11 December 2025
EMA/CHMP/245110/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Livmarli

International non-proprietary name: maralixibat chloride

Procedure No. EMEA/H/C/005857/X/0015

Note

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

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List of abbreviations

AE	Adverse event
ALGS	Alagille syndrome
AUC	Area under the concentration–time curve
$AUC_{0\text{-}inf}$	Area under the plasma drug concentration-time curve extrapolated to infinity
AUC_{last}	From time zero to the last measurable concentration after dosing
BA	Bile acid
BCS	Biopharmaceutical classification system
C4	7αc4 = 7α-hydroxy-4-cholesten-3-one
CI	Confidence interval
CHMP	Committee for Medicinal Products for Human use
CPP	Critical Process Parameter
C_{max}	Maximum concentration of drug in plasma
CV	Coefficient of variation
eAF	Electronic application form
EC	European Commission
EU	European Union
fBA	Faecal bile acid
GI	Gastrointestinal
GLSMR	Geometric least squared mean ratio
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
IBAT	Ileal bile acid transport inhibitor
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IR	Immediate release
KF	Karl Fischer titration
MO	Major objection
NLT	Not less than
PD	Pharmacodynamic
Ph. Eur.	European Pharmacopoeia

AE	Adverse event
PK	Pharmacokinetic
PFIC	Progressive familial intrahepatic cholestasis
QC	Quality Control
QTTP	Quality target product profile
RH	Relative Humidity
sBA	Serum bile acid
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopeia
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

Mirum Pharmaceuticals International B.V. submitted on 10 October 2024 an application for an extension of the marketing authorisation.

The MAH applied for an addition of new strengths (10 mg, 15mg, 20 mg and 30 mg) in combination with the addition of a new pharmaceutical form pharmaceutical form (tablet). The RMP was proposed to be updated in accordance.

The MAH applied for the following indication for Livmarli 10 mg, 15mg, 20 mg and 30 mg tablets:

Livmarli is indicated for the treatment of:

- Cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older,
- Progressive familial intrahepatic cholestasis (PFIC) in patients 3 months of age and older.

1.2. Legal basis

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (c) and (d) - Extensions of marketing authorisations

Livmarli, was designated as an orphan medicinal product on 18 December 2013 in the following condition: Treatment of Alagille syndrome (EU/3/13/1214) and Treatment of progressive familial intrahepatic cholestasis (EU/3/13/1216).

The indications which are the subject of this application for the new tablet formulation/strengths fall within the existing authorised indications for Livmarli and within the above-mentioned orphan designations.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0488/2023. At the time of submission of the application, the PIP P/0488/2023 covering the application was completed. The PDCO issued an opinion on compliance for the PIP P/0488/2023. This application did not include new data generated in accordance with the PIP. Results of studies conducted in compliance with this agreed paediatric investigation plan were implemented in previous procedures in the Summary of Product Characteristics.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Protocol assistance

The MAH received protocol assistance from the CHMP on the development for the indication from the CHMP on 12 October 2023 (EMA/SA/0000146162) and 21 March 2024 (EMA/SA/0000163014). The protocol assistance pertained to *quality, non-clinical, and clinical* aspects.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: N/A

The application was received by the EMA on	10 October 2024
The procedure started on	31 October 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	3 February 2025
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	n/a
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 January 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	27 February 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	22 May 2025
The PRAC Rapporteurs Assessment Report	30 June 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	1 July 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 July 2025
The CHMP Rapporteurs updated Assessment Report	17 July 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	24 July 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	19 August 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	04 and 12 September 2025
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	18 September 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on	29 October 2025

Oral explanation took place on	11 November 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Livmarli on	11 December 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Livmarli 9.5 mg/ml oral solution (maralixibat) has been authorized in EU under exceptional circumstances for the "treatment of cholestatic pruritus in patients with ALGS 2 months of age and older" on the 9th of December 2022, and for the "treatment of PFIC in patients 3 months of age and older" on the 28th June 2024.

Alagille syndrome (ALGS) is an inherited multi-organ disease of variable severity caused by heterozygous mutations in either JAG1 or NOTCH2. The most prominent feature of the disease is cholestasis caused by paucity of biliary ducts, and which itself manifests as scleral icterus, conjugated hyperbilirubinaemia, and potentially hepatomegaly. The increased level of bile acids in the serum usually causes severe pruritus.

Progressive Familial Intrahepatic Cholestasis (PFIC) is a group of rare inherited diseases of hepatocellular origin resulting in disrupted bile acid transportation, leading to accumulation of bile acids within the liver with all characteristic features of intrahepatic cholestasis and progressive liver damage.

Both conditions manifest early in childhood.

2.1.2. Epidemiology

Both, ALGS and PFIC are rare diseases.

2.1.3. Biologic features

Key component of both conditions is development of intrahepatic cholestasis with increase in levels of serum bile acids (sBA), bilirubin and other parameters indicating progressing liver damage.

2.1.4. Clinical presentation, diagnosis and prognosis

The diagnosis of ALGS and PFIC is usually made early in life. Manifestations of intrahepatic cholestasis become apparent early in childhood with hyperbilirubinaemia, pruritus, xanthomas, icterus, etc. Patients with ALGS additionally display cardio-vascular, renal, skeletal, ophthalmologic, facial abnormalities. Patients suffer from developmental delay.

In both conditions, the intrahepatic cholestasis ultimately leads to liver cirrhosis/liver failure.

2.1.5. Management

As mentioned above, Livmarli oral solution (9.5 mg/ml) is approved for treatment of pruritus in ALGS and for treatment of PFIC from the age of 2 and 3 months respectively.

Also, selective ileal bile acid transport (IBAT) inhibitor, odevixibat has been approved in roughly similar indications under the trade names Bylvay (EMEA/H/C/004691; treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older) and Kayfanda (EMEA/H/C/006462; treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older).

No other medicinal products are approved. Choleretic agents Ursodeoxycholic Acids (UDCAs) and other therapies (cholestyramine, rifampin, naltrexone) are used for the management of pruritus but typically have limited success.

Surgical interventions, such as surgical biliary diversion (SBD) (partial internal biliary diversion and ileal exclusion) and liver transplantation are conducted in the patients with progressed liver damage and/or intractable pruritus.

2.2. About the product

This procedure concerns a line extension (Livmarli 10 mg, 15 mg, 20 mg, and 30 mg tablets) to the licenced product Livmarli 9.5 mg/mL oral solution (EU/1/22/1704/001).

The active ingredient in Livmarli is maralixibat, which is a highly potent Intestinal Bile Acid Transporter (IBAT) inhibitor. Maralixibat-mediated blockade of intestinal reabsorption of Bile Acids (BAs) by IBAT inhibition interrupts the enterohepatic circulation, thereby increasing faecal bile acid excretion and lowering serum bile acid levels.

Maralixibat is minimally absorbed due to its large molecular weight (~710 Da) and the presence of a positively charged quaternary nitrogen atom, therefore maximizing the local exposure of the molecule to its target in the intestinal wall and minimizing unnecessary systemic exposure. Due to the minimally absorbed nature of maralixibat, it has not been possible to consistently document the plasma pharmacokinetics (PK) of maralixibat at therapeutically relevant doses because oral dosing results in very low plasma drug levels. The absolute bioavailability of maralixibat has not been determined in humans and is estimated to be below 1% (EPAR Livmarli EMA/864249/ 2022).

Dose-proportionality as a method of PK characterisation at the time of initial marketing authorisation was also hampered by the fact that the compound is poorly absorbed. There was an indication of increasing concentration/exposure with doses higher than 20mg, but a clear linear relation could not be demonstrated. No relevant differences were detected between single and multiple doses of the compound, although a formal evaluation of time-dependency was not conducted (but considered acceptable). A high variability of PK parameters was obvious from the data. In the 100mg dosing group (oral solution) of the food effect study MRX-102, the coefficient of variation for $AUC_{0\text{-}inf}$ and Cmax is 73% and 52%, respectively.

The primary route of maralixibat excretion is faecal and metabolism of maralixibat is minimal (>94% unchanged in faces).

A new pharmaceutical form of Livmarli, a tablet formulation, has been developed for use by patients who can reliably swallow tablets and prefer a solid formulation. Both, the oral solution and tablet dosage forms share the same active ingredient, indications, dosing regimen, and route of administration. The proposal for this line extension refers to the fact that older patients (adolescents and adults) will well be able to swallow tablets. They can thus avoid the rather less convenient

procedure of dosing with the available liquid dosage form which requires careful drawing of the dose into the syringe to avoid over/insufficient dosing.

Additionally, this formulation does not contain propylene glycol (PG), that may pose a risk of PG-related toxicity, especially in patients with affected liver function.

2.3. Type of Application and aspects on development

The development plan of this new oral dosage form of maralixibat (tablet) was previously presented to CHMP/SAWP in the context of a first protocol assistance procedure submitted on 13 July 2023. The aim of this first interaction with the Agency was to seek advice on the Applicant's proposed development plan and related data package (initial protocol assistance). The advice given in October 2023 mainly referred to the following issues:

- Rationale for using in vitro dissolution in support of a waiver for in vivo bioavailability or bioequivalence data requirements
- The plan for manufacturing registration batches of drug product; the proposed bracketing and rolling submission approach for the drug product registration stability plan, and the plan to do a concurrent release of drug product process validation batches

Based on the data and justification provided by the applicant, the CHMP agreed on the proposed quality aspects, but objected to the proposal of using in vitro dissolution in support of a waiver of an in vivo bioavailability and bioequivalence data requirements. The following issues were brought forward:

- Incompleteness of the documentation that the compound belongs to BCS Class III (highly soluble but poorly absorbed), and the fact that even if the classification is accepted, the use of a BCS-based biowaiver approach would be hampered by the fact that excipients are not similar, and the approach refers to similar pharmaceutical forms.
- The presentation of comparative dissolution profiles, which did not include early time-points for dissolution and were generally not conducted according to the requirements of the ICH M9 and bioequivalence guidelines. Moreover, comparative data as such were thought to be questionable since the comparator oral solution possesses a dissolution of 100% by definition.
- No presentation of any reasoning why a bioequivalence (BE) or PD-equivalence approach would not be feasible, based on the potential for increased sensitivity of analytical methods, and/or use of high(er) doses. The Applicant was made aware that the development of the new dosage form would regularly require the conduct of a BE study.

To address these recommendations, the Applicant sought Follow-Up Protocol Assistance which was submitted in January 2024. The Applicant at that time presented the following:

- An updated discussion on the BCS class of the active substance, further substantiating the high solubility of the compound across the relevant pH range.
- Updated documentation of dissolution profiles for the different strengths of the new solid dosage form using the United States Pharmacopeia Apparatus.
- Evaluation of the feasibility of comparative PK studies and PD equivalence of clinical equivalence studies.
- Proposal for the study protocol for a comparative bioavailability clinical study.

CHMP at that time still had an issue with the fact that a discussion on the influence of micelle formation as mentioned in the previous advice letter was not included. There are indications that micelle

formation (Critical Micelle Concentration=0.6mg/mL) leads to better in vitro dissolution for higher dose strengths. As the products are taken 30 min before or during a meal and the drugs are due to their low permeability expected to remain in the intestinal lumen, the influence of food on the performance and local site of action of the new product in the gastrointestinal tract in comparison to the marketed oral solution also would need to be thoroughly discussed.

In addition, the occurrence of the "coning effects" in the dissolution experiments newly presented would need to be documented properly together with the reasons for the occurrence of this effect. The recommendation to perform additional dissolution experiments with a basket apparatus at 100 rpm according to the ICH M9 guideline was given.

With regard to the comparative bioavailability study, it was accepted that a bioequivalence study in the strict (with a confirmatory approach) sense would not be possible due to issues with assay sensitivity as well as variability, but the study could contribute to overcome the potentially unconvincing character of the BCS-based biowaiver argumentation, and potential issues with the dissolution profiles.

CHMP considered the Applicant's approach to be overall acceptable and concluded that most probably the decision would be based on the totality of data.

2.4. Quality aspects

2.4.1. Introduction

This line extension concerns the addition of four strengths of a finished product tablet formulation. Each tablet contains 10 mg, 15 mg, 20 mg or 30 mg of the active substance maralixibat, which is present as the salt maralixibat chloride. This line extension is in addition to the already authorised oral solution formulation.

Other ingredients are Lactose monohydrate, microcrystalline cellulose, crospovidone (Type A), silicon dioxide, glyceryl distearate Type I.

The finished product is available in a high-density polyethylene (HDPE) bottle with a child resistant cap as described in section 6.5 of the SmPC.

2.4.2. Active Substance

The information with respect to the active substance is the same as the approved oral solution formulation.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The tablets contain maralixibat chloride equivalent to 10 mg, 15 mg, 20 mg, or 30 mg of maralixibat and have the following appearance:

Livmarli 10 mg tablets
White to off-white round tablets, of 6.35 mm in diameter, and debossed with "MRX" on one side, "10" on the other side.

Livmarli 15 mg tablets

White to off-white oval tablets with dimensions of 4.75 mm x 10.50 mm and debossed with "MRX" on one side, "15" on the other side.

Livmarli 20 mg tablets
White to off-white round tablets of 8.00 mm in diameter and debossed with "MRX" on one side, "20" on the other side.

Livmarli 30 mg tablets
White to off-white round tablets of 9.20 mm in diameter and debossed with "MRX" on one side, "30" on the other side.

The aim was to develop immediate release tablets of various strengths suitable for the intended patient population who can swallow such dosage forms. The approved oral solution dosage form could be used in patients who would experience swallowing difficulties with the tablets. The development of the tablet dosage form built upon knowledge gained during the approval of the oral solution.

The quality target product profile (QTPP) for the tablets was defined and is outlined in Table 1, this allowed for identification of potential critical quality attributes. While potential for tablet administration to children was defined in the QTPP the final indication includes adults and adolescent patients.

Table 1: Quality Target Product Profile

QTPP Elements	Target	Justification
Route of Administration	Oral	Oral dosage form is selected for maralixibat because the drug target (ASBT) lies on the apical side of the intestinal surface.
Dosage Form	Solid Oral	Tablets are proposed as an option in addition to the previously developed oral solution for adolescent children who are capable of swallowing tablets. Tablets will not be scored to avoid disproportionate dosing.
Pharmacokinetics	Immediate Release	Maralixibat chloride is highly water soluble and minimally absorbed after oral administration. No contributions from the formulation are needed to enhance availability to the target.
Dosage Strength	10 mg	The strength (based on maralixibat free base) is selected so that patients of different body weights can receive prescribed doses by taking the appropriate tablet.
	15 mg	
	20 mg	
	25 mg	
	30 mg	
	50 mg	
Stability	At least 24 months shelf-life at controlled room temperature.	Adequate stability to ensure drug safety and efficacy within the specified shelf life.
Container Closure System	Suitable container closure system to achieve the target shelf-life and to ensure drug product integrity during storage and shipping.	To provide adequate protection for the drug product throughout its shelf life.
Alternative Route of Administration	None	The drug target (IBAT) lies on the apical side of the intestinal surface. The compound is minimally absorbed. Therefore, the oral route is the most appropriate route for drug administration.

Abbreviations: ASBT = apical sodium dependent bile acid transporter

The active substance synthesis is the same as per the currently approved oral solution and no new information has been provided. The applicant has demonstrated that the polymorphic form (form II) is stable during the manufacture/storage of the tablets. The active substance is highly soluble; however particle size reduction was necessary to enable the solid dosage form manufacturing process and

improve content uniformity of the tablets. This milling step takes place as the first step of the finished product manufacturing process and the particle size distribution is controlled as an in-process control.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The excipients are considered suitable for the intended patient population.

The development of the manufacturing process has been adequately described, the applicant selected and developed a standard direct compression manufacturing process that utilises a common blend for all strengths. In addition to the proposed 10 mg, 15 mg, 20 mg, and 30 mg strengths, the applicant presented supportive development data from the manufacture of 25 mg and 50 mg strengths by the same process and formulation. The information gained during the development was used to define process parameters and in-process controls relevant to the proposed commercial process.

The applicant aimed to develop a product that would be therapeutically equivalent to the solution formulation. The applicant requested a BCS biowaiver approach for the tablet formulation, claiming that the active substance exhibits high solubility and low permeability (BCS class III). A BCS biowaiver approach alone was not supported, as the dosage forms are not the same, in addition the excipients are qualitatively and quantitatively different due to the different dosage forms and formulations. The applicant was requested to substantiate the therapeutic equivalence of the products please refer to the clinical section of this report for further information. Following this clinical review, the tablet formulation was considered acceptable based on the totality of data presented.

The development information presented regarding dissolution and the experimental conditions used was originally not considered acceptable. The information provided was not consistent with respect to the method being used and it was not clear which apparatus was being used, and which parameters were being applied. Considering the applicant's claim of a BCS class III highly soluble active substance a major objection (MO) was raised on this aspect to clarify the data presented. To resolve this MO the applicant clarified the dissolution testing conditions and corrected the discrepancies in the apparatus and operating parameters of the method descriptions. With the revised information the dissolution performance of the finished product was suitably clarified, and it was accepted that the active substance is highly soluble.

The discriminatory power of the dissolution method proposed for QC release was initially not demonstrated by the applicant, as this could impact the ability of the method to detect relevant changes in product performance an MO was raised on this aspect. This MO also encompassed a number of related deficiencies on dissolution including that the method needed to be consistently defined, and comparative dissolution data for commercial batch sizes was also requested. To resolve these aspects the applicant clarified the intended dissolution method for QC release. It was also demonstrated that the chosen method was suitably discriminatory. The applicant provided dissolution data for commercial scale batches of the finished product that demonstrated similar dissolution results. The applicant clarified in their response the intended QC dissolution limit, however this limit was not acceptable as the discriminatory potential of the dissolution method was demonstrated only for earlier time-points. This aspect of the MO was therefore maintained, and the applicant was requested to tighten the QC dissolution limit. The applicant tightened the dissolution limit as requested and provided data stability data showing this tightened limit was achieved for the stability batches, this resolved the outstanding aspect of this MO.

The primary packaging is a high-density polyethylene (HDPE) bottle with child resistant cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site. Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product

The manufacturing process consists of five main steps: milling, blending, compression, primary packaging, secondary packaging. The process is considered to be a standard manufacturing process.

Critical process parameters (CPPs) were evaluated as part of a risk assessment based on ICH Q8(R2) principles. Based on the risk assessment performed for the manufacture of MRX Tablets, all process steps were determined to be of relatively low risk. CPPs were identified and the defined ranges for these process parameters are adequate justified. Additionally, the in-process controls described are appropriate to ensure the overall quality of the finished medicinal product. There are no intermediates isolated during the manufacturing process of MRX Tablets.

The applicant proposes concurrent validation of the finished product manufacturing process as described in Annex 15 of the EU GMP guidelines, the product is intended for an orphan indication and the volumes produced are low. Based on the knowledge gained through development and presented batch history, the risk of concurrent validation from a quality viewpoint is low and the approach is therefore acceptable. The same approach was applied previously for the authorised oral solution formulation.

It is considered that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. The information provided concerning the proposed bulk-hold time is sufficient.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form description (visual), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), water content (KF), content uniformity (Ph. Eur.), dissolution (HPLC), microbiological quality (Ph. Eur.).

The proposed test parameters are acceptable for an immediate release tablet, and the proposed limits were set based on batch data, stability data and relevant guidelines.

The limits for potential degradation products are set in line with ICH Q3B requirements, one degradation product is present above the relevant qualification threshold. The applicant has suitably qualified the impurity based on toxicological considerations.

The applicant's initially proposed limit for the assay value was not acceptable, the applicant had proposed a limit at release and shelf life, however, this limit was wider than 95-105% and an MO was raised as sufficient justification for this had not been presented in line with the requirements of Directive 2001/83/EC. To resolve this MO the applicant tightened the limit for assay.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of

Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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

Batch analysis results were provided for batches manufactured during the development program, including batches of commercial batch size, this confirms the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from 4 commercial scale batches of the 10 mg and 30 mg finished product strengths stored for up to 24 months under long term & intermediate conditions (25 ºC / 60% RH & 30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal products are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. A bracketing approach was applied for the strengths, and the testing encompassed the highest and lowest strengths proposed for authorisation. Supportive stability testing data was also provided for a 50 mg strength which is not subject to a request for authorisation but was produced from the same common blend. Stability data concerning small scale developmental batches was also provided as additional supportive data.

Samples were tested for description, assay, degradation products, water content, dissolution, microbiological quality. The analytical procedures used are stability indicating. At long term an accelerated storage conditions the product remained within specification and no trends were observed.

With respect to ongoing stability programs, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. An increase in degradation of products was seen upon exposure to light and the finished product is considered to be photosensitive.

The applicant performed in-use stability studies simulating room temperature conditions (15-25 ºC & 37.5% RH) on one batch of the 10 mg & 50 mg strengths for 100 days. No out of specification results or significant trends were noted and the in-use stability was confirmed after 100 days. Considering the results of the in-use stability studies and the other stability data provided, an in-use shelf life is not required in the product information.

Based on available stability data, the proposed shelf-life of 24 months and store in the original package in order to protect from light as stated in the SmPC are acceptable.

2.4.3.5. Adventitious agents

It is confirmed that lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure three MOs concerning quality were raised, these related to the information provided to dissolution data provided to substantiate the dissolution performance of the active substance, the definition of the dissolution method proposed for QC release of the finished product along with the discriminatory power of this method, and the limit proposed for the assay value for the finished product. To resolve MOs the applicant provided further information on the dissolution of the active substance to substantiate its high solubility and corrected inconsistencies in the descriptions of some of the dissolution experiments. The dissolution method proposed for QC release was clarified and the discriminatory power of this method substantiated. Following further request the applicant also suitably tightened the limit proposed for QC release to be in accordance with the discriminatory power of the method. The MO related to the assay value was resolved when the applicant tightened the proposed finished product specifications in line with the request.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

A new pharmaceutical form of Livmarli, a tablet formulation, has been developed for use by patients who can reliably swallow tablets and prefer a solid formulation. Both the oral solution and tablet dosage forms share the same active ingredient, indications, dosing regimen, and route of administration.

No new non-clinical data has been submitted for this procedure apart from an Environmental risk assessment (ERA).

2.5.2. Ecotoxicity/environmental risk assessment

The applicant considered that the authorisation of the new pharmaceutical form applied for will not lead to changes in the anticipated environmental exposure. This is justified by the fact that the maralixibat oral solution and maralixibat tablet share the same active ingredient, indications, dosing regimen, and route of administration.

The CHMP noted that in compliance with the guideline on the environmental risk assessment of medicinal products for human us (EMEA/CHMP/SWP/4447/00 Rev. 1) an increase in environmental exposure may be expected when e.g. the maximum daily dose is increased. As for the new pharmaceutical form the maximum recommended daily doses for the indications ALGS & PFIC are slightly increased, i.e. for PFIC from 57 mg (oral solution) to 60 mg (tablets) and for ALGS from 28.5 mg (oral solution) to 30 mg (tablets). However, under consideration of the orphan status for both indications and the changes in the dosing regimen a $PEC_{surface\ water}$ of 0.00105 µg/l can be calculated for the new pharmaceutical form applied for (tablets). This PEC is slightly higher than the PEC for the oral solution ($PEC_{surface\ water}$ of 0.00094 µg/l) and falls clearly below the action limit of 0.01 µg/l as well.

Table 2:Summary of main study results

Substance (INN/Invented Name): maralixibat chloride			
CAS-number (if available): 228113-66-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow} (taken from previously submitted ERA)	OECD 123	1.54	Potential PBT N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (based on prevalence data)	0.00105	µg/L	> 0.01 threshold N

2.5.3. Discussion on non-clinical aspects

Maralixibat is already used in existing marketed products and no significant increase in environmental exposure is anticipated. For the new pharmaceutical form applied for (tablets) a $PEC_{surface\ water}$ of 0.00105 µg/l can be calculated. This PEC is slightly higher than the PEC for the oral solution ($PEC_{surface\ water}$ of 0.00094 µg/l) but falls clearly below the action limit of 0.01 µg/l as well.

Therefore, maralixibat is not expected to pose a risk to the environment.

2.5.4. Conclusion on the non-clinical aspects

Maralixibat chloride PEC surface water value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Maralixibat is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Type of Study	Study Identifier	Objective(s) of the Study	Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	# of Subj.	Population	Duration of Treatment	Study Status; Type of Report
Relative bioavailability	MRX-103	Evaluate pharmacokinetics of single doses of 100-mg maralixibat as liquid formulation and tablet formulation in healthy participants	Open-label	Maralixibat 100-mg oral solution (10.5 mL × 9.5mg/mL) and maralixibat oral tablet formulation (2 × 50-mg tablets)	14	Healthy subjects	Single dose Two 3-day treatment periods	Complete; full clinical study report

To support this procedure, one clinical study is submitted: Study MRX-103 is an exploratory comparative bioavailability study comparing the current oral solution (9.5 mg/ml) with the new tablet formulation using the 50 mg strength (not intended for marketing). Additionally, results of an *in vitro* dissolution test of the lowest and the highest to-be-marketed dose strengths of Livmarli tablet formulation (10 mg and 30 mg) and argumentation supporting the claim of the Class III BCS for active substance, maralixibat, have been provided.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Phase I clinical study MRX-103: This was a Phase 1, open-label, randomized study to assess the relative bioavailability of tablets versus liquid formulation of maralixibat in healthy adult participants.

Study Objectives:

• The primary objective was to evaluate the pharmacokinetics of single doses of 100-mg maralixibat administered as the liquid formulation (10.5 mL × 9.5 mg/mL maralixibat oral solution) and the tablet formulation (2 × 50-mg tablets) in healthy participants.

• The secondary objective was to assess the safety and tolerability of single oral doses of 100 mg of the liquid formulation (10.5 mL × 9.5 mg/mL maralixibat oral solution) and tablet formulation (2 × 50 mg) of maralixibat in healthy participants.

Study design

Study MRX-301 was single-centre, open-label, randomized, one-cohort study of 100-mg dose of a liquid maralixibat solution compared with a 100-mg dose of a tablet maralixibat formulation in 14 healthy participants. The clinical part of the study was initiated 30th October 2023 and completed on 10th November 2023.

The 28-day screening period was followed by two 3- day Treatment Periods (~72 hours between study drug administrations), and with a follow up telephone call 7 days from the final study drug administration. Participants reported to the clinic on Day -1, fasted overnight for a minimum of 10 hours, and received a maralixibat dose (depending on the randomization order of either 2x50-mg tablets or a 100-mg solution, i.e., 10.5 ml of 9.5 mg/ml oral solution) on Day 1. Fasting continued for further 4 hours.

During each treatment period, PK samples were obtained before study drug administration and at selected times through 24 hours after study drug administration (time-points were 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after dosing. A total of 24 PK blood samples (2 Periods with 12 PK collection times) were collected from each participant.

Analyses

Exploratory analyses were conducted. Standard PK parameters were assessed.

A post hoc analysis of C4 as a PD marker of decreased absorption of bile acids in the intestines (i.e., of the effective IBAT inhibition) was presented with the responses to the Day 120 list of questions and the Day 180 list of outstanding issues. These results are presented in the PD part of this report.

The use of sBA as a biomarker in this healthy population was not employed, as sBA levels are low in healthy subjects under fasting conditions and a further decrease in levels associated with maralixibat treatment is challenging to reliably detect after a single dose due to the sBA variability and diurnal effects.

Population

Healthy volunteers were included.

Results

Fourteen participants were included: 7 were assigned to treatment sequence 1 (oral solution – tablet) and 7 to treatment sequence 2 (tablet – oral solution).

Of the fourteen participants, 6 were females and 8 males. Participants' ages ranged from 19 to 48 (mean: 33.6 years) years, BMI from 23.0 to 31.5 kg/m2 (mean: 27 kg/m2). Participant height and weight ranged from 154.6 to 189.5 cm (mean: 167 cm) and 61.4 to 102.3 kg (mean: 76 kg), respectively. 6 subjects were white, 7 – black or African American, and 1 – "multiple".

All participants completed the study and were included into the PK and statistical evaluation.

There were 9 protocol deviations altogether, the majority of which concerned deviations in the timing of the meals with minimal premature serving. 2 deviations concerned delays in sample collection, one with 3:24 minutes, and the other with 1 minute deviation. One deviation concerned a delay in the follow-up telephone call. All were rated as clinically not important.

PK analysis included a total of 336 time points (i.e., 12 samples per subject during each of both treatment periods with liquid and tablet formulation: once before maralixibat administration and at 11 time points post-dose). In 90 samples maralixibat concentrations were below limit of quantification (BLQ). These included 28 pre-dose samples, 61 samples after the last quantifiable concentration, and one occurred before the first quantifiable concentration (i.e., 62/308, 20% of the samples post-dose has MRX BLQ). All BLQ samples were treated as zero in the analysis. All 14 participants provided enough data points after Cmax to complete the maralixibat plasma concentration-time profiles and to determine the terminal slope.

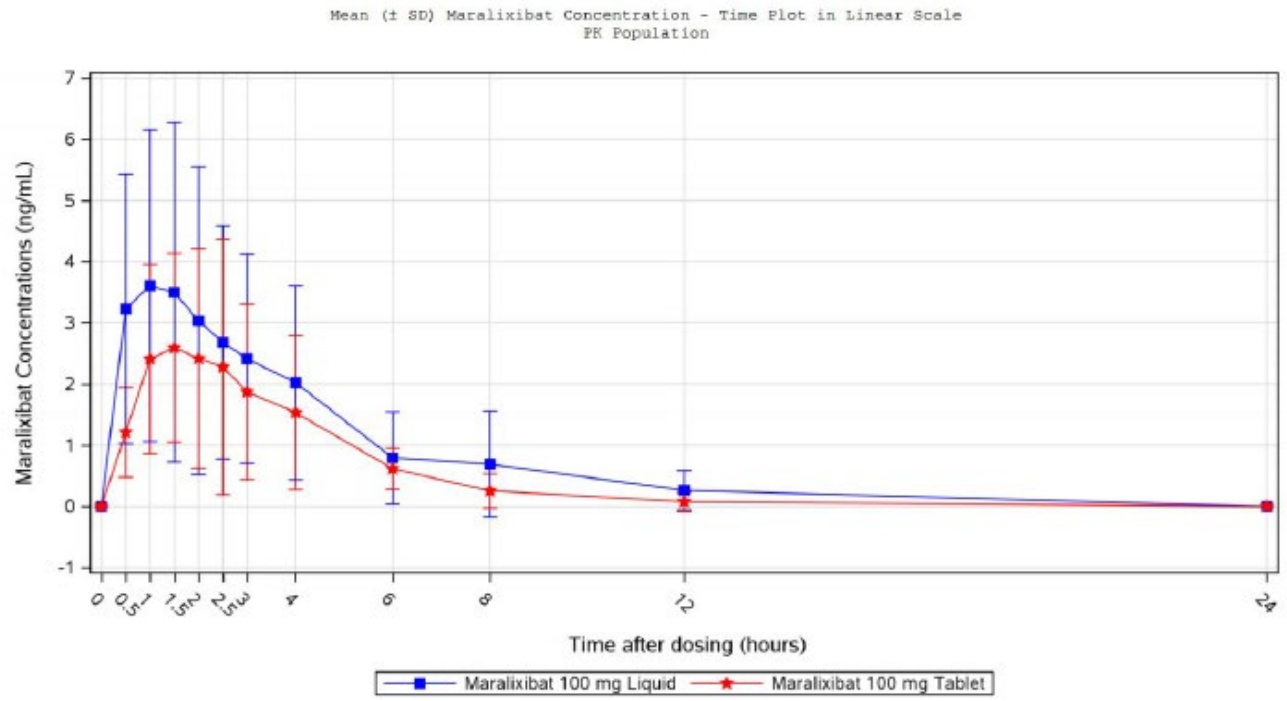
The plasma drug levels after oral administration of either formulation were very low. No plasma drug level above 10 ng/mL was observed at any timepoint. All subjects on liquid formulation had systemic concentrations of maralixibat at the first post-dose sampling time (0.5 h), while at least half of the subjects had no measurable MRX concentrations at the same time point after intake of tablet. At all sampling timepoints, systemic concentrations of maralixibat (mean and median) were higher after intake of liquid formulation (difference in mean/median values ranging between about 30% and 60% in the first 1-1.5 h post-dose). At 12 hours post study drug administration, plasma maralixibat concentrations were minimal, and by 24 hours, concentrations were BLQ for both formulations, indicating that the drug had been eliminated from the blood within 24 hours in both cases. The study drug remained in the body for 3 hours longer after administration of liquid formulation compared to the tablet formulation. The median duration of detectable maralixibat exposure (as calculated with T_{last}) was 10 hours for the liquid formulation and 7 hours for the tablet formulation, although the range was similar for both formulations (~3.9 to 12 hours).

Administration of maralixibat in liquid formulation resulted in a higher geometric mean plasma Cmax compared to the tablet formulation (3.62 ng/mL vs. 2.48 ng/mL) and a more rapid T max (1 h vs. 1.5 h). Both formulations exhibited similar λz and T ½ values, indicating comparable rates of maralixibat elimination. Half-life was determined in 13 participants with 2.58 h for the liquid, and 2.41 h for the tablet formulation.

Both AUClast and AUCinf values were higher for the maralixibat liquid formulation compared to the tablet. The extrapolated area for AUC was high, i.e., >20% in 3 subjects on tablet formulation and 2 after intake of oral solution (between 24.441 and 41.681%) and in 2 cases (one tablet, one oral solution), AUCinf and AUCextrapol could not be estimated.

The concentration time profiles are shown in the figure 1:

Figure 1: Concentration time-profile for maralixibat liquid and tablet formulations (linear scale)



The participant plasma levels and plasma PK parameters showed high variability, with a CV% for group Cmax of 63% for the liquid formulation and 71% for the tablet formulation, a CV% for group AUClast of 73% for the liquid formulation and 74% for the tablet formulation, and a CV% for group AUCinf of 72% for the liquid formulation and 62% for the tablet formulation.

Table 3 Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	**AUC_{0-t}** **xg/ml/h**	**$AUC_{0-\infty}$** **xg/ml/h**	**C_{max}** **xg/ml**	**t_{max}** **h**
Test (tablet)	10.78 ±7.94	13.21 ±8.23	3.04 ±2.17	1.5 (0.98; 2.53)
Reference (oral solution)	16.39 ±11.98	18.37 ±13.24	4.32 ±2.72	1.0 (0.50; 3.93)

Ratio (90% CI)	**0.71** (0.56, 0.90)	**0.77** (0.62, 0.95)	**0.68** (0.56, 0.83)	

AUC_{0-t} - Area under the plasma concentration curve from administration to last observed concentration at time t.

AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

$AUC_{0-\infty}$ - Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}

C_{max} - Maximum plasma concentration

t_{max} - Time until Cmax is reached

Additional data provided with the responses to the LoOI:

In addition to the scientific information presented thus far, a mechanistic model was used to assess the impact of formulation change on the drug concentration-time profile in the human gastrointestinal regions, especially focused on the lumen of the ileum, which is the site of action for maralixibat. The solubility data, in vitro dissolution data and the in vitro permeability data generated were used to simulate the luminal drug concentration profile of maralixibat oral solution and tablets, using a therapeutic dose of 30 mg. Dosing under fasted conditions was simulated to mimic the prandial conditions from the MRX-103 exploratory relative bioavailability study. Additionally, dosing under fed prandial conditions was simulated based on the method of administration.

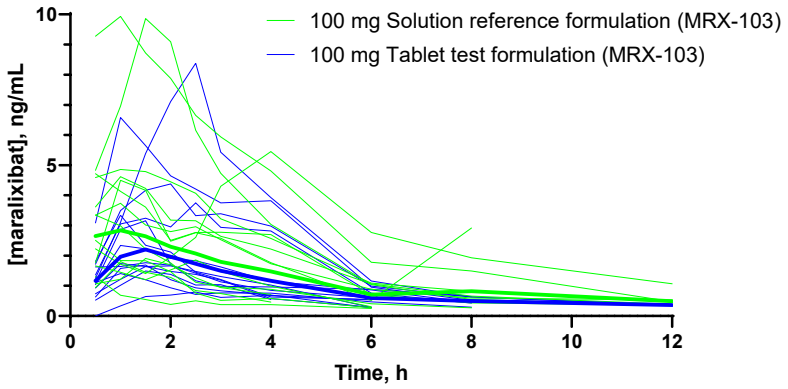
Based on the modelling and simulation the MAH concluded that the data support the knowledge that the drug is highly soluble and the tablets undergo rapid dissolution at different pH conditions, and that the tablet formulation and oral solution reach similar concentrations in the lower gastrointestinal region (especially in the ileum, the site of action of maralixibat) regardless of fasted or fed conditions.

Additional data provided with the response to the 2nd D180 LoOI:

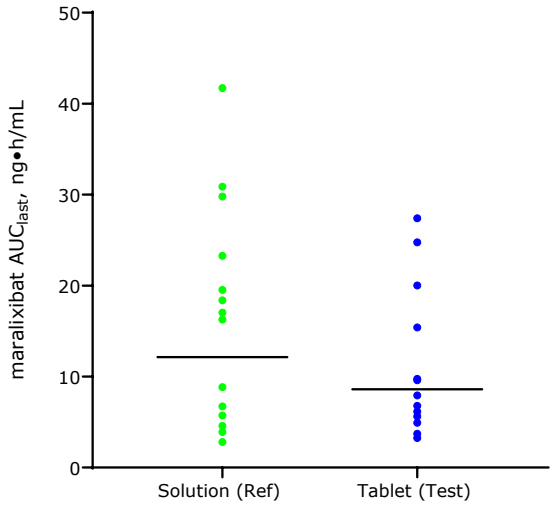
It was argued by the MAH that the oral-solution formulation exhibited a wide (>10-fold) exposure range among 14 participants, whereas exposures with the tablet formulation, although variable, fell within the range observed for the oral solution (Figure below). For the oral solution, AUC_0–last ranged from 2.81 to 41.7 ng·h/mL (n=14); for the tablet formulation, AUC_0–last ranged from 3.26 to 27.4 ng·h/mL (n=14).

Figure 2: Individual and Geometric Mean a) Plasma Concentration Versus Time Profiles and b) AUC_{last} of Maralixibat After Single Oral Solution or Tablet Doses Administered to Healthy Adult Participants Under Fasted Conditions

a)



b)



Thin line=individual profile; thick line=geometric mean

The study MRX-103 was designed as a crossover study to minimise between-subject variability; nevertheless, AUC variability was comparable to or higher than in previous studies (i.e., parallel-group setting). It was further asserted by the applicant that no scientific basis exists for within-subject variability to exceed between-subject variability, and that the variability observed in the oral-solution arm (>10-fold exposure range), considered by the applicant to underlie the 23.4% difference versus the tablet, represents an outlier relative to the broader clinical PK dataset. On this basis, the applicant argued that robust statistical conclusions are limited for a drug with minimal and variable systemic absorption. Despite the wider exposure range for the oral solution, the tablet-to-solution point estimate Geometric least squared mean ratio (GLSMR 77%) was noted to fall only slightly below the conventional 80% lower bound and, in the applicant's view, does not constitute a major PK deviation given the variability and the limited clinical relevance of systemic exposure.

2.6.2.2. Pharmacodynamics

Primary and Secondary pharmacology

Post hoc analysis of 7αC4 (referred to as "C4")

The following additional information was submitted during procedure:

The PD evaluation was performed in a post hoc analysis from the MRX-103 study samples. Plasma samples at predose and 24-hour postdose maralixibat administration were analysed for 7αC4 concentration via a validated LC-MS/MS assay. The 24-hour timepoint was selected as it was the last postdose timepoint collected in the MRX-103 study. Additionally, the predose and 24-hour postdose timepoints were collected at a similar time of day, thus potentially correcting for diurnal effects of the C4 assessment. The bioanalytical study report CMS-MIRUM-C4-001 with the raw data was submitted.

Study samples were collected between 30OCT2023 and 03NOV2023, stored at -80°C, and analysed for C4 concentration on 25APR2024. Long term stability data provide stability coverage at -80°C for this time period.

To allow for the calculation of the geometric mean, a single negative change from baseline value was excluded from the calculation for each formulation type (n=13 per formulation). The geometric mean (SD) C4 changes from baseline were 9.49 (3.17) ng/mL and 12.0 (5.21) ng/mL for the maralixibat tablet and liquid formulations, respectively.

Figure 3: Box and Whisker Plot of 7αC4 Plasma Change from Baseline – Study MRX-103 Liquid Formulation versus Tablet Formulation

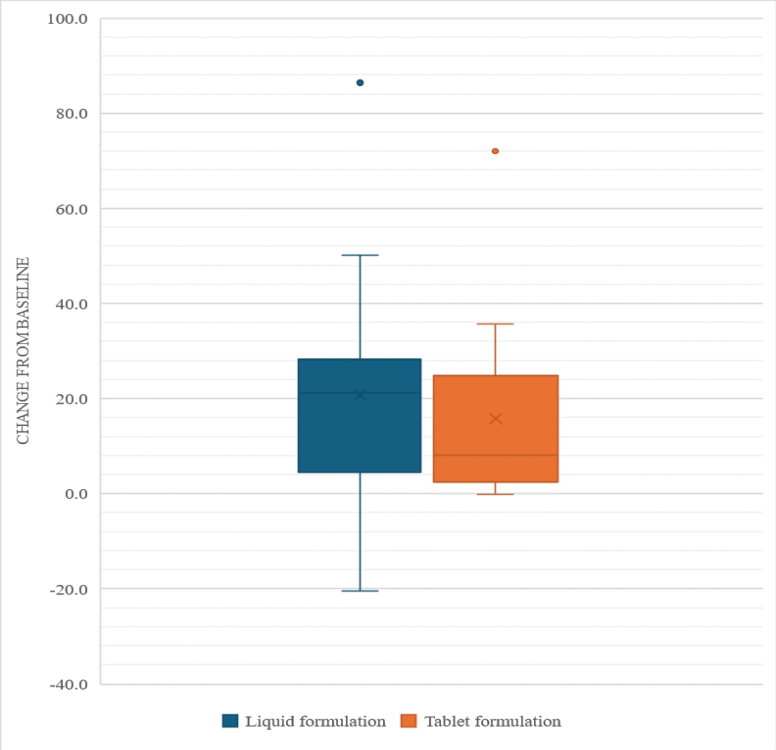
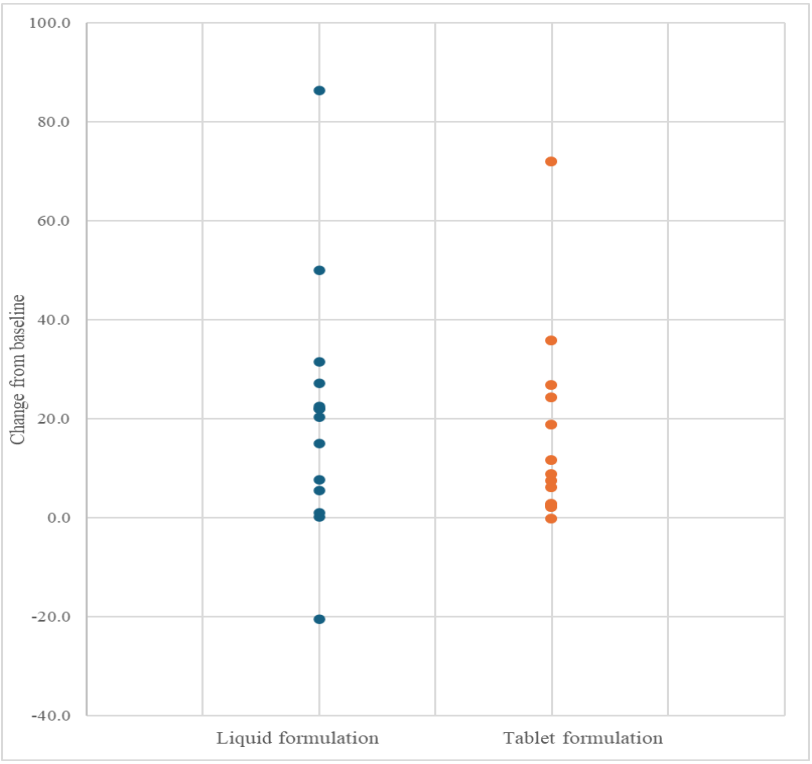
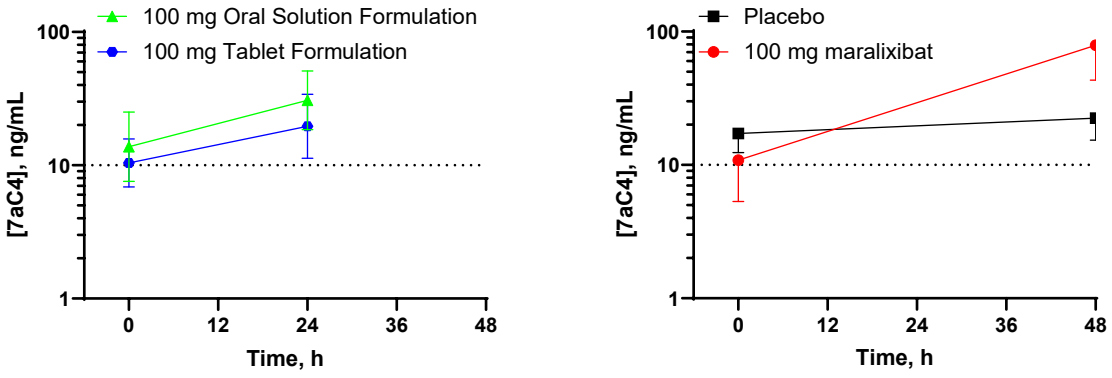


Figure 4: Individual Subject 7αC4 Plasma Change from Baseline Values – Study MRX-103 Liquid Formulation versus Tablet Formulation



To provide context for the observed changes in C4 in Study MRX-103, available C4 data at baseline and after two oral doses of either placebo or 100 mg maralixibat are presented in the Figure below (Study SHP625-101, right graph). The data demonstrate that changes from baseline with placebo (no PD effect expected) in Study SHP625-101 are negligible, while the magnitude change from baseline after a dose of 100 mg maralixibat in MRX-103 (either as a tablet or oral solution; Figure below, left graph), is detectable and consistent with the change from baseline slope after 100 mg maralixibat in Study SHP625-101 (Figure below, right graph) in the Applicant's opinion.

Figure 5: Geometric mean (95% CI) Baseline and Postdose 7αC4 Concentrations After Oral Doses of Maralixibat or Placebo Administered to Healthy Adult Participants Under Fasted Conditions



Source: Study MRX-103 (left graph) after single dose; Study SHP625-101 (right graph) after 2 doses.

Additionally, the individual subject C4 baseline and post dose concentrations are presented in below Figure as intra-subject comparisons.

Figure 6: Individual Baseline and Postdose 7αC4 Plasma Concentrations After a Single Oral Dose of Maralixibat Oral Solution or Tablet Formulation to Healthy Adult Participants Under Fasted Conditions in Study MRX-103

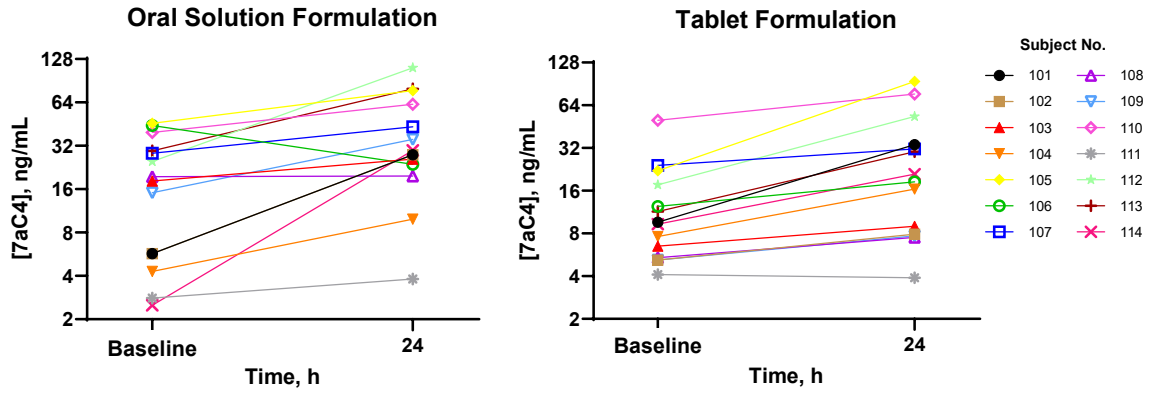
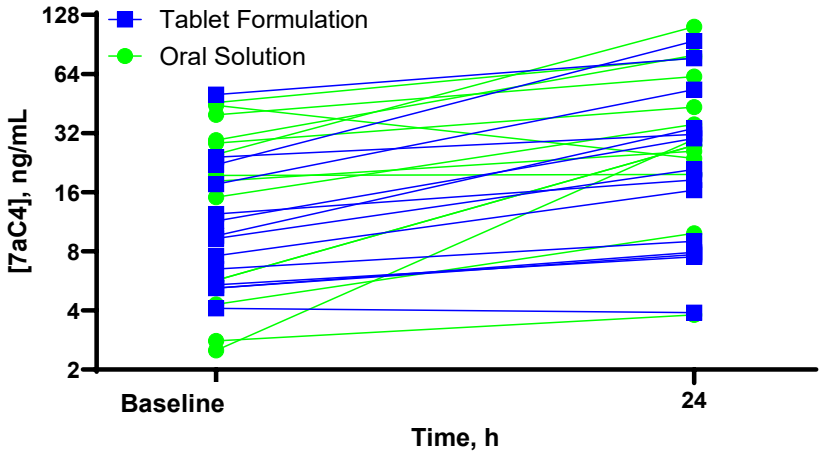


Figure 7: Overlay of Individual Baseline and Postdose 7αC4 Plasma Concentrations After a Single Oral Dose of Maralixibat Oral Solution or Tablet Formulation to Healthy Adult Participants Under Fasted Conditions in Study MRX-103



The raw data per patient have been listed in the table below.

Analysis of the raw data of C4 from the MRX-103 study in regard to the reference value of ULN shows that 4 subjects (from 14) on liquid formulation and 2 subjects (from 14) on tablet formulation had C4 concentrations above the ULN 24 h post-dose.

From the 4 subjects with diarrhoea on liquid solution, two subjects () had C4 >ULN, or close to ULN, and two () had normal C4 with post-treatment change that was larger on liquid formulation. Notably, the subjects with C4 >ULN/close to ULN had higher post-dose concentrations of C4 and larger change in C4 concentrations after intake of tablet formulation but did not develop diarrhoea. I.e., the subject had C4 increase from 22.1 ng/ml to 94.1 ng/ml, and from 45.8 ng/ml to 77.4 ng/ml on tablet and oral solution, respectively. Subject had C4 increase from 50.2 ng/ml to 76.9 ng/ml and 39.6 ng/ml to 62.1 ng/ml on tablet and liquid formulations, respectively.

Additional data provided:

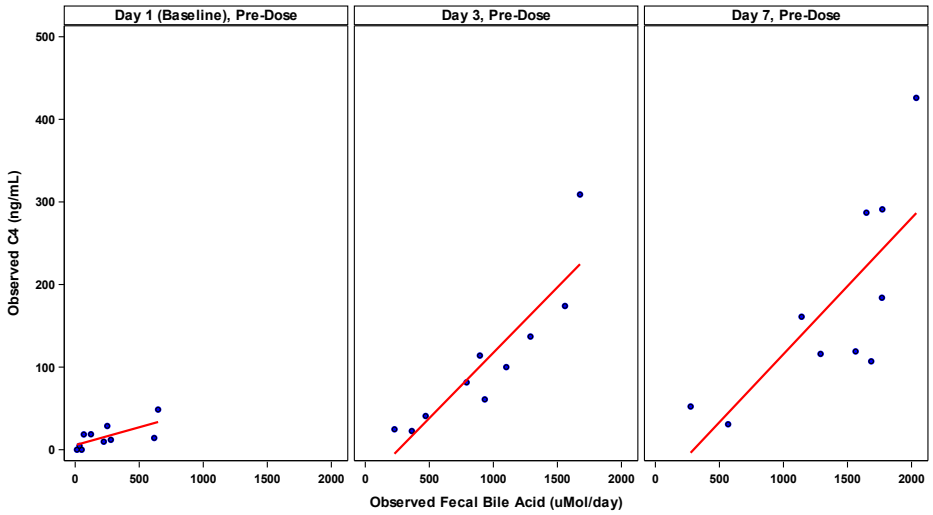
Additional post hoc analyses based on the data from earlier studies to support reliability of C4 as a PD parameter was provided.

Post hoc correlation analysis between C4 and faecal bile acid (fBAs) was conducted based on the data from the phase 1 study in healthy volunteers Study SHP625-101 on once daily 100 mg maralixibat (oral solution) or placebo administered over 7 days under modified fed (intake of maralixibat 30 min before the meal) conditions.

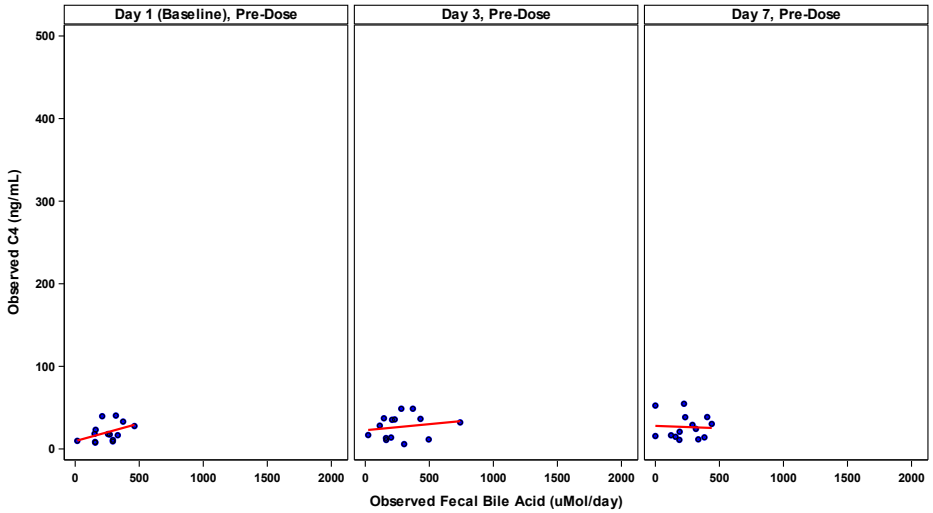
Baseline fBA concentrations were low and no relevant correlation was shown, but concurrent increases in 7αC4 and fBA with repeated maralixibat dose were observed. No changes (and absence of correlation) were observed on placebo. (see the figures with scatter plots and the Spearman correlation coefficients and corresponding p-values in the table below).

Figure 8: Scatter Plots of Observed 7αC4 versus Faecal Bile Acid Concentrations after Dosing Maralixibat or Placebo to Healthy Participants across Dosing Days

a) 100 mg maralixibat cohort in Study SHP625-101



b) Placebo cohort in Study SHP625-101



C4=7αC4. Baseline total faecal bile acid (fBA) is the average of fBA values from Day -2, Day -1, and predose on Day 1. Day 3 is the average of Days 2 and 3. Day 7 is the average of Days 6 and 7.

Table 4: Correlations of Observed 7αC4 versus Faecal Bile Acid Concentrations and Change from Baseline Response after Dosing Maralixibat or Placebo to Healthy Participants across Dosing Days in Study SHP625-101

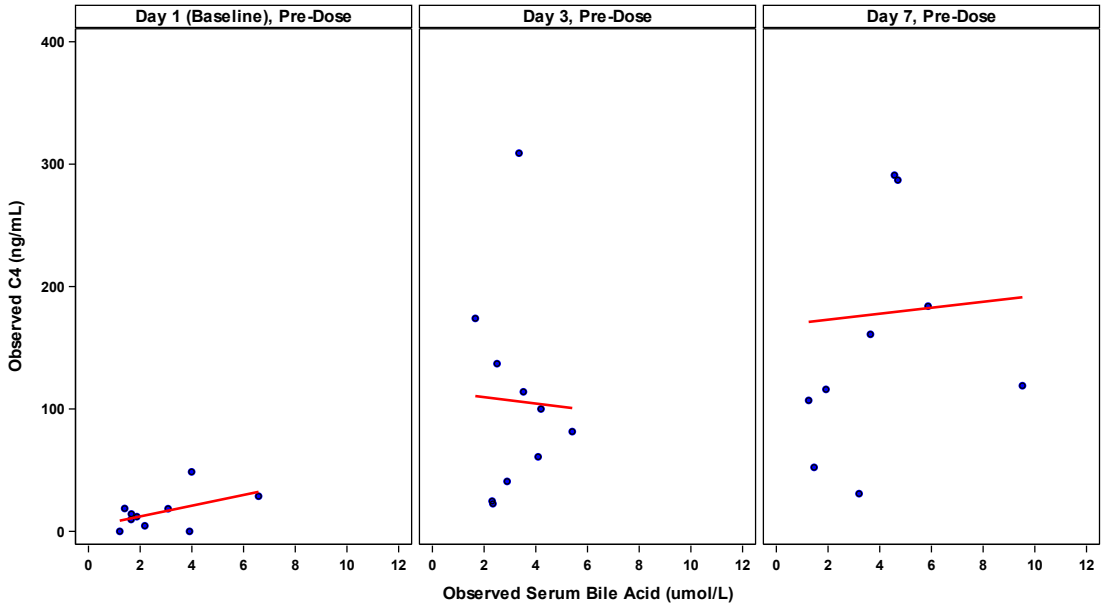
Treatment	Parameter	7αC4		
		Baseline	Day 3 Predose	Day 7 Predose
100 mg maralixibat	fBA	0.7112 (0.0211)	0.9273 (0.0001)	0.8061 (0.0049)
	fBA CFB	NA	0.9394 (<0.0001)	0.6485 (0.0425)
Placebo	fBA	0.4286 (0.1263)	0.1342 (0.6474)	0.0946 (0.7477)
	fBA CFB	NA	-0.6176 (0.0186)	-0.0462 (0.8755)

CFB=change from baseline; fBA=faecal bile acids; NA=not available.
Note: Spearman correlation coefficients (corresponding p-values) are presented. Baseline total fBA is the average of fBA values from Day -2, Day -1, and predose on Day 1. Day 3 is the average of Days 2 and 3. Day 7 is the average of Days 6 and 7.

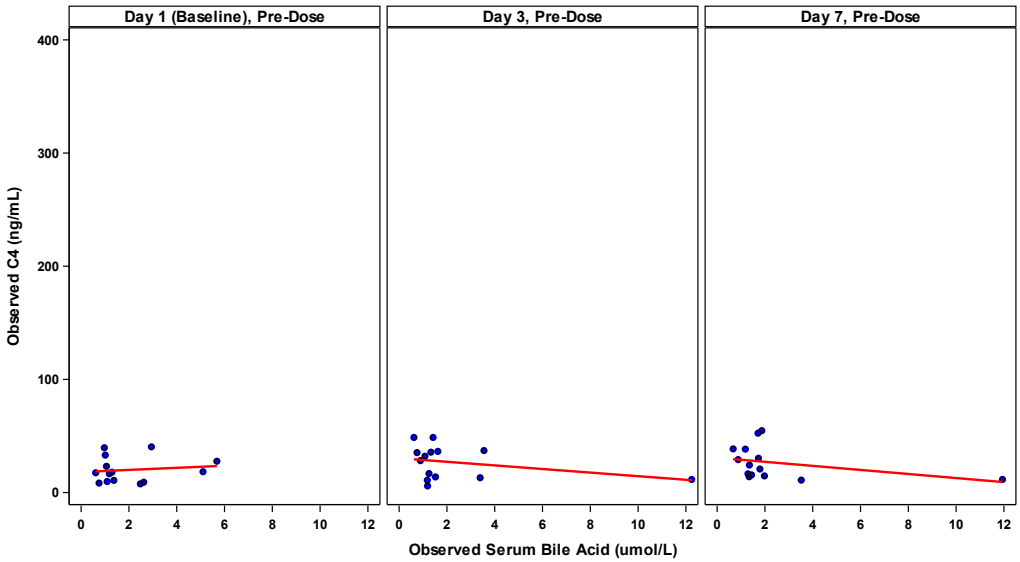
Correlation analysis between the levels of C4 and serum bile acids on 100 mg maralixibat showed increased C4 levels on days 3 and 7 without considerable changes in the sBA concentrations. No changes were seen on placebo.

Figure 9: Scatter Plots of Observed 7αC4 versus Serum Bile Acid Concentrations after Dosing Maralixibat or Placebo to Healthy Participants across Dosing Days

a) 100 mg maralixibat cohort in Study SHP625-101



b) Placebo cohort in Study SHP625-101



C4 levels in blood inform on the hepatic bile acid synthesis. C4 increases when intestinal absorption of bile acids is reduced/excretion of bile acids with faeces is increased. Elevated levels of C4 in after maralixibat dosing are interpreted as evidence of effective IBAT inhibition, and a modest rise from baseline 24 hours after a single fasted dose in healthy participants is likely expected. Maintained levels of serum BA in spite of increased C4 can be explained with compensatory mechanisms (increased production of BA ensures maintained levels of sBA in spite of decreased reabsorption on maralixibat), and by the fact that sBA was evaluated under fasted condition, when the levels are the lowest (postprandial changes were not evaluated). In the applicant's opinion these data show the ability of C4 to adequately reflect IBAT inhibition in the intestines.

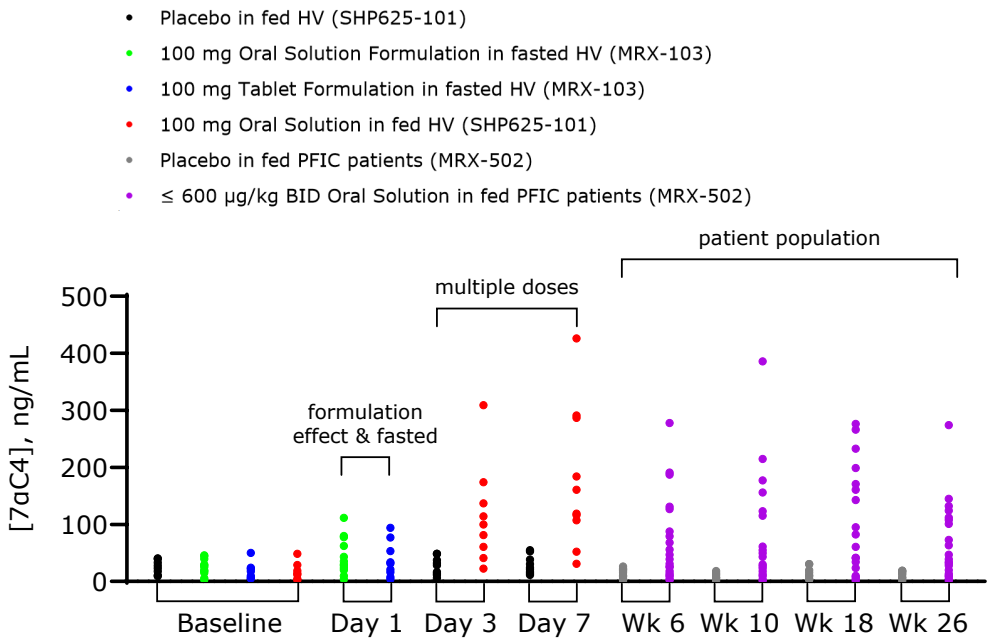
The applicant claims that in **Study MRX-103**, a PD effect (change from baseline in C4 concentrations) with a similar magnitude was observed for the tablet and oral-solution formulations, when maralixibat was administered under fasted conditions, as in other studies. To substantiate this statement C4 data were plotted across selected studies (Figure 11), including maralixibat studies in healthy participants and in patients where C4 data were available and study design allowed single-timepoint evaluation.

As shown in Figure 11, a detectable change from baseline in C4 after a single assessment under maralixibat exposure was observed across all evaluated healthy-participant studies. Study SHP625-101 showed a change-from-baseline response after 100 mg maralixibat under fed conditions (within 30 minutes of a meal) and after multiple doses; despite variability, the magnitude exceeded that in MRX-103, consistent with multi-day dosing, whereas placebo produced no increase across multiple doses.

In **PFIC patients (Study MRX-502)** with moderate-to-severe cholestasis, baseline C4 levels were expected to be lower than in healthy participants owing to chronic inhibition secondary to bile-acid accumulation (as reflected in the placebo data); relative to placebo, dosing $\leqslant$600 µg/kg maralixibat under fed conditions and after multiple doses yielded a variable yet detectable PD response within the ranges of MRX-103 and SHP625-101.

Overall, the applicant argues that the available data in healthy participants and patients indicate that C4 is an adequate PD biomarker of IBAT inhibition. Cross-study measurements are considered by the applicant to support the conclusion that no major formulation-related differences were observed in Study MRX-103 and that the PD response is clinically meaningful in view of the study design and biomarker variability.

Figure 10: Individual Baseline and Postdose 7αC4 Concentrations After Oral Doses of Maralixibat or Placebo Administered to Healthy Adult Participants (Fasted or Fed) or Patients across Studies



HV=healthy volunteers.
Note: Fed prandial condition represented by dosing within 30 min of a meal.

Pharmacodynamic Biomarker Similarity across Formulations/additional PD analyses (MRX-103 study)

Analysis of covariance (ANCOVA) of C4 change from baseline was performed for 13 evaluable participants who received both formulations n the crossover study MRX-103 (Table 5). The model included sequence, subject-within-sequence, period and treatment (formulation) as fixed categorical effects and baseline C4 value (ln-transformed) as a continuous covariate. Mean (geometric mean, GM) and variability (geometric coefficient of variation, gCV %) are presented for each formulation together with the geometric least-squares means (GLSM) and the tablet-to-solution geometric least-squares mean ratio (GLSMR) with its 90 % confidence interval. The results show that the baseline-adjusted GLSMR for tablet versus solution was 0.60 (90 % CI 0.29–1.24).

Table 5: Analysis of Covariance of 7αC4 Change from Baseline for the Maralixibat Tablet and Oral Solution Formulations in MRX-103

Formulation	**Tablet**		**Solution**		**Tablet to Solution**
Parameter	**GM (gCV%)**	**GLSM**	**GM (gCV%)**	**GLSM**	**GLSMR (90% CI)**
7αC4 Change from Baseline (n=13)	9.49 (167)	7.10	12.0 (378)	11.8	0.60 (0.29–1.24)

Note: ANCOVA model with sequence, subject-within-sequence, period, and treatment (formulation) as fixed categorical effects, as well as the continuous fixed covariate of baseline results as ln-transformed data.

Table 6 summarises responder analyses of categorical fold-increase in 7αC4 from baseline for each formulation. Participants were classified into predefined categories of fold change (<1.5, 1.5–2, >2–3, >3–4, >4). Among participants treated with the oral solution, 4 of 14 (29 %) demonstrated >4-fold increases in C4, whereas only 1 of 14 (7 %) reached this category on the tablet. Less stringent response categories showed a more balanced distribution across formulations.

Table 6: Categorical Fold Increase in 7αC4 Change from Baseline for the Maralixibat Oral Solution and Tablet Formulations in MRX-103 (5 Categories)

	Fold Increase in 7αC4 Change from Baseline n (%)				
Fold Change Category	**<1.5**	**1.5–2**	**>2–3**	**>3–4**	**>4**
Oral Solution	4 (29)	3 (21)	3 (21)	0 (0)	4 (29)
Tablet Formulation	4 (29)	4 (29)	4 (29)	1 (7.1)	1 (7.1)

- ***BCS Class***

Solubility

Solubility of the maralixibat drug substance in 0.1N HCl, pH 4.5 acetate buffer, water, and pH 6.8 phosphate buffer was evaluated by adding approximately 25 mg of maralixibat drug substance to 10-mL aliquots of the different buffers. The solutions were heated to 37°C and stirred for 2 hours. The samples were centrifuged, and the supernatant analysed by high performance liquid chromatography. The solubility results are presented in the table below. The results show that 100% of the maralixibat substance goes into solution under these conditions.

Table 7: Solubility of 25 mg Maralixibat Drug Substance in 10 mL of Buffers at 37°C

Buffer	Measured Concentration of Maralixibat in Buffer (mg/mL)
0.1N HCl	2.57
pH 4.5 acetate buffer	2.67
Purified water	2.77
pH 6.8 phosphate buffer	2.64

The drug substance did not precipitate out of solution through the duration of evaluation, thereby aligning with the BCS definition of highly soluble.

Equilibrium solubility experiments have been performed by the Applicant using the shake flask method to determine solubility in three pH buffers at pH 1.2, 4.5, and 6.8 using a shake-flask technique, to dissolve approximately 76 mg of maralixibat chloride in 20 mL of buffer to demonstrate that the maximum daily dose of 30 mg BID will be easily dissolved in 250 mL of gastric media. The pH of each test solution was measured after the addition of maralixibat chloride drug substance and did not change at the end of the 24-hour equilibrium study. The results indicated that the 24-hour equilibrium solubility of maralixibat chloride drug substance remains effectively constant (3.69–3.77 mg/mL) across a range of 1.2 to 6.8 pH. This concentration is significantly higher than 0.24 mg/mL of maralixibat in solution as expected when dosing 30 mg tablets, BID in 250 mL of gastric media demonstrating that the drug substance is highly soluble, rapidly dissolves, and is in solution for at least 24 hours.

Table 8: pH Solubility of Maralixibat Chloride over 24 hours

Time	Concentration (mg/mL)		
	pH 1.2	**pH 4.5**	**pH 6.8**
15 min	3.29	3.74	3.51
30 min	3.63	3.75	3.75
45 min	3.64	3.88	3.77
60 min	3.67	3.60	3.73
24 hr	3.75	3.69	3.77

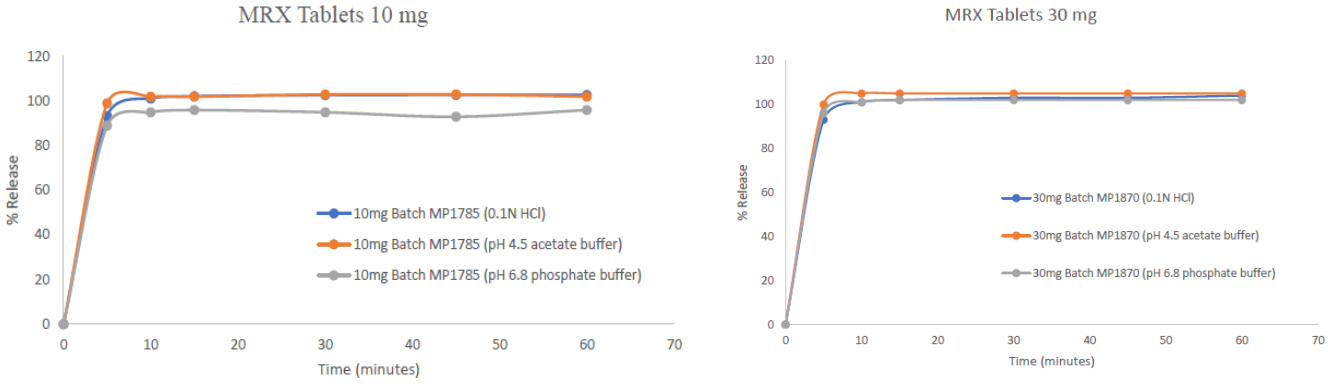
The Applicant argues that the highest strength of maralixibat tablet for this registration procedure is 30 mg, which would result in a GI concentration of approximately 0.12 mg/mL of maralixibat drug substance using the standard GI volume estimate of 250 mL and concludes that drug substance is at least 20 times more soluble than this value at the gastro-relevant pH range from 0.1N HCl – pH 6.8. In the Applicant's opinion, these results establish that the drug substance is solubilized at all required doses in biorelevant conditions, as defined in ICH M9 and maralixibat can be considered a BCS Class III compound. In addition, because the site of action for IBAT inhibition is located at the luminal surface of ileal enterocytes in the terminal 25% of the small intestine, the complete dissolution of the maralixibat tablet before it reaches the site of action is adequate to ensure the same availability of drug at the site of action with the tablet compared to the liquid formulation, in the Applicant's opinion.

- ***In vitro dissolution test***

To demonstrate that Livmarli tablets would be completely dissolved and remain dissolved throughout the GI tract when it reaches its site of action, three tests for dissolution of tablet formulations (10 mg and 30 mg strengths; the highest and the lowest strengths to be marketed) were performed in biorelevant dissolution media such as 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer and using USP Apparatus.

The dissolution profile of the proposed maralixibat tablets included the 5-minute and 10-minute measurements, demonstrating over 90% drug release within 10 minutes in all biorelevant media used for testing, and complete dissolution within 60 minutes (see figures below).

Figure 11: Dissolution profile of Maralixibat tablets, 10 mg and 30 mg in 0.1N HCl, pH 4.5 Acetate Buffer, and pH 6.8 Phosphate Buffer



2.6.3. Oral explanation

The company presented their position on this line extension procedure, and in particular on the demonstration of therapeutic equivalence, to the CHMP at oral an explanation on 11th November 2025. The main arguments brought forward were the following:

Systemic bioequivalence is of minimal relevance as maralixibat is minimally absorbed and the efficacy is local in terminal ileum. The totality of evidence generated demonstrates the two formulations are sufficiently similar to establishing a positive benefit-risk for the tablet formulation

- Very rapid in vitro dissolution ensures tablets behave like oral solution at site of action
- Same maralixibat concentration predicted at target site for tablets and oral solution formulation
- Similar PK profile in rBA Study MRX-103 between the two formulations considering the PK variability
- Similar magnitude of effect on 7αC4, PD biomarker on IBAT mechanistic pathway

2.6.4. Discussion on clinical pharmacology

The applicant pursues a line-extension for its product Livmarli 9.5 mg/mL, oral solution, in form of a new solid oral dosage form (tablet) to be used by adults and older paediatric patients.

Four different dose strengths, 10mg, 15mg, 20mg and 30mg are planned to be marketed.

The active substance maralixibat, a selective inhibitor IBAT, is absorbed minimally (bioavailability estimated as <1% after intake of oral solution) and acts locally in the terminal ileum at the apical membrane of the enterocytes. Thus, this drug product does not need to be systemically absorbed for pharmacological activity.

Generally, in those cases where the test product is an oral solution which is intended to be bioequivalent to another immediate release oral dosage form, bioequivalence studies are required (EMA Guideline on investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 2010).

As maralixibat is an active substance locally acting in the intestine, in addition, the requirements of the Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev. 1, Corr.1*, 2018), apply. According to this guidance therapeutic/PD equivalence study would be expected.

However, standard requirements such as confirmatory PD/therapeutic equivalence study in target population were regarded not feasible due to the rarity of the disease and highly vulnerable population (ALGS, PFIC). Conduct of an adequately powered BE study in healthy volunteers was considered challenging given very low systemic availability (<1%) of maralixibat and high PK variability.

Recognising these constraints, the CHMP accepted a limited data package proposed by the applicant, i.e., proof of very fast *in vitro* dissolution and exploratory evidence of similar BA in healthy subjects. Additionally, potential impact of food/food contents on efficacy of maralixibat was indicated as a relevant aspect in the CHMP scientific advice. It was agreed these two main data packages would likely serve as the basis for decision.

The Applicant has, thus, submitted: 1. data from an *in vitro* dissolution testing of the lowest and the highest to-be-marketed Livmarli tablet strengths (10 mg and 30 mg), and 2. data from one exploratory clinical comparative BA study in 14 healthy volunteers. Additionally, comparison of the PK parameters across two studies MTX-103 (Tablet and oral solution, 100 mg single dose) and MTX-102 study (oral

solution, 30 mg, 45 mg, and 100 mg single dose) to claim dose-linearity and similarity of exposure across studies have been provided.

2.6.4.1. BCS Class/Solubility of maralixibat and in vitro dissolution testing

2.6.4.1.1. BCS Class – solubility of maralixibat

Maralixibat is claimed to possess high water solubility and is a BCS Class III compound according to the applicant. The summary results indicate high equilibrium solubility of maralixibat chloride considering the highest single therapeutic dose. The solubility remains effectively constant (3.69-3.77 mg/mL) over a time-period of 24 hours across a pH range of 1.2 to 6.8. Compliance with the requirements of ICH M9 was confirmed. It is assumed that solubility of maralixibat remains constant regardless of the chosen formulation and under similar conditions as soon as the substance is released.

Maralixibat is surface-active compound with a CMC of approximately 0.6 mg/mL in water under ambient conditions. Surfactants exist as monomers below the CMC and the rate of dissolution is dependent on the concentration gradient between the undissolved solids and dissolved monomers in solution. Once the micelles are formed, they prevent monomer accumulation and provide a driving force for dissolution, allowing the drug substance to directly integrate into micelles thereby increasing the rate of solubilization. For maralixibat, a slower dissolution phase at concentrations < 0.6 mg/mL (i.e., below CMC) and a significantly faster dissolution phase when the concentration reaches > 0.6 mg/mL have been reported.

2.6.4.1.2. In vitro dissolution testing

The performed in vitro dissolution experiments with the (USP apparatus, 37°C±0.5°C, compendial media, number of samples (n=12)) are in line with the conditions stipulated by ICH M9. The experiments were only performed with the new tablet formulation with the 10 mg and the 30 mg strengths. Omission of the 15 mg and 20 mg tablet strengths is acceptable, since manufacturing with the same process and quantitative proportionality in composition have been demonstrated.

The experiments showed a very rapid dissolution (≥ 85% within 15 Minutes) for all media and for both strengths of the tablet formulation.

2.6.4.2. MRX-103 Study

Study design and study population

This was a phase I open-label randomised cross-over study in healthy volunteers evaluating relative BA of Livmarli tablets against Livmarli oral solution 9.5 mg/ml. Tablet strength (i.e., 50 mg) and the applied dose (100 mg MRX) were higher than the to-be-marketed tablet strengths and the recommended maximum daily dose. This was accepted, as with recommended dose (max. 30 mg per intake) measurable systemic exposure might not have been reached.

The study size, population, design, objective, study procedures, and evaluated parameters are accepted. This was an exploratory study that cannot confirm or reject presence of bioequivalence, and the data should be seen as one piece of the totality of evidence on PK similarity of tablet vs. oral liquid formulation, that by extension may be assumed as similarity in PD/efficacy.

Data are available from all 14 subjects included. No major protocol deviations have been reported.

2.6.4.2.1. Bioanalytical method validation and bioanalysis of study samples in study MRX-103

For study MRX-103, the previously fully validated method of quantitative assessment of maralixibat in human plasma was transferred from the site. Study MRX-103 maralixibat PK samples were analyzed at the new site,

The documentation of analytical methods therefore comprises a Method Transfer Report (dated 06 June 2024; amended final report comprising partial and cross validation results), as well as the "on-study" bioanalytical report for study MRX-103.

Both, partial and cross-validations are burdened with deficiencies.

For study MRX-103, increase in measured plasma concentrations, that was apparently associated with the method transfer (~20-27% higher at the new facility based on the limited data available) should not have any relevant impact on the outcome, since both pharmaceutical dosage forms are expected to be affected in a similar manner.

However, a direct comparison of results from study MRX-103 with results from previous studies in which bioanalysis was conducted at the previous site is not supported by adequate cross-validation and is therefore considered to be of limited value only and does not allow firm conclusions.

Additionally, in study MRX-103 AUCinf values are not regarded robust, since in >20 % of the observations AUCextrap was either greater than 20% (24% - 42% in 3 subjects on tablet formulation and 2 after intake of oral solution) or AUCinf and AUCextrapol could not be estimated at all (2 cases, one tablet, one oral solution).

2.6.4.2.2. Bioanalysis of study samples in study MRX-103

The bioanalysis of the study samples in study MRX-103 does not fully comply with regulatory guideline recommendations.

Method MARLHPP is not fully suitable for bioanalysis of study samples in study MRX-103 as the validated LLOQ at 0.25 ng/mL is not sensitive enough in relation to the obtained Cmax values in this study (>5% Cmax). This precluded guideline-compliant quantification of pre-dose concentrations and carry-over in this study and may have additionally affected the reliability of the AUCextrapol /AUC measures. The results from study MRX-103 should therefore be interpreted with caution.

Importantly, although study MRX-103 is a comparative BA study, not all samples per subject were analysed together in one analytical run, contrary to ICH M10 guideline recommendations and equally contrary to the applicable policy. In addition, the chromatographic integration modes and parameter settings additionally differed for individual samples and between analytical runs, respectively, which all may have impacted the results. Although ISR results may be considered somewhat reassuring, being consistent even in cases where the smoothing factor differed from that used in the original sample analysis, the samples selected by the applicant for ISR do not represent the type of samples that are most sensitive to changes in smoothing factor.

In view of these findings, the applicant provided the GLP/GCP inspection history of the and sites by US FDA, respectively, including issued establishment inspection reports (EIR). Regarding the most recent remote inspection carried out by US FDA at the site in Jan 2025, the applicant declared that it specifically addressed study MRX-103 and that no observations were noted at the close of audit in this remote inspection.

2.6.4.2.3. MRX-103 study – PK data

Comparative pharmacokinetics - absorption rate

Overall, data suggest that systemic exposure to MRX after intake of the tablet formulation remains very low in line with the approved oral solution. Both formulations exhibited comparable half-lives (2.58 hours for the liquid, and 2.41 hours for the tablet formulation) and rates of maralixibat elimination. At 12 hours post study drug administration, plasma maralixibat concentrations were minimal, and by 24 hours, concentrations were BLQ for both formulations, indicating that the drug had been eliminated from the blood in both cases. Consequently, no new safety concerns are raised.

The study data showed some differences in the PK profiles of the proposed tablet and approved oral solution of Livmarli. The absorption rate after intake of the test (tablet) formulation was clearly lower than that of the reference (oral solution):

- Tablet formulation showed less steep upward slope, lower Cmax (2.48 ng/mL vs. 3.62 ng/mL), and later Tmax (1 h vs. 1.5 h) compared to liquid formulation.
- Maralixibat was not measurable at the first post-dose sampling time (0.5 h) in at least half of the subjects on tablet, whereas all subjects on oral solution had maralixibat measured at the same time point.
- Almost half (6/14) of the subjects had Tmax already at 0.5 h post-dose (i.e., first post-dose sampling point) on liquid formulation, while no such cases were observed on tablet formulation.

Comparative pharmacokinetics - systemic exposure

Also, systemic exposure to MRX was lower on the test formulation (tablet) compared to the reference (oral solution):

- Both AUClast and AUCinf values were lower after intake of tablets (Ratios of GSLM and 90% CI were 0.71 [0.56, 0.90] and 0.77 [0.62, 0.95], respectively).
- Cmax showed even larger difference, with GSLM ratio (90%CI) of 0.68 (0.56, 0.83); Systemic concentrations of maralixibat (mean and median) were lower after intake of tablets by about 30-60% (mean/median values) during the first 1-1.5 h post-dose.
- At 12 hours post study drug administration, at least half of the subjects on tablet had no measurable MRX concentrations, while majority of the subjects had MRX > BLQ on liquid formulation as judged from the median values of actual concentration measurements.
- Maralixibat remained in the body 3 hours longer after administration of liquid formulation compared to the tablet formulation (median Tlast 10 and 7 h post-dose, respectively).

Systemic availability of MRX is not directly relevant for exerting PD/efficacy. However, it may be an indicator of different pattern of transportation of maralixibat to target location (e.g., due to the need of tablet dissolution in vivo).

Whether the difference observed in the PK profiles and BA will translate into lower efficacy of Livmarli tablets compared to Livmarli 9.5 mg/ml solution is unclear. Importantly, comparative BA of the test vs reference product was evaluated under optimal conditions when all procedures were strictly standardised (on site clinical setting, strictly defined procedures of drug intake, 10 h fasting time prior and 4 h after to drug intake, healthy population, within-subject comparison) and presence of potential confounders was minimised (e.g., food intake, intake of other medications).

PBPK modelling - assumptions and limitations

In order to address the concern of different/lower concentrations of maralixibat at target location on tablet a PBPK model was built using in vitro measurements, estimated or default (from the software) values for the different physicochemical and biopharmaceutical parameters for maralixibat. Since no observed data are available in the GI tract, the simulations are based on many assumptions which cannot be validated, thus leading to high uncertainties in the simulated concentrations. Therefore, the model-based simulations cannot be considered supportive for any statement on concentration-time curves in the different sections of the GI tract and these data are not considered in this assessment.

Food effect and administration recommendation

Since intake of Livmarli (tablets and oral solution) is recommended up-to 30 min before, or with meal, it is reasonable to assume that in vivo dissolution of Livmarli tablets, and, consequently, drug release and subsequent drug delivery may be disturbed because of food intake. Adequacy of the recommendations on administration of Livmarli tablets was, thus, questioned, and discussion of alternative recommendations considering in vivo dissolution speed were requested. The Applicant states that the chosen tablet formulation is disintegrated in the stomach within 7.5 min (observation based on an in vitro testing) and is dissolved also very fast. The formulation contains standard excipients and that no interaction would be expected in terms of tablet dissolution, transit time, or absorption in the gut.

Additionally, the applicant agreed to modify the dosing recommendation such that Livmarli tablets are to be taken 30 minutes before a meal (previously: "*up to 30 minutes before, or with a meal*"). The revised instruction aims to minimise the potential impact of food on tablet dissolution and drug delivery

Post hoc PD analysis: rationale for selecting C4

In order to substantiate close similarity of the tablet vs. liquid formulation, the applicant has provided a post hoc PD analysis choosing C4 as a parameter. The applicant argues that sBA is unsuitable as a PD parameter in the case of MRX-103, as the study was conducted in healthy subjects under fasting conditions and healthy subjects under fasting conditions already have low levels of sBA, so that sBA reducing effects of maralixibat would not have been seen. Omission of sBA for assessment of PD was accepted.

From published literature the following is known about C4:

· Camilleri et al., (2009) report that in healthy adult cohorts the 5th-95th percentile for serum C4 was approximately 6-60.7 ng/mL (n=111 controls in one study). Mayo Clinic Laboratories lists adult reference values ≈2.5-63.2 ng/mL (fasting sample recommended; https://www.mayocliniclabs.com/api/sitecore/TestCatalog/DownloadTestCatalog?testId=607699);

- Diurnal changes in C4 are known with two peaks around 1 p.m. and late in the evening;
- Collection of blood samples for analyses is recommended early in the morning (before 9 a.m.), as this allows avoid diurnal peaks.

Since in the MRX-103 C4 samples were collected and compared before 9 a.m., the chosen timepoint of 24 post-dose is accepted. However, the exploratory nature and limited amount of information are acknowledged.

A number of published studies suggests roughly 2-4-fold increase in C4 after treatment with IBAT inhibitor, or bile acid sequestrants. However, no concrete values (nominal or relative) were detected that would fit with a definition of clinically relevant change. Thus, the single source of the reference is the defined range of normal values and the ULN of 63.2 ng/ml, that can be used as clinically relevant threshold for changes in C4.

Group level comparison of C4 24h post-ingestion of maralixibat (tablet vs. oral solution) showed that level of increase in geometric mean after tablet formulation was about 21% lower compared to oral solution. The boxplots displaying group-level change in C4 (mean/median, etc.) and individual changes in C4 showed large overlap.

With responses to the raised requests, several post hoc analyses on C4 were presented:

ANCOVA model adjusted for baseline C4 values showed high variability with tablet formulation displaying lower level of change in C4 (GLSM ratio of 0.6). 90% CI of tablet versus solution formulation overlaps 1, but the lower bound is at 0.29. Therefore, no conclusion on equivalence is possible based on these results: it can neither be excluded that mean change in C4 from baseline is the same for the two formulations, nor that it is relevantly different.

In addition, a sensitivity analysis to understand if the 7αC4 magnitude change from baseline was meaningful, a Wilcoxon signed-rank test was performed for each formulation. The analyses demonstrated that statistically significant increases in 7αC4 were observed after 100 mg maralixibat was dosed as either the tablet (p=0.0002) or the oral solution (p=0.0023) formulations. The analysis shows that the mean change in C4 from baseline was statistically significant, but this non-parametric test does not provide an effect estimate such that it cannot be concluded whether the change was meaningful. Even if it was, this would only be a necessary condition for change in C4 being a meaningful parameter to indicate change/pharmacodynamic activity but not a sufficient condition to conclude that it is a meaningful parameter for evaluation of PD equivalence.

A Wilcoxon rank sum test was used to evaluate if a difference between C4 change from baseline was observed across formulations. This analysis did not demonstrate statistical significance (0.4823). However, absence of statistical significance does not indicate that the C4 PD response was similar for the tablet and oral solution formulations as claimed by the applicant but only that the data do not provide sufficient evidence to reject the hypothesis of equal response for the two formulations (absence of evidence is not evidence of absence).

Responder analyses (categorical fold-increase definitions; MRX-103) showed that 4 of 5 participants with >4-fold increases in C4 were on oral solution. Less stringent response definitions yielded more balanced distributions.

To better understand the relevance of the C4 data, further information from previous studies was provided:

Robustness of C4 and C4 variability

To assess the robustness and consistency of C4 as a parameter, data over time are relevant and can be derived from multiple-dose studies on placebo. Such data are available from the parallel-group studies SHP625-101 (Phase 1 in healthy volunteers, conducted under highly standardized conditions; in-clinic setting) and MRX-502 (Phase 3 study in the PFIC population, with less standardized conditions).

In study **SHP625-101**, the baseline mean (SD) value of serum C4 concentration on placebo was 20.021 (11.3) ng/mL and remained relatively consistent over two post-baseline measurement timepoints (day 3 and day 7), with mean and median changes ranging between 6.1 and 7.5 ng/mL. The minimum and maximum changes on placebo ranged from -26.4 to 30.7 ng/mL at days 3 or 7.

Data from the PFIC population (**study MRX-502**) have been summarized in the cross-study comparison (see the figure below). Baseline values (data not summarised, but available in the study report) of C4 were very low (lower than those in the healthy population), which is attributed to the suppression of C4 due to excess concentrations of bile acids in this cholestatic condition. Changes in C4 concentrations over time on placebo were in the range of those observed in healthy population (i.e., SHP625-101 study).

These data are reassuring and suggest that C4 value appears to be somewhat variable but remains sufficiently constant over time to be used for longitudinal analysis.

Sensitivity of C4 as a PD parameter

Correlation analysis was done between C4 and faecal bile acids (fBAs) after dosing 100 mg maralixibat as the oral solution or placebo in healthy participants in **Study SHP625-101**.

Scatter plots of the observed C4 vs. **faecal bile acid concentration** show gradual increase of C4 with increased amount of fBAs on maralixibat, while no such effect was seen on placebo.

Spearman correlation coefficients showed reasonable correlation between C4 and fBA after dosing maralixibat that is not observed after dosing placebo, or at the baseline.

The absence of correlation under placebo or at baseline likely reflects low sensitivity of this analysis at normal levels of C4 and fBA. Correlation appears only at elevated post-dose concentrations. The cross-treatment difference in correlation at the baseline raises questions regarding the test sensitivity. However, impact of variability may not be excluded.

Similar analyses conducted for C4 and **serum bile acids (sBA)** in the same population (study SHP625-101) did not reveal any correlation. Scatter plots show sBA concentration remaining within the same narrow range, while C4 values increase on 100 mg maralixibat. The stable levels of sBA may have been maintained by increased compensatory synthesis of bile acids, as suggested by the increased levels of C4 in these subjects. Additionally, the pre-dose sBA levels are likely to be the least informative for assessing PD effects, as they showed very low baseline sBA levels with limited potential for further reduction. Thus, this correlation analysis does not provide additional relevant evidence to substantiate (or to object) the use of C4 as PD marker.

To summarize, data on placebo suggest that C4 may be a potentially suitable parameter for longitudinal assessment, but its sensitivity for detecting changes across treatments (especially in the absence of several baseline and post-baseline values) remained unclear.

In this respect, C4 data collected on various doses of MRX in the SHP625-101 study are of interest. These data showed that pre-dose concentrations of C4 on treatment with MRX overlapped between 100 mg MRX QD and 50 mg MRX QD substantially.

The absence of a clear dose–response effect in the study SHP625-101 questions the sensitivity of C4 to distinguish between formulations. However, relevant limitation of the evaluated cross-treatment comparison is that this was tested in a parallel group design and small sample and might have been influenced by confounders, which are not present in a cross-over design.

Thus, the provided C4 analyses, which are based on a single measurement before and 24 h post-dose, are regarded insufficiently robust to draw conclusions regarding similarity or dissimilarity of the tested formulations.

Diarrhoea as possible PD parameter

Four cases of drug-related diarrhoea were reported in the study MRX-103, all 4 on oral solution. Since diarrhoea is an established ADR of maralixibat and other IBAT inhibitors and is directly related to the excess excretion of bile acids via faeces, such imbalanced occurrence of this AE raised the question of possible higher BA excretion on oral solution compared to the tablet formulation.

However, evaluation of possible association between the incidence of diarrhoea and either plasma drug AUC or C4 did not reveal clear patterns, and the issue was not further pursued.

2.6.4.3. Overall assessment of formulation similarity

The tablet formulation was regarded as different from the already approved oral solution. Therefore, BCS-based waiver was not acceptable and additional data on similar bioavailability were needed.

The conducted comparative bioavailability study in small set of healthy volunteers showed some differences between the PK profiles of the tablet and the oral solution, suggesting that maralixibat might have had slower and delayed absorption after intake of tablet formulation. It is of note that maralixibat shows a very low bioavailability (<1%) and very high systemic variability. Additionally, the study was a small exploratory study and the bioanalytical methodology used was considered insufficiently sensitive. The Applicant argued that the exposure range of tablet formulation fell within the broader range observed on the oral solution. Additionally, data showed high variability (>10-fold range of exposure on oral solution) and the sample was small, which makes drawing robust statistical conclusions impossible. Overall, the 23.4% difference in the exposure of the tablet vs. oral liquid formulation, and the tablet-to-solution point estimate (GLSMR 77%) that falls only slightly below the conventional 80% lower bound, should not be considered a major PK deviation given the variability and the limited clinical relevance of systemic exposure, given the local mode of action of maralixibat.

In addition, several risk minimisation measures are implemented to limit potential differences between the new tablet and approved liquid formulation:

a) The indication was restricted to adolescents and adults, in whom more accurate weight-based dosing is feasible and issues related to tablet intake are not expected;

b) Dosing recommendations were modified to ensure more accurate dosing (within 92 -120% range of the recommended weight-based dose) and to minimise the impact of food on the *in vivo* dissolution of Livmarli tablets (to be administered 30 min before food intake);

c) A warning was added to section 4.4 of the SmPC, stating that when patients are switched from Livmarli oral solution to Livmarli tablets, efficacy should be monitored based on signs and symptoms, and patients should be switched back to Livmarli oral solution if efficacy is not maintained.;

d) Efficacy of this product is regularly monitored within this marketing authorisation under exceptional circumstances. The Applicant committed to report new data of efficacy / lack of efficacy with the switch from Livmarli oral solution to the tablet formulation. The CHMP recommended the collection of these data using the ongoing study MRX-803 and reporting during annual reassessments.

2.6.5. Conclusions on clinical pharmacology

Whilst the use of a BCS based biowaiver approach is not possible the PK study MRX-103 showed overlapping concentrations of maralixibat in plasma. Differences in the PK/BA were observed, but these were likely impacted by small sample, high variability, low sensitivity of the bioanalytical test, etc. Given the very fast *in vitro* dissolution profile of the tablet formulation, the standard excipients not affecting GI transit, and the modified recommendation to take tablets 30 min before meals, it is assumed that the in vivo dissolution will also be sufficiently fast and undisturbed., The tablet formulation is expected to deliver maralixibat to the target location in a similar pattern as the oral solution. In addition, several risk minimisation measures are implemented to limit potential differences between the new tablet and approved liquid formulation.

2.6.6. Clinical efficacy

2.6.6.1. Dosing recommendations, dosing regimen, and tablet palatability

With the response to the LoOI, the applicant updated the dosing table for Livmarli tablets to ensure most of the patients are within 95%–120% of the recommended dose, including the use of multiple tablets to deliver the recommended dose.

The following modifications have been included in the revised dosing tables in the SmPC to accommodate this proposal:

- The starting dose for all new patients in ALGS and PFIC will be administered using Livmarli Oral Solution.
- The dosing table for patients receiving Livmarli Tablets for the treatment of ALGS has been updated to start at 33 kg body weight.
- The dosing table for patients receiving Livmarli Tablets for the treatment of ALGS has been updated to include the 25 mg dose (delivered using a combination of commercially available tablet strengths) for patients in the 56–65 kg body weight group.
- The dosing table for patients receiving Livmarli Tablets for the treatment of PFIC has been updated to include the 25 mg dose (delivered using a combination of commercially available tablet strengths) for patients in the 37–43 kg body weight group.
- The dosing table for patients receiving Livmarli Tablets for the treatment of PFIC has been updated to include the new 35 mg dose (delivered using a combination of commercially available tablet strengths) for patients with body weight 56 kg or higher.

Starting Dose using Livmarli Oral Solution

For new patients starting Livmarli, the dosing table is updated to administer the starting dose (ALGS 190 mcg/kg; PFIC 285 mcg/kg) using Livmarli oral solution. This will allow flexibility for dose titration in the patients when starting therapy. This also allows transition of ALGS patients from Livmarli Oral Solution to Livmarli Tablets at 33 kg body weight, instead of the previously proposed 44 kg body weight. This change does not impact patients who are already receiving the target dose of Livmarli Oral Solution (ALGS 380 mg/kg; PFIC 570 mcg/kg) and transition to Livmarli Tablets.

Target Dose using Livmarli Tablets

Patients with body weight 33 kg or higher, new and existing, with ALGS or PFIC, can transition to tablets for the target dose (ALGS 380 mcg/kg; PFIC 570 mcg/kg) using the 15 mg, 20 mg, 25 mg, 30 mg, and 35 mg doses when they start taking the tablet formulation. Some of the doses, such as 25 mg, may be administered using 2 tablets (the 10 mg and 15 mg tablets).

A new 35 mg dose is proposed for patients with body weight of 56 kg or higher, receiving Livmarli tablets for the treatment of PFIC, to ensure they are receiving 95% or higher of the recommended dose of maralixibat. These modifications ensure most of the patients receiving Livmarli tablets are within the 95%–120% recommended dose range.

The only exceptions are the 42 kg-weighing patients receiving the maintenance dose for ALGS using Livmarli tablets, who will receive 94% of the recommended dose, and the 43 kg-weighing patients receiving the maintenance dose for ALGS using Livmarli tablets, who will receive 92% of the recommended dose.

The final agreed revised dosing tables for Livmarli tablets are presented in Table 9 and Table 10.

The final agreed individual body weight and dose comparisons for Livmarli tablets are presented in Table 11 and Table 12.

Table 9: Individual Dose by Patient Weight for ALGS

Patient Weight (kg)	Dosage 190 mcg/kg	Dosage 380 mcg/kg
33 to 43	Livmarli Oral Solution	15 mg
44 to 55		20 mg
56 to 65		25 mg
66 or higher		30 mg

Table 10: Individual Dose by Patient Weight for PFIC

Patient Weight (kg)	Dosage 285 mcg/kg	Dosage 570 mcg/kg
33 to 36	Livmarli Oral Solution	20 mg
37 to 43		25 mg
44 and above		30 mg

Table 11: Individual Body Weight and Dose Comparison for ALGS Patients

Patient Weight (kg)	Dose 380 mcg/kg Tablet Strength (mg)	% of Recommended Dose 380 mcg/kg
33	15	120
34	15	116
35	15	113
36	15	110
37	15	107
38	15	104
39	15	101
40	15	99
41	15	96
42	15	94
43	15	92
44	20	120
45	20	117
46	20	114
47	20	112
48	20	110
49	20	107
50	20	105
51	20	103
52	20	101
53	20	99
54	20	98
55	20	96
56	25	118
57	25	115
58	25	113

Patient Weight (kg)	Dose 380 mcg/kg Tablet Strength (mg)	% of Recommended Dose 380 mcg/kg
59	25	112
60	25	110
61	25	108
62	25	106
63	25	104
64	25	103
65	25	101
66	30	120

*Fixed dose in ALGS patient's weight-band "66 kg or higher".

Table 12: Individual Body Weight and Dose Comparison for PFIC Patients

Patient Weight (kg)	Dose 570 mcg/kg Tablet Strength (mg)	% of Recommended Dose 570 mcg/kg
33	20	106
34	20	103
35	20	100
36	20	98
37	20	95
38	25	115
39	25	113
40	25	110
41	25	107
42	25	104
43	25	102
44 or higher*	30	120

*Fixed dose in PFIC patient's weight-band "56 kg or higher".

2.6.7. Discussion on clinical efficacy

Claimed indication

Upon CHMP request the applicant agreed to amend the indication of the tablet formulation to treatment of adolescents and adults only. This change was requested because the to-be-marketed tablet formulation is not suitable for patients as young as 2 months (ALGS) or 3 months (PFIC), as previously claimed. In very young patients, the available tablet strengths do not allow accurate weight-based dosing, swallowing of intact tablets cannot be assured, and variability in delivery relative to the approved oral solution is likely.

Dosing recommendations, dosing regimen, and tablet palatability

The applicant initially proposed to align tablet dosing with the oral solution. During the procedure, it was requested that the applicant restrict dosing recommendations to 95–120% of the calculated weight-based dose (ideally 100–120%).

With the response to the LoOI, broader range of 92-120% was proposed, as it was argued by the applicant that more precise dosing with the proposed tablet strengths is not possible.

The maximum fixed dose of maralixibat in PFIC population has been increased to 70 mg/day from 57 mg/day with the oral solution. This was not accepted, and the 35 mg BID dose was removed to keep the maximum fixed dose limited to 30 mg BID (corresponds to 570 µg/kg BID, the weight-based dose at 52 kg BW).

The Applicant also proposed that titration is recommended only with the oral solution, which allows prescription of the tablet formulation in patients with BW as low as 33 kg (instead of 44 kg as recommended in the previously). This was implemented in 4.2 of the SmPC. The proposed dosing regimens are accepted.

The size and shape of a tablet are fundamental to the ability of a child to swallow it. Therefore, justification in support of chosen size and shape of tablets was provided. The submitted evidence is limited, but overall acceptable. There was an uncertainty regarding the palatability of the 10 and 15 mg strength tablets in younger patients (body weight less than 33 kg) due to their size. However, this issue is no longer relevant, given the restriction of indication to adolescent and adults.

Generally, dosing regimens with 4 tablet strengths (10 mg, 15 mg, 20 mg, and 30 mg) for two different indications and two treatment phases (titration step and maintenance) is complex and may lead to patients dosing errors. Although marketing only 2 dividable tablet strengths (e.g., 10 mg and 15 mg) would offer more convenience, ease in terms of prescription, use and minimise dosing errors; the Applicant has explained that the packages are colour coded, and the different strengths have distinct appearance to prevent dosing errors. Dosing errors will also be monitored in the post-marketing safety reports. The CHMP considered these measures are acceptable.

2.6.8. Conclusions on the clinical efficacy

Overall, based on the data presented, the proposed dosing regimens are accepted and expected to produce the same level of efficacy as the oral formulation. Patients switching to the tablet will be monitored as a precautionary measure as reflected in the SmPC and the applicant will collect this information as part of study MRX-803 and report during the regular annual reassessments.

2.6.9. Clinical safety

Safety of Livmarli 9.5 mg/ml oral solution was assessed at the time of its marketing authorisation and extension of indication procedure. Limited additional data to support the safety and tolerability of the tablet formulation of maralixibat, was provided in this application from the open-label, randomized Phase 1 Study MRX-103.

Safety parameters assessed in Study MRX-103 included laboratory evaluations, physical examinations, vital signs, ECGs, and TEAEs.

Details of study participant disposition, exposure, and baseline characteristics are described in section on clinical pharmacology.

2.6.9.1. Patient exposure

Fourteen adult healthy volunteers received both the liquid formulation and the tablet formulation containing 100 mg maralixibat as a single dose. The duration of the study was approximately 6 weeks.

2.6.9.2. Adverse events

Higher proportion of patients reported treatment emergent AEs (TEAEs) after intake of liquid formulation compared to tablets (3/7 [42.9%] vs 0 [0%] during treatment sequence 1 and 4/7 [57.1%] vs. 2/7 [28.6%] during treatment sequence 2, respectively). Drug-related TEAEs were reported only on liquid formulation (3/7 [42.9%] and 4/7 [57.1%] during treatment sequences 1 and 2, respectively).

The most frequently reported TEAEs were diarrhoea (4/14 [28.6%] subjects during both treatment sequences) and headache (2/14 [13.3%]). All AEs on oral solution (4 – diarrhoea, 2 – headache, and 1 case of nausea, abdominal pain, dyschezia, and flatulence each) were considered drug related. Two AEs on Livmarli tablet (dyschezia and nausea) were qualified as drug related.

The severity of all TEAEs was Grade 1, which is mild. All TEAEs resolved.

There were no serious adverse events or AEs that led to participant withdrawal or death. No adverse events of special interest were reported for this study.

2.6.9.3. Serious adverse event/deaths/other significant events

None reported.

2.6.9.4. Laboratory findings

No relevant findings observed.

2.6.9.5. Discontinuation due to adverse events

No cases reported.

2.6.9.6. Post marketing experience

No post authorisation data was submitted.

2.6.10. Discussion on clinical safety

The data on safety of Livmarli Tablet formulation are derived from a small Phase I study (MRX-103) in healthy volunteers (n=14) and single administration of a 100 mg dose MRX tablets. The same subjects also received a single dose of 100 mg MRX in form of the approved oral solution (9.5 mg/ml).

In this study TEAEs, safety laboratory parameters, ECG and physical exam were collected. No new safety signals were detected, and no safety concerns are raised.

MRX showed overall favourable safety profile (most frequent TEAEs were diarrhoea and headache) that is in line with the known safety profile of MRX. However, proportion of subjects with at least one AE was clearly higher after intake of oral solution and all AEs on oral solution were considered drug related, while none of the 2 AEs on Livmarli tablet were qualified as drug-related. Most importantly, the AE with the highest frequency, i.e., diarrhoea, is a well-known symptom associated with increased bile acid concentration in faeces (e.g., during BA malabsorption).

From the safety database, all the adverse reactions reported in clinical trials have been included in the SmPC.

2.6.11. Conclusions on the clinical safety

In a small Phase I study (MRX-103), intake of 100 mg single dose MRX as tablet and oral solution (9.5 mg/ml) was well tolerated and showed favourable safety profile in healthy volunteers. No new safety signals were detected.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Hepatotoxicity Medication error resulting from erroneous dosing (LIVMARLI oral solution only)
Missing information	Long-term safety Long-term safety of chronic exposure to propylene glycol in PFIC patients (LIVMARLI oral solution only)

PFIC=progressive familial intrahepatic cholestasis

2.7.2. Pharmacovigilance plan

Table Part III.3: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Date**
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
MRX-803 (former MRX-311): "Long-Term Safety and Clinical Outcomes of Livmarli in Patients with Alagille Syndrome and Progressive Familial Hepatic Cholestasis" Low-intervention clinical study	The objectives are to: • evaluate the long-term safety • evaluate the long-term efficacy (impact on liver related events/clinical outcomes, growth and development)	Hepatotoxicity Medication error resulting from erroneous dosing (LIVMARLI oral solution only) Long-term safety Long-term safety of chronic exposure to propylene glycol in PFIC patients (LIVMARLI oral solution only)	Submission of feasibility assessment (PFIC cohort)	28 September 2024
			Protocol submission	28 December 2024
			SAP submission	Within 6 months of study start
			Interim report	Within 5 years from study start
			Interim results	Yearly reporting with annual reassessment

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Date**
Planned				
Submission of yearly updates on any new information concerning the safety and efficacy of maralixibat. Ongoing	In order to ensure adequate monitoring of safety and efficacy of maralixibat in the treatment of patients with ALGS and PFIC.	Hepatotoxicity	Annual report	Yearly reporting with annual reassessment
Category 3 – Required additional pharmacovigilance activities				
MRX-503: "An Open-label Extension Study to Evaluate the Long-term Safety and Efficacy of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC)" Ongoing	Primary objective: To evaluate the long-term safety and tolerability of maralixibat. Secondary objective: To evaluate the long-term efficacy of maralixibat, including the maintenance of severity and frequency of pruritus as well as serum bile acids (over time and growth in the primary cohort	Hepatotoxicity Long-term safety	End date of collection (LPO):	23 April 2025
			Final report of study results (final CSR):	Q4 2025
MRX-502, MRX-503, MRX-800, MRX-801: "A retrospective study to compare impact of maralixibat treatment on long-term clinical outcomes against historical control in the patients with PFIC" Planned	Primary objective: To evaluate the long-term effects on liver related events and clinical outcomes	Hepatotoxicity Long-term safety	Final report of study results (final CSR):	Q4 2025

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date

ALGS=Alagille syndrome; CSR=clinical study report; EMA=European Medicines Agency; EC=European Commission; LPO=last patient out; PFIC=progressive familial intrahepatic cholestasis; Q=quarter; SAP=statistical analysis plan.

2.7.3. Risk minimisation measures

Safety Concern	Routine Risk Minimisation Activities
Hepatotoxicity	Routine risk communication: SmPC sections 4.2, 4.3, 4.4, and 4.8 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: *LIVMARLI 9.5 mg/mL oral solution* Close monitoring is advised for ALGS patients with end-stage liver disease or progression to decompensation per SmPC section 4.2. Liver function tests should be monitored in patients prior to start and during treatment with maralixibat per SmPC section 4.4. *LIVMARLI 19 mg/mL oral solution* ALGS: Close monitoring is advised for patients with end-stage liver disease or progression to decompensation per SmPC section 4.2. PFIC: Livmarli should be used with caution in patients with moderate hepatic impairment. Close monitoring is advised in patients at risk of decompensation per SmPC section 4.2. Liver function tests should be monitored in patients prior to start and during treatment with maralixibat per SmPC section 4.4. LIVMARLI tablets ALGS: Close monitoring is advised for patients with end-stage liver disease or progression to decompensation per SmPC section 4.2. PFIC: No dose adjustment is required for patients with mild and moderate hepatic impairment. Close monitoring is advised in patients at risk of progression to decompensation per SmPC section 4.2. Liver function tests should be monitored in patients prior to start and during treatment with maralixibat per SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription

Medication error resulting from erroneous dosing (LIVMARLI oral solution only)	Routine risk communication: SmPC sections 4.2, 4.4, and 4.9 PL section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Separate SmPCs are provided for LIVMARLI 9.5 mg/mL oral solution and LIVMARLI 19 mg/mL oral solution. The outer and inner packaging for LIVMARLI 19 mg/mL oral solution includes an additional green box feature that differentiates the LIVMARLI 19 mg/mL oral solution outer packaging from the LIVMARLI 9.5 mg/mL oral solution outer packaging. Restricted medical prescription
Long-term safety	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription
Long-term safety of chronic exposure to propylene glycol in PFIC patients (LIVMARLI oral solution only)	Routine risk communication: SmPC sections 4.2, 4.3, 4.4, 4.6, and 4.9 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription

ALGS=Alagille syndrome; PFIC=progressive familial intrahepatic cholestasis; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 7.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. 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.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Livmarli 9.5 mg/ml oral solution. The bridging report submitted by the MAH has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Livmarli (Maralixibat) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Livmarli 9.5 mg/ml oral solution (maralixibat) has been authorized in EU under exceptional circumstances for the treatment of cholestatic pruritus in patients with ALGS 2 months of age and

older on the 9th of December 2022, and for the treatment of PFIC in patients 3 months of age and older on the 28th of June 2024. A new pharmaceutical form of Livmarli, a tablet formulation, has been developed for use by patients who can reliably swallow tablets and prefer a solid formulation. The proposed indications were the same for the new pharmaceutical form but the MAH agreed during this line extension procedure to amend the indication for this new tablet formulation to adolescents and adults only based on CHMPs concerns on suitability of the tablet for patients as young as 2 months (ALGS) or 3 months (PFIC). In very young patients, the available tablet strengths do not allow accurate weight-based dosing, swallowing of intact tablets cannot be assured, and variability in delivery relative to the approved oral solution is likely.

ALGS and PFIC are genetic diseases which manifest from early childhood and are associated with intrahepatic cholestasis. Both conditions belong to the group of rare diseases and are associated with typical symptoms and signs of progressing cholestasis with liver damage, failure/cirrhosis.

3.1.2. Available therapies and unmet medical need

Livmarli oral solution (9.5 mg/ml) is approved for treatment of pruritus in ALGS and for treatment of PFIC from the age of 2 and 3 months respectively.

Also, selective ileal bile acid transport (IBAT) inhibitor, odevixibat has been approved in similar indications under the trade names Bylvay (EMEA/H/C/004691; treatment ofPFIC in patients aged 6 months or older) and Kayfanda (EMEA/H/C/006462; treatment of cholestatic pruritus in ALGS in patients aged 6 months or older).

The newly proposed oral formulation for Livmarli is an immediate release tablet formulation. It shares with the oral solution the same active ingredient and route of administration.

By introducing the new solid oral formulation, in patients who are able to swallow tablets (e.g., adolescents and adults) may be able to avoid the less convenient procedure of dosing with the currently available liquid dosage form which requires careful drawing of the dose into the syringe to avoid over/insufficient dosing.

Additionally, this formulation does not contain propylene glycol (PG). Even though PG is considered generally safe excipient, safety risks of chronic/long-term exposure, especially in patients with affected liver function are unknown.

3.1.3. Main clinical studies

The clinical development for the Livmarli tablets consists of one exploratory Phase I, open-label, randomised, crossover study to investigate the relative bioavailability of the new tablet formulation against the approved oral solution in healthy subjects (Study MRX-103).

• The primary objective was to evaluate the pharmacokinetics of single doses of 100-mg maralixibat administered as the liquid formulation (10.5 mL × 9.5 mg/mL maralixibat oral solution) and the tablet formulation (2 × 50-mg tablets) in healthy participants.

• The secondary objective was to assess the safety and tolerability of single oral doses of 100 mg of the liquid formulation (10.5 mL × 9.5 mg/mL maralixibat oral solution) and tablet formulation (2 × 50 mg) of maralixibat in healthy participants.

Standard PK parameters were assessed: Maximum observed plasma concentration (Cmax), the area under the plasma concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC0-t), and the AUC from time zero to extrapolated infinity (AUC0-∞). No formal testing

of bioequivalence or relative bioavailability was done, but geometric least squares means (GLSMs) and 90% confidence intervals (CIs) were calculated. A post hoc analysis of the biomarker of increased bile acid production (7αC4 – "C4"; at single timepoints of baseline and 24 h post-dose) have been provided with responses.

Safety assessments included adverse events (AEs), clinical laboratory assessments, ECG, vital signs, and physical examination.

In order to demonstrate the very fast dissolution of tablet formulation, *in vitro* dissolution testing of the tablet formulations (10 mg and 30 mg strengths; the highest and the lowest strengths to be marketed) was performed in biorelevant dissolution media such as 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer (500 ml), using the USP Apparatus 1 (basket) at a recommended stir speed of 100 rpm at 37°C±0.5°.

3.2. Favourable effects

Efficacy was considered demonstrated based on 1. proof of very fast *in vitro* dissolution and 2. evidence of similar BA compared to the authorised oral solution in healthy subjects (see below).

No new clinical efficacy data has been provided.

3.3. Uncertainties and limitations about favourable effects

The PK study MRX-103 was a small study (n=14), not designed to formally test bioequivalence. Very low bioavailability of maralixibat and very high variability make the characterisation of PK profiles and the demonstration of bioequivalence/similar BA challenging. Therefore, generally PK comparisons lack robustness.

A lower and slightly delayed exposure to maralixibat was observed with the tablet formulation. However, systemic exposure to maralixibat is not directly relevant for efficacy because maralixibat is locally acting in the gastrointestinal tract and poorly absorbed the clinical relevance of this difference is considered low.

PD activation was demonstrated by means of increase in C4 PD parameter on both formulations. However, the data carry multiple limitations and deficiencies, so that no firm conclusions on PD effects and their comparability between the formulations can be drawn.

The study was conducted under fasted conditions using supratherapeutic doses, so that impact of concomitant food intake on the *in vivo* dissolution of the tablets and of the active substance (micelle building) at the recommended dose is uncertain. The uncertainty related to data generalisability is, however, addressed with several risk minimisation measures:

- The dosing recommendations were tightened to better reflect the weight-based dosing and intake of the tablet formulation 30 min prior to the meals is recommended to minimised the potential impact of food on the in vivo dissolution.
- The warning that efficacy should be monitored after switching from oral solution to Livmarli tablets was added in section 4.4 of the SmPC.

Additionally, the Applicant commits to the post-approval collection of the data on efficacy after switch from oral solution to tablet formulation. The CHMP recommended the collection of this data using the ongoing study MRX-803 and reporting during annual reassessments.

The drug-related AEs typical for increased BA elimination via faeces, such as e.g., diarrhoea, were not reported on Livmarli tablet, but were present on oral solution in the same subjects. This difference in safety profile may be a reflection of weaker/absence of PD effects of a tablet formulation compared to more pronounced effects of the liquid formulation. However, causal relationship with the systemic availability of MRX or with C4 activation could not be established from the limited data.

3.4. Unfavourable effects

In the Phase I study (MRX-103), intake of 100 mg single dose MRX as tablet and oral solution (9.5 mg/ml) was well tolerated and showed favourable safety profile (most frequent TEAEs were diarrhoea and headache) in healthy volunteers. No new safety signals were detected.

3.5. Uncertainties and limitations about unfavourable effects

Safety conclusions are limited by the small sample size (n=14) and the study setting (healthy volunteers). Long term safety of the new tablet formulation will be followed as part of the regular PSURs submissions.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The new tablet formulation of Livmarli is a propylene glycol free formulation that offers higher convenience of use in adolescents and adults during maintenance treatment. These benefits are regarded clinically relevant. Therapeutic similarity for the tablet of this locally in the GI-tract acting product to the oral solution was sufficiently demonstrated mainly based on overlapping plasma concentrations of maralixibat in PK study MRX-103 and the very fast *in vitro* dissolution profile of the tablet formulation based on which the tablet formulation is expected to deliver maralixibat to the target location in a similar pattern as the oral solution. Uncertainties related to the limited data package, to the absence of supportive PD and efficacy data, and adequacy of dosing regimen, are considered sufficiently addressed through the more precise dosing regimen, modified recommendation on drug administration and advice to monitor efficacy after switch from Livmarli oral solution to Livmarli tablet formulation. Further, the MAH, as part of the existing specific obligations, will monitor post-approval efficacy data on patients switching to the tablet of Livmarli.

Overall, the clinical safety data presented was limited as new data came only from a study with healthy volunteers. The systemic exposure to maralixibat was lower with the tablet formulation than with the oral solution and no new safety signals were reported. The safety profile of Livmarli tablet formulation is expected to be in line with the known safety profile of the compound based on the PK bridging.

3.6.2. Balance of benefits and risks

Very fast in vitro dissolution of the new tablet formulation was demonstrated, and the used excipients are not expected to influence maralixibat transportation along the GI tract.

The PK study MRX-103 showed largely overlapping systemic exposure to maralixibat on both formulations, with some differences in the absorption profile. Given the observed very low systemic availability and very high PK variability the differences are not considered to indicate major dissimilarity between the new tablet and approved liquid formulations.

The uncertainties related to lack of PD data and external validity have been addressed by modifications in the SmPC (i.e., modified lower age limit, dosing regimen, warning to monitor efficacy). Further monitoring of the cases of lack of efficacy on Livmarli tablets, and reassessment of benefit/risk will take place in the post-approval phase (e.g., via the ongoing SOBs).

Additional considerations on the benefit-risk balance

Livmarli oral solution is approved under exceptional circumstances, and this line extension also falls under the same MA.

3.7. Conclusions

The overall benefit/risk balance of Livmarli 10 mg, 15 mg, 20 mg, 30 mg tablets is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Livmarli is not similar to Bylvay within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Livmarli 10 mg, 15 mg, 20 mg, 30 mg tablets is favourable in the following indication(s):

Livmarli tablets is indicated in adults and adolescents 12 years and older for the treatment of:

- Cholestatic pruritus in patients with Alagille syndrome (ALGS),
- Progressive familial intrahepatic cholestasis (PFIC).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Livmarli subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures for Livmarli 9.5 mg/mL Oral Solution**

  Due to the propylene glycol content in order to minimise the important potential risks "Medication error resulting from erroneous dosing (PFIC patients)" the MAH should make available in each Member State (MS) where Livmarli is marketed:

  - A dosing guide developed to help physicians to guide patients for the dosing schedule, volume and required syringe size to be used.
  - A patient booklet where the physician will enter the date, patient's weight, calculated dose and volume and required syringe size to be used.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

The MAH shall complete, within the stated timeframe, the below measures:

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	**Due date**
In order to further characterise the long-term safety and efficacy of maralixibat in the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) and in the treatment of patients with PFIC, the MAH shall conduct and submit the results of study LEAP (MRX-803) according to an agreed protocol.	Annual (within annual reassessment)
In order to ensure adequate monitoring of safety and efficacy of maralixibat in the treatment of patients with Alagille syndrome (ALGS) and Progressive familial intrahepatic cholestasis (PFIC), the MAH shall provide yearly updates on any new information concerning the safety and efficacy of maralixibat.	Annual (within annual reassessment)