# ORPHABASE STUDY PROTOCOL

## PASS Information

| | |
|---|---|
| **Title** | **Orphacol® patient surveillance database (Orphabase)** |
| **Protocol version identifier** | Version 2.1 |
| **Date of last version of protocol** | 15 April 2024 |
| **EU PAS register number** | EUPAS37229 |
| **Active substance** | Cholic acid (ATC code: A05AA03) |
| **Medicinal product** | Orphacol 50 mg and 250 mg hard capsules |
| **Product reference** | EMEA/H/C/001250 |
| **Procedure number** | Not applicable |
| **Marketing authorisation holder(s)** | Theravia<br>16 rue Montrosier<br>92200 Neuilly-sur-Seine<br>France |
| **Joint PASS** | No |
| **Research question and objectives** | To increase the amount of available data on the treatment of inborn errors in primary bile acid synthesis due to 3β-HSD deficiency or Δ4-3-OxoR deficiency with Orphacol® in infants, children, adolescents and adults, and especially data on initial efficacy and safety of treatment with cholic acid. |
| **Country(-ies) of study** | France, Germany, Italy, Switzerland, UK, Sweden, Spain, Denmark<br>Additional countries might be added to this list as treating physicians/patients are identified and enrolled |
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## Marketing authorisation holder(s)

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## Signature page for the investigator

I confirm that I have read and that I understand this protocol, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects. Information taken from the study protocol may not be disseminated or discussed with a third party without the express consent of the sponsor.

Investigator's name:

Signature:

Date:

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## 2. List of abbreviations

| | |
|---|---|
| 3β-HSD | 3β-hydroxy-Δ5-C27-steroid oxidoreductase |
| ALT | Alanine amino-transferase |
| AP | Alkaline phosphatase |
| AST | Asparate amino-transferase |
| CHMP | Committee for Medicinal Products for Human Use |
| cm | centimeters |
| FAB-MS | Fast Atom Bombardment/Mass Spectrometry |
| GC-MS | Gas Chromatography/Mass Spectrometry |
| GCP | Good Clinical Practices |
| HCP | Healthcare Professional |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ID | Identification |
| kg | kilograms |
| MAH | Marketing Authorisation Holder |
| mm | month |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PSUR | Periodic Safety Update Reports |
| QP | Qualified Person |
| SADR | Serious Adverse Drug Reaction |
| SAE | Serious Adverse Event |
| SmPC | Summary of Product Characteristics |
| yyyy | year |
| Δ4-3-OxoR | Δ4-3-oxosteroid 5β-reductase |

## 3. Responsible parties

**Sponsor :**
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**List of Investigators:**

Please refer to the separate Annex I of this protocol for a list of principal investigators and coordinating investigators in each participating country.

# 4. Abstract

Title
Orphacol® patient surveillance database (Orphabase)

Rationale and background
Orphacol® (cholic acid) is indicated for the treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase (3β-HSD) deficiency or $\Delta^4$-3-oxosteroid 5β-reductase ($\Delta^4$-3-oxoR) deficiency. Both deficiencies are extremely rare genetic disorders. Due to this rarity, the available clinical data on the efficacy and safety of cholic acid in the treatment of 3β-HSD and $\Delta^4$-3-oxoR deficiencies is more limited than for more common diseases.

Orphacol was approved on 13 September 2013 in the European Union under exceptional circumstances. This Patient Surveillance Database is a specific obligation of the Marketing Authorisation for Orphacol®, and its protocol is part of the current product Risk Management Plan approved by the European Medicines Agency. Data collected as part of this protocol is used as a basis for annual reassessment of the marketing authorisation and compilation of the Periodic Safety Update Reports.

Research questions and objectives
The objectives of this ongoing surveillance protocol is to increase the amount of available data on the treatment of inborn errors in primary bile acid synthesis due to 3β-HSD deficiency or $\Delta^4$-3-OxoR deficiency with Orphacol® in infants, children, adolescents and adults, and especially data on initial efficacy and safety of treatment with cholic acid.

Study design
Multi-centre, multi-national, retrospective and prospective observational study to collect patients' clinical information (treatment, safety and efficacy data) of patients receiving Orphacol® for the treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase (3β-HSD) deficiency or $\Delta^4$-3-oxosteroid 5β-reductase (Δ4-3-oxoR) deficiency.

Patients treated with Orphacol® will be asked for consent to participate in the study database.
Orphacol® is indicated for the treatment of inborn errors in primary bile acid synthesis due to 3-β-Hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase deficiency or $\Delta^4$-3-Oxosteroid-5-β-reductase deficiency in infants, children, adolescents and adults. Therefore, the patients included in the patient database will include infants, children and adolescents.
The parents or guardians of the paediatric patients will sign an informed consent form on behalf of the patient. A new informed consent will be obtained by the physician when paediatric patients will become adults.

For the patients that consent for participation, HCP will review the medical records and will enter the following information in the database:
- Demographic data for the patient
- Last laboratory data available before start of treatment with cholic acid
- Laboratory data right after start of treatment with cholic acid

Laboratory data available at each follow-up visit after start of treatment with cholic acid.

Population
Patients of any age treated with Orphacol® for inborn errors in primary bile acid synthesis due to 3β-Hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase deficiency or $\Delta^4$-3-Oxosteroid-5β-reductase deficiency.

Variables
The collected data consist in the following:
- Demographic and familial data
- Diagnostic information
- Treatment
- Serious Adverse Events/Reactions

Data sources
Patients medical records

Study size
Due to the rarity of the indications, no formal sample size can actually be calculated. It is expected that the number of inclusions will not exceed 100 patients. All possible patients will be enrolled in the study, and the study will continue as long as deemed necessary by Theravia, the regulatory authorities and the participating treating physicians.

Data analysis
Exploratory statistical methods may be used for analyses of the data.

Milestones
Data is analysed at time of PSURs (safety) and annual reassessments (efficacy and safety).

## 5. Amendments and update

| Protocol version | Date | Modified section | Amendment or update | Justification |
|---|---|---|---|---|
| V1.0 (as part of RMP v2.2) | 03/12/2010 | N/A | N/A | N/A |
| V1.1 (Non-substantial modifications only) | 18/01/2018 | Entire document | Formatting (e.g. addition of title page, synopsis, version number and date, signature pages, etc.). | To allow having a clean protocol following template required by ethics committees |
| | | Section 10.1 | Update with regards to link and screenshots from the database. | To reflect the updates made to the online database |
| | | Section 4 | Modification of the format of collection of the date of birth: previously as DD-MM-YYYY, now as MM-YYYY. | As collection of full date of birth in not allowed in some Member States. Such modification still allows analysis of patients according to their age without impacting the scientific interpretation nor the safety of patients included in the study. |
| | | Section 4 | Addition of a field in the "Diagnostic Information" data to be collected. | To allow physician to mention that diagnosis was performed with other suitable technique than the FAB-MS or GC-MS. This is in line with the LEG-005 procedure at the EMA level, where this modification was made to the SmPC of the product to allow diagnosis to be made by other techniques than FAB-MS or GC-MS (diagnosis of bile acids in urine). |
| | | Section 5 | Deletion of the sentence "Follow-up on a patient's SAE/SADR will be stopped as soon as the patient has been withdrawn from the ongoing surveillance protocol" | This does not reflect the process performed in reality, as a follow-up is performed until resolution of the event (even if the patient withdraws from the database during the resolution process). |
| | | Appendices | Removal of the attachment of educational material. | This material is approved separately by the local competent authorities in each Member State where Orphacol is commercialized (approval of the educational |

| Protocol version | Date | Modified section | Amendment or update | Justification |
|---|---|---|---|---|
| | | | | material is not granted by Ethics Committee, whereas approval for conduct of the patient surveillance database is usually granted by Ethics Committees only). Instead, a sentence has been added to clarify that "approved educational material are available in PDF format for the countries where they are approved by local authorities" when the user connects to the database. |
| V2.0 | 04/02/2020 | Entire document | Update template of protocol | Template for PASS study required by EMA was used for creating v2.0 of the protocol (Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies (EMA/623947/2012). |
| | | Summary and section 9.1 Study design | Modification of the study design from retrospective design to retrospective and prospective design (in study synopsis) | No change is proposed to the data collection itself, to the database itself, nor to the analysis of the data. This proposed modification concerns only wording in the design of the study.<br><br>Indeed, until now, mainly patients treated for a long-time were included in the database, thus justifying the retrospective design of the study as mainly past data were being collected from those patients. However, more and more new patients are being enrolled which have been treated with Orphacol since their diagnosis and included in the database since the very beginning of their treatment with Orphacol. In such case, for those patients, it is mainly prospective data that will be collected at the time they sign the ICF. Theravia therefore believes that the proposed change in the design name better depicts |

| Protocol version | Date | Modified section | Amendment or update | Justification |
|---|---|---|---|---|
| | | | | the actual practice of data collection for the patient surveillance database. |
| | | 9.7 Data Analysis | Section not existing in previous protocol version | This section was added to follow the Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies (EMA/623947/2012).<br><br>The information provided in this section follows the Statistical Analysis Plan, used for preparation of the annual reassessments. |
| | | 12 Plans for disseminating and communicating study results | Section not existing in previous protocol version | This section was added to follow the Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies (EMA/623947/2012).<br><br>The information provided in this section clarifies the current process and planned process for disseminating and communicating study results. |
| V2.1 | 15/04/2024 | Entire document | Modification of the name and the contact details of the Sponsor | Since 18 April 2023 the registered name of the company “Laboratoires CTRS” has been changed to “Theravia”. Theravia is an official MAH from 15 May 2023. |

## 6. Milestones

| Milestone | Planned date |
|---|---|
| Start of data collection | 20 November 2006 |
| End of data collection | Not known yet. This protocol will be continued as long as deemed necessary by Theravia, the regulatory authorities and the participating treating physicians. |
| Study progress reports | At each annual reassessment (efficacy and safety)<br>At each PSUR (safety) |
| Registration in the EU PASS Register | 16 September 2020; EUPAS37229 |
| Final report of study results | Not known yet. This protocol will be continued as long as deemed necessary by Theravia, the regulatory authorities and the participating treating physicians. |

## 7. Rationale and background

This Patient Surveillance Database is a specific obligation of the Marketing Authorisation for Orphacol®, and its protocol is part of the current product Risk Management Plan approved by the European Medicines Agency. Data collected as part of this protocol is used as a basis for annual reassessment of the marketing authorisation and compilation of the Periodic Safety Update Reports.

Cholic acid is a primary bile acid. Primary bile acids are biosynthesised in the liver of healthy mammals and are key constituents of normal bile. Cholic acid is the predominant primary bile acid in human bile.

Orphacol® (cholic acid) is indicated in the European Union for the treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase (3β-HSD) deficiency or $\Delta^4$-3-oxosteroid 5β-reductase ($\Delta^4$-3-oxoR) deficiency. Both deficiencies are extremely rare genetic disorders. Due to this rarity, the available clinical data on the efficacy and safety of cholic acid in the treatment of 3β-HSD and $\Delta^4$-3-oxoR deficiencies is more limited than for more common diseases.

The liver disease associated with 3β-HSD and $\Delta^4$-3-oxoR deficiencies due to the production of hepatotoxic bile acid precursors is progressive and, if untreated, leads to death due to cirrhosis and liver failure, usually within the first years of life. Oral administration of cholic acid, the substance missing in an affected patient, will inhibit the production of these bile acid precursors by down-regulating cholesterol 7α-hydroxylase, the rate limiting enzyme in bile acid synthesis. In addition, it will provide a stimulus for bile flow facilitating the hepatic clearance of toxic bile acid precursors and toxic substances, including bilirubin. Furthermore, it will improve growth by facilitating the absorption of fat-soluble vitamins and fat.

The patient population includes infants and toddlers (28 days – 23 months), children (2-11 years), adolescents (12-18 years) and adults (>18 years).

Cholic acid is formulated as 50 mg and 250 mg hard capsules.

The daily dose of cholic acid is 5 to 15 mg/kg in adults and children. In adults, the daily dose should not exceed 500 mg, corresponding to the total amount of primary bile acids synthesised per day in a normal adult human. The dosage must be adjusted for each patient in a specialised unit according to blood and/or urine chromatographic bile acid profiles and liver function tests. Treatment is chronic and, in the absence of other treatment options that may arise in the future, for life.

Janhel et al. (2017) published the data from the European survey which identified 63 patients (55 with 3b-HSD and 8 with D4–3-oxoR deficiency) in 21 countries and determined a prevalence of 3β-HSD and Δ4-3-oxoR of 0.99 and 0.14 per 10 million in Europe, respectively. These prevalence figures actually show a wide disparity, with 4.02, 1.98, and 1.69 per 10 million in France, Italy, and UK, respectively. Janhel et al. interpreted this disparity due to the lack of knowledge on diagnosis and lack of availability of diagnosis methods in the countries with the lower prevalence or in the countries that didn't report any patient.

The biggest cohort of patients treated with Orphacol in Europe was reported from France by Gonzales at al. (2009 and 2018). Fifteen patients with either 3β-HSD (13 patients) or Δ4-3-oxoR (2 patients), treated with cholic acid, were followed-up for more than 20 years. Those patients were treated with Orphacol since August 2007. The authors concluded that oral cholic acid therapy is a safe and effective long-term treatment for those patients.

One case report from Bossi et al. (2017) presents data from a patient in Italy successfully treated with Orphacol.

To Theravia knowledge, no further data is publicly available reporting efficacy and safety of Orphacol in 3β-HSD and Δ4-3-oxoR patients in Europe. The objective of the Orphabase study is therefore to allow a long-term collection of efficacy and safety data on the product, on additional patients outside of France.

## 8. Research questions and objectives

For the ongoing surveillance of patients being treated with Orphacol®, Theravia has developed a patient database. This database has two main intended functions: first, as a central tool for all Health Care Professionals (HCPs) treating patients with Orphacol® to record and access information regarding patient clinical information. In addition, Theravia will provide educational material on the diagnosis and treatment of 3β-HSD and $\Delta^4$-3-oxoR deficiencies to Health Care Professionals through the web site that serves as portal to the patient database. Second, the database will be available to Theravia in order to have access to treatment, safety and efficacy data that can be communicated to Regulatory Authorities. Such data are in principle available from the regular (at least annual) clinical and laboratory investigations in

patients, and the database will serve to capture this information in a central location. These data will be used to further increase the available safety and efficacy data and refine the therapeutic recommendations as required.

The primary objective of this ongoing surveillance protocol is to increase the amount of available data on the treatment of inborn errors in primary bile acid synthesis due to 3β-HSD deficiency or $\Delta^4$-3-OxoR deficiency with Orphacol® in infants, children, adolescents and adults, and especially data on initial efficacy and safety of treatment with cholic acid.

# 9. Research methods

## *9.1. Study design*

Multi-centre, multi-national, retrospective and prospective observational study to collect patients' clinical information (treatment, safety and efficacy data) of patients receiving Orphacol® for the treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase (3β-HSD) deficiency or $\Delta^4$-3-oxosteroid 5β-reductase (Δ4-3-oxoR) deficiency.

The retrospective data collection concerns patients that have been diagnosed long time ago and treated with other options before they start Orphacol treatment: either with other cholic acid than Orphacol or with other medications (like Ursodeoxycholic acid, for example), and for whom legacy data is collected from the start of treatment until the date of signature of the ICF. The prospective data collection concerns the patients who continue the treatment with Orphacol, as well as the new patients who start Orphacol treatment right at the diagnosis and who are included in the database at the very beginning of their treatment, and for whom the data that is collected does not yet exist at time of signature of the ICF.

The primary criteria for efficacy evaluation are measurement of blood biochemistry parameters, in particular the levels of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin and Vitamin E.

## *9.2. Setting*

The study population consists in patients of any age treated with Orphacol® for inborn errors in primary bile acid synthesis due to 3β-Hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase deficiency or $\Delta^4$-3-Oxosteroid-5β-reductase deficiency.
The selected investigators are hospital-based Health Care Professional (HCP) managing patients of any age suffering from inborn errors in primary bile acid synthesis and treated with Orphacol®.

- Inclusion criteria

All patients treated with Orphacol® and having signed an informed consent form can be included in the patient database.

- Exclusion criteria

No exclusion criteria.

- Withdrawal criteria

A patient will be withdrawn from the patient database when retracting his informed consent.

It is the treating physician's responsibility to decide if a patient should stop the treatment and document this in the database.

- Special population

Orphacol® is indicated for the treatment of inborn errors in primary bile acid synthesis due to 3-β-Hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase deficiency or $\Delta^4$-3-Oxosteroid-5-β-reductase deficiency in infants, children, adolescents and adults. Therefore the patients included in the patient database will include infants, children and adolescents.
The parents or guardians of the paediatric patients will sign an informed consent form on behalf of the patient. A new informed consent will be obtained by the physician when paediatric patients will become adults.

- Treatment of patients

The patients will be treated by the physician under his/her responsibility and as per the indications of the Orphacol® SmPC and the standard of care.

## *9.3. Variables*

The collected data consists in data available from the patients medical records. The following data will be collected in the patient database on each patient:

- Date (mm/yyyy),
- Age (precisely),
- Size, Weight,
- Deficiency: [3β HSD] or [$\Delta^4$-3-oxoR]

**Demographic and familial data:**

1. Patient unique identification code (generated by the database administrator)
2. Sex
3. Date of birth (month and year only)
4. Number of siblings living (today)
5. Number of siblings who have died, and those who have probably died from the same disease
6. Number of living siblings with the same disease
7. Parental consanguinity

**Diagnostic Information:**

1. Date
   Age (yyyy/mm)

   Height (cm)

   Weight (kg)

2. Results:
   Fast Atom Bombardment/Mass Spectrometry (FAB-MS)
   and/or Gas Chromatography/Mass Spectrometry (GC-MS)
   or any other suitable analytical technique to detect abnormal bile acid metabolites
   If available: disease gene sequence data

3. Kind of Deficiency: [3β HSD] or [$\Delta^4$-3-oxoR]

4. Clinical Examination
   *a.* Icterus (jaundice)
   b. Pruritus
   *c.* Steatorrhoea
   d. Nausea
   *e.* Ascites
   *f.* Hepatomegaly
   *g.* Splenomegaly
   h. Rickets

   <u>Functional signs at diagnosis and after:</u>
   - Blood Biochemistry:
     - AST, ALT, Gamma-GT, Alkaline Phosphatase [AP]
       bilirubin (total), Serum-conjugated bilirubin

       total cholesterol, triglycerides

       Vitamin A, Vitamin D, Vitamin E, Vitamin K

       Bile Acids (total)

     - Oncological exploration: serum alpha-fetoprotein
     - Serum iron
     - 25-OH serum vitamin D
     - Cytology-Blood cell count
     - Haemostasis: fibrinogen, Quick time, Factor 11, Factor VII +X, Factor V
       *Bile acids in serum*
     - Primary Bile Acids: Cholic acid, Chenodeoxycholic acid
     - Secondary Bile Acids: Deoxycholic Acid, Lithocholic Acid,
       Ursodeoxycholic acid, total Biliary Acid, ratio Cholate/Chenodeoxycholate

- Urinary Biochemistry
  - Creatinine
    *Bile acids in urine*
  - Primary Bile Acids: Cholic acid, Chenodeoxycholic acid
  - Secondary Bile Acids: Deoxycholic acid, Lithocholic acid, Ursodeoxycholic acid, Hyododeoxycholic acid, Hyocholic Acid, Total Secondary Bile Acids

Histology / Medical imaging at diagnosis and after:

- Abdominal Scan,
  Liver
  Spleen
  Hepatosplenomegaly
  Adenopathy
- Abdominal ultrasound
  Liver
  Gallbladder
  Dilated bile ducts
  Hilum
  Spleen
  Kidneys

- Cardiac Doppler
- Excrement Investigation
- Liver biopsy

Treatment and others

- Cholic acid: posology
- Associated or simultaneous treatment: drug and posology
- Other investigations or observations
- Adverse Events

**Treatment**

- Orphacol®: Dose/day
- Other treatment
  - In relation to the Disease
  - Without relation to the Disease

**Serious Adverse Events/Reactions**

- Information on SAE/SADR: event/reaction, seriousness criteria, date of occurrence, relevant tests, concomitant drugs, outcome
- Was the SAE/SADR declared to national authorities?

- Copy of the pharmacovigilance declaration submitted to the national authority

### *9.4. Data sources*

Data source consists in patients' medical records. Source data will be recorded by a HCP under the treating physican's responsibility.

### *9.5. Study size*

Due to the rarity of the indications, no formal sample size can actually be calculated. It is expected that the number of inclusions will not exceed 100 patients. All possible patients will be enrolled in the study, and the study will continue as long as deemed necessary by Theravia, the regulatory authorities and the participating treating physicians.

### *9.6. Data management*

A simple database was chosen by Theravia as the approach to data collection that addresses best the requirement for collection of particularly safety data in an extended patient population. A more formalised approach, for example a patient registry or an observational study, would introduce an excessive financial and administrative burden for this very small patient population, and for Theravia as a Small Enterprise.

The database is set up in a way that treating health care professionals can enter treatment and safety information on their patients. Such data are available at every examination of a patient during establishment of the diagnosis, titration of the appropriate cholic acid dose, and during the regular follow-up investigations. The database serves to capture this information, for the reference of the health care professional and for analysis by Theravia and Regulatory Authorities.

Theravia controls and maintains the database. The database will use internationally recognized programmes like Access or Excel.

The flow chart depicted in Figure 1 sets out how authorized persons are able to access:
- general information regarding inborn errors of primary bile acid synthesis;
- pharmacovigilance information and
- clinical information regarding patient sets being treated with Orphacol®.

Access to the database is set up as a tier system, whereby entry into the database is identification (ID) and password sensitive.

Health Care Professionals may request access to the database by their own initiative, or after having been contacted by Theravia. Additionally, as few laboratories have the analytical capacities for the analyses of serum and urine bile acid metabolites required for diagnosis,

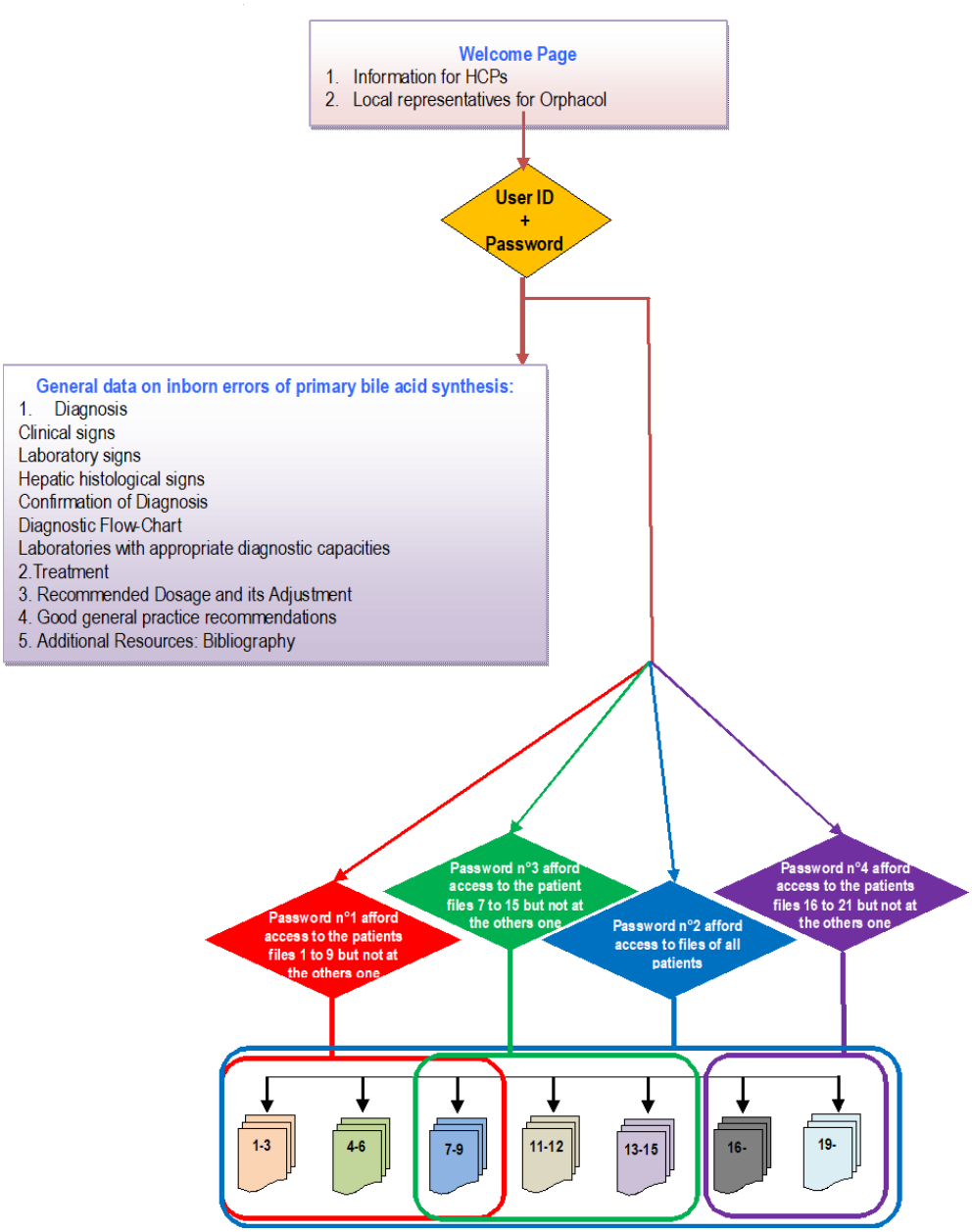
Theravia will establish and/or maintain close contact to these laboratories in order to ensure that HCPs are systematically informed about the availability of the patient database resource.

As shown in Figure 1 of the protocol, there is an access control to the Orphacol® Patient Surveillance Database. A first access to a welcome web page is open to all visitors and contains high-level information on inborn errors of bile acid synthesis destined to HCPs.

In order to gain access to the restricted level General data on inborn errors of primary bile acid synthesis, users need to request a user ID and password from the MAH. This access control is intended to ensure that only properly qualified HCPs have access to this information, as required legally in a number of Member States.

The web site is non-promotional and open for inspection by Regulatory Authorities for adherence to this requirement.

**Figure 1: Flow chart for accessing the patient database**



Controlled access level

Below are the instructions on how a health professional will enter the patient database and Orphacol® Educational website and Patient Database and what information will be available for him/her at this level of access. The aim of this level of access is to disseminate information to physicians and other HCPs that will help them to correctly identify and initially treat patients with 3β-HSD deficiency or $\Delta^4$-3-oxoR deficiency.

**1.** Access the web site via the electronic address
www.databaseorphacol.com
Documentation on Orphacol® providing information on the possibility to access the website will be distributed to the EU Reference Centres for the disease.

**2.** Enter your User ID and your Password
User ID: **1234567890**
Password: **C2TOROS9**
The password will be granted by Theravia upon receipt of a request by email. The requestor will have to provide Theravia with a statement confirming that he/she is a health care professional.

**3.** Available information (content may change according to local requirements)

I. General data on:
Inborn errors of primary bile acid synthesis

II. Diagnosis
   a. Clinical signs
   b. Laboratory signs
   c. Hepatic histological signs
   d. Confirmation of Diagnosis
   e. Diagnostic Flow-Chart
   f. Laboratories with appropriate diagnostic capacities

III. Treatment
   a. Restoration of the bile acid-dependent component of bile flow
   b. Inhibition of the production of hepatotoxic and cholestatic primary bile acid precursors
   c. Improvement of the child's growth

IV. Recommended dosage of cholic acid to treat *3β-hydroxy-*$\Delta^5$*-*$C_{27}$*-steroid dehydrogenase/isomerase* and $\Delta^4$*-3-oxosteroid-5β-reductase* deficiencies

V. Good general practice recommendations for patients with 3β-HSD deficiency or $\Delta^4$-3-oxoR deficiency, including appropriate measures to prevent hepatic impairment, such as a healthy diet and low alcohol intake, vaccination against hepatitis, and avoidance of hepatotoxic xenobiotics, including medicinal products.

VI. Additional Resources
   a. Link to the Orphacol EPAR and product information on the Agency's web site
   b. Bibliography

All educational material on this web site will be prepared in accordance with the approved product information, national competent authority requirements. Approved educational material are available in PDF format for the countries where they are approved by local authorities.

Patient database

In this patient database section, HCPs will be able to view their patients' information including demographics and family history, diagnostics, treatment and adverse events, as well as adding new patient.

HCPs have access to a data entry interface that will enable them to enter the data listed above (see section 4) as they are generated during the treatment of their patients.
Data that have been entered will be reviewed for consistency by Theravia before definite inclusion into the database. Potential data queries will be resolved in direct interaction with the reporting physician.

Monitoring

The database will be monitored for effectiveness by the following measures:

- Due to the low number of patients, treatment centres and hence treating physicians, Theravia will be aware of most or even all physicians that are treating patients with 3β-HSD deficiency or $\Delta^4$-3-oxoR deficiency. It will therefore be possible to link commercial information with the registration of HCPs with the web site, and to take contact individually with HCPs to motivate them to participate in the data collection effort.

- A patient will be followed at least once a year by the treating physician once the treatment with Orphacol® is well-established. Therefore, Theravia can monitor whether the information for any given patient has been updated in the corresponding time span, and therefore again stimulate data entry by HCPs.

- Data are entered by the HCP or delegated person under the respective treating physician's responsibility. The data will be reviewed for consistency at least once per year by Theravia before definite inclusion into the database, as per the Theravia Quality Assurance procedures. Potential data queries will be resolved in direct interaction with the reporting HCP.

Quality Control and Quality Assurance

Data are entered by an HCP or delegated person under the treating physician's responsibility. The data will be reviewed for consistency at least once per year by Theravia before definite

inclusion into the database, as per the Theravia Quality Assurance procedures. Potential data queries will be resolved in direct interaction with the reporting HCP.

## *9.7. Data analysis*

Descriptive statistics are used to describe the included patients. Blood biochemistry parameters are described using best and worst values (either as categorical then quantitative variables) in each treatment period. Then, mean values per patient of each blood biochemistry parameters are described in each treatment period, and comparisons between treatment periods using the Wilcoxon's test for paired data are performed.
Graphical representations (boxplot and individual time-response graphs) are generated.

Analysis population will comprise all patients treated with Orphacol®, having signed the ICF, without deviation and for whom the type of deficiency is available.

Disposition of patients
Number and percentage of patients in the following populations will be described:

- Patients for whom the type of deficiency is available
- Patients treated with Orphacol® (i.e. with at least one start date of Orphacol® in the database)
- Patients included in the analysis population

A flowchart presenting the populations will also be provided.
In addition, the number of patients included in the analysis population will be described according to the year of the last data point and according to the type of deficiency.
A listing by patient of durations of observation under the different treatment periods will be provided including the following variables: site + patient code, type of deficiency, durations for the different treatment periods (No treatment (calculated from birth of patient) / Ursodeoxycholic acid (UDCA) / UDCA+CA / CA monotherapy).
Additional information such as total number of visits and the additional visits (since the 12 September of the previous year) according to the patient will also be provided.

Statistical methodology

Statistics is outsourced to the CRO administrating the database, ICTA PM.

*General principles:* All statistical analyses will be performed on the analysis population defined above.

*Softwares*: Statistical analyses will be performed by ICTA PM with SAS® version 9.2 or higher (SAS institute, North Carolina, USA).

*Descriptive statistics*: Descriptive statistics will be summarized depending on the nature of the analysed variables:

- Quantitative variable: number of data available, number of missing data, mean, standard deviation, first quartile (Q1), median, third quartile (Q3), minimum and maximum

- Qualitative variable: number of data available, number of missing data, frequency and percentage for each modality. Missing data will not be taken into account for percentage calculation.

*Management of missing or incomplete data*: Missing data will not be replaced.

*Presentation of results*: The statistical outputs will be produced in British English.
For summary statistics of quantitative parameters, the following number of decimal places (dp) will be presented:

- Mean, standard deviation, median, Q1 (first quartile) and Q3 (third quartile) with one more dp than the raw data
- Minimum and maximum with the same number of dp as the raw data

The percentages of each modality of qualitative variable will be presented with one more dp than the raw data. The p-values will be presented with four decimals.

*Validation levels*: A single programming is planned for this study and will be performed by the statistician in charge of the study.
An internal review by the statistician in charge of the project will be performed, including SAS® programming, SAS® logs and outputs, and edition of the tables, figures and listings (TFL). Then, an external review of the TFL will be performed by the ICTA PM Project Manager and Medical Writer.

Demographic and other baseline characteristics

Demographic and other baseline characteristics will be described according to the type of deficiency (3β-HSD / Δ4-3-oxoR).

- Year of birth, in classes (1980-1985 / 1986-1990 / 1991-1995 / 1996-2000 / 2001-2005 / 2006-2010 / 2011-2015 / 2016-2020). Additional classes may be added over time based on the data in the database
- Age at diagnosis, in classes (<3 months / [3 months;6 months] / ]6 months;12 months] / ]12 months;36 months] / ]3 years;10 years] / ]10 years;15 years] / >15 years). The day of birth will be imputed to the 15th of the month
- Gender (Male/Female)
- Treatment centre (Centre 001/Centre 002/Centre 003/Centre 004/Centre 005/Centre 006/Centre 007/Centre 008). Additional centres may be added over time based on the data in the database
- Cholic acid treatment duration, in classes (≤1 year / ]1 year;2 years] / ]2 years;3 years] / ]3 years;5 years] / ]5 years;10 years] / ]10 years;15 years] / ]15 years; 20 years] / >20 years). The end date of cholic acid will be the date of the database lock if treatment is still ongoing at that date.

Analysis of endpoints

Analysis of endpoints will be performed according to the type of deficiency, if the sample size is sufficient.

*Comparison of blood biochemistry parameters (categorical analysis)*
The best/worst categorical values will be described in each treatment period.

This endpoint will compare in pairs the best categorical values of blood biochemistry parameter in the following treatment periods: UDCA, UDCA+CA, CA first year, CA second year, CA after second year and CA monotherapy (i.e. CA pooled), versus the worst categorical values in the following treatment periods: no treatment and UDCA. In total, 11 pairwise comparisons will be performed using the McNemar's test at level 0.05:

- Best categorical value in UDCA vs worst categorical value in no treatment period
- Best categorical value in UDCA+CA vs worst categorical value in no treatment period
- Best categorical value in CA first year vs worst categorical value in no treatment period
- Best categorical value in CA second year vs worst categorical value in no treatment period
- Best categorical value in CA after second year vs worst categorical value in no treatment period
- Best categorical value in CA monotherapy (CA pooled) vs worst categorical value in no treatment period
- Best categorical value in UDCA+CA vs worst categorical value in UDCA
- Best categorical value in CA first year vs worst categorical value in UDCA
- Best categorical value in CA second year vs worst categorical value in UDCA
- Best categorical value in CA after second year vs worst categorical value in UDCA
- Best categorical value in CA monotherapy (CA pooled) vs worst categorical value in UDCA

Any other pairwise comparison might be added if other treatment options were used before treating with CA (e.g. CDCA).

These analyses will be performed for each blood biochemistry parameter (alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma-glutamyl transferase (GGT), total bilirubin, alkaline phosphatase (ALP) and vitamin E).
A sensitivity analysis will be performed, comparing in pairs the worst categorical value of each blood biochemistry parameter in the treatment periods defined above, versus the worst categorical value in no treatment and UDCA periods.

*Assessment of the effect of treatment periods on levels of blood biochemistry parameters*
This analysis will assess the effect of treatment periods on levels of blood biochemistry parameters (see classifications in section 6.2). Ordinal logistic models (or logistic models, see section 6.2) will be used, taking account that the measurements were repeated within the subjects and therefore that the outcomes (i.e. blood biochemistry parameters) in the treatment periods were not independent. Supposing that outcomes within the subjects are correlated, generalized estimating equations (GEE) method will be used to control for possible underestimating of the variance which can lead to artificially low p-values.

The primary analysis will consider the best categorical values of blood biochemistry parameter. The effect of treatment periods will be assessed with pairwise comparisons. In total, 11 ordinal logistic models with repeated measures will be performed (odds ratio (OR), 95% confidence intervals (CI) and p-values will be presented).

This analysis will be performed for each blood biochemistry parameter (ALAT, ASAT, GGT, total bilirubin, ALP and vitamin E).

A sensitivity analysis will be performed, considering the worst categorical values of blood biochemistry parameters.

*Stability of blood biochemistry parameters within CA period*
In order to examine the stability of the outcomes (i.e. blood biochemistry parameters) within CA period, ordinal logistic model (or logistic model, see section 6.2) with repeated measures and GEE estimates will be used (OR, 95% CI and p-values will be presented). The explicative variable will be the treatment period with the following modalities: CA first year, CA second year and CA after second year.

The primary analysis will consider the best categorical values of blood biochemistry parameter will be considered.

This analysis will be performed for each blood biochemistry parameter (ALAT, ASAT, GGT, total bilirubin, ALP and vitamin E).

A sensitivity analysis will be performed, considering the worst categorical values of blood biochemistry parameters.

*Comparison of blood biochemistry parameters (quantitative pooled analysis)*
In this section, all values of each blood biochemistry parameter will be considered. The mean value per patient of each blood biochemistry parameter for each treatment period (the CA pooled period will not be taken account) will be calculated.

These values will be described in each treatment period.

Comparison of the mean values between each treatment period (UDCA, UDCA+CA, CA first year, CA second year and CA after second year vs no treatment and UDCA) will be performed using the Wilcoxon's test for paired data at level 0.05.

*Graphical representations*
Mean values of each blood biochemistry parameter (see section 4.3.4) will also be presented through boxplots graph at each treatment period.

The evolution of blood biochemistry parameters will be presented through graphs according to the duration of observation, for both patients with Δ4-3-oxoR deficiency and patients with 3β-HSD deficiency.

## *9.8. Quality control*

Data are entered by a HCP or delegated person under the treating physician's responsibility. The data will be reviewed for consistency at least once per year by Theravia before definite inclusion into the database, as per the Theravia Quality Assurance procedures. Potential data queries will be resolved in direct interaction with the reporting HCP.

### *9.9. Limitations of the research methods*

Major limitations of this study are its still small sample size (preventing any complex data analyses) and its observational nature (possibly impacting data quality increasing the risk of missing data). Other limitation is the patients' medical records (source data itself) which cannot be verified nor validated.

### *9.10. Other aspects*

Not applicable.

## 10. Protection of human subjects

Each patient accepting to participate in the study will have to sign an informed consent form (ICF). If the patient is minor, then his legal representatives will be asked to participate and to sign the ICF.

The collection of data is conducted in accordance with General Data Protection Regulation 2016/679 in force. The patients are informed accordingly in the ICF.

The consent of the patient or his or her parent or guardian to the collection of the above defined medical data will be obtained and filed by the treating physician. Theravia will systematically request a proof of signature of the informed consent (acknowledgment from the physician that the ICF has been signed), as per current internal processes.

The proof of signature of a new informed consent will be requested by Theravia when paediatric patients will become adults.

The national requirements in every country where a patient will be treated will be clarified in detail and on a case by case basis as patients are identified. For patients treated in France, the French Commission Nationale de l'Informatique et des Libertés (National informatics and civil liberties commission; CNIL) has been notified regarding the patient database (declaration number: 1210041).

This protocol will be approved by the relevant authorities, including European Medicines Agency and national competent authorities/local Ethics Committees where required.

## 11. Management and reporting of adverse events/adverse reactions

A serious adverse event/reaction (SAE/SADR) is one which:

- is fatal or life threatening,
- is permanently or significantly disabling,

- results in congenital abnormality or birth defect, or
- requires in-patient hospitalization or prolongation of hospitalization
- is assessed as serious for other medically important condition as defined by the physician.

An unexpected adverse event/reaction is one which:
- is not previously reported in the Section 4.8 of the Orphacol® SmPC, or
- is symptomatically and pathophysiologically related to a reported toxicity but differs because of greater severity or increased frequency.

The physician is responsible for reporting to his national authorities the adverse reactions observed with Orphacol® as per the local requirements.

Collection of information

Information on the adverse events/reactions to Orphacol® can be collected in the patient database. The SAE/SADR should be reported in the Serious Adverse Events/Reactions section of the patient database.

The following information is requested:
- Information on SAE/SADR: event/reaction, seriousness criteria, date of occurrence, relevant tests, concomitant drugs, outcome
- Was the SAE/SADR declared to national authorities?
- Copy of the pharmacovigilance declaration submitted to the national authority

A warning system will inform Theravia of the posting of any SAE/SADR information in the safety database. This information will be immediately retrieved by Theravia for regular pharmacovigilance data processing, as per current processes in place.

## 12. Plans for disseminating and communicating study results

Interim, study progress reports are submitted to the European Medicines Agency at every annual reassessment as required, and safety data analysed as part of PSUR, as required. The same reports or their summaries might be communicated to participating investigators as well.

The final study results and reports will be submitted to national competent authorities/local Ethics Committee where required, as well as to participating investigators.

## 13. References

Bossi et al. (2017)
Janhel et al. (2017)
Gonzales et al. (2009)
Gonzales et al. (2018)