No. 20B: ANOVA Summary Table - Liposome encapsulated doxorubicin

Liposome encapsulated doxorubicin			
Parameters	**ANOVA p-values***		
Effects	**C_{max}**	**AUC_{0-t}**	**$AUC_{0-\infty}$**
Sequence	0.6661	0.7245	0.5455
Period	0.1213	0.4264	0.2287
Formulation	0.9001	0.5686	0.5034

*** Effect was tested at 5% level of significance. If p-value is < 0.05 it was considered significant**

Mean plasma concentration (ng/mL) of **Total Doxorubicin** vs. Time (h) plot for Test (T) and Reference (R) formulations:

PCLPL-200-17 (Total Doxorubicin)



% extrapolated AUC was more than 20% for the following subjects:

Treatment R: 23-02 (P-II) and 23-04 (P-I)
Treatment T: 10-01 (P-II), 23-03 (P-I), 23-04 (P-II)

No pre-dose sample was >5% C_{max}.

Table No. 20C: ANOVA Summary Table – Total Doxorubicin

Total doxorubicin			
Parameters	**ANOVA p-values***		
Effects	**C_{max}**	**AUC_{0-t}**	**$AUC_{0-\infty}$**
Sequence	0.5959	0.9720	0.8839
Period	0.0609	0.4255	0.4367
Formulation	0.9494	0.7062	0.3661

*** Effect was tested at 5% level of significance. **If p-value is < 0.05 it was considered significant**

The test by reference geometric least square mean ratio and 90% confidence interval obtained for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for the three primary analytes are as follows:

Parameter	**Geometric Least Squares Mean Ratio (T/R) % (N=59*)**	**90% Confidence Interval**

Free doxorubicin		
Cmax	100.71	89.41 - 113.44
AUC_{0-t}	96.92	86.40 - 108.72
$AUC_{0-\infty}$	100.91	89.20 - 114.16
Liposome encapsulated doxorubicin		
Cmax	99.37	91.44 - 107.98
AUC_{0-t}	97.59	90.96 - 104.70
$AUC_{0-\infty}$	97.83	92.69 - 103.25
Total doxorubicin		
Cmax	100.32	92.40 - 108.92
AUC_{0-t}	101.97	93.64 - 111.05
$AUC_{0-\infty}$	104.33	96.61 - 112.66

* N=54 for $AUC_{0-\infty}$ of Free doxorubicin

The coefficients of variation (CV (%)) corresponding to intra-subject variability C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 40.15%, 38.65% and 39.71% for Free doxorubicin, 27.52%, 23.14% and 17.65% for Liposome encapsulated doxorubicin and 27.20%, 28.24% and for Total doxorubicin.

Partial AUCs for liposomal encapsulated doxorubicin

Partial AUCs (AUC_{0-48h} and $AUC_{48-336h}$) for liposomal encapsulated doxorubicin are required according to guidance "Pegylated liposomal doxorubicin hydrochloride concentrate for solution 2 mg/mL product-specific bioequivalence guidance", which was only adopted after protocol finalisation. Therefore, additional statistical tests were performed on this parameter and the data provided in an addendum to the study report.

Geometric Least Squares Mean and its ratio (T/R), Intra subject CV (%), 90% confidence interval and Power for AUC_{0-48h} and $AUC_{48-336h}$ for Liposome encapsulated doxorubicin are presented in the following table:

Liposome encapsulated doxorubicin						
Parameter (units)	Geometric Least Squares Mean (N = 59)			90% Confidence Interval	Intra-Subject Variability CV (%)	Power (%)
	Test (T)	Reference (R)	% Ratio (T/R)			
AUC_{0-48} (ng.hr/mL)	1307718.30	1318719.92	99.17	91.35% - 107.65%	27.14	99.72
AUC_{48-336} (ng.hr/mL)	1974304.34	2022036.07	97.64	91.17% - 104.57%	22.55	99.98

ANOVA Summary Table for Liposome encapsulated doxorubicin:

Liposome encapsulated doxorubicin		
Parameters	**ANOVA p-values***	
Effects	**AUC_{0-48}**	**AUC_{48-336}**
Sequence	0.7503	0.5594
Period	0.2067	0.3998
Formulation	0.8666	0.5670

*** Effect was tested at 5% level of significance. If p-value is < 0.05 it was considered significant**

The p-values obtained from ANOVA for sequence, period and formulation effects were greater than 0.05 for AUC_{0-48} and AUC_{48-336} for Liposome encapsulated doxorubicin, which indicates that sequence, period and formulation effects were statistically not significant at 5% level of significance.

Results – Secondary parameters:

The secondary PK parameters comprised t_{max}, $t_{1/2}$, k_{el}, AUC_{0-48hr}, $AUC_{48-336hr}$, $AUC_{\%\ Extrapolated}$, V_d and CL – for details please refer to the Clinical Assessment Report.

Secondary pharmacokinetic data were presented for all three forms of doxorubicin and for the metabolite doxorubicinol.

Mean plasma concentration (ng/mL) of **Doxorubicinol** vs. Time (h) plot for Test (T) and Reference (R) formulations:

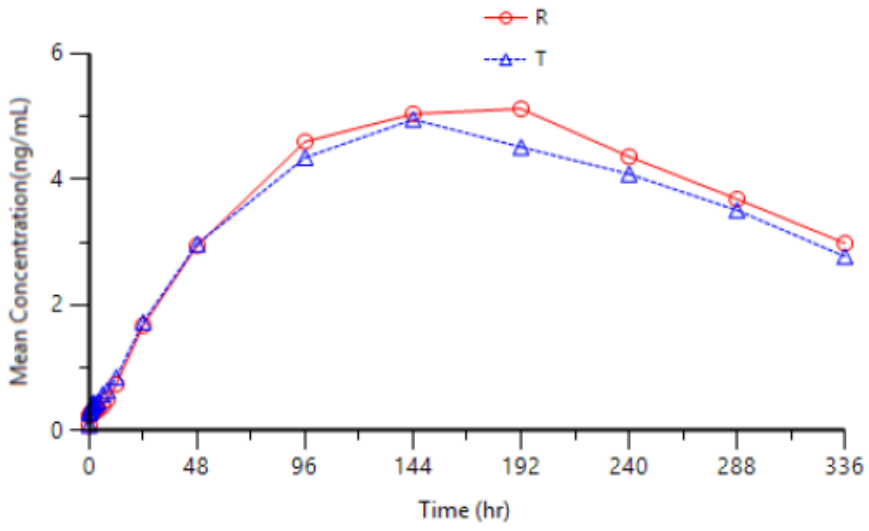


Table No. 20D: ANOVA Summary Table – Doxorubicinol

Doxorubicinol			
Parameters	**ANOVA p-values***		
Effects	**C_{max}**	**AUC_{0-t}**	**$AUC_{0-\infty}$**
Sequence	0.4542	0.3760	0.9799
Period	0.4764	0.4973	0.5514
Formulation	0.7960	0.3864	0.9617

*** Effect was tested at 5% level of significance. If p-value is < 0.05 it was considered significant**

The test by reference geometric least square mean ratio obtained for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for doxorubicinol are as follows:

Parameter	**Geometric Least Squares Mean Ratio (T/R) %**	**90% Confidence Interval**
Doxorubicinol		
C_{max}	98.96	Not analysed
AUC_{0-t}	96.26	Not analysed
$AUC_{0-\infty}$	99.63	Not analysed

Only 54 and 46 subjects were available for AUC_{0-inf} of doxorubicinol with reference and test product, respectively.

However, among others, the final GCP inspection states that, "Due to the lack of documentation of the actual dispensing of the IMP and its quality control measures it could not be verified, whether the dispensing was correctly done and whether the patients received the correct dose. Hence, there is a concern that errors in dispensing have jeopardized the validity of the pharmacokinetic data." Therefore the validity of the above described primary and secondary PK results is questionable.

3.3.2. Pharmacodynamics

Not applicable.

3.3.3. Discussion on clinical pharmacology

The pivotal clinical study for this hybrid application is a bioequivalence study to establish essential similarity between Doxorubicin Hydrochloride Tillomed and the reference product Caelyx®.

The design of the BE study (randomised, two-period, two-sequence, single dose, crossover) is in line with the requirements outlined in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01 – January 2010) and thus appropriate. The CHMP guidance for "Pegylated liposomal doxorubicin hydrochloride concentrate for solution 2 mg/ml product- specific bioequivalence guidance (EMA/CHMP/800775/2017)" was also taken into account.

The analytical methods for the determination of Doxorubicinol, free doxorubicin, total doxorubicin and liposomal doxorubicin in K_2EDTA human plasma as well as respective validations are described adequately; acceptance criteria are within a plausible range and were fulfilled. The bioanalytical methods demonstrate acceptable performance and are suitable for the determination of Doxorubicinol, free doxorubicin, total doxorubicin and liposomal doxorubicin in K_2EDTA human plasma over the calibration ranges.

Considering the pharmacokinetic profile of the reference product Caelyx (apparent half-life 45.2 to 98.5 hours in breast cancer patients according to Caelyx SmPC, 2017) the washout period of 28 days was more than 5 half-lives and is considered long enough to avoid potential carry-over effects.

The test by reference geometric least square mean ratios including 90% confidence intervals were provided for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for the three analytes free Doxorubicin, liposome encapsulated Doxorubicin and total Doxorubicin.

The results are well in line with the acceptance criteria set in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) and support the notion of bioequivalence between the reference and test product. The statistical analysis by ANOVA model on log transformed pharmacokinetic parameters with Sequence, Subject (Sequence), Period and Treatment as fixed effects is appropriate and in line with the above Guideline. It should however be noted that non-significance of the results does not fully exclude any sequence, period or treatment-by-period interactions due to the possible low power of the test.

Secondary pharmacokinetic data were presented for all three forms of doxorubicin and for the metabolite doxorubicinol. In general, the secondary parameters were similar between test and reference product and support the notion of bioequivalence between the two products. During the EMA GCP inspection only one of the study centres could be visited. However, critical findings from the inspection lead to the conclusion that the site did not meet GCP requirements questioning the validity of the pharmacokinetic data. (**MO**)

In response to the D180 LoOI, the applicant has presented the individual demographic data for the included subjects and for the subjects that have completed the trial, as well as descriptive statistics presented by overall subjects and by sequence. For subjects that have completed the trial, the mean and CV% for age, height, weight and BSA was similar for the two sequences, which assures a homogeneous sampling from the patient population.

Furthermore, it is noted that for several patients there is a long delay from last platinum regimen For some of them there are more than 6 episodes of platinum exposure, which would indicate platinum re-challenge, but for others it is $\leq$ 6, i.e. probably limited to first line therapy. It is not reported if those patients were on non-platinum chemotherapy other than PLD. Resistance to platinum-based treatment is defined as disease progression $\leqslant$6 months after completing a platinum-based regimen (previously classified as 'platinum-resistant' relapse) or who fail to respond at all to first-line treatment or relapse within 4–6 weeks after last platinum dose (previously classified as 'platinum-refractory'). Patients with relapsed ovarian cancer, who are potentially platinum-responsive, should receive platinum re-challenge. Patients for whom platinum-based chemotherapy might not be the best option, are a heterogeneous group, containing both patients with early symptomatic relapse or progression during prior platinum-based chemotherapy and patients with platinum intolerability. These patients should be offered a non-platinum regimen (as per ESMO guideline[1]).

For the pivotal bioequivalence PK study, the inclusion criteria were: "Patients with advanced ovarian cancer who have failed a first-line platinum-based chemotherapy regimen and who are already receiving or scheduled to start Doxorubicin Hydrochloride liposomal injection 50 mg/m2 dose as monotherapy as per Investigator judgment." Failing platinum-based chemotherapy is in line with the PLD indication. Cases of platinum intolerance have also been included in the trial. The inclusion in the trial occurred from 1-86 months after the last platinum treatment. The justification for inclusion in the PDL trial was in line with protocol criteria in the majority of the cases as per Investigator's judgement, as well as due to high biomarker (CA-125) or because already on doxorubicin treatment.

The provided concomitant medication data is acknowledged, and most of the medication pertains to prophylaxis as per protocol. In response to the D180 LoOI, the applicant performed a risk analysis regarding possible interferences with the analytical method used for the determination of encapsulated and free doxorubicin, also covering selectivity of the method and interference with concomitant drugs.

Several PK parameters of free doxorubicin ($AUC_{0-\infty}$, K_{el}, $t_{1/2}$, $AUC_{extr,apolated}$, V_d, C_L) were evaluated in 59 subjects for test product, but only in 56 subjects for the reference product. Similarly, the evaluation of $AUC_{0-\infty}$, K_{el}, $t_{1/2}$, $AUC_{extrapolated}$, V_d, and C_L for doxorubicinol was only conducted in 46 and 54 subjects

[1] Annals of Oncology 30: 672–705, 2019 doi:10.1093/annonc/mdz062 Published online 2 May 2019

for the reference and test product, respectively. The applicant revised the determination of the terminal rate constants for individual subjects for free doxorubicin and encapsulated doxorubicin, and the statistical analyses for the affected PK parameters (K_{el}, $t_{1/2}$ and AUC_{0-inf}) as requested.

The applicant conducted a re-calculation of the PK parameters for the analyte doxorubicinol including the geometric LSM ratio and 90% CI for AUC_{0-inf} and the revised data confirms the valid BE criteria for this analyte. Module 1.5.2 was revised accordingly.

Nevertheless, the conclusions of the GCP inspection challenge the reliability of the PK data, thus questioning data acceptability.

3.3.4. Conclusions on clinical pharmacology

The final GCP inspection states, among others, that "Due to the lack of documentation of the actual dispensing of the IMP and its quality control measures it could not be verified, whether the dispensing was correctly done and whether the patients received the correct dose. Hence, there is a concern that errors in dispensing have jeopardized the validity of the pharmacokinetic data."

The inspectors further conclude that findings observed at the analytical laboratory trigger serious concerns in relation to the plausibility and credibility of the reported PK concentrations, and they recommend not using the reported PK data for evaluation by the assessors.

Owing to these critical findings of the GCP inspection questioning the validity of the PK results, bioequivalence between test and reference product cannot be considered established.

3.3.5. Clinical efficacy

No efficacy studies were performed by the applicant.

Literature data on clinical efficacy is provided in the Clinical Overview, which is acceptable for this type of application.

Dose-response studies and main clinical studies

Not applicable

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

Not applicable

Supportive study(ies)

Not applicable

3.3.6. Discussion on clinical efficacy

Extensive data has been published regarding efficacy of liposomal doxorubicin in the treatment of the sought indications. A sufficient number of studies have been reviewed by the applicant and the clinical studies demonstrate the efficacy of pegylated liposomal doxorubicin. Treatment is considered justified for the proposed indications.

Doxorubicin Tillomed was developed as a hybrid version of the product Adriamycin and a generic to the existing licensed product Caelyx®. The active ingredient and the route of administration are the same for both products. Both products are concentrates for solution for infusion, and the excipients of Tillomed's product are qualitatively identical to those of the Caelyx®. The proposed drug product is regarded as pharmaceutically equivalent to Caelyx® based on information provided in the dossier.

The conclusion of clinical efficacy of the applied product relies on the proof of bioequivalence between Doxorubicin hydrochloride pegylated liposomal Tillomed and the reference product Caelyx 2 mg/ml concentrate for solution for infusion.

3.3.7. Conclusions on clinical efficacy

Conclusions on the clinical efficacy of Doxorubicin hydrochloride pegylated liposomal Tillomed are based on establishment of bioequivalence between Doxorubicin hydrochloride pegylated liposomal Tillomed and Caelyx 2 mg/ml concentrate for solution for infusion. However, due to critical GCP findings regarding the BE study, bioequivalence cannot be regarded as established (see 3.3.4).

3.3.8. Clinical safety

Product name

As stated above, following a number of reports of serious medication errors, some leading to death, and after consultation with EMA's safety committee (PRAC), the CHMP and CMDh agreed on actions to reduce the risk of mix-up between liposomal and non-liposomal formulations of the same active substance. Therefore the applicant was asked to adopt the following points:

- for medicinal products with an 'international non-proprietary name (INN)+company or trademark' name, the name should be changed to incorporate the qualifier 'pegylated liposomal' between the INN and the company name or trademark;
- the currently existing EDQM standard term 'dispersion', which includes liposomes in its definition, should be used consistently throughout the product information.

The requested changes in the product information were finally implemented and thus, the respective major objection on clinical safety has been appropriately addressed.

Patient exposure

The details of duration and extent of exposure of study drugs (Test Product 'T' and Reference Product 'R') to the subjects during the clinical phase of the bioequivalence study PCLPL-200-17 are provided below:

Period	Formulation	Dose	No. of subjects administered	Duration	Exposure
Period-I	Test product 'T': Doxorubicin 2mg/mL concentrate for solution for Infusion (Pegylated Liposomal Doxorubicin Hydrochloride)	50 mg/m^2	29	1 hour ± 05 minutes	Single dose
	Reference product 'R': Caelyx 2mg/mL concentrate for solution for infusion	50 mg/m^2	37	1 hour ± 05 minutes	Single dose
Period-II	Test product 'T': Doxorubicin 2mg/mL concentrate for solution for Infusion (Pegylated Liposomal Doxorubicin Hydrochloride)	50 mg/m^2	35	1 hour ± 05 minutes	Single dose
	Reference product 'R': Caelyx 2mg/mL concentrate for solution for infusion)	50 mg/m^2	26	1 hour ± 05 minutes	Single dose

However, one of the critical GCP findings pertains to concerns about the correct handling and dosing of the IMP, which was not adequately documented and traceable. Therefore, the validity of the clinical safety data and the following evaluation of (S)AEs are questionable.

Adverse events

During the conduct of the study, 98 adverse events were observed among 32 patients. Out of 98 adverse events, 17 were reported prior to administration of investigational products, 35 and 46 were reported after administration of test and reference products, respectively. Adverse events were mild (52), moderate (40) and severe (6) in nature. Out of 98 adverse events, certain (4), possible (26), probable / likely (18) and unlikely (50) were related to the IPs.

In total, AEs only observed with the test product occurred in 7 MedDRA PTs, whereas AEs only observed with the reference product were present in 16 MedDRA PTs.

Serious adverse events and deaths

No deaths and only three SAEs were reported in the bioequivalence study.

Two of the three SAEs were reported after treatment with the reference drug:

One subject (17-01) experienced the SAE of "Bone Marrow Suppression", which was "likely/probably" related to study IPs and occurred during Period I after treatment with the reference product. This SAE occurred on a single episode and was resolved after 6 days without sequelae.

One subject (17-03) experienced the SAE of "Febrile Neutropenia with Acute Gastroenteritis", which was of 'certain' relationship with study IPs and occurred during Period I after treatment with the reference product. This SAE occurred on a single episode and was resolved after 5 days without sequelae.

The following SAE was reported after treatment with the test drug:

One subject (12-03) experienced the SAE of "inferior wall ischemia", which was "possibly" related to study IPs and occurred during Period II. The subject was discontinued from the study due to this SAE.

Laboratory findings

Clinically significant abnormalities found for individual subjects during assessment of post study clinical laboratory values and the causative effect of study drug to the abnormality were recorded. The causality of the study drug for abnormality in any of the parameters was judged at the discretion of Principal Investigator.

According to the study report of Study PCLPL-200-17, abnormal laboratory values were observed in the study. However, no summary of these values was presented.

Safety in special populations

Literature data provided by the applicant are considered adequate in light of the Caelyx SmPC.

Immunological events

One AE is presented as autoimmune neutropenia. No other immunological events are reported. There are two infusion related reactions, but not mentioned as an immunological event.

Safety related to drug-drug interactions and other interactions

A literature overview on DDI data was provided in CTD Module 2.5.

Discontinuation due to AES

One subject was discontinued from the study due to a SAE, as described above.

Post marketing experience

Not applicable

3.3.9. Discussion on clinical safety

In this hybrid application the safety characterisation of Doxorubicin Hydrochloride Tillomed is based in part on historical data of liposomal doxorubicin hydrochloride and in part on safety data observed in the bioequivalence study between the test product and Caelyx. The available literature is adequately summarised and discussed in Module 5.2 Clinical Overview.

In study PCLPL-200-17, 98 AEs were observed in total, of which 17 occurred before drug administration, whereas 35 and 46 were reported after administration of test and reference products, respectively. There was no general pattern of AEs per system organ class occurring more often in any of the two treatments.

In total, Adverse Events that were only observed with the test product occurred in 7 MedDRA PTs, whereas AEs only observed with the reference product were present in 16 MedDRA PTs.

However, though summarised by treatment, in the initial study report the applicant did not specify if the adverse events occurred in treatment period 1 or 2. An overview of AEs by treatment and study period was provided in response to the D180 LoOI.

Cardiac toxicity is well described for anthracyclines and, although liposomal doxorubicin formulations have a better safety profile, several cardiac disorders are common adverse effects observed during Caelyx treatment (Caelyx SmPC, 2017). In the present study, however, there was only one AE of cardiac disorder, namely myocardial ischaemia in one patient treated with test product. Based on the

single occurrence of this AE and the known incidence of cardiac disorders related to treatment with Caelyx, no conclusions can be drawn on a clinically relevant difference between the test and reference product in regards to myocardial ischaemia.

No deaths and only three serious adverse events were reported in the bioequivalence study.

Two SAEs were observed after administration of reference product in study period I and were considered likely and certainly related to the reference product. Both of them resolved without sequelae.

The SAE observed in one subject after treatment with test product, which was possibly related to study drug, occurred in period II. Therefore, it is not entirely clear if it was caused by the administration of the test product or by a delayed effect of the reference product, although a delayed effect is not likely with this kind of event.

Most AEs observed more frequently with test than reference product in the bioequivalence study are described as common AEs in the Caelyx SmPC. It is therefore not of concern that such events were observed in the present study, even with a slightly higher incidence for the test product compared to the reference product.

Liposomal doxorubicin has been in clinical use for over a decade, and its toxicity profile is well characterised; it has been shown to be favourable over non-liposomal doxorubicin, which is adequately supported by literature data presented in the Clinical Overview.

A major objection has been raised regarding the potential mix-up between liposomal and non-liposomal formulations of the same active substance and the resulting risk of medication errors. The product name needs to incorporate the qualifier 'pegylated liposomal' in order to avoid confusion between liposomal and non-liposomal formulations of the same active substance. Furthermore, the EDQM standard term ‘dispersion’, which includes liposomes in its definition, should be used consistently throughout the product information. Finally, the product information was amended accordingly.

3.3.10. Conclusions on clinical safety

Among others, the final GCP inspection states that, “Due to the lack of documentation of the actual dispensing of the IMP and its quality control measures it could not be verified, whether the dispensing was correctly done and whether the patients received the correct dose. Hence, there is a concern that errors in dispensing have jeopardized the validity of the pharmacokinetic data.”

This also relates to the validity of the clinical safety data, since toxicities and adverse events depend on the administered dose, which, according to the GCP inspectors, could not be verified.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

3.4.2. Discussion on safety specification

As this is a well-known product, no additional pharmacovigilance activities and risk minimisation measures have been proposed by the applicant, which is accepted.
Therefore, the list of summary of safety concerns does not include any important identified and potential risks and missing information.

3.4.3. Conclusions on the safety specification

As no additional pharmacovigilance activities and risk minimisation measures have been proposed by the applicant, all safety concern have been deleted, which is accepted.

3.4.4. Pharmacovigilance plan

The PRAC Rapporteur is of the opinion, that the reference product has been in post-authorisation use for a long time and all risks are well known and well managed. No additional PhV activities are needed.

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.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

3.4.5. Risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

In line with the reference product, the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

3.4.6. Conclusion on the RMP

The Application of MA of Doxorubicin Hydrochlorid Tillomed was submitted in accordance with Article 10 (3) – hybrid application of the reference product Adriamycin 2 mg/ml solution of injection which has no additional risk minimisation activities. Routine PhV is considered sufficient to identify and characterise the risks of the product. No additional risk minimisation measure is required.

The PRAC Rapporteur fully supports recommendation of CHMP Rapporteur to delete all safety concerns proposed by the applicant.

The RMP Part III-VI is acceptable.

3.5. 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.

Following the BREXIT, the QPPV and PSMF location should be changed as planned (**OC**).

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.>

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

Doxorubicin Hydrochloride Tillomed is developed as a generic of the reference medicinal product Caelyx® and is designed to have the same indications and posology as Caelyx®.

The applicant proposes the same indications and posology for their product as the reference product Caelyx®:

- As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.
- For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.
- In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.
- For treatment of AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (<200 CD4 lymphocytes/mm3) and extensive mucocutaneous or visceral disease.
  Caelyx may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other anthracycline).

4.1.2. Available therapies and unmet medical need

The clinical efficacy of Doxorubicin Hydrochloride Tillomed is concluded based on studies conducted with the reference product Caelyx, which is an established treatment option for the above-mentioned malignancies.

4.1.3. Main clinical studies

The pivotal clinical study was performed to demonstrate the bioequivalence to the reference product Caelyx®. Study PCLPL-200-17 was a multicentre, open label, randomized, balanced, two-treatment, two-period, two-sequence, single dose, two-way crossover, bioequivalence study in female patients

with advanced ovarian cancer; of 67 included subjects 59 were considered for PK analysis and statistical evaluation.

The bioequivalence study was conducted with the highest dose applied in any of the indications as per SmPC of the reference product, thus covering the full dose range of liposomal doxorubicin hydrochloride.

4.2. Favourable effects

According to the documentation submitted by the applicant, the test by reference geometric least square mean ratios and confidence intervals for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for the three analytes free doxorubicin, liposome encapsulated doxorubicin and total doxorubicin are within the acceptance criteria set out in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). The same applies to the partial AUCs (AUC_{0-48h} and $AUC_{48-336h}$) calculated for liposome encapsulated doxorubicin. Thus, in principle, the results support the notion of bioequivalence between the reference and test product.

Additionally, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, were determined for the metabolite doxorubicinol. The test by reference geometric least square mean ratios of these parameters further support the notion of bioequivalence between test and reference product for the main metabolite doxorubicinol. Also, the secondary parameters were similar between test and reference product.

The p-values obtained from ANOVA for Formulation, Sequence and Period effects were greater than 0.05 for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for all three analytes and for the partial AUCs of encapsulated doxorubicin, indicating that formulation, sequence and period effects were statistically not significant at the 5% significance level.

4.3. Uncertainties and limitations about favourable effects

The conclusion of the GCP inspection is:

"Due to the lack of documentation of the actual dispensing of the IMP and its quality control measures it could not be verified, whether the dispensing was correctly done and whether the patients received the correct dose. Hence, there is a concern that errors in dispensing have jeopardized the validity of the pharmacokinetic data.

The observed findings give reason for serious concerns in relation to the plausibility and credibility of the PK concentrations reported. Therefore, the inspectors recommend not using the reported data for the evaluation by the assessors."

4.4. Unfavourable effects

Liposomal doxorubicin has been in clinical use for over a decade and its safety profile is well characterised and has been shown to be favourable compared with non-liposomal doxorubicin formulations. The safety data provided from the BE study did not detect any new or unexpected findings.

4.5. Uncertainties and limitations about unfavourable effects

Due to the lack of documentation of the actual dispensing of the IMP and its quality control measures it could not be verified, whether the dispensing was correctly done and whether the patients received the correct dose. Hence, there is a concern that errors in dispensing have jeopardized the validity of the safety data.

4.6. Effects Table

Not applicable

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Liposomal doxorubicin has been in clinical use for over a decade and its safety profile is well characterised and has been shown to be favourable compared with non-liposomal doxorubicin. However, there is a risk of mix-up between liposomal and non-liposomal formulations of the same active substance; the product name was amended as recommended by the CHMP in order to mitigate the risk of potentially serious medication errors.

In this hybrid application, a reliable bridge to the reference product needs to be established by means of a valid bioequivalence exercise in order to claim similarity to the reference product in efficacy and safety. The applicant conducted a BE study and the submitted PK results seemed to support bioequivalence. However, the GCP inspection of the pivotal BE study PCLPL-200-17 raises serious concerns in relation to the plausibility and credibility of the PK data. Therefore, it is concluded that the reported data cannot be used for the assessment of bioequivalence between Doxorubicin Tillomed and the reference product Caelyx.

4.7.2. Balance of benefits and risks

In view of the GCP inspection questioning the plausibility and credibility of the PK results the benefit/risk balance of Doxorubicin Tillomed is negative.

4.7.3. Additional considerations on the benefit-risk balance

Not applicable.

4.8. Conclusions

The overall B/R of Doxorubicin hydrochloride pegylated liposomal Tillomed is negative.

User consultation

The Readability User Test of the PIL for Doxorubicin Hydrochloride Tillomed took place in Bedfordshire, UK from 2019-03-15 to 2019-03-20.

The Package Leaflet has been user tested as required in EC Directive 2001/83/EC as amended by Directive 2004/27/EC and achieved a satisfactory result.

Discussion of the main test:

In the main test, the readability and comprehensibility of the PIL was tested on 10 persons each in two test cycles, giving a total of 20 participants.

The target of 90% of participants being able to find each item of information and 90% of these participants being able to show that they had understood it was met for all 12 questions.

The success criteria were achieved with each question.

Therefore the PIL can be related as readable and comprehensive according to the guidelines of the European Commission.