Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

URSODEOXYCHOLIC ACID

Delursan
Ursofalk

UK/W/036/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	29th October 2012
Date of finalisation of PAR:	12th November 2012

INDEX

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section IX
INN (or common name) of the active substance(s):	Ursodeoxycholic acid
MAHs:	See section IX
Pharmaco-therapeutic group (ATC Code):	Bile and Liver therapy
Pharmaceutical form(s) and strength(s):	Tablets: 250 mg, 500 mg Capsules: 250 mg Oral suspension: 250 mg/5 ml

I. EXECUTIVE SUMMARY

Ursodeoxycholic acid (UDCA), a naturally occurring hydrophilic bile acid, derived from cholesterol, is present as a minor fraction of the total human bile acid pool. Oral administration of UDCA increases this fraction in a dose related manner, to become the major biliary acid, replacing/displacing toxic concentrations of endogenous hydrophobic bile acids that tend to accumulate in cholestatic liver disease. It also appears that UDCA has a choleretic effect which increases bile acid output and bile flow from the liver. Furthermore, UDCA reduces the ratio of cholesterol in biliary fluid primarily by dispersing the cholesterol and forming a liquid-crystal phase. Overall the exact mechanism of action has not been fully elucidated.

UDCA medicines have a licensed adult indication for the treatment of cholesterol gallstones, primary biliary cirrhosis (PBC) and in some EU countries bile reflux gastritis. However, in some EU countries (France, Greece, Hungary, and Netherlands) UDCA preparations are also licensed for the treatment of primary sclerosing cholangitis and cystic fibrosis associated liver disease which are more frequently observed in children and adolescents.
A currently approved UK SmPC contains the following information about the paediatric use of ursodeoxycholic acid: '*Section 4.2: There are no age restrictions on the use of* UDCA*. Children: Cholesterol rich gallstones are rare in children but when they occur, dosage should be related to bodyweight.'* However no paediatric indications or exact posology is specified.

UDCA containing products are available as capsules, tablets and suspension. Of note, MAH 1 markets capsules, tablets and suspension formulations, where as MAH 2 holds market authorization only for film coated tablets.

On 25th August 2011, one MAH (referred to as MAH1 in this document) submitted data for ursodeoxycholic acid, in accordance with Article 45 of the Paediatric Regulation. A few months later - on 29th November 2011 - the MHRA also received a request from another MAH (referred to as MAH2 in this report) to participate in this work-sharing procedure and consequently MAH2 joined the procedure on 1st December 2011.

Both MAHs' data packages have been assessed and the preliminary assessment report was circulated to member states on 20th February 2012 at day 70 of the procedure. Comments were received from five member states (DE, SE, NL, HU and IE) which were incorporated into the rapporteur's report and request for additional information. The day 89 report was sent to the MAHs on 22nd March 2012 and responses were received from MAH1 and MAH2 in June 2012. Both MAHs' response data sufficiently addressed the list of questions from the rapporteur and the MSs. Following circulation of the day 90 assessment report in September 2012, comments were received from five member states (NL, FR, HU, SE and IE); all were in agreement with the Rapporteur's overall conclusions and recommendations. The day 120 report was circulated and the procedure finalised on 29th October 2012. An update to the list of medicinal products and MAHs (section IX of the final assessment report) was made on 31st October 2012.

RECOMMENDATION

Based on the review of the presented paediatric data on ursodeoxycholic acid, the rapporteur considers that the currently available evidence only supports UDCA's use in hepatobiliar disorder associated with cystic fibrosis in children aged 1 month to less than 18 years. Treatment with UDCA in this paediatric condition is considered to be safe and effective at a dose

of 20 mg/kg/day in 2-3 divided doses with an increase up to 30 mg/kg/day if necessary based on clinical response.

It has been demonstrated in short-term as well as long-term use (up to 12 years) that UDCA is able to improve/normalise hepatic transaminases, improve hepatic metabolism of essential fatty acids and bile flow in children with cystic fibrosis. Moreover, there is some evidence suggesting that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepato-biliary changes if given at early stage of CFAHD. Treatment with UDCA should be started as soon as the diagnosis of CFAHD is made in order to maximize treatment effectiveness because if significant liver cirrhosis is already manifested a normalisation of liver function may not be expected.

UDCA has been in most trials safe and well tolerated, even at high doses up to 45 mg/kg/day and also in preterm infants. However, careful titration of UDCA dose is needed in paediatric patients with significantly decreased bile outflow. There is evidence available in the literature that UDCA administration has been associated with serious hepatic and extra-hepatic morbidites in cases of unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia, therefore it is considered justified to contraindicate UDCA's use in paediatric patients with this condition. Furthermore, although a potential safety concern recently emerged regarding long-term high-dose UDCA treatment in adult patients with primary sclerosing cholangitis (PSC) this is not considered relevant to the paediatric CF population.

Both MAHs' submitted lists of paediatric adverse events fall within the company's core safety profile. It has been noted that a significant number of non-serious ADRs fell within SOC: 'Skin and subcutaneous tissue disorders' and therefore the MAHs are advised to closely monitor this in the future.

Furthermore, in light of the newly proposed paediatric indication MAHs are requested to submit a Risk Management Plan (RMP) to address the identified risks for the paediatric population in accordance with the new pharmacovigilance legislation at the time of the variations to implement the new indication. This has to be done in line with the current CMDh advice, which can be found at the following link
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Pharmacovigilance_Legislation/CMDh-257-2012-Rev2-2012_07.pdf

Summary of outcome

SmPC and PL changes are proposed in sections 4.1, 4.2, 4.3 and 5.1.
Of note, MAH 2 does not hold marketing authorization for a paediatric formulation suitable for use in children under 6 years of age therefore the final SmPC change recommendations in section 4.1 vary based on the formulation (see below).

☐ No change

☒ Change

☐ New study data: <section(s) xxxx, xxxx>

☐ New safety information: <section(s) xxxx, xxxx>

☐ Paediatric information clarified: <section(s) xxxx, xxxx>

☒ New indication: sections 4.1, 4.2

Final SmPC recommendations

a) Suspension

Section 4.1 Therapeutic indications
Paediatric population
Hepatobiliar disorder associated with cystic fibrosis in children aged 1 month to less than 18 years

Section 4.2 Posology and method of administration
Paediatric population
Children with cystic fibrosis aged 1 month to less than 18 years: 20 mg/kg/day in 2-3 divided doses, with a further increase to 30 mg/kg/day if necessary

Section 4.3 Contraindications
Paediatric population
Unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia

Section 5.1 Pharmacodynamic properties
Paediatric population
Cystic fibrosis
From clinical reports long-term experience up to 10 years and more is available with UDCA treatment in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepato-biliary changes if given at early stage of CFAHD. Treatment with UDCA should be started as soon as the diagnosis of CFAHD is made in order to optimize treatment effectiveness.

b) Tablets, Capsules

Section 4.1 Therapeutic indications
Paediatric population
Hepatobiliar disorder associated with cystic fibrosis in children aged 6 years to less than 18 years

Section 4.2 Posology and method of administration
Paediatric population
Children with cystic fibrosis aged 6 years to less than 18 years: 20 mg/kg/day in 2-3 divided doses, with a further increase to 30 mg/kg/day if necessary

Section 4.3 Contraindications
Paediatric population
Unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia

Section 5.1 Pharmacodynamic properties
Paediatric population

Cystic fibrosis

From clinical reports long-term experience up to 10 years and more is available with UDCA treatment in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepato-biliary changes if given at early stage of CFAHD. Treatment with UDCA should be started as soon as the diagnosis of CFAHD is made in order to optimize treatment effectiveness.

II. INTRODUCTION

II. 1. MAH 1

On 25th August 2011, MAH 1 submitted the following 4 documents for ursodeoxycholic acid, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use:

- Clinical expert overview of the use of UDCA preparations in children
- Core Safety Profile for UDCA (Final assessment report of PSUR Work-sharing procedure MT/H/PSUR/0001/001)
- *Study URU-3/NEO:* Influence of bile acids on postnatal development in preterm infants during the first weeks of life.
- *Study URC-17/CCF*: A 2-year prospective double blind randomised cross-over trial to evaluate the effect of ursodeoxycholic acid on histology in children with cystic fibrosis liver disease.

The MAH individually reviews the major indications and chronic cholestatic liver diseases in children: Cystic fibrosis (CF), Byler's disease or Progressive Familial Intrahepatic Cholestasis (PFIC), Alagille syndrome (AS), Biliary atresia (BA), Total parenteral nutrition associated cholestasis (TPNAC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC). The MAH acknowledges that many of these studies were conducted in the 80s and early 90s in small study populations. Nevertheless, in the MAH's view they demonstrate that the use of UDCA for treatment of cholestatic liver diseases may be effective at least in some indications. In addition, treatment with UDCA was shown to be safe in children, even in high doses (up to 45 mg/kg/day) in preterm neonates, infants and small children. Moreover, the Core Safety Profile (CSP) for UDCA resulting from the PSUR Work-sharing procedure MT/H/PSUR/0001/001 in 2009 does not generally restrict the use of UDCA in any paediatric subset, therefore the MAH is of the view that the statement in the currently approved SmPC in section 4.2 "*There are no age restrictions on the use of UDCA 250 mg/ml suspension"* is justified.

UDCA products are licensed in adults for the treatment of cholesterol gallstones, primary biliary cirrhosis (PBC) and in most EU countries bile reflux gastritis. However, in certain parts of Europe other indications are also licensed, such as:

- o Liver diseases caused by primary sclerosing cholangitis (HU)
- o Symptomatic treatment of cholestatic syndromes of various etiology such as sclerosing cholangitis (EL)
- o Chronic (≥ 6 months) mild to moderate severe hepatobiliar disorder (hepatobiliair disorders at least up to 2-3 times the standard value) as result of cystic fibrosis (CF) in children and adolescents (NL)

UDCA products are licensed via national procedures in most European countries.

MAH1 recommends the following approach to updating the SmPC:

- ➢ In countries where UDCA preparations are approved only for the indications cholesterol gallstones, PBC and for UDCA capsules in addition bile reflux gastritis they suggest to include the following information in Section 4.2 of the SPC:

"Children and adolescents

Cholesterol gallstones and PBC (and bile reflux gastritis) are very rare in children and adolescents. Therefore there are only limited data on the efficacy and safety in the paediatric population available.
When these conditions occur in children or adolescents the administration of UDCA/…/ should be based on body weight.
In general there are no age restrictions on the use of UDCA /…/."

- In countries where UDCA preparations are in addition approved for other types of cholestasis they propose to include the following information in Section 4.2 of the SPC:

"Children and adolescents
Cholesterol gallstones and PBC (and bile reflux gastritis) are very rare in children and adolescents. Therefore there are only limited data on the efficacy and safety in the paediatric population available in these indications.
There is limited experience with UDCA in treatment of other types of paediatric cholestasis.
When these conditions occur in children or adolescents the administration of UDCA/…/ should be based on body weight.
In general there are no age restrictions on the use of UDCA /…/."

- In the Netherlands the following posology is included in the SmPC for children suffering from cystic fibrosis. This information should be maintained:

"Treatment of hepatobiliar disorders as a result of cystic fibrosis: Dosage of ursodeoxycholic acid for treatment of hepatobiliar disorder as result of cystic fibrosis is 15-20 mg/kg/day, corresponding with 2 – 5 capsules, to be taken in 2 – 3 portions during the day."

II. 2. MAH 2

On 8th December 2011, MAH 2 submitted the following 3 documents for ursodeoxycholic acid, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use:

- A critical literature overview assessing the paediatric data available for the following indications : cholestatic liver diseases or conditions, biliary atresia (BA), cystic fibrosis (CF), primary sclerosing cholangitis (PSC), progressive familial intrahepatic cholestasis (PFIC), gallstone disease (cholelithiasis), total parenteral nutrition associated liver disease (PNLD), cholestasis, non-alcoholic steatohepatitis (NASH), hematopoietic stem cell transplantation (HSCT),
- Approved SmPC/leaflet
- Complete bibliography from literature data.

The MAH's critical literature overview concludes that despite the paucity of large scale, prospective, blinded, RCTs investigating the use of UDCA in children, the overall scientific literature provides consistent evidence of its efficacy and safety in some indications such as CF, BA after successful portoenterostomy, PSC and TPN-associated cholestasis. For some indications, evidence of efficacy in children is less consistent although UDCA is widely used in practice (e.g. PFIC). The MAH claims that UDCA improves liver function tests in all indications and depending on the pathology, it has also been shown to have a beneficial effect on the symptomatology (jaundice, pruritus). Doses used in the scientific literature usually range from 10 – 30 mg/kg/day causing only a few adverse events. Mild diarrhea has been reported in a few studies and involving a very limited number of patients.

The MAH advises some precautions and contraindications for the use of UDCA in the above-mentioned indications:

- UDCA should not be used in cases of obstruction of bile ducts (e.g. failure of portoenterostomy in BA);
- In PSC, doses should not exceed 20 mg/kg/day;
- Administration of UDCA in TPN-associated cholestasis should be restricted to preterm or VLBW infants that are not suffering from severe concomitant infections or diseases as a study has demonstrated deleterious effects of UDCA administration in severely ill neonates.

MAH 2 did not propose any wording to update the currently approved SmPC.

III. SCIENTIFIC DISCUSSION

III.1 Information on the pharmaceutical formulation used in the clinical studies

Ursodeoxycholic acid is a naturally occurring bile acid found in small quantities in normal human bile and in larger quantities in the biles of certain species of bears. It is a bitter-tasting white powder consisting of crystalline particles freely soluble in ethanol and glacial acetic acid, slightly soluble in chloroform, sparingly soluble in ether, and practically insoluble in water.
Ursodeoxycholic acid preparations are available as capsules (250mg), tablets (150mg, 300mg) and suspension (250mg/5ml) in most EU countries.
In study URU-3/NEO (which recruited preterm infants <34 weeks gestational age) a suspension form of UDCA was administered. Before use, bottles containing the suspension as a thixotropic mixture were well shaken to liquefy the content. Then 0.1ml aliquots (corresponding to 5mg UDCA) of the suspension were removed with a sterile pipette or syringe and were diluted with sterile water in the appropriate ratio for the individual patient to give a total volume of 1 ml. In case of transpyloric feeding suspension was given through a feeding tube.
The other submitted clinical study medication formulation (Study URC-17/CCF; recruited children aged 6.5 – 17 years) is not specified in the submitted manuscript and abstracts.

MAH 2 states that UDCA prescribed to children is done off-label, with dosages extrapolated from adult data through body weight and surface area calculations. Furthermore, the lack of pharmaceutical formulations proper for children favors the manipulation of “homemade” oral preparations by hospital pharmacies. This is associated with unknown bioavailability and stability of the resulting product; moreover derivation from solid to liquid often requires addition of artificial flavours and therefore adds the risk of hypersensitivity reactions. These homemade preparations can generate improper dosage and unpredicted adverse events and therefore well-formulated and quality-controlled liquid formulations approved by health regulatory authorities are necessary.

Rapporteur’s Comment
MAH 1 did not provide quality information about the formulations of UDCA they hold license for. According to SmPC section 6.1, MAH 1’s UK licensed UDCA liquid suspension 250mg/5ml is comprised of the following excipients: benzoic acid (E210), microcrystalline cellulose, carboxymethyl-cellulose sodium, sodium chloride, sodium citrate, citric acid anhydrous, glycerol, propylene glycol, xylitol, sodium cyclamate, lemon flavouring (Givaudan 87017), purified water. Based on this data the following issues were raised regarding the excipients:

- The use of benzoic acid as a preservative in an oral liquid, particularly when used in neonates is of concern as the Reflection paper: Formulations of choice for the paediatric population (CHMP/PEG/194810/2005) specifically states: Neonates are unable to conjugate benzoic acid efficiently and this is of great importance to the use of benzyl alcohol as an excipient in this age group since its metabolite benzoic acid can accumulate and is toxic. Furthermore, in developing pharmaceutical preparations for use in preterm infants, neonates and young children benzyl alcohol/benzoic acid/sodium benzoate should be carefully evaluated and may be best avoided. The MAH should discuss and justify the use of benzoic acid if they wish to retain all paediatric age groups in section 4.2 of the SmPC.
- There is clear risk for accumulation as this medication would be administered long-term in chronic cholestatic conditions. The MAH should confirm the amounts of each excipient present, as it is unclear whether each 5ml spoonful contains 1.5mg or 7.5mg of benzoic acid (WHO currently accept 5mg/kg/day as an ADI, but not specifically in neonates, where numerous concerns regarding safety have been raised).
- Concerns about the use of propylene glycol have been raised as well. 5ml UDCA suspension contains only 10mg propylene glycol but again there is the risk of accumulation with long-term administration (WHO ADI 25mg/kg/day).
- Furthermore, the MAH should determine the overall sodium content as sodium is present in a number of excipient sources, including sodium chloride.
- The use of sodium cyclamate as a sweetening agent also needs justification (ADI is 0-11mg/kg/day (http://ec.europa.eu/food/fs/sc/scf/out53_en.pdf), each 5ml contains 5mg) as due to safety concerns it is banned in the US.

Based on a dosing regime of 20mg/kg/day UDCA, an infant of 5 kg weight at 1 month of age would receive a daily dose of 100mg per day (2-3 doses), or 2 x 1ml doses. Therefore the volumes of suspension are acceptable, providing an appropriate measuring device is used. However, if UDCA was to be used in preterm infants, development of a more dilute suspension would be needed to allow safe dosing.
In summary, the rapporteur is of the view that the MAH should provide quality information and discuss the use of excipients and where necessary justify in relation to the suitability of the formulation to the proposed paediatric population.

MAH 2 markets only 250 mg and 500 mg tablets. The rapporteur fully agrees that age-appropriate quality controlled liquid formulations are needed for the paediatric population to allow more exact dosing and to avoid dosing errors and therefore would strongly encourage the development of such product.

III.2 Non-clinical aspects

1. Introduction

Non-clinical studies have not been provided or summarized by MAH 1 on Ursodeoxycholic acid.

MAH 2 summarized an *in vitro* pre-clinical pharmacology study available in the literature, which was conducted in immature rat neurons at conditions mimicking those of hyperbilirubinaemic newborns (Vaz et al. 2010). This study showed that administration of a glycine-conjugated form of UDCA (glycoursodeoxycholic acid) protected neurons from neurotoxicity due to hyperbilirubinemia and thus, UDCA could be beneficial in preventing neonatal unconjugated bilirubin-induced encephalopathy, particularly in premature infants.

No pre-clinical information is available in the currently approved SmPC in Section 5.3.

2. Discussion of non clinical aspects

Ursodeoxycholic acid (UDCA), a hydrophilic bile acid, derived from cholesterol, is present as a minor fraction of the total human bile acid pool. Oral administration of UDCA increases this fraction in a dose related manner, to become the major biliary acid, replacing/displacing toxic concentrations of endogenous hydrophobic bile acids that tend to accumulate in cholestatic liver disease. In addition, other mechanisms of action include cytoprotection of the injured bile duct epithelial cells, inhibition of apotosis of hepatocytes, immunomodulatory effects, and stimulation of bile secretion by hepatocytes and cholangiocytes.

UDCA reduces the ratio of cholesterol in biliary fluid primarily by dispersing the cholesterol and forming a liquid-crystal phase. The exact mechanism of action has not been fully elucidated.

Rapporteur's Comment

The rapporteur is of the view that the information provided on non-clinical aspects is not fully relevant to ursodeoxycholic acid as the study compound was glycoursodeoxycholic acid, not UDCA; therefore its inclusion in the SmPc is not justified.

III.3 Clinical aspects

1. Introduction

Both MAHs provided clinical expert overviews of the available information on the clinical efficacy of ursodeoxycholic acid in patients with different forms of chronic cholestatic liver disease. Each condition has a dedicated chapter in the MAHs' clinical overviews comprising of the description of the condition, the role of UDCA in the treatment of the disease and a comprehensive literature review including the study abstracts in a table format. All of these conditions are discussed individually under section II.3.2.b (Clinical efficacy) of this report.

In addition, two MAH 1 sponsored clinical study reports were submitted:

- *Study URC-17/CCF:* A 2 year prospective double blind randomised cross-over trial to evaluate the effect of ursodeoxycholic acid on histology in children with cystic fibrosis liver disease.
- *Study URU-3/NEO:* Influence of bile acids on postnatal development in preterm infants during the first weeks of life.

The details and assessment of these studies can be found under the relevant condition's heading i.e. Cystic fibrosis associated liver disease (URC-17/CCF) and Total parenteral nutrition associated cholestasis (URU-3/NEO) in section II.3.2.b.

2. Clinical overview

a. Pharmacokinetics

The currently approved UK SmPC Section 5.2 reads: "Ursodeoxycholic acid occurs naturally in the body. When given orally it is rapidly and completely absorbed and undergoes first pass metabolism and enterohepatic recycling. It is 96-98% bound to plasma proteins and efficiently extracted by the liver and excreted in the bile as glycine and taurine conjugates. In the intestine some of the conjugates are deconjugated and reabsorbed. The conjugates may also be dehydroxylated to lithocolic acid, part of which is absorbed, sulphated by the liver and excreted via the biliary tract."

MAH 1 did not provide any data on the pharmacokinetic properties of UDCA.

MAH2 provided the following pharmacokinetic information:

Technologies used to study ADME in adults usually require larger sample volume than can be collected from newborn infants. In a first study, Vuong et al. (2010) demonstrated a 'single-drop' analytical capacity for quantifying tracer labelled compounds in neonates using accelerator mass spectrometry (AMS) to quantify the concentration of sub-therapeutic doses of ^{14}C-labeled compounds in single drops (5 - 25 ml) of biological fluids, such as obtained from a heel prick drop of blood/ECF. PK data from 3 neonates dosed at 37, 120 and 370 Bq of ^{14}C-labeled ursodiol were used to demonstrate the value of AMS in neonatal research, this technique allowing for much lower sample volumes and radiological exposure while providing accurate PK measurements.
In a second trial performed by the same group of investigators (Baillie et al. 2011), the pharmacokinetics of ursodiol were studied in 5 neonates. Subjects did not have cholestasis and caloric intake was parenteral. Non-compartmental analysis showed that the UDCA concentrations were dose-proportional. Compartmental analysis yielded a 3-compartment model with a gall bladder compartment. The apparent Vdist was 145 ± 31 ml; T-half was 20.3 ± 5.5 hr. The model was extended to represent cholestasis and predict changes in bile release. The authors concluded that AMS and PK/PD modelling provide validated, essential tools for neonatal PK and trial design. AMS sensitivity allows a significantly lower tracer dose. Low intra-subject variability indicated that AMS provides useful data supporting modelling and insight into UDCA PK. High inter-subject variability implied significant physiological variability between newborns. Modelling suggested several experiments to reduce the variability. The PK model constructed from AMS data could be used to study bile flux in cholestatic patients.

Rapporteur's Comment
The first study submitted by MAH 2 (Vuong et al 2010) aimed to evaluate accelerator mass spectrometry (AMS) as a tool for neonatal PK modelling rather than providing PK information about UDCA. The authors state that "further discussion of the results or any conclusions about the behavior of neonatal biliary systems in response to small ursodiol doses is beyond the scope of this report which serves to introduce the concept of AMS tracing 14C compounds in neonates."
MAH 2's second study (Baillie et al. 2011) aimed at analysing ursodiol PK in neonates, however only limited data have been submitted (only a conference abstract). Although the study included small numbers (n=5) and described high inter-subject variability between newborns, it may still provide valuable PK data in neonates. Therefore MAH 2 is requested to provide more details of this study if available.

The rapporteur is of the view that the pharmacokinetic properties described in the currently approved SmPC may be significantly different in the paediatric population. Intestinal absorption as well as the hepatic extraction of bile acids from portal venous blood is immature in young children and this may affect the PK of UDCA. The MAHs should provide any available pharmacokinetic data relevant to paediatric use.

b. Clinical efficacy

The MAHs covered the following conditions in their clinical overviews:

Table 1. Conditions reviewed

MAH 1	MAH 2
Cystic fibrosis associated liver disease (CFLD)	Cystic fibrosis associated liver disease (CF)
Progressive familial intrahepatic cholestasis (PFIC)	Progressive familial intrahepatic cholestasis (PFIC)
Biliary atresia (BA)	Biliary atresia (BA)

TPN associated cholestasis (TPNAC)	TPN associated cholestasis (PNLD)
Primary sclerosing cholangitis (PSC)	Primary sclerosing cholangitis (PSC)
Primary biliary cirrhosis (PBC)	Liver transplantation
Alagille syndrome (AS)	α_1 –antitrypsin deficiency
	Autoimmune hepatitis
	Non-alcoholic steatohepatitis (NASH)
	Hematopoietic Stem Cell Transplantation (HSCT)
	Viral hepatitis
	Hepatobiliary scintigraphy

The rapporteur discusses conditions covered by both MAHs first, followed by each MAH's additional data. In order to avoid confusion MAH 1's abbreviations of conditions are used in this report (see left column above). Furthermore, MAH 1 provided a conclusion about each condition, whereas MAH 2 included a summary of conclusions (see at the end of this section).

- ***Conditions covered by both MAHs***

- **CYSTIC FIBROSIS ASSOCIATED LIVER DISEASE**

Study URC-17/CCF
The role of ursodeoxycholic acid on histological changes in children with cystic fibrosis liver disease – a prospective study
Background: Study URC-17/CCF was submitted by MAH 1. It was an investigator initiated study for which MAH 1 provided the study medication. Neither a Clinical Study Report nor an accepted full text publication is available at MAH1 but only an unpublished manuscript as well as abstracts.

Study centers: Single center: Birmingham Children's Hospital NHS Trust

Study period:(first enrolment): March 1993 Phase of development: II
(last completed): March 1996

Objectives: The primary objective was to evaluate the effect of ursodeoxycholic acid on histology in children with cystic fibrosis liver disease.

Methodology: prospective, randomized, double-blind, cross-over trial of UDCA (20 mg/kg/day) orally versus placebo (20 mg/kg/day) for one year each.

Number of patients
21 patients were enrolled to the study (M:F 14:7), median age 9 yr 11mts (range 6.5-17yr)
Group A (n=9): Placebo 1 year, than UDCA 1 year
Group B (n=12): UDCA 1 year, than placebo 1 year

Methods:
Children with hepatomegaly/hepatosplenomegaly and/or abnormal hepatic biochemistry on 2 occasions over a 6 month period were randomised to group A (placebo/UDCA) or group B (UDCA/placebo). Liver biopsy was performed at annual intervals at entry, cross-over and completion. Cirrhosis was noted and each biopsy was scored for steatosis, portal fibrosis and cholangitis. A mean score was calculated for each category and compared using the t-test.

Results:
18/21 children completed the study, mean age 10.3 yr (range 6.5 to 17.1 yr) 11 :7 M:F.
The study reported significant improvement in transaminases in both treatment groups whilst the patients were taking UDCA [group A had a median fall of 55.5 (26.5 to 65.5), $p<0.02$ and group B had a median fall of 25 (-4 to 82.5), $p<0.07$)]. Following withdrawal of UDCA in group B at cross-over when the children commenced placebo, the ALT increased by a median rise of 50 (9 to 118), $p<0.02$. Overall there was a statistically significant effect of UDCA on ALT in both groups ($p<0.001$).
4 patients out of 8 in group A and 4 out of 10 in group B had cirrhosis at entry and did not change during the study. One child from group A and 2 from group B developed cirrhosis at 1 and 2 yr respectively. There was no significant deterioration in histological findings in either group irrespective of whether they received UDCA or placebo. However, at 2 years deterioration in steatosis and portal fibrosis was seen in those patients who had received UDCA late (group A, n=8) compared to those who had received UDCA earlier in the course of the trial (group B, n=10). There was a significant UDCA treatment effect on histological score ($p = 0.01$), particularly in stabilizing the progression of portal fibrosis ($p = 0.02$).
Chemical cholangitis was improved at 2 years in group B (early UDCA).
USS findings were a poor indicator of underlying liver disease and had poor correlation with histology (3 out of 8 children with a normal ultrasound score had abnormal histology with features of steatosis, cholangitis and biliary fibrosis).

Conclusion:
The authors concluded that UDCA may moderate chemical cholangitis, portal fibrosis and steatosis if given early enough in the course of CF-liver disease, but has no effect on progression of cirrhosis in already established liver disease. No correlation was found between ultrasound findings and liver histology concerning cirrhosis (under-estimation with ultrasound).

Rapporteur's Comment
The rapporteur shares the author's view that although the number of children recruited in the study is small (n=21), it is one of the largest prospective controlled studies available to date in children with CF. Furthermore, the methodology is of great value as it uses liver biopsy as well as ultrasound to assess the degree of CF associated liver disease.
In the rapporteur's view the most significant confounding factor of this study is that many of the children already had advanced liver disease at entry level and were less likely to benefit from UDCA. In addition, there was a remarkable difference in the initial baseline histology findings between the treatment groups: 78% (7/9) of GroupA vs. 58% (7/12) of GroupB were either cirrhotic or had focal biliary fibrosis.
Analysis of sexes are not reported in the manuscript, however it is noted that significantly more males than females were enrolled: 14 vs 7, respectively. There are reports in the literature that male sex may be a predisposing factor for CFLD, therefore this may have had a confounding effect on results as well (Colombo et al 1994).
Despite these limitations the rapporteur shares the authors' conclusion that UDCA therapy significantly improved liver transaminases and may prevent histological deterioration in portal fibrosis if started early.

MAH 1 also provided a comprehensive literature overview of cystic fibrosis related liver disease:

Cystic fibrosis (CF) is an autosomal recessive disease effecting 1 in 2000-4500 newborns (Colombo et al. 2000). The life expectancy of these patients has been extended through improved pulmonary, nutritional and general medical care however the incidence of recognizable hepatobiliary complications has increased. Data derived from autopsy studies indicate a progressive increase in prevalence of CF-associated liver disease (CFLD) with age, from 10 % in infants to 72 % in adults. The hepatobiliary disease, which often is asymptomatic, can be severe. The major concern is the focal biliary cirrhosis occuring in about 25-30 % of the young CF patients, which progresses to multilobular biliary cirrhosis in 5 to 10 % of cases (Balistreri 1997).
UDCA, at present, is the first line therapy in patients with CF associated hepatobiliary liver disease. In principle, the main goals of therapy are to decrease bile viscosity, replace hepatotoxic bile acids and prevent progression to cirrhosis. The efficacy of UDCA has been demonstrated in a series of controlled and uncontrolled studies showing the following results:

Controlled clinical trials
Placebo-controlled, double-blind trials to evaluate the efficacy of UDCA in CF associated cholestasis were perfomed by Bittner et al. (1991), Colombo et al. (1993), Lepage et al. (1997), Merli et al. (1994) and Spray et al. (2000a, b). Studies comparing CFLD to other conditions such as CF without cholestasis or no-treatment groups were described by Kapustina (2003) and O'Brien et al. (1992, 1996).
These controlled studies show that UDCA led to a significant decrease of the serum liver enzymes AST, ALT and AP compared to placebo or no treatment. A significant improvement in γGT was noted by Colombo et al. (1996) and O'Brien et al. (1992, 1996). Moreover, a significant decrease in glutamate dehydrogenase (GLDH) has been reported by Bittner et al. (1991). There were also improvements in 5'-nucleotidase levels and bile flow. The Shwachman Score, a summary score of general activity, physical examination, nutrition and chest radiography findings, improved significantly with UDCA (Colombo et al. 1996)
With regard to the effect of UDCA on the nutritional status and fat absorption, the results are diverging. An improvement of the fatty acid metabolism and the absorption of the essential fatty acid (EFA) and retinol status has been observed by Lepage et al. (1997) at a UDCA dosage of 15 mg/kg/day (with an increase to 30 mg/kg/day). However, this has not been observed by Merli et al (1994) who used a lower UDCA dose of 10-12 mg/kg/day in a small group of CF patients with advanced liver disease. An effect of UDCA on the vitamin E absorption was also demonstrated by Thomas et al. (1995) in a single case placebo-controlled pharmacokinetic trial with vitamin E. A single dose of 250 mg UDCA increased the vitamin E absorption in comparison to placebo as demonstrated by the concentration-time curves.

Dose finding studies
Beside the already cited study of Lepage et al. 1997, who described the benefit of UDCA dose-increase from 15 mg to 30 mg/kg/day in CF patients who did not show a 50% decrease of ALT or AST or both within 2 months, three other dose-finding studies have been submitted by MAH 1 (Colombo et al. 1992 b, van de Meeberg et al. 1997, Setchell et al. 1994).

Colombo et al. (1992b) demonstrated a dose-dependent UDCA bile enrichment after oral dosing with UDCA to patients with CF-associated cholestasis, going from 5 to 20 mg UDCA/kg/day, which was highly correlated with the decrease of serum liver enzymes and serum UDCA concentrations, but there was no correlation between administered UDCA dose and serum UDCA concentrations. As demonstrated by Setchell et al. (1994), 20 mg UDCA/kg/day seemed to be the optimal dose of UDCA, at least in the used study population. A further increase of the UDCA dose to 30 and 40 mg/kg/day even caused a decrease in UDCA bile enrichment. Van de

Meeberg et al. (1997) also demonstrated that a UDCA dose-increase from 10 to 20 mg/kg/day further improved the liver serum enzymes. The biliary enrichment of UDCA at an oral UDCA dose of 20 mg/kg/day is nearly comparable to those values seen in other chronic cholestases, like PBC, at even lower UDCA dosages. As stated by Colombo et al. (1992c), CF patients need higher doses of UDCA to compensate for poor intestinal absorption.

In addition, El-Rifai et al. (2003) reported a higher proportion of UDCA relative to all bile acids in blood of children with chronic cholestasis (mean age: 4 years) when UDCA was taken in 3 divided doses per day as compared to 2 divided doses per day. They also observed significant improvement of liver function tests with higher UDCA serum proportions (> 54% of total serum bile acids) in contrast to those with lower proportions of UDCA in serum. The authors recommended to monitor the proportion of UDCA in serum and to adjust/increase the UDCA dose in order to obtain high serum levels.
Scher et al. (1997) reported treatment of two cholestatic infants with CF on UDCA treatment with doses of 40 mg UDCA/kg/day. After an initial response the dose was reduced to 30 mg/kg/day with good therapeutic efficacy. However, a further dose reduction to 20 mg/kg/day led to worsening of the disease, which improved again by dose-increase.

Plotting the degree of biliary enrichment of UDCA obtained from cholestatic CF patients against the daily UDCA dose shows a linear dose-dependency with a very high coefficient of regression (see *Figure 1*; r= 0.9638). Compared to healthy subjects or to patients without overt metabolic liver diseases (patients with gallstones or hyperlipidemia), the degree of biliary UDCA enrichment in CF-patients is smaller**.** However, linear regression lines of both groups run exactly parallel to each other, indicating similar dose-depenedent mechanisms of absorption and enrichment in both patient groups. The degree of biliary enrichment of UDCA in CF patients is even lower than that in PBC patients which also shows a linear regression line running parallel to that of healthy-liver subjects and to that of CF patients. To obtain a degree of approximately 45% of biliary UDCA enrichment, which was shown to be associated with therapeutical efficacy in many trials, for the treatment of cholesterol gallstones a dose of 10 mg/kg/day is sufficient, whereas PBC patients require an UDCA dose of 15 mg/kg/day and CF patients even seem to need doses of 25 mg UDCA/kg/day.

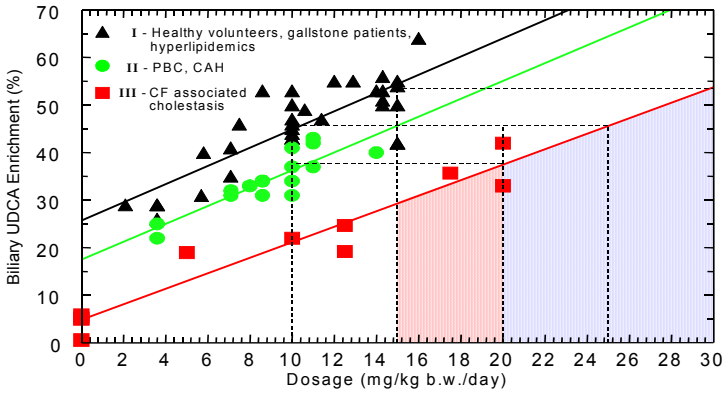

***Figure 1**: Biliary UDCA enrichment in dependence on the daily UDCA dose in healthy subjects, gallstone patients and patients with hyperlipidemia (Group I - healthy liver subjects), as well as in patients with PBC and chronic active hepatitis/CAH (Group II), and patients with CF-associated cholestatic liver disease (Group III).* Red shaded area below the CF-regression line characterizes the presently performed UDCA therapy (dosage range 15-20mg/kg/day);the blue shaded area characterizes the theoretically optimized UDCA dosage area for CF-patients (20-30 mg/kg/day) with the optimum mean value of 25 mg/kg/day.

MAH 1 states that it can be extrapolated from this figure that a dose of 20 mg UDCA /kg/day as it was used in many trials must be considered to be in the lower range of optimal efficacy and therefore, may not be the optimal dose for these patients. Following these conclusions and dependent on the severity of the CF-associated liver disease/cholestasis, an UDCA dose range between 20 and 30 mg/kg/day is expected to result in an optimised efficacy. This is a dose range which recently has been used successfully in a study by Kapustina (2003).
Furthermore, MAH 1 concluded that as treatment with UDCA does not resolve the underlying cause of the cholestasis it should be continued long-term without a dose reduction in CF-associated liver disease. For optimal therapeutic efficacy monitoring of the UDCA serum concentration and, if possible, of the UDCA bile enrichment would be recommended in combination with serum liver function parameters.

Non-controlled, open clinical trials, case reports

Almost all non-controlled studies support the positive results observed in the controlled and dose-finding studies, if performed with dosages higher than 10 mg/kg/day and especially, when treatment with UDCA was continued over a longer period. Even studies performed at a dose-range of 10-15 mg or 10-20 mg UDCA/kg/day showed improvement of laboratory parameters already after 2 months of treatment (Nakagawa et al. 1990).
As stated by Colombo et al. (2001), 60% of the patients (n=57, aged 5.8±2.8 y) showed under a median UDCA therapy duration of 6 years of complete normalisation of the biochemical liver serum parameters without any evidence of progression of the liver disease. Patients who did not respond with a normalisation of the biochemical serum parameters to UDCA treatment at a dose of 20 mg/kg/day showed a progression of the disease. Predictive of non-response were the existence of liver cirrhosis already before start of UDCA, and scintigraphic picture of an apparently normal biliary drainage before start of therapy. The authors concluded that the more favourable clinical response in patients with biliary drainage impairment suggests that the flushing effect of UDCA, induced at the biliary tree level, by dissolving biliary plugs which obstruct intrahepatic ducts, is a relevant mechanism of action in this patient population. It is possible that in patients with apparently normal biliary drainage, different pathogenic mechanisms are involved, which may affect liver cells rather than cholangiocytes.
Also, Kappler et al. (2001) observed during 6.5-years of UDCA treatment with 20 mg/kg/day a consistent normalisation of the liver function parameters AST, ALT, γGT and GLDH in 53% of the patients (n=31), while only one non-compliant patient developed portal hypertension. As compared to patients before start of UDCA therapy, 9 patients had developed severe liver disease at a mean age of 7.6 years (range: 2-15 years) which took 2.9 years (range: 2-4.7 years) from first elevated serum liver enzymes until manifestation of sever liver disease with thrombocytopenia and hypersplenism.
Lindblad et al. (1998) observed that if UDCA was given at a dose of 10-15 mg/kg/day for a 2-year period, the echogenicity of the liver by ultrasonography did not progress. Liver histology from biopsies showed a time-dependent improvement after 1 and 2 years towards decrease of inflammation, bile duct proliferation and fibrosis. Electronmicroscopy showed an improvement in the number and shape of microvilli.
Nousia-Arvanitakis et al. (1998, 2001) described 12 and 14 years follow up periods, respectively, in 70 patients (aged 2-29 y) in whom UDCA at a dose of 20 mg/kg/day was started after a 4 years observation period. During these 4 years without UDCA, a progression of the focal biliary cirrhosis (FBC) and nodular biliary cirrhosis (NBC) was seen at a rate of 1 patient pro year. After

start of UDCA therapy, progression of pathological changes in NBC was arrested, ultrasound image showed an increased number of normalisation, the number of patients with focal biliary cirrhosis decreased from n=30 (at 4 years) to n=1 (at 14 years) and liver enzymes (γGT, ALT, AST) had returned to normal within 1 year. Although hepatospleno-megaly persisted, the size of liver and spleen decreased.
A dramatic improvement/normalisation in two severely cholestatic infants with CF (ages 9 days and 6 weeks, respectively) has been reported with 40 mg and 20 mg/kg/day UDCA dose, respectively (Scher et al. 1997). At 2 and 3 years of age, respectively, these children had no signs of liver disease under constant UDCA therapy.
An improvement of the nutritional status and body growth has partially been observed (Colombo et al. 1990, Cotting et al. 1990, 1992).

MAH 1 concluded that dose-finding trials, placebo-controlled and controlled trials as well as open-label trials have demonstrated that 15 - 20 mg UDCA/kg/day should be considered as the normal effective dose for treatment of CF-associated cholestatic liver disease. This is confirmed by a recent review which considers 20 mg/kg/day as the optimum dose for cholestatic diseases in paediatric CF patients (Colombo et al. 2006). Most important is a start of therapy as soon as possible after having diagnosed the hepatobiliary disease in order to prevent progression from the focal biliary cirrhosis to nodular biliary cirrhosis. It has been demonstrated in short-term as well as long-term use (up to 12 years) that UDCA is able not only to prevent progression, but also to reverse these hepatobiliary changes in a high number of patients if therapy has started early enough. If liver cirrhosis is already manifested, a normalisation of liver function can not be expected. It has also been demonstrated that UDCA might have a positive effect on nutrition and absorption of fat-soluble vitamins as well as on growth development and muscle mass of children if given at an adequate dosage. At dosages below 15 mg/kg/day none or only marginal effects might be seen especially if given only for a short period of time, for weeks or few months.
UDCA was in all trials, even in doses up to 45 mg/kg/day, well tolerated, almost without any drug-related side effects. Also, preterm neonates tolerated enterally administered UDCA suspension from their third day of life without any side effects. UDCA, therefore, is a safe and efficient drug for treatment of CF-associated liver disease which might be given from the first days of life.

MAH 2's overview on cystic fibrosis associated liver disease was less detailed however included most of the above described studies. In addition, MAH 2 referred to MAH 1's study (Spray et al. 2010, Study URC-17/CCF) and another study not mentioned by MAH1 (Siano et al 2010):

Aside from improvement in liver function tests, Spray et al. (2000) and Lindblad et al. (1998) have demonstrated a significant treatment effect of long-term UDCA treatment (1 and 2 years, respectively) on portal fibrosis (Spray et al., 2000) or inflammation and/or bile duct proliferation (Lindblad et al., 1998), suggesting that UDCA could have exerted direct cytoprotective and immunomodulatory effects, aside from its choleretic effect (O' Brien et al., 1996).

As meconium ileus has been detected as a risk factor for the development of liver disease in CF children, Siano et al. (2010) evaluated the effect of early treatment with UDCA in preventing chronic liver disease in children presenting with meconium ileus at birth. A lower prevalence of CF-related liver disease was observed in the group treated with UDCA before the onset of signs and symptoms of liver disease compared to those which were treated with UDCA only at the onset of symptoms.

Rapporteur's Comment
The MAHs provided an extensive literature review of the use of ursodeoxycholic acid in patients with CF. In addition; the rapporteur would like to draw attention to a report about UDCA's

possible mechanism of action in CFLD. Smith et al. found elevated endogenous UDCA in children with CF without liver disease (compared to children with CFLD and normal controls) which may suggest the possibility of a successful adaptive response to cholestasis with a protective role against liver injury in these patients. If so, it provides indirect support to the therapeutic exogenous enrichment of CF bile with UDCA in patients with CFLD, especially if it is detectable and treated early (Smith et al. 2004).

Study URC-17/CCF and a more recently published study (Siano et al. 2010) suggest treatment with UDCA could improve CFLD outcome if started early in the disease i.e. in most cases in childhood. Siano et al. looked at 26 children with CF with meconium ileus, assigned into two groups: group 1 treated early with UDCA (UDCAe) and group 2 treated at the onset of CFLD (UDCAd). A higher prevalence of CFLD was observed in the UDCAd group with a statistically significant difference at 9 years of age. The rapporteur shares the authors' conclusion that early treatment with UDCA may be beneficial in patients at risk of developing CFLD.

The rapporteur is of the view that although ursodeoxycholic acid is not licensed for CF associated liver disease, it is widely used in both adult and paediatric clinical practice. The rapporteur would like to draw attention to the recently published consensus guidelines for the management of cystic fibrosis-associated liver disease which was supported by the European Union Sixth Framework Programme (Debray et al. 2011). This document states that CF related liver disease has a cumulative incidence of 27% to 35%, without incidence cases after the age of 18 years. In a prospective study, the incidence of CFLD was 2.5 per 100 patient years during the first 10 years of life (95%CI: 1.8-3.3), declining sharply during the second decade. Liver failure usually occurs later, after the paediatric age. The rapporteur is of the view that these data highlight the therapeutic need for delaying the progression of CF associated liver disease in children and fully agrees with the authors that treatment should be started as soon as the diagnosis of CF associated liver disease is made. The guidelines recommend a daily dose of 20 mg/kg in multiple divided doses (at least twice/day) because of incomplete intestinal absorption. It is not clearly stated in the guidelines whether this dose is applicable to children as well. Furthermore the paper advises that evaluation of indices of cholestasis and cytolysis should be performed 3 and 6 months from initiation of therapy to test for the efficacy of UDCA and the dose should be increased if necessary.
Despite these guidelines routine use of UDCA remains controversial. A letter to the editor in response to the above mentioned guidelines reads: "Simply put, at present, there are no convincing data to demonstrate that UDCA is efficacious or harmful in CFLD. Future studies…are needed before firm recommendations for or against the use of UDCA can be made" (Ooi et al 2011).
In addition, a Cochrane review published in 2010 concluded that there is insufficient evidence to justify UDCA's routine use in cystic fibrosis (Cheng et al. 2010). However, the review was based only on three randomised controlled trials (Colombo 1996, Merli 1994, O'Brien 1992) involving 118 participants aged 4 to 32 years. The exact number of participating children is not reported; it is estimated around 70 of which 55 were included in one study (Colombo 1996). Furthermore, the dose of UDCA given in the reviewed studies ranged from 10 to 20 mg/kg/day (compared to the optimal dose 20 to 30 mg/kg/day). The authors acknowledged UDCA's effect on reduction of raised liver enzymes to normal, however noted that it is difficult to draw conclusions given the small number of patients.
The rapporteur would like to highlight the available data on UDCA's widespread off-label paediatric use throughout Europe. The British National Formulary for Children 2011-2012 lists 'Improvement of hepatic metabolism of essential fatty acids and bile flow, in children with cystic fibrosis' as an indication for UDCA with a recommended dose of 15 -20 mg/kg twice daily (30-40 mg/kg/day) from 1 month to 18 years of age. In addition, several hospital guidelines on paediatric CF prove that there is a wide spread off-label UDCA use in children with CF in the UK. For example, recent clinical guidelines from the Royal Brompton hospital recommend the

following UDCA use in children with CF: "Ursodeoxycholic acid (increases bile flow): 10-15mg/kg twice daily. It is well tolerated with main side effect of diarrhoea, in which case reduce the dose…. In cases of significant liver disease, 5-15mg/kg three times daily may be used." (Balfour-Lynn et al 2011). Furthermore, in French hospitals between July and December 2008 Ursodeoxycholic acid was the 8th most frequently off-label prescribed oral drug in the European Medicines Agency's Report on the survey of all paediatric uses of medicinal products in Europe (December 2010). The indication for this off-label use was not specified in the report.
Currently only the Netherlands has cystic fibrosis listed among the licensed indications for UDCA. The MAH proposes to maintain the current wording of the Dutch SmPC regarding of the indication ('Chronic (≥ 6 months) mild to moderate severe hepatobiliar disorder as result of cystic fibrosis in children and adolescents') and dosing (15-20 mg/kg/day in 2-3 divided doses).This approach is not supported by the rapporteur as UDCA should be started as soon as the diagnosis of CFLD is made to delay the progression of the disease. Furthermore, based on the above described dose finding studies an initial dose of 20 mg/kg/day should be recommended with a further increase up to 30 mg/kg/day if necessary.

In summary, based on the assessment of the available data the rapporteur is of the view that the presented data is robust enough to support adding the paediatric indication of ***'Hepatobiliar disorder associated with cystic fibrosis in children aged 1 month to less than 18 years'*** to the SmPC. Although Study URC-17/CCF aimed at evaluating the effect of UDCA on histology in children with CFLD, in the rapporteur's opinion the available evidence is not robust enough to show that UDCA prevents progression of CFLD, even if started early enough in the course of the disease. Therefore adding 'prevention of liver cirrhosis' as an indication for UDCA use is not considered justified by the rapporteur.
As the aim of UDCA therapy in children is delaying progression of liver disease and therefore therapy should be started as soon as the diagnosis of CFLD is made, the target population of ***1 month to less than 18 years*** is justified in the rapporteur's opinion. Several of the submitted studies recruited children as young as 1 month of age and UDCA was considered to be safe and efficacious in the very young as well. However, in the rapporteur's view there is not enough evidence available in the literature about UDCA's effectiveness in infants with CFLD younger than 1 month of age. Furthermore, UDCA therapy would not be started in this age group as the diagnosis of cystic fibrosis associated liver disease is usually made > 1month of age.
In the rapporteur's view the recommended dosing regime of ***20 mg/kg/day in 2-3 divided doses with an increase up to 30mg/kg/day*** is well supported by the submitted dose finding and biliary enrichment studies. Of note, the British National Formulary for Children 2011/2012 is in line with this recommendation:
"Improvement of hepatic metabolism of essential fatty acids and bile flow, in children with cystic fibrosis: Child 1 month–18 years: 10–15 mg/kg twice daily; total daily dose may alternatively be given in 3 divided doses."

- **BYLER'S DISEASE or PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS**

Byler's Disease synonymous to Progressive Familial Intrahepatic Cholestasis (PFIC) is a rare autosomal recessive form of intrahepatic cholestasis in which genes coding for membrane transport proteins involved in bile formation are affected. It is a fatal disease, leading to death within few years during childhood due to a high rate of progression to cirrhosis and end-stage liver disease. The onset of the Byler's Disease is typically in the first 6 month of life with cholestasis, hepatomegaly, severe pruritus, growth failure, and fat-soluble vitamins deficiency. Treatment primarily aims to relieve symptoms and to retard decompensation.

MAH 1 summarized 8 open label pilot studies and case reports and concluded that:
UDCA treatment in doses of 15 – 30 mg/kg/day have shown to markedly reduce the degree of pruritus, hepatosplenomegaly and biochemical parameters of liver injury (bilirubin, ALT), as well as hepatotoxic endogenous detergent-like bile acids. Liver histology shows a reduced degree of fibrosis in children with normalised liver function parameters, indicating that, under continuous UDCA treatment, liver transplantation might be prevented in patients who respond biochemically. As stated by Jaquemin (1999, 2000), UDCA is effective in all subtypes of PFIC to a fair proportion of children.

MAH 2 submitted the following additional information:
Recent molecular studies have allowed the identification of different forms of PFIC (PFIC types 1, 2 and 3) due to specific defects of hepatocellular transport proteins encoded by different genes (Colombo et al., 2011).
Jacquemin et al. (1997) have observed similar improvement of cholestasis with UDCA treatment in children, whether patients had normal serum GGT (PFIC types 1 and 2) or elevated levels of serum GGT (PFIC type 3). In their study, an improvement in parameters of cholestasis was observed in 61% of patients with normal GGT (types 1 and 2) and in 71% of those with type 3 PFIC.
Colombo et al. (2011) undertook mutation analyses in a case series of children with PFIC-3 to analyze the relationship between ABCB4 genotypes and severity of symptoms, response to UDCA and outcome of disease. UDCA treatment (14 to 51 mg/kg/day) was started at the time of diagnosis. Jaundice resolved in four (4) out of 12 patients who were jaundiced at onset. Response to treatment was complete with normalization of liver biochemistry in 10 subjects (37%); all of them had a mild genotype with benign substitutions on both alleles or a single mutated allele. Of the remaining 17 children, 13 showed partial response (jaundice clearance, but persistent biochemical abnormalities and progression of fibrosis) and 4 did not respond at all. All except 2 of these 17 patients had severe genotype (disease-causing mutations on both alleles). The authors concluded severe ABCB4 genotypes are associated with reduced liver expression and function of ABCB4 protein, lack of response to UDCA, and evolution to cirrhosis and end-stage liver disease.
David-Spraul et al. (2010) analyzed ATP8B1 or ABCB11 mutations and response to UDCA treatment (dose of 600 mg/m^2 of body surface) in children with PFIC-1 or PFIC-2 presenting with normal GGT levels but signs and symptoms of cholestasis such as pruritus, jaundice, hepatomegaly and elevated bile acid concentrations. In terms of treatment strategy, the authors' policy was to use UDCA as first-line therapy as soon as possible and to discuss other alternatives such as biliary diversion (BD) or liver transplantation (LT) depending on the outcome with UDCA. Fourty-nine (49%) percent of PFIC-1 children (9/13) and 72% of PFIC-2 children (21/29) had a complete or intermediate long-lasting response to UDCA with some reaching adolescence on UDCA treatment without the need for BD or LT.

Rapporteur's Comment
PFIC is a rare condition (estimated incidence between 1/50,000 and 1/100,000 births).
The rapporteur shares MAH 1's view that based on the studies available in the literature UDCA could be considered in the initial management of children with all types of PFIC. However, questions remain regarding the posology and duration of UDCA treatment as no randomized controlled studies have been carried out in children.
MAH 2 also concludes that evidence of UDCA's efficacy in this condition is less consistent although it is widely used in practice.
In summary, the rapporteur is of the view that UDCA's use in PFIC can not be routinely recommended at present.

- **BILIARY ATRESIA**

MAH 1 submitted 5 studies and provided the following summary:
Biliary atresia is a common disorder of unknown aetiology, affecting about 1 in 8,000 to 15,000 live births in the first month of life, and it accounts for approximately one third of all cases of cholestasis in infants (Suchy et al. 2002) in which a persistent necro-inflammatory process leads to fibro-obliteration of the extrahepatic bile ducts. The destructive process affects the intra- as well as the extrahepatic bile duct segments. The disease is rapidly progressive leading to cirrhosis in many patients as early as 4 months of age. Biliary atresia is the most frequent indication for liver transplantation in the paediatric population (Balistreri 1996b), required in about 60 – 84% of all patients with biliary atresia during their lifetime. Beside liver transplantation, there is no specific therapy of biliary atresia. As an interim therapy, bile flow can be re-established in about 80% of infants if they are referred for surgery (hepatoportoenterostomy, Kasai-portoenterostomy) within 60 days after birth, but the success rate drops dramatically to under 20% in those older than 90 days at the time of operation.
UDCA at a dose of 15 – 20 mg/kg/day has shown to reduce pruritus, increase bile flow in some children and improve liver function parameters and growth, in preparation for liver transplantation. However, UDCA does not appear to alter the outcome of the disease (Balistreri 1997). Infants who had a Kasai portoenterostomy, following treatment with solumedrol, steroids and indefinitely UDCA plus antibiotics, required less liver transplantations and bilirubin levels decreased more frequently than in infants who were treated with antibiotics and only occasionally with UDCA (Meyers et al. 2003).

MAH 2 provided additional information from more recent studies published in the literature.
The only therapeutic option for reestablishing bile flow in neonates with BA is the Kasai procedure or portoenterostomy. Adjunct medical therapy is used after portoenterostomy to prevent bacterial cholangitis, optimize nutritional status and improve cholestasis (Willot et al., 2008). The adjuvant effect of UDCA given alone or as part of a combination treatment (together with steroids and/or phenobarbital and/or vitamin or taurine supplementation) in infants having undergone Kasai portoenterostomy for biliary atresia was examined in 3 retrospective cohort studies (Kobt 2008: n=108 infants; Smaropoulos et al., 2006: n=4 infants; Stringer et al., 2007: n=50 infants) and 2 prospective open-label studies (Willot et al., 2008: n=16 infants; Yamashiro et al., 2006: n=16 infants). UDCA was used or had been used at doses ranging from 10 to 25 mg/kg/day depending on the study.
Long-term administration of UDCA significantly improved cholestasis and final outcome following successful portoenterostomy, more patients clearing their jaundice and surviving longer with their native livers (Smaropoulos et al., 2006; Stringer et al., 2007; Willot et al., 2008). Yamashiro et al. (2006) also showed that UDCA may be of significant benefit in the treatment of essential fatty acids deficiency in these patients.
In these studies, UDCA was well tolerated, even at the higher dose of 25 mg/kg/day used by Willot et al. (2008) for 18 months. In the latter prospective trial, because children in this center are routinely treated with UDCA shortly after Kasai portoenterostomy, a discontinuation / reintroduction methodology was used. UDCA had to be resumed in 13 out of 16 children because of worsening of liver function.

However, in children with unsuccessful portoenterostomy and without recovery of a good bile flow, UDCA administration has been associated with serious hepatic and extra-hepatic morbidities (Alvarez 2008). This was also observed by Kobt 2008 in a review of a historical cohort where the surgical intervention was successful in restoring bile flow in only 19.8% of patients and in which UDCA administration at 20 mg/kg/day lead to faster development of liver injury. Therefore, MAH 2 claims that the beneficial effect of UDCA administration post-portoenterostomy in infants with BA would be dependent on a good postoperative biliary

drainage; and obstruction of extrahepatic bile ducts such as failure of portoenterostomy in BA should be considered a contraindication to administration of UDCA.

Rapporteur's Comment
It is noted that MAH 1 did not provide a conclusion whether UDCA should be used for the treatment of biliary atresia. However the studies submitted by MAH 1 were old, conducted using very limited number of patients and assessed the efficacy of UDCA during the peri-operative period early in life. Only one of the studies was placebo-controlled and although it proves that UDCA is efficacious in reducing pruritus, it failed to show improvement in survival or need for transplantation.
MAH 2 provided more up to date information and included studies (3 retrospective cohort, 2 prospective open label) using larger number of infants. Williot et al. (2008) demonstrated, using a discontinuation/reintroduction methodology that UDCA therapy results in improvement of liver function in children with biliary atresia who had a successful surgery and that these beneficial effects persist for several years after the Kasai intervention. Yamashiro et al also showed improvement, but only if the patients were not jaundiced i.e. had successful Kasai procedure. Stringer et al. used UDCA with dexamethasone therefore the beneficial effects can not be clearly attributed to UDCA.
Kobt et al (2008) and Alvarez et al (2008) observed serious hepatic and extra-hepatic complications when UDCA was administered without recovery of good bile flow following portoenterostomy. See section II.3.2.c on Clinical safety.
In the rapporteur's opinion, additional studies are needed to provide robust evidence for the use of UDCA in children with biliary atresia. Of note, the currently approved SmPC in section 4.3 also lists "occlusion of the biliary tract" as a contraindication.
In summary the rapporteur is of the view that UDCA's use in this condition can not be routinely used at present.

- **TOTAL PARENTERAL NUTRITION ASSOCIATED CHOLESTASIS (TPNAC)**

MAH 1 submitted a self sponsored study (Study URU-3/NEO) in addition to a clinical overview of TPNAC:
Total Parenteral Nutrition (TPN) can cause hepatobiliary alterations, ranging from asymptomatic biochemical indicators of liver abnormalities, to biliary sludge, fatty liver, and cholestasis, with the potential for progression to end-stage liver disease. TPN-induced cholestasis (TPNAC) is best known in infants, especially in preterm neonates and those with low birth weight (less than 1500 g), and especially in those on long-term TPN. The incidence of TPNAC in premature infants ranges from around 20% to 80% (more than 60 days TPN) and even up to 90% with TPN more than 90 days (Balistreri 1996b).
The positive effect of UDCA at doses of 15-45 mg/kg b.w./day has been demonstrated in several small pilot trials, showing a fast decrease and normalisation especially of bilirubin, but also of the serum liver enzymes in many patients (Cojin et al. 1993; 1994; Immacolata et al. 1996; Levine et al. 1999). In contrast to patients without treatment, UDCA treatment prevented gallstone formation, cholangitis and cholecystectomy if administered to premature infants with TPNAC 4 weeks after start of TPN (Cojin et al. 1994). TPNAC-induced hepatobiliary symptoms like jaundice, hepatomegaly and splenomegaly disappeared within 1-2 weeks of UDCA therapy (Immacolata et al. 1996).
Cojin et al. (1993, 1994) have shown in their publications that in infants who do not respond adequately to an initial dose of 15-20 mg/kg b.w./day an escalation of the UDCA dose up to 45 mg/kg b.w./day can be helpful.

Al-Hathlol et al. (2006) and Chen et al. (2004) successfully treated preterm infants with very low birth weight and intractable TPNAC within two weeks after withdrawal of total parenteral nutrition with 15 – 20 mg/kg/d UDCA.
Cholestasis of neonates or children of up to 11 years of age who developed irreversible intestinal failure as a result of a small bowel syndrome or other conditions were treated successfully or partially successfully with 30 mg UDCA/kg/d (De Marco et al. 2006).
UDCA has been shown in all these pilot trials to be safe in preterm infants, even in doses up to 45 mg/kg bw./day.
The safety and efficacy of a suspension containing 50 mg/ml UDCA - which is specifically adequate for the dosing of neonates, infants and small children - has also been investigated in a placebo-controlled trial in preterm neonates to whom the suspension was given from the 3rd day of life (Clinical Study report URU-3/NEO by Moro 2001).

Study URU-3/NEO [MAH 1 sponsored study]
Influence of Bile Acids on Postnatal Development in Preterm Infants during the First Weeks of Life. A Controlled Study with Ursodeoxycholic Acid
Study centers: Single center: Division of Perinatal Pathology, University of Milan in Italy

Study period:(first enrolment): August 1998 Phase of development: II
(last completed): March 1999

Objectives: The primary objective was to evaluate whether bile acid supplementation with ursodeoxycholic acid (UDCA) shortens the duration of total/supplementary parenteral nutrition and increases fat absorption in preterm infants during the first weeks of life. In addition, the influence of UDCA therapy on growth, nutritional status and occurrence of TPN-induced cholestasis was evaluated. The effect of UDCA on bile acid concentration in the duodenum, serum, faeces, and urine was to be evaluated, too, in order to show any possible positive treatment effects on the nutritional status of the neonate

Methodology: single center, randomized, double-blind, placebo-controlled, parallel group study

Number of patients (planned and analyzed):30 patients planned, 15 in each treatment group (UDCA vs. placebo), 32 (16 vs. 16) included, 25 (14 vs. 11) in intention-to-treat analysis and 19 (10 vs. 9) in per protocol analysis

Diagnosis and main criteria for inclusion: Preterm infants with gestational age ≤ 34 weeks as estimated by the Dubowitz method requiring total parenteral nutrition during the first days of life and birth weight appropriate or small for gestational age according to Lubchenco's intrauterine growth chart

Test product, dosage and mode of administration, batch-number: Suspension containing ursodeoxycholic acid 5% (5 g in 100 ml), 5 mg per kg body weight and day (for approximately three days, period 1), followed by 10 mg per kg body weight and day until the last day of supplementary nutrition (period 2), and 20 mg per kg body weight and day from then onwards (period 3) administered through a gastric/enteric tube divided in four doses; batch no.: 96H16; Study Code: URU-3/NEO

Duration of treatment: From the 3rd day of life until 4 to 6 weeks of life

Criteria for evaluation:
Efficacy: time to achieve full enteral feeding (no. of days), percentage of fat absorption (periods 2 and 3), lipase activity in duodenal aspirate, nutritional status (anthropometric data: length, weight, head circumference; end of periods 2 and 3) and the occurrence of cholestasis (defined as an increase above baseline of biochemical markers of cholestasis: serum bilirubin, ALP, gamma-GT and serum total bile acid; end of periods 2 and 3)

Safety: routine clinical measurements (temperature, oxygen saturation, acid/base status in blood, plasma sodium and potassium), serum measurements (AST, ALT, albumin, total protein, total and direct bilirubin), pH of duodenal aspirate (no data available), routine urine analysis, physical examination (abdominal distension), measurement of preprandially gastric residual and other clinical signs of feeding tolerance

Statistical methods: ITT- and PP-analysis, Mann-Whitney test, Cox regression analysis and appropriatedescriptive statistics were used.

Efficacy results:

- *Time to achieve full enteral feeding*

The time to achieve full enteral feeding as the first primary endpoint was calculated as 19.4 ± 5.2 [19.5] days in the UDCA-group and as 23.7 ± 10.3 [22.0] days in the placebo-group (p = 0.4089, Mann-Whitney test, two-tailed). After adjustment for gestational age, the risk ratio for the treatment groups was 1.058 indicating no benefit for any of the treatments in the Cox regression analysis. Without adjustment the risk ratio was 0.499 (95% confidence interval: 0.202 to 1.230) in favor of UDCA. Likewise, further exploratory analyses revealed no significant differences between the treatment groups.

- *Fat excretion*

The proportion of excreted fat at the end of the study which was used as the second primary endpoint was almost identical in both treatment groups: 42.2 ± 17.9 [46.9]% in the UDCA-group and 43.8 ± 25.6 [29.9]% in the placebo-group (p = 0.9472, Mann-Whitney test, two-tailed).

- *Secondary efficacy parameters*

No relevant differences between the treatment groups were observed for the remaining secondary efficacy parameters.

Safety results:
Only one adverse event was reported in this study. The only adverse event occurring in the placebo-group was a general infection due to candida. The event was assessed as not related to study medication. However, it was severe and serious, but the patient recovered completely. The only clinically relevant abnormalities were observed in one patient of the UDCA-group and concerned the parameters BUN (102 mg/dl), total bilirubin (12.99 mg/dl), and creatinine (1.66 mg/dl) at baseline. All values were within the reference range at the next examination.

MAH 1 concluded that TPNAC in infants/children as well as in adults can be treated efficiently and safely with UDCA doses of 15-20 mg/kg/day. If patients do not respond within a reasonable time, the UDCA dose might be increased to 30 and further to 45 mg/kg/day.
Furthermore, the investigators of Study URU-3/NEO concluded that treatment of preterm infants with UDCA may result in a reduction of the time to achieve full enteral feeding. However, this reduction was not significant in the present trial due to the higher gestational age in the UDCA-group. For the other efficacy parameters no relevant differences between the treatment groups were observed. Treatment with study medication was safe and well-tolerated.

MAH 2 submitted the following additional information:
Progression to biliary cirrhosis and the development of portal hypertension and liver failure occurs in a minority who then require liver or combined liver and intestinal transplantation (Kelly 2010). The pathogenesis is multifactorial and is related to prematurity, low birth weight, duration of PN, short bowel syndrome requiring multiple laparotomies and recurrent sepsis. Other important mechanisms include lack of enteral feeding which leads to reduced gut hormone secretion, reduction of bile flow and biliary stasis which leads to the development of cholestasis, biliary sludge and gallstones, which exacerbate hepatic dysfunction, especially in premature neonates with immature hepatic function. In order to improve bile flow and reduce the formation of biliary sludge, UDCA may be advantageous and is commonly prescribed (Kelly 2010). Hagadorn et al reported that the use of UDCA has increased 86% in 220 US NICUs between 1999 and 2004 (Hagadorn et al., 2009).

A number of studies have reported biochemical resolution in infants with cholestasis on long-term PN due to prematurity and / or low birth weight (Arslanoglu et al., 2008; Gauzon et al., 2009; Gokmen et al., 2010) or intestinal failure due to short bowel syndrome (SBS) or other causes (Cowles et al., 2010 De Marco et al., 2006). Two of these studies were randomized, placebo-controlled trials (Arslanoglu et al., 2008; Gauzon et al., 2009), one was a prospective cohort study (De Marco et al., 2006) and the last 2 were retrospective analyses. Doses used were ranging from 5 mg/kg/day to 30 mg/kg/day and were usually part of a rehabilitation program consisting of cycling of PN, enteral and oral stimulation and UDCA treatment. No side effects associated with the use of UDCA were reported in these studies where UDCA was administered as a solution or suspension.
The MAH points out that the patient population treated in these studies was free of severe associated illnesses. Arslanoglu et al. (2008) enrolled only premature neonates that were otherwise free or congenital abnormalities, chromosomal aberrations, congenital infections or severe neonatal diseases. In the study by De Marco et al. (2006), intestinal failure led to PN and only PN-related cholestasis was studied, excluding other possible causes such as active liver infections, primary metabolic disorders, cystic fibrosis, autoimmune diseases, neoplastic diseases, biliary tract diseases including cholelithiasis and bacterial cholangitis and toxic injury.

De Marco et al. (2006) have shown that UDCA was effective in controlling PN-associated cholestasis. In addition the authors reported that UDCA was as effective in children with short bowel syndrome (SBS) and extensive small bowel loss as in those with normal intestinal length. Therefore, absorption of UDCA occurred in the former even with an extreme reduction of functioning intestinal surface involving the ileum where the main absorption of UDCA usually occurs. De Marco et al. (2006) attributed this efficacy to the fact that some passive non-ionic diffusion of UDCA was demonstrated in the small intestine, that treatment was started early and that high doses (30 mg/kg/day) were used. Cowles et al. (2010) have concluded that, in the short-term, development of intestinal failure-associated liver disease can be prevented or reversed in a large number of patients by a multidisciplinary approach involving UDCA administration.

Rapporteur's Comment

Study URU-3/NEO (MAH1 sponsored study)
The rationale behind this study is that difficulty in fat digestion is the limiting factor for enteral feeding tolerance in premature infants and therefore bile acid supplementation with UDCA may improve nutritional care. This is due to the immaturity of the enterohepatic circulation in infants resulting in a very small bile acid pool, lack of anaerobic flora in large intestines and immaturity of intestinal absorption and hepatic extraction of bile acids.

The rapporteur shares MAH 1's conclusion that in theory UDCA may reduce the time to achieve full enteral feeding in preterm infants however the results were not significant enough to prove this. This is possibly due to the higher gestational age and birth weight in the UDCA group.
MAH 1 claims that the difference in body weight between the treatment groups persisted for a long time, but was no longer present at the end of the study. The rapporteur notes that there was a steady weight loss from day 30 in the UDCA group, whereas the body weight continued to rise in the placebo group. This was not discussed by MAH 1 or the authors. Furthermore, more information is needed on the significant difference in study duration between the placebo and UDCA groups (37.4 $\pm$ 10.6 (32.5) vs 50.5 $\pm$ 19.8 (45) days) respectively).
In summary, the rapporteur is of the view that the observation of a constant and significant reduction of γGT activity over time in the UDCA group is the most important finding of this study and as such, warrants further investigation evaluating the potential prophylactic use of UDCA to prevent cholestasis in infants who receive prolonged parenteral nutrition.

MAH 1, in addition to study URU-3/NEO in infants with TPNAC, has presented a literature overview regarding the use of UDCA in TPN associated cholestasis. The submitted studies included another prospective, randomised double-blind, placebo-controlled trial by Arslanoglu et al. (2008). The study consisted of the following periods: Period 0: period of randomization; Period 1: began on day 3 of life. Infants received total PN and UDCA 5 mg/kg/d or placebo suspension; Period 2: began with the initiation of enteral feeding. UDCA 10 mg/kg/d or placebo suspensions was given until the last day of PN; Period 3: started on the day when full enteral feeding was achieved. UDCA 20 mg/kg /d or placebo suspension was given till the last day of the study. The UDCA-treated infants reached full enteral feeding approximately 2 days earlier than did the placebo-treated infants (18.6$\pm$5.8 vs 20.4$\pm$8.6 days, respectively). When this parameter was adjusted for gestational age, the risk ratio was 1.09, indicating no significant benefit for any treatment. For the secondary outcome measures, growth, nutritional status, and metabolic status were similar in both groups. Regarding markers of cholestasis, γGT activity declined continuously and significantly throughout the intervention period in the UDCA group, and in the placebo group it increased during the PN period and then declined slightly without any statistical significance. In the UDCA group, aspartate aminotransferase and alanine aminotransferase activities declined significantly ($P<0.05$), whereas in the placebo group aspartate aminotransferase activity remained unchanged and alanine aminotransferase activity increased ($P>0.05$).

MAH 2 submitted one additional claimed to be randomised controlled trial however Garson et al's study is a 2 year retrospective study and available only in Spanish.
Gokmen et al (2010) compared oral erythromycin, UDCA and placebo treatment in preterm infants and concluded that erythromycin is the most effective in facilitating enteral feeding and ursodeoxycholic acid is the most effective in preventing cholestasis in VLBW infants. The rapporteur was unable to find any more data about this study as MAH 2 submitted only a short abstract. MAH 2 is asked to provide more information about this RCT as it may provide valuable data for the assessment of UDCA's efficacy for TPNAC.

Kelly et al. (2010) recently reported that oral administration of UDCA may improve bile flow and reduce gall bladder stasis, although there is little data to suggest that prophylactic use prevents the onset of PNLD.
In summary, the rapporteur acknowledges that there is wide off label use of UDCA in this indication and there is some evidence suggestive of a role for UDCA in the prophylaxis and treatment of TPNAC. However in the rapporteur's opinion, there is not enough robust evidence on the effectiveness of ursodeoxycholic acid in paediatric patients with TPN associated cholestasis therefore its use can not be routinely recommended at present.

- **PRIMARY SCLEROSING CHOLANGITIS**

PSC in children is - like in adults - primarily observed in males and is predominantly associated with inflammatory bowel diseases (IBD). The overall median survival rate of these children is 10 years from clinical onset (Debray et al. 1994). Primary sclerosis cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammation with progressive obliterative fibrosis of the intrahepatic and/or extrahepatic bile ducts. The prevalence of PSC in children was reported to be lower than in adults (0.23 versus 1.11 cases per 100,000 person-years for children versus adults, respectively) in a Canadian population-based analysis (Kerkar and Milot, 2010). In children, PSC is linked, not only with IBD and autoimmune hepatitis (overlap syndrome), but with a variety of other disorders, including immunodeficiencies, neoplasms, trauma and conditions associated with choledocholithiasis and may also be present in the neonatal period. Although PSC has been considered as a common cause of cholestatic liver disease in adults for some time, diagnosis of SC in children and adolescents has evolved in the last two decades with increased awareness of the condition (Kerkar and Miloh, 2010).

MAH 1
There are only very spare data available about the treatment of PSC in children with UDCA.
Bousvaros et al. (1995) observed in a 12-months trial in 15 PSC patients associated with IBD a decrease of ALT and ALP during 6 and 12 months therapy with UDCA at a dose of 13.8 mg/kg/day. However, a similar response was observed in PSC patients not treated with UDCA.
In another trial, PSC patients treated only with UDCA (n=13), or in combination with immunosuppressive medications (n=14; corticosteroids with or without azathioprine) did show only an initial clinical and biochemical improvement, but did not prevent progression of liver disease (Feldstein et al. 2003). Only Tsimbalova et al. (2003) described a positive effect of UDCA at a dose of 15 mg/kg/day in addition to 5-ASA and corticosteroid therapy in 5 PSC patients (age: 3-18 years; 1 with Crohn's disease, 4 with ulcerative colitis). They found a decrease of hepatomegaly, transaminases and γGT. In addition, UDCA prolonged the remission for 1 year in these patients.
MAH 1 concluded that the present data do not allow a conclusion whether or not UDCA is effective in PSC in children.

MAH2
Most clinical trials involving patients with PSC have been performed in adults. Some of these have included adolescents, aged 13 years old or older (Charatcharoenwitthaya et al., 2008; Garioud et al., 2010). These studies used doses ranging from 13 to 15 mg/kg/day and reported no side effects. As adolescents were not analyzed separately from adults, the results from these studies in terms of efficacy are difficult to apply to the pediatric population *per se*.

The following three clinical trials have been conducted specifically in the pediatric population (Feldstein et al., 2003; Gilger et al., 2000; Miloh et al., 2009). The experience from the retrospective cohort analysis performed by Miloh et al. (2009) prove dramatic improvement in liver enzymes in children treated with UDCA as was the case with Feldstein et al. (2003). In the study by Miloh et al. (2009), 47 pediatric patients with PSC were treated with UDCA at doses of 20 to 30 mg/kg/day for a median follow-up of 78 months. No side effects were reported. Most of the children with PSC had IBD or autoimmune overlap and advanced fibrosis at diagnosis. Gilger et al. (2000) have also shown that UDCA at a dose of 17 mg/kg/day in children with PSC provided a significant biochemical improvement for up to 20 months without side effects.

Milot et al (2009) concluded that prospective randomized controlled trials of therapy of PSC in children, although desirable, are nearly impossible to power and alternative ways to address this issue are greatly needed. A randomized, double-blind, placebo-controlled, multicenter trial of high-dose UDCA (28-30 mg/kg/day) in adults had to be stopped early because of an enhanced risk in the UDCA group for death or liver transplantation and serious adverse events, particularly in those with advanced disease. Therefore, caution should be exercised in using UDCA at a dosage > 20 mg/kg/day in children with PSC (Ibrahim and Lindor, 2011). Given the existing data in both children and adults and the lack of other therapeutic alternatives, Kerkar and Miloh (2010) suggested that all children with PSC be treated with UDCA at doses not exceeding 20 mg/kg/day.

Rapporteur's comments
Primary sclerosing cholangitis (PSC) is a licensed indication in adults in some European countries. The incidence of PSC is seemingly increasing in children as a result of increased use of cholangiographic screening techniques in children with inflammatory bowel disease. The underlying pathogenesis remains poorly understood and, as a result, therapeutic agents that halt disease progression and improve prognosis are lacking. PSC treatment is mainly supportive and directed at controlling cholestatic symptoms and preventing complications. The rapporteur shares Ibrahim et al. conclusion that UDCA is helpful in inducing biochemical improvement; however prospective multicenter trials in children with PSC are needed to determine a benefit of this agent (Ibrahim et al 2011).
MAH 2 submitted more recent and therefore more informative studies about this condition.
In addition, the rapporteur identified a recent Cochrane review (2011) which concluded that the evidence does neither support nor refute the use of bile acids for primary sclerosing cholangitis. However, bile acids seem to lead to a significant improvement in liver biochemistry. Therefore, more randomised trials are needed before any of the bile acids can be recommended for this indication (Poropat et al.2011).
In summary, the rapporteur is of the view that there is not enough data available to allow a conclusion about UDCA's effectiveness in children with PSC and therefore its routine use cannot be recommended at present.

As an outcome of the rapporteur's literature review about UDCA's use in PSC a significant safety concern was identified. A very recently published study found that long-term use of high-dose UDCA (28-30 mg/kg/d) is associated with an increased risk of colorectal neoplasia in patients with ulcerative colitis (UC) and PSC (Eaton et al. 2011). The rapporteur is of the view that the MAHs should discuss this issue after reviewing any available safety information.

- **STUDIES OF VARIOUS CHRONIC CHOLESTASIS IN CHILDREN**

MAH 1
There are some placebo-controlled trials (Levy et al. 1990; Paradis et al. 1993) as well as open clinical trials (El-Rifai et al. 2003; Kardorff et al. 1996; Narkewicz et al. 1998) which included a combination children with different chronic cholestatic liver diseases such as Alagille Syndrome, biliary atresia, Byler's disease/PFIC, cystic fibrosis-associated cholestasis, and others, in which results were pooled and presented together. In total there are 141 children in the age range between 4 months and 18 years, and the duration of treatment with UDCA varied between 3 months (Levy et al. 1990) and 4 years (El-Rifai et al. 2003). All trials showed improvements in liver function parameters and partially in pruritus, except in the 3-monthly trial performed by Levy et al. (1990) in which UDCA was administered at a dose of only 10-12 mg/kg/day. Most trials did not differentiate between the different cholestatic diseases, which makes an individual evaluation and interpretation of results difficult. Only Paradis et al. (1993) evaluated the results

of his study by disease. The UDCA bile enrichment was at least in the group of CF patients 31% and in the group of North American Indian Childhood Cirrhosis (NAIC) 37% at an UDCA dose of 15-30 mg/kg/day; serum liver enzymes improved significantly in the children with CF, NAIC and biliary atresia, and in some a normalisation was observed. However, 4 children deteriorated who then subsequently improved after stopping UDCA (Paradis et al. 1992; Section on safety).
MAH 1 concluded that UDCA improved serum liver enzymes in children with various cholestatic liver diseases. Low doses of UDCA (10-12 mg/kg/day) and treatment for short treatment periods were ineffective. These results are in agreement with the data reported for the individual cholestasis as described in the sections above.

MAH 2
In addition to the above mentioned studies, MAH 2 submitted 2 retrospective cohort reviews in neonates with various cholestatic etiologies:

Table 2 - Summary of Studies in Neonates – Cholestasis of Various Etiologies

Reference	Population characteristics	UDCA dosage	Results
Kobt, 2009 (Retrospective cohort review)	496 neonates with neonatal hepatitis and 97 with paucity of intrahepatic bile duct (10 with Alagille syndrome, 54 with non-syndromic PIBD and 33 with vanishing bile duct syndrome); neonatal hepatitis was idiopathic in 76.8% of neonates and attributable to infectious (the vast majority) or congenital metabolic disorders	20-40 mg/kg/day for a mean duration of 319.2 & 368.8 days for neonatal hepatitis and PIBD, respectively	UDCA was ineffective in management of cholestasis in these pediatric cohort and its use was associated with morbidities and worse outcome that compromised their QOL
Tufano et al., 2009 (Retrospective cohort review)	27 children with neonatal cholestasis of various etiologies and multifactorial in 92.5% of them (prematurity, asphyxia, PN, chromosomal disorder, infections, sepsis); 92.5 % were preterm and 81% of these were of VLBW; all preterm infants suffered from concomitant clinical disorders such anemia, respiratory problems, cardiac and neurological anomalies; 21/27 experimented 25 episodes of sepsis	30 mg/kg/day for 3 weeks	UDCA did not significantly affect clinical and biochemical course of cholestasis in this patient cohort

MAH 2 stated that these studies gave results that seem to be in contradiction with those found in studies examining the effects of UDCA administration on homogeneous populations of infants suffering from cholestasis of a unique etiology (e.g. biliary atresia or TPN associated with prematurity, VLBW and intestinal failure). It was pointed out by the MAH that the heterogeneous populations studied in these 2 trials were composed of very severely ill neonates, with cholestatic liver disease being often associated with infections and sepsis, whereas in the former studies, patients were free of severe associated illnesses. The latter could then constitute a contraindication to the use of UDCA in this neonatal context, especially with regards to infectious hepatitis. Indeed, Kobt et al. (2009) have pointed out that complications seen in their trial could be partly attributable to the glucocorticoid immunosuppressives effects of UDCA. With regards to the lack of efficacy of UDCA observed in the study by Tufano et al. (2009), the same arguments could apply, together with the fact that comparison between UDCA-treated and untreated patients was performed after a very short period of time (3 weeks).

Rapporteur's Comment
In the rapporteur's opinion due to the limitations of the submitted studies, robust conclusions can not be drawn. However, the rapporteur is of the view that the MAHs should further explore the available evidence on UDCA's effectiveness in the treatment of pruritus in paediatric cholestatic liver diseases. Also see comments on Alagille syndrome.

- **MAH 1 additional information**

  - **PRIMARY BILIARY CIRRHOSIS**

PBC (Primary Biliary Cirrhosis) is a chronic cholestatic liver disease primarily occuring in women and is usually diagnosed at ages between 30 and 50 years. It is characterised by a destruction of the intralobular bile ducts, leading eventually to cirrhosis. Currently, treatment with UDCA is the only approved treatment of this disease. It improves liver function parameters and stops histologic progression of the disease, particularly if treatment is started in early stages and with adequate doses. Biochemical responders have been shown to have a similar mortality without liver transplantation as an age- and sex-matched normal population.
PBC is very rarely seen in paediatric patients. However, Dahlan et al. (2003) reported for the first time two PBC cases diagnosed in 15- and 16-years-old girls. In addition to these two cases there is another case report in the literature of a 17 year old girl with a histological stage II PBC who was treated with 2 g UDCA/day and her liver enzymes (AST, ALT, AP, γGT) and total bilirubin nearly normalized under this therapy. (Floreani et al. 2006)

MAH1 concluded that PBC in children/adolescents is very rare. However, UDCA seems to be effective, at least in high doses (2 g/day) as published in a case report. The usually recommended dose of UDCA for PBC in adults is about 15 mg/kg/day, corresponding to about 1 g/70 kg/day.

Rapporteur's Comment
Primary biliary cirrhosis is one of the licensed indications of UDCA in adults in Europe.
The rapporteur is of the view that PBC is extremely rare in children and the paediatric cases (three case reports in 15-17 year old girls) identified in the literature do not offer robust evidence of the effect of UDCA treatment in this condition.
MAH 2 did not present any data in this condition.

  - **ALAGILLE SYNDROME**

Alagille Syndrome, synonymous to Ateriohepatic dysplasia and Syndromic paucity of the intrahepatic bile ducts is a chronic intrahepatic cholestasis occuring in about 1 of 70,000 live births (Suchy et al. 2002) characterised by a decreased number or paucity of interlobular bile ducts and various extrahepatic congenital malformations. The disease usually is not associated with liver cirrhosis and has a low mortality rate (Ballistreri 1996). Clinical manifestations include intense pruritus, starting by the 4^{th} to 6^{th} month of life, often intractable and disturbing sleep an daily activities. The disease is also characterised by an increase of serum cholesterol, sometimes up to 2000 mg/dl, and cutaneous xanthoma formations. Due to an intraluminal bile acid deficiency in the intestine, the patients are at risk of fat-soluble vitamin deficiency which can be manifested as degenerative neurological diseases (Ballisteri 1996b).
MAH 1 submitted an open label pilot study (Ballisteri et al 1993) which demonstrated that UDCA at a dose of 15 – 20 mg/kg/day lead to a fast decrease of the severity of pruritus in the majority

of patients within 2 to 3 weeks from start of therapy. A dose increase to 30 – 45 mg UDCA/kg/day in non-responding patients caused an increase of the response rate. In addition, there was a significant reduction or even normalisation of serum liver parameters (bilirubin, ALT, AST, ALP) and cholesterol levels.
Two case reports (Clerici et al 1990, Krawinkel et al 1994) were also submitted in children aged 10 years and 3 years, respectively. These reports also showed marked improvement in liver function parameters and decrease of pruritus with a dose of 10-15 mg/kg/day.

MAH 1 concluded that as the treatment periods in all the above published studies were only short (6 – 36 months), it is not known whether UDCA can prevent progression. However, the MAH also claims that UDCA is the drug of first choice for the treatment of pruritus and cholesterolaemia in children with Alagille syndrome. The recommended dose in this condition is 15-20 mg UDCA/kg/day and an increase up to 30 and 45 mg/kg/day in patients who don't respond.

Rapporteur's Comment
The rapporteur is of the view that the studies provided by MAH 1 (2 case reports and 1 open label study) are considered too limited to offer robust evidence on UDCA's efficacy to prevent liver disease progression in Alagille syndrome and therefore its use can not be routinely recommended.
However, there is some evidence that UDCA may improve pruritus in Alagille's syndrome and some other paediatric cholestatic conditions. The MAH is advised to submit additional data on UDCA's potential use for 'Treatment of pruritus in paediatric cholestatic liver disease'.

- **MAH 2 additional information**

  - **GALLSTONE DISEASE (CHOLELITHIASIS)**

The prevalence of gallstone disease in adults is much higher than in children (1.9% in children versus 9.5% and 18.9% in male and female adults, respectively). Guidelines for management of cholelithiasis are available in adults and treatment of radiolucent gallstones with UDCA has been well documented. On the contrary, little is known about the natural history and management of cholelithiasis in childhood (Della Corte et al., 2008).
Only a few trials have addressed the medical treatment of gallstones in children. Most of these studies have not generated very positive results as to the efficacy of UDCA in dissolving gallstones (Cebe et al., 2011; Della Corte et al., 2008; Nordin et al., 2010; Tsai et al., 2005). Nordin et al. (2011) have shown complete resolution of choledocholithiasis in 3 cases of infants treated with UDCA (dose and duration not specified) and antibiotics for associated low-grade cholangitis. In the study by Tsai et al. (2005), a very small subset of infants (n=6) with gallstone of unspecified nature were treated with UDCA (dose not specified) for a mean duration of 11 months. None of them had any degree of stone resolution.
In two retrospective analyses of cases of children with gallstones (mean age of approximately 7 years old in both trials), gallstone dissolution with UDCA treatment was analyzed with respect to the nature and/or number of stones (Cebe, 2011; Della Corte et al., 2008). Cebe (2011) treated 17 patients with UDCA (dose and duration not specified). Reduction in stone size occurred in 6 patients (35%), complete dissolution in 3 patients (17.5%), whereas there was no reduction of stone size in 8 patients (47.5%). Children with a single stone of < 5 mm (n=4), all had a complete dissolution of stone or reduction in stone size. However, children with a single stone > 5 mm or multiple stones were the ones who predominantly had no reduction in stone sizes and no one had complete dissolution of stones.

Della Corte et al. (2008) analyzed the effect of UDCA treatment at a mean dose of 25 mg/kg/day (range 18-30) for a median period of 13 months in 83 children with echographic evidence of cholelithiasis (median maximum diameter of gallstones of 8 mm, range: 2-45 mm). Thirty-three (39.8%) children had radiolucent gallstones, 17 (20.4%) had radio-opaque gallstones while 33 (39.8%) did not undergo radiographic examination. All children completed the therapy without adverse events. Dissolution of gallstones occurred in only 6 /83 children (7.2%; 4 with radiolucent gallstones and 2 with unknown radiologic aspect) and recurrence occurred in 3 of them. This study showed that UDCA was ineffective in dissolution of gallstones in the vast majority of cases. However, UDCA had a positive effect on the symptoms i.e. determining the disappearance of abdominal discomfort in the vast majority of the symptomatic children treated (64.7% of the total population). The authors concluded that, unless larger series are performed to determine the natural history of cholelithiasis in childhood, UDCA should not be used in pediatric gallstones, except in symptomatic children with contraindications to cholecystectomy in order to reduce the clinical symptoms.
MAH 2 concluded that contrarily to adults, the effects of UDCA administration in gallstone disease have not been extensively studied in children and the benefit of UDCA administration in this context is not obvious. However, studies performed in children with gallstones have not explored the potential benefit of UDCA with respect to the chemical composition of these cholelithiases (cholesterol gallstones or not).

Rapporteur's Comment
MAH 2 provided a comprehensive literature overview of paediatric cholelithiasis and UDCA's potential role in treating this condition.
In recent years following the extensive use of ultrasound scanning an increased number of children with cholelithiasis has been identified. As opposed to the adult population, female predominance is only seen after the age of 14 years and there is an association with some risk factors such as familial cholelithiasis, obesity and haemolytic disorders. The therapeutic strategies are very heterogenous and consist of medical, surgical or expectant management.
Mehmood et al. (2010) reported that cholelithiasis is an atypical and under-diagnosed cause of abdominal pain in childhood and that the true prevalence may be higher than reported. 32 patients under the age of 15 were included in their retrospective single hospital based study and 2 of them treated with UDCA had a successful resolution. Overall the authors recommended surgical intervention for patients with symptomatic biliary lithiasis.
The rapporteur shares MAH 2's view that the available information is too limited to support UDCA's use in paediatric cholelithiasis. Furthermore, the literature suggests surgical management of symptomatic patients and in asymptomatic cases the 'wait and see approach' is preferred, leaving little room for pharmaceutical treatment, especially as the efficacy of UDCA treatment has not been demonstrated.

- **CHOLESTASIS – OTHER ETIOLOGIES**

The effect of UDCA administration has also been studied in a few other conditions associated with cholestasis such as biliary cirrhosis following hepatic artery thrombosis (HAT) after liver transplant (Bilik et al., 1995), α_1- antitrypsin deficiency (Lykavieris et al., 2008) and autoimmune hepatitis (Miyake et al., 2009).

Early initiation of UDCA at a dose of 15 mg/kg/day immediately after HAT in 3 children prevented interlobular fibrosis and cholestasis. However, initiation of treatment at 4 or 6 months in 2 other children, when considerable fibrosis of the graft had already taken place, did not have any beneficial effect as progression towards cirrhosis and need for re-transplantation was observed. No UDCA-related side effects were observed. MAH 2 concluded that early initiation of

UDCA after **liver transplantation and HAT** might have a protective effect on the graft. However, given the very small sample size in this study, other trials would be warranted to confirm this finding.

Forty-two children with **α_1 –antitrypsin deficiency** were administered UDCA 30 mg/kg/day. Liver function test results normalized in 22/42 children treated for a mean duration of 2.6 years. In 16 of them, UDCA was discontinued and relapse was observed in 11/16 followed by return to normal after UDCA was recommenced. Eleven children had an improvement in LFTs after mean treatment duration of 2.3 years, and 9 had no improvement with evolution toward cirrhosis requiring liver transplant. Combined initial values of GGT ≤ 5x ULN and total bilirubin ≤ 66 µmol/L were associated with normalization of LFTs in 90% of children whereas no beneficial effect was seen in children with the most severe liver involvement. The authors concluded that, because of the lack of side effects of UDCA and the lack of available medical treatment of this condition, it would be reasonable to recommend its use in children using levels of GGT and total bilirubin as decision tools as these seem to have prognostic value for the efficacy of treatment.

The efficacy of UDCA alone or in combination with prednisolone has also been tested in 147 Japanese patients with **autoimmune hepatitis (AIH)** which included some adolescents (range: 16 – 79 years old). Cumulative incidence of the normalization of serum transaminase levels was 64% in the UDCA group, 95% in the combination group (UDCA plus prednisolone) and 94% in the prednisolone group. The authors concluded that UDCA monotherapy is effective for some AIH patients. However UDCA monotherapy is not recommended for patients with high-grade inflammatory activity or poor residual capacity of liver function because they may reach liver failure before achievement of remission. The application of this study to the pediatric population is limited since results from adolescents were not analyzed separately from the adult population.

Rapporteur's Comment
The rapporteur fully endorses the above discussion of UDCA's potential use in the treatment of liver transplantation, α_1 –antitrypsin deficiency and autoimmune hepatitis, however the presented evidence is too limited to support its routine use in these conditions.

- **<u>OTHER POTENTIAL INDICATIONS NOT RELATED TO CHOLESTASIS</u>**

Studies performed in adults with **non-alcoholic steatohepatitis** (NASH) have generated conflicting results. Two randomized control trials showed no improvements in liver enzymes or histology when UDCA was used as treatment for NASH in adults patients. In contrast, an other group of investigators showed that 2 years of UDCA treatment at a dose of 12-15 mg/kg/day in combination with vitamin E improved ALT levels in NASH patients (Barshop et al., 2008; D'Adamo et al., 2009; Lenta et al. 2010).
Few data are available in children (Barshop et al., 2008; D'Adamo et al. , 2009; Lenta et al. 2010). In fact, only one study was conducted in children. In this prospective, controlled study by Vajro et al. (2000), 31 obese children (mean age, 8.7 years) with non-alcoholic fatty liver disease (NAFLD) were divided into 4 groups: patients able to follow a low-calorie diet, UDCA (10 – 12.5 mg/kg/day) given alone or added to the diet, and untreated patients. Children were followed-up for a period of 6 months.
Diet alone determined weight loss and resolved biochemical liver abnormalities in all patients. Addition of UDCA to the diet was no more efficacious than weight loss alone. UDCA alone was ineffective for the treatment of liver abnormalities in all cases, and results did not differ from those observed in the untreated control group. Improvement of ultrasonographic abnormalities was observed in patients who lost weight, irrespective of UDCA administration. No adverse events were reported in this study with respect to UDCA administration.

In view of these preliminary results, D'adamo et al. (2009) do not recommended to treat NAFLD in children, as its efficacy is still unproven. Further studies with higher doses used alone or in combination with vitamin E and for a longer duration are needed to really assess the potential benefit of UDCA in pediatric patients with NASH (Lenta et al., 2010; Vajro et al., 2000).
MAH 2 concluded that UDCA does not seem to have any positive effect in children suffering from NASH and authors do not recommend its use.

Toxicity related to radiotherapy and chemotherapeutic agents (regimen-related toxicity; RRT) accounts for 20% to 50% of transplant-related mortality among patients undergoing unrelated donor **hematopoietic stem cell transplantation (HSCT)** for acute lymphoblastic leukemia (ALL). Veno-occlusive disease (VOD) of the liver, which occurs in 5% to 60% of HSCT patients, is a sporadic early RRT syndrome with a high mortality rate. Poor outcomes have also been linked to other toxicity syndromes, among which idiopathic pneumonia syndrome and severe oral mucositis (Thornley et al., 2004).
Two groups of investigators, investigating ways of reducing RRT after HSCT in children have mentioned their routine use of UDCA together with other agents such as leucovirin and vitamin E or tinzaparin as supportive care protocols (Duggan et al., 2003; Qureshi et al., 2008).
Three studies have prospectively (Thornley et al., 2004) or retrospectively (Brown and Talamo, 2003; Lakshminarayanan et al., 2010) explored the efficacy of UDCA in combination with other agents in preventing VOD or other RRT syndromes in children undergoing HSCT.
In 37 children (mean age 8 years old), the use of UDCA (15 mg/kg/day) in combination with folinic acid, vitamin E and parenteral nutrition resulted in a signicant decreased prevalence and severity of mucositis, less severe hepatic toxicity and decreased time to engraftment when compared to historical controls (Thornley et al., 2004). In this study, the incidence of VOD was not significantly different.
In a retrospective study, Brown and Talano (2003) have shown that UDCA (30 mg/kg/day) in combination with heparin was a more effective strategy than heparin alone to prevent VOD following HSCT in children. In another retrospective review of 188 patients with high-risk HSCT treated with a combination of heparin, glutamine and UDCA (10 mg/kg/day), only one patient developed VOD (Lackminarayanan et al., 2010). The authors concluded that this supportive combination treatment was effective in preventing VOD in this paediatric population.
MAH 2 concluded that some positive results of UDCA administration have been found in alleviating regimen-related toxicity in children undergoing HSCT and it is routinely used in some centres, together with other agents, as part of supportive care.

Prevention of graft rejection after liver transplantation was studied in a subgroup of 15 children in a multicenter double-blind randomized controlled trial involving also adult patients. UDCA was given at a dose of 15 mg/kg/day for 3 months starting on the first day post-op. No difference between the UDCA and the placebo group were observed with regards to frequency of acute rejection, patient survival and graft survival. UDCA was generally well tolerated with minimal side effects (Keiding et al., 1997).

Since apoptosis plays an important role in the pathogenesis of viral hepatitis and it affects not only hepatocytes but also immune cells, Reizis et al. (2005) have conducted an open-label, randomized, placebo-controlled trial in 145 children with **viral hepatitis A, B or C** to study the effect of UDCA (10-15 mg/kg/day) on apoptosis of peripheral blood lymphocytes (PBL). The levels of PBL apoptosis showed significant correlation with the severity of the disease. Both the course and outcome of the disease and the apoptosis of PBL were significantly improved by UDCA treatment.

Diagnostic applications:
Early differentiation of extrahepatic biliary atresia from intrahepatic causes of cholestasis in neonates is of utmost importance, since early surgery of biliary atresia significantly improves the

outcome. **Hepatobiliary scintigraphy** is an integral part of diagnostic investigations of these patients and an excellent non-invasive method. However its specificity for diagnosis of biliary atresia is far from optimal.
Two studies have been performed using UDCA in order to try to improve the specificity of hepatobiliary scintigraphy (Khorasani and Mansouri, 2009; Poddar et al., 2004).
By using oral administration of UDCA (20 mg/kg every 12 h for 48 to 72 h) prior to scintigraphy, Poddar et al. (2004) were able to significantly improve the specificity in excluding extrahepatic biliary atresia from 54.3% to 88.6%. In another trial, Khorasani and Mansouri (2009) compared pre-treatment with phenobarbital with pre-treatment with UDCA in improving the specificity for diagnosis of biliary atresia by hepatobiliary scintigraphy. Compared to phenobarbital, UDCA administered at a dose of 20 mg/kg/day for 5 days had fewer complications and was more efficient in diagnosing extrahepatic biliary atresia (80% versus 96.6% specificity for phenobarbital and UDCA, respectively).

Rapporteur's Comment
The rapporteur is of the view that although UDCA use may be beneficial in the above discussed conditions, the available evidence is not robust enough to support its routine use at present.

c. Clinical safety

MAH 1
The use of UDCA in children and adolescents for treatment of cholestatic liver diseases has been shown to be safe, even in high doses of up to 45 mg/kg/day in preterm neonates, infants and small children for treatment duration of up to 2 years. Diarrhoea has been reported in few cases (Bittner et al. 1991). However, Paradis et al. (1992, 1993) reported 4 infants in a double-blind cross-over trial using a UDCA dose of 15 mg/kg/day (1 with α1-antitrypsin deficiency, 2 with biliary atresia, 1 with biliary atresia + Alagille Syndrome) with deterioration of the liver function tests, mild diarrhoea and tense ascites, anorexia or pruritus with improvement after stopping UDCA. As 3 of these children had biliary atresia and were at age 4 to 20 months, these children might have had probably complete liver cirrhosis. Kardorff et al. (1996) reported 3 of a total of 20 children who developed pruritus or increasing pruritus under the UDCA therapy. However, it was not mentioned what type and stage of disease these children had.
MAH 1 stated that UDCA as suspension has been used from third day of life, in addition to TPN, with increasing doses from 5 to 20 mg/kg/day in preterm neonates without any known liver disease (Clinical Study Report URU-3/NEO). Similarly, Levine et al. (1999) reported about the use of UDCA dosages of 15-30 mg/kg/day without any side effects in preterm neonates with TPNAC.
MAH 1 concluded that in general, UDCA has been shown to be very safe, even if used in preterm neonates few days after birth. However, MAH 1 advises that children with biliary atresia and advanced stages of liver disease (cirrhosis) should be treated with care. It would be advisable to start treatment at low dose in those children with careful monitoring of their therapy.

MAH 2
MAH 2 did not extensively discuss UDCA's safety profile in the critical literature overview, however provided the following precautions and contraindications for the use of UDCA:

- UDCA should not be used in cases of obstruction of bile ducts (e.g. failure of portoenterostomy in BA);
- In PSC, doses should not exceed 20 mg/kg/day;
- Administration of UDCA in TPN-associated cholestasis should be restricted to preterm or VLBW infants that are not suffering from severe concomitant infections or diseases as a study has demonstrated deleterious effects of UDCA administration in severely ill neonates.

Rapporteur's Comments

The rapporteur shares MAH 1's view that UDCA has proven to be a safe medication in a large number of paediatric studies, even when used in premature infants.

However there are a few paediatric studies in the literature which reported serious adverse events with the use of UDCA. Paradis et al. (1992) reported 4 infants with severe underlying cholestatic liver disease (1 with α1-antitrypsin deficiency, 2 with biliary atresia, 1 with biliary atresia and Alagille Syndrome) and complete cirrhosis who deteriorated while on UDCA and showed improvement after stopping therapy. The rapporteur shares the authors' conclusion that caution and careful dosing should be used with UDCA when treating children with significantly decreased bile outflow.

UDCA administration has been associated with serious hepatic and extra-hepatic morbidities in cases of unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia (Alvarez 2008). This was also observed by Kobt et al (2008) in a review of a historical cohort of infants with extrahepatic biliary atresia following portoenterostomy where UDCA administration at 20 mg/kg/day lead to faster development of liver injury.

Of note, the currently approved UK SmPC in section 4.3 also lists "occlusion of the biliary tract" as a contraindication. Based on these facts, the rapporteur is of the view that UDCA should not be used in children with biliary atresia and unsuccessful portoenterostomy or without recovery of good bile flow and therefore inclusion of this information in Section 4.3 of the SmPC is considered justified.

Kotb et al (2009) also identified several hepatic complications associated with the use of UDCA in their cohort of infants with neonatal hepatitis, such as vanishing bile duct syndrome, liver cell failure, ascites, and higher rate of relapse and progression of disease in already resolved cholestasis. The authors concluded that UDCA's use was associated with morbidities and worse outcome affecting their quality of life. The rapporteur noted that 76.8% of cases were idiopathic neonatal hepatitis and parental consanguinity was present in 39.8% of infants; both of these factors may have confounding effects. The rapporteur is of the view that, both studies by Kotb et al. had significant limitations and therefore need careful interpretation.

Safety concerns also emerged regarding UDCA's use in adults with primary sclerosing cholangitis. A very recently published study found that long-term use of high-dose UDCA (28-30 mg/kg/d) is associated with an increased risk of colorectal neoplasia in patients with ulcerative colitis (UC) and primary sclerosing cholangitis (PSC) (Eaton et al. 2011).

Furthermore, another study in adults receiving 28-30 mg/kg/day UDCA for PSC reported that the risk of reaching a primary endpoint of cirrhosis, varices, cholangiosarcoma, liver transplantation, or death was 2.3 times greater for patients on UDCA than for those on placebo. The rapporteur shares the authors' conclusion that the possibility of hepatotoxic bile acids being produced from unadsorbed UDCA may be a potential explanation (Lindor et al. 2009).

At this time no other reports could be found in the literature which would raise concern about UDCA use in cholestatic diseases other than in cases of obstruction of bile ducts and PSC. The rapporteur is of the view that the MAHs should discuss these safety concerns further and provide any relevant safety data.

Furthermore, as discussed in section II.3.2.(Clinical efficacy), UDCA is not routinely recommended for use in TPN associated cholestasis, however MAH 2 is asked to justify the recommendation that precaution is needed when UDCA is administered to severely ill neonates with TPN associated cholestasis as the referenced study is not cited.

Paediatric safety report

MAH 1 submitted the Core Safety Profile (CSP) for UDCA resulting from the PSUR Work-sharing procedure MT/H/PSUR/0001/001 in 2009. The work-sharing procedure covered the Safety Report (PSUR) period from 1st January 2004 to 30th November 2008. Malta acted as Rapporteur and five other EU member states (FR, UK, SE, IE, BE) provided comments on the Assessment Report.

TABLE OF ADVERSE DRUG REACTIONS (ADRs)					
	Serious		**Nonserious**		**Total**
System Organ Class (SOC)	**Listed**	**Unlisted**	**Listed**	**Unlisted**	
Congenital and familial and genetic disorders		1			**1**
Gastrointestinal disorders			6	4	**10**
General disorders and administration site conditions				1	**1**
Musculoskeletal and connective tissue disorders				2	**2**
Nervous system disorders				3	**3**
Respiratory thoracic and mediastinal disorders				1	**1**
Skin and subcutaneous tissue disorders		1	5	3	**9**
Total	**0**	**2**	**11**	**14**	**27**

During the period under review only 2 serious ADRs were reported in relation to ursodeoxycholic acid administration. Both these ADRs were unlisted and their potential impact on the product's overall safety was discussed and assessed. One case concerned a 31 year old oncology patient being administered 33 concomitant drugs for leukaemia and purulent coxitis. He developed toxic epidermal necrolysis and died after 2 months. Due to the high number of concomitant medications the case was not assessed further and both the MAH and the rapporteur were of the opinion that the benefit-risk balance of UDCA remains unchanged. The other serous ADR concerned a pregnant female who was initiated treatment with UDCA capsules for treating intrahepatic cholestasis of pregnancy. After 15 weeks of treatment her baby was born and it was later reported that the child had white spots on the teeth. A dentist assessed the event as possibly related to UDCA. The PSUR rapporteur requested that in future pregnancy related ADRs to collect information on gestational age at the initiation of UDCA therapy to assess any teratogenic effects.

Furthermore, the PSUR rapporteur noted that most of the non-serious ADRs fell within SOCs: 'Gastrointestinal disorders' and 'Skin and subcutaneous tissue disorders'. In view of this, the rapporteur highlighted that close monitoring of future ADRs classified under these clinical categories is warranted.

The exposure to the capsule, suspension and tablet formulations during the period under review was 665,347 patient treatment years. The cumulative safety data from spontaneous reporting, clinical studies and the review of the medical literature confirmed a good safety profile for the products and no ongoing safety issues were apparent at the time of the report. No further action was deemed necessary.

Rapporteur's Comment

The rapporteur noted the above work-sharing procedure's outcome and changes to the SmPC. However, MAH 1 did not provide the actual PSUR report or any information about the paediatric cases included in the reporting period. The final assessment report is informative regarding the 2 unlisted serious adverse events, however the non-serious adverse events should be described in more detail by MAH 1 including the age of the affected patients.
MAH 2 did not provide any detailed safety information.
Both MAHs are requested to review their post-marketing safety database in order to identify any paediatric safety reports since UDCA has been licensed.

d. Conclusion

MAH 1
In respect of the paediatric population the MAH's report concludes that:
"…the use of UDCA for treatment of cholestatic liver diseases may be effective at least in some indications. In addition, treatment with UDCA was shown to be safe in children and adolescents, even in high doses (up to 45 mg/kg bw/day) in preterm neonates, infants and small children. Therefore, the statement included in the posology section of the SPC and PIL of UDCA preparation in most EU countries "There are no age restrictions for the use of UDCA" appears appropriate and justified."

MAH 2
Despite the paucity of large scale, prospective, blinded, RCTs using UDCA in children, the overall scientific literature provides evidence of its efficacy and safety in some indications such as CF, BA after successful portoenterostomy, PSC and TPN-associated cholestasis in neonates and children. Many authors have strongly recommended the use of UDCA in these conditions. For some indications, evidence of efficacy in children is less consistent although UDCA is widely used in practice (e.g. PFIC). Depending on the pathology, it has also been shown to have a beneficial effect on the symptomatology (jaundice, pruritus) and in some cases, can delay disease progression.

3. Discussion on clinical aspects

The submitted studies review a variety of cholestatic conditions where the use of UDCA may be beneficial. The efficacy information from these studies reviewed here confirms the effectiveness of UDCA based on the expected mechanism of action. Despite its wide paediatric off-label use in paediatric cholestatic liver disease, the available data is limited to provide enough evidence to prove its efficacy in most of these conditions. Many of the submitted studies were conducted over a decade ago and only in small study populations. Furthermore, due to the low paediatric prevalence rate of some cholestatic conditions, very few randomized controlled studies were carried out. Therefore it is concluded by the rapporteur that for Progressive familial intrahepatic cholestasis (Byler's disease), Biliary atresia, Total parenteral nutrition associated cholestasis, Primary sclerosing cholangitis, Primary biliary cirrhosis, Alagille syndrome, Liver transplantation, α_1 –antitrypsin deficiency, Autoimmune hepatitis, Non-alcoholic steatohepatitis, Hematopoietic stem cell transplantation, Viral hepatitis and Hepatobiliary scintigraphy UDCA could be effective in selected paediatric patients but currently there is not robust enough evidence to strongly support these indications for the paediatric population.

The majority of the existing information on paediatric use of UCDA is regarding the treatment of Cystic fibrosis associated liver disease (CFLD). UDCA dosage of 20 mg/kg/day is considered to be safe and effective in this condition with a further increase up to 30 mg/kg/day if necessary.

UDCA has proven to be a safe medication in a large number of paediatric studies in a dose range of 15-45mg/kg/day, even when used in premature infants. However, in view of the identified serious adverse events (see section 2.c) careful titration of UDCA dose is needed in paediatric patients with significantly decreased bile outflow (advanced cirrhosis, failure of portoenterostomy in biliary atresia) and in primary sclerosing cholangitis (PSC), starting with a low dose and carefully titrating until the desired clinical response is achieved.

IV. RAPPORTEUR'S CONCLUSION AND RECOMMENDATION AT DAY 70

Following thorough review of the literature and submitted data on the use of ursodeoxycholic acid in paediatric conditions, the currently available evidence only supports its use for **hepatobiliar disorder associated with cystic fibrosis in children aged 1 month to less than 18 years**. Treatment with UDCA in this paediatric condition is considered to be safe and effective at a dose of **20 mg/kg/day in 2-3 divided doses, with a further increase to 30 mg/kg/day if necessary**. It has been demonstrated in short-term as well as long-term use (up to 12 years) that UDCA is able to improve/normalise hepatic transaminases, improve hepatic metabolism of essential fatty acids and bile flow in children with cystic fibrosis if therapy has started early enough. If liver cirrhosis is already manifested, a normalisation of liver function can not be expected. It has also been suggested that UDCA might have a positive effect on nutrition and absorption of fat-soluble vitamins as well as on growth development and muscle mass of children if given at an adequate dosage. At dosages below 15 mg/kg/day, no or only marginal effects might be seen, especially if given only for a short period of time, for weeks or few months. Furthermore, UDCA may be effective in decreasing pruritus in children with cholestatic liver disease; however no relevant data has been presented by either MAH.

The rapporteur would like to emphasise that although the evidence assessed during this procedure was not considered robust enough to support any of the other potential uses of UDCA, it is not proposed to delete any currently nationally approved paediatric indications. Furthermore, assessment of adult indications falls outside the scope of this procedure.

UDCA was in most trials, even in doses up to 45 mg/kg/day and in preterm infants, safe and well tolerated. However, careful titration of UDCA dose is needed in paediatric patients with significantly decreased bile outflow (advanced cirrhosis, failure of portoenterostomy in biliary atresia). Furthermore, a potential safety concern regarding long-term high-dose UDCA use in adult patients with primary sclerosing cholangitis (PSC) was identified based on a recent study report (Lindor et al 2009).

As a conclusion, upon receipt of the requested additional data the paediatric aspects of the SmPC for ursodeoxycholic acid should be updated in the relevant sections. The currently approved SmPC states in section 4.2*:"There are no age restrictions on the use of UDCA".* However, the rapporteur is of the view that as the presented evidence only supports UDCA's use in children aged 1 month to less than 18 years with cystic fibrosis, therefore this statement is not acceptable for this particular indication. However it needs to be highlighted that the rapporteur is not proposing to delete already existing indications and as such, this statement may be needed for other nationally approved uses of UDCA. Of note, any changes of adult indications do not form part of this procedure.
In section 4.2, comprehensive dosing recommendations should be available for the paediatric population under a separate heading. Regarding safety of UDCA, the MAH should review the available paediatric information on adverse reactions and update sections 4.3, 4.4 and 4.8 accordingly.

Based on the currently available information the rapporteur proposes the following wording to update SmPCs (however this may change upon receipt of additional information from MAHs):

Section 4.1 Therapeutic indications
Paediatric population
Hepatobiliar disorder associated with cystic fibrosis in children aged 1 month to less than 18 years

Section 4.2 Posology and method of administration
Paediatric population
Children with cystic fibrosis aged 1 month to less than 18 years: 20 mg/kg/day in 2-3 divided doses, with a further increase to 30 mg/kg/day if necessary

Section 4.3 Contraindications
Paediatric population
Unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia

V. MEMBER STATES' COMMENTS (DAY 85)

Following the circulation of Day 70 PdAR, comments were received from five member states: DE, SE, NL, HU and IE.

Three member states (DE, HU, IE) supported the rapporteur's conclusions and the request for additional data.

Two member states (NL, SE) did not support the rapporteur's proposed SmPC wording. Their comments were taken into consideration and incorporated in the revised report which was circulated to the MAHs.

VI. ADDITIONAL CLARIFICATIONS REQUESTED AT DAY 89

The MAHs were requested to provide additional information on the following:

- UDCA's potential paediatric use in the currently licensed adult indications not covered by the clinical expert overview (bile reflux gastritis)
- UDCA's efficacy in the treatment of pruritus in paediatric cholestatic liver diseases
- Discussion of the evidence available highlighting the long-term efficacy and safety outcome of UDCA treatment of paediatric hepatobiliary disorder associated with cystic fibrosis
- Use of excipients in UDCA suspensions
- Paediatric pharmacokinetic data, if available
- Study URU-3/NEO: explanation of weight loss in UDCA group
- Review of the MAHs' post-marketing safety database in order to identify any paediatric safety reports since UDCA has been licensed
- Discussion of efficacy and safety in infants with TPN associated cholestasis
- Discussion of the recently emerged carcinogenicity safety concerns in adults with PSC

- Proposals for paediatric SmPC text in sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2. The proposal should be justified by supporting data from the MAH databases and relevant published data.

VII. ASSESSMENT OF RESPONSE TO QUESTIONS

Following the circulation of Day 89 PdAR, the following responses were received from the MAHs with regards to the additional clarifications requested in section V:

1) UDCA's potential paediatric use in the currently licensed adult indications not covered by the clinical expert overview (bile reflux gastritis)

MAH 1
A literature research (search profile *"Ursodeoxycholic Acid"[Mesh] AND ("bile reflux gastritis" OR gastr*)*", restricted to "humans" and articles in English language) yielded 42 hits. These and references from a local database on publications on bile reflux disease (containing 81 publications) were screened manually in title and eventually in abstracts and in the full publication for data on the use of UDCA in paediatric patients with bile reflux disease. We could not find any publication with paediatric patients treated with UDCA for bile acid induced gastritis, dyspepsia or similar disease. Based on the results of theses searches it appears that there are no relevant publications on the use of UDCA in paediatric bile reflux disease.

MAH 2
A literature search on Pubmed has been performed using the following key words: bile reflux gastritis AND (paediatric OR children) AND (ursodiol OR UDCA OR ursodeoxycholic acid) without any limits of language. No data have been found regarding the paediatric use of UDCA in bile reflux gastritis. Thus, results of the initial literature search related to UDCA in the paediatric population had covered all indications for which data were available in this patient population.

Rapporteur's Comment
Based on the provided extensive literature search both MAHs reviewed all potential paediatric use of ursodeoxycholic acid as requested through this paediatric work-sharing procedure. Issue resolved.

2) UDCA's efficacy in the treatment of pruritus in paediatric cholestatic liver diseases

MAH 1
Pruritus is a well known symptom of many chronic cholestatic disorders in both adults and children. Pruritus occurs in different intensities and severities ranging from mild forms to severe forms with persistent active scratching with evident skin abrasions, cutaneous mutilation, haemorrhage and scarring. Many parents of children with cholestatic disorders regard pruritus to be the most incapacitating symptom of their child's chronic liver disease.
In the treatment of adult patients with cholestasis, UDCA is not generally considered to lessen cholestatic itch with the exception of pruritus which is associated with intrahepatic cholestasis of pregnancy. Due to its effect on liver enzymes, histology, reduction of complications and putatively also mortality without liver-transplantation, UDCA is considered the medicinal treatment of choice in primary biliary cirrhosis (PBC) which presents with pruritus as a symptom. However, a consistent effect of UDCA on pruritus was reported only in few studies, whereas most studies did not report any significant general effect of UDCA on pruritus. Moreover, pruritus

or exacerbation of pruritus were reported anecdotally associated with UDCA treatment. In cases where pruritus is suspected to occur as an adverse drug reaction, it is recommended to restart the treatment with a reduced daily UDCA doses which then should be slowly increased to the recommended dose range of 14 ± 2 mg/kg body weight/day.
Desmond et al. (2007) describe 22 adult patients with cystic fibrosis associated hepatobiliary disorders (CFAHD) (mean age at diagnosis of CFAHD: 23, range 8-47 years) who were treated with a median daily dose of 11.3 mg UDCA/kg body weight (range 7 – 22 mg) for a median duration of 3.6 years. UDCA treatment was associated with an improvement in hepatobiliary symptoms including pruritus, fatigue and right upper quadrant pain which were prevalent in 50% of the patients in the pre-UDCA period and in 4% in the post-UDCA period. In intrahepatic cholestasis of pregnancy (ICP), UDCA (10 – 20 mg/kg body weight per day) is established as an effective and safe treatment also relieving pruritus. Lindor & Burnes (1991) described a 56-year old patient with pruritus under total parenteral nutrition (TPN). Under the treatment with 600 mg/day UDCA pruritus disappeared.

In their review on treatment of cholestatic pruritus in children Cies & Giamalis (2007) summarise: "Depending on the underlying disease state resulting in cholestasis, UDCA …[as other agents such as phenobarbital, bile sequestering agents and opioid antagonists]… appears to be most effective for treating pruritus related to intrahepatic cholestasis in children. However, due to the different mechanisms of cholestatic pruritus there are no guidelines or algorithms to guide therapy with the different agents for children. Combination therapy including UDCA may be effective. An agent should be selected based on the patient's concurrent diseases and current medication regimen. UDCA is safe and inexpensive, with documented efficacy for pruritus associated with intrahepatic cholestasis in children."

Reports of UDCA treatment on pruritus in paediatric patients with:

- progressive familial intrahepatic cholestasis (PFIC; Byler's disease)
Balli (1992) reported 2 paediatric cases with PFIC who were treated with 20 mg/kg body weight/day UDCA. Pruritus improved in both patients. Jankowska et al (1996) treated 24 paediatric PFIC patients with 15 mg/kg body weight/day UDCA (in two daily doses) for a mean duration of 26 months. In 4 children pruritus was relieved completely. In addition, 12 children experienced a marked decline in pruritus. Jacquemin et al. (1997) treated 39 paediatric patients with PFIC with 600 mg/m² (corresponding approximately to 20 – 30 mg/kg body weight) /day UDCA for 2 to 4 years. Pruritus disappeared or diminished significantly in 15 children in whom liver function tests normalised under UDCA treatment. Interruption of the treatment with UDCA induced a relapse of pruritus in some patients who improved again when UDCA was restarted.
Takahashi et al (2007) report the treatment of one paediatric case with PFIC type 2 with a heterozygous mutation in the ABCB11 gene. Initially, pruritus persisted under treatment with UDCA (20 mg/kg body weight/day). However, after hospital admission (for liver transplantation) the pruritus disappeared and bilirubin as well as liver function parameters, except for alkaline phosphatase decreased. These improvements were interpreted as a late effect of UDCA therapy.

- Alagille syndrome
Clerici et al. (1990) desribed a 10 year old patient with Alagille syndrome whose pruritus markedly decreased under treatment with 10 mg/kg body weight/day UDCA. Krawinkel et al. (1994) described a 3 year old patient with Alagille syndrome whose pruritus was found to be decreased after a few weeks of treatment with 15 mg/kg body weight/day UDCA.

- Various cholestatic disorders
Balistreri et al. 1989 treated 5 children (age: 7 months – 19 years) with intrahepatic cholestasis as well as 5 patients (age: 5 – 16 weeks) with extrahepatic cholestasis due to biliary atresia with

15 mg UDCA/kg body weight/day for 48 to 188 days. In 3 of 5 of the patients with intrahepatic cholestasis, a marked decrease of pruritus was reported.
Levy et al. (1990) reported the short term (3 months) effects of UDCA treatment (10 – 12 mg/kg body weight/day) in 9 paediatric patients with various chronic cholestatic disorders (4 with Alagille syndrome, 3 with biliary atresia, 2 with idiopathic etiologies) who all suffered from intractable pruritus. Pruritus remained unchanged in 7 children, improved in one and worsened in one. (No further details are given in the abstract publication.)
Balistreri et al. (1993) report on paediatric patients with various forms of intrahepatic cholestasis, among them 31 patients with Alagille syndrome and 27 patients with PFIC who all had persistent, generalised pruritus of varying degrees which had been refractory to multiple medications, including cholestyramine and, in some cases, to partial external biliary drainge. Patients were treated initially with doses of 15 mg/kg body weight/day UDCA in three divided doses and all other antipruritic medications were discontinued. In patients whose pruritus did not improve after 2 to 3 weeks the UDCA dose was serially increased to 30 mg/kg body weight/day and then to 45 mg/kg body weight/day. In the majority of patients with chronic intrahepatic cholestasis who received UDCA for at least one month there was a clinical and biochemical improvement. In 15 of the 31 patients with Alagille syndrome, pruritus improved after one month under treatment with 15 mg/kg/day UDCA. The dose of UDCA was increased in 16 patients and pruritus improved in additional 11 patients. In 3 of 5 non-responding patients, partial external biliary diversion was carried out which led - in combination with UDCA – to a relief of pruritus.
The same authors reported also treatment of paediatric patients (<4 months of age) with biliary atresia with extra- and intrahepatic cholestasis. There was a decrease in the degree of pruritus in the patients treated with 15 – 30 mg/kg /day UDCA. An increase in pruritus was noted in several patients after discontinuation of the UDCA treatment even if survival or need of liver transplantation was not affected.
Kardorff et al. (1996) treated 20 children with various forms of cholestatic diseases with UDCA in the dose range of 7 – 26 mg/kg bodyweight/day for 24 months. Pruritus improved in 4 patients but pruritus arose newly or deteriorated in 3 other patients.
Narkewicz et al. (1998) reported that the treatment of children with various cholestatic disorders with UDCA (dose 15 – 20 mg/kg body weight/day) led to an improvement of pruritus in all children. Interruption of UDCA treatment after 12 months led to the re-appearance or worsening of pruritus. Dinler et al. (1999) treated 24 paediatric patients with various forms of intrahepatic cholestasis (7 with neonatal hepatitis, 7 with PFIC, 10 with idiopathic intrahepatic cholestasis) with 15 – 20 mg/kg body weight/day UDCA for 12 months. Pruritus was ameliorated in all patients; it disappeared completely in 4 patients. Batta et al. (2005) reported treatment with 300 mg UDCA/day for 6 months in 4 paediatric subjects with cholestasis due to familial unconjugated hypercholanemia. Pruritus did not resolve on UDCA treatment while it was reduced to a minimum after treatment with conjugated cholic acid.

<u>- Cystic fibrosis associated liver disease</u>
In contrast to most other cholestatic disorders, in cystic fibrosis associated liver disease (CFAHD), pruritus is not mentioned as a predominant symptom (Colombo et al. 2006; Herrmann et al. 2010) and also reports on the effects of UDCA treatment in CFAHD on this symptoms are rare.

<u>- Reports of induction or worsening of pruritus by UDCA treatment</u>
Besides the cases of induction or worsening of pruritus under treatment with UDCA described already above - Kardorff et al.(1996) and Levy et al.(1990) - van de Meeberg et al (1997) performed a dose-finding study with 30 CFAHD patients. Two patients included in this study, one treated with 10 mg/kg body weight/day UDCA, the other treated with 20 mg/kg body weight/day UDCA, developed severe pruritus under treatment with UDCA and therefore dropped out of the study. In this study, pruritus was considered the only side effect of the treatment, even if the causal relation to UDCA is considered to remain uncertain.

Paradis et al (1993) report on a double-blind, placebo-controlled crossover study with 65 children with cholestatic disorders due to various diseases (21 with CFAHD, 15 with North American Indian childhood cholestasis, 6 with biliary atresia, 5 with Alagille syndrome) who were treated with 15 mg/kg body weight/day UDCA. If there was no AST reduction of at least 50 % within 2 months, the UDCA dose was doubled to 30 mg/kg body weight/day. In one infant increasing pruritus and anorexia occurred (Paradis et al. 1992).
The classic cholestatic liver diseases PBC and primary sclerosing cholangitis (PSC) are rare in paediatric patients as are publications on the use of UDCA in paediatric patients with cholestatic diseases. In the only publication available on paediatric patients with PBC, Dahlan et al. 2003, a 16 year old girl with stage II PBC at diagnosis developed intractable pruritus despite the treatment with 1250 mg/day UDCA. This patient had finally a successful liver transplantation. No pruritus was mentioned in a second case described in this publication.

MAH1's conclusion
There is evidence for the efficacy of UDCA in the treatment of pruritus in paediatric patients with various forms of intrahepatic cholestatic liver disease particularly in those with PFIC and Alagille syndrome. If treatment with standard doses of UDCA (15 – 20 mg/kg /day) does not relieve pruritus within some weeks, the dose might be increased up to 45 mg/kg/day for a trial. However, in rare cases, pruritus or deterioration of pruritus seemed to be triggered by use of UDCA.

MAH 2
Most studies investigating the efficacy and safety of UDCA treatment in the paediatric population have only focused on biochemical markers of cholestasis or cholangitis, as well as tried to evaluate the effect on the progression of liver disease. The effect of UDCA on pruritus has been less often reported, since this symptom is not predominant in all conditions in which UDCA could be effective. Therefore, the efficacy of UDCA in treating pruritus in children has been reported in a limited number of conditions where pruritus is more often observed and also more troublesome.

Chronic intrahepatic cholestasis: Alagille syndrome, PFIC and others
The predominant features of chronic intrahepatic cholestasis such as Alagille syndrome and progressive familial intrahepatic cholestasis (PFIC), also called Byler's disease, are growth failure and intractable itching, which is often of such severity as to interfere with daily activities and sleep (Balisteri 1993). In a multicenter, open-label, pilot trial of UDCA, Balisteri (1993) have been evaluating the effect of UDCA on 31 patients suffering from Alagile syndrome and 27 with PFIC (the majority) or idiopathic intrahepatic cholestasis. All patients received initially a dose of 15 mg/kg/day and if there was no improvement in the degree of pruritus after 2-3 weeks, the dose was serially increased to 30 mg/kg/day and then to 45 mg/kg/day. All patients had persistent, generalized pruritus of varying degrees (active scratching with or without evident skin abrasions, or cutaneous mutilation, hemorrhage and scarring evident) which had been refractory to multiple medications including cholestyramine and in some cases, to partial external biliary drainage.
Of the 31 patients with Alagille syndrome, 15 had a beneficial clinical response after 1 month. For the 16 non-responsive patients, UDCA dose was increased and pruritus was ameliorated in an additional 11. Five patients were non-responsive to doses as high as 45 mg/kg/day. In 3 of these patients, partial external biliary diversion was carried out in combination with UDCA and led to successful results. The authors noted that the responsive patients were older (mean age 10.1 years) than the non-responsive ones (mean age 3.5 years). Of the 27 patients with Byler's disease or idiopathic intrahepatic cholestasis, 23 noted an improvement in the degree of pruritus at a dose of 15 mg/kg/day. By increasing the dose, one additional patient became responsive and combining with partial external biliary diversion was an effective measure in one in the 3

remaining unresponsive patients. No adverse events related to the administration of UDCA were noted in either group during the 6-month period of UDCA treatment.
Dinler (1999) also conducted a prospective trial in pediatric patients (range 1.5 months to 15 years) with intrahepatic cholestasis (neonatal hepatitis: 7; PFIC: 7; idiopathic intrahepatic cholestasis: 10) treated with UDCA at a dose of 15-20 mg/kg/day for 12 months. Pruritus was ameliorated in all patients and itching completely disappeared in 16.7% of them. No adverse effects of therapy were noted.
Narkewicz (1998) conducted a 2.5-year, open-label, crossover study to determine the effects of UDCA on the clinical symptoms and biochemical test results of 13 patients (mean age: 13.1 ± 2.1 years) with intrahepatic cholestasis (Cystic Fibrosis: 6; Alagille syndrome: 4; PFIC: 2; non-syndromic intrahepatic bile duct paucity: 1). UDCA (15–20 mg/kg daily) was given for 12 months and then discontinued for 6 months, followed by retreatment for another 12 months. Patients did not receive any concomitant choleretic therapy (e.g., phenobarbital, cholestyramine) during the study. Of the six patients who had reported pruritus, all experienced an improvement in their symptoms after treatment with UDCA. Three patients reported worsening of pruritus on discontinuation of ursodiol and required retreatment with UDCA.
Krawinkel (1994) also noted a decrease in the degree of pruritus in a patient with Alagille syndrome after a few weeks of treatment with 15 mg/kg/day UDCA.

Biliary atresia
A prospective, randomized, double-blind, placebo controlled trial was also conducted by Balisteri (1993) in 29 subjects with biliary atresia having undergone hepatoportoenterostomy. Subjects received either placebo (n = 15) or UDCA at a dose of 15-30 mg/kg/day (n = 14) for up to 24 months. There was a decrease in the degree of pruritus in the UDCA group and an increase in pruritus was observed in several patients after discontinuation. A decrease in pruritus was also noted in several patients following the transition from placebo to UDCA. No side effects were noted.

Other trials
Kardoff (1996) and Levy (1990) have also studied, among other parameters, the effect of UDCA administration on pruritus in children with chronic cholestatic liver diseases. In the study by Kardoff (1996), 20 children (biliary atresia: 10; Alagille syndrome: 4; Byler's disease: 3; intrahepatic biliary hypoplasia: 3) were treated with a mean dose of 13 mg/kg/day (range: 7 – 26) for a duration of 24 months. During the first year of treatment, pruritus was improved only in 4 patients
Levy (1990) could not demonstrate beneficial effects on pruritus after treatment of 9 children (Alagille syndrome: 4; biliary atresia: 3; idiopathic etiologies: 2) with UDCA at a dose of 10-12 mg/kg/day for 3 months. Pruritus remained unchanged in 7 children, improved in one and worsened in one. One possible explanation for this lack of effect on pruritus in this trial could be the low dose used (10-12 mg/kg/day).

MAH 2's conclusion:
Intractable pruritus can severely alter the quality of life in children with some cholestatic liver diseases. Like for other cholestatic diseases in children, controlled trials are needed to truly define the role UDCA may have with regards to the treatment of pruritus. However, in view of the beneficial effects noted in preliminary studies, Balisteri (1997) stated that UDCA should be the drug of choice for pruritus in Alagille syndrome. This could also apply to other causes of chronic cholestasis such as PFIC, biliary atresia or idiopathic intrahepatic cholestasis, especially when other medical treatments, including cholestyramine have failed. As demonstrated in the study by Balisteri (1993), dose should be increased and adjusted until a decrease in pruritus is obtained and UDCA treatment could also be combined with partial external biliary diversion for the more refractory cases.

Rapporteur's Comments
Both MAHs provided a comprehensive summary of available data on UDCA's efficacy in reducing pruritus in various cholestatic liver diseases in children. The rapporteur considers that the currently available evidence suggests some efficacy in these conditions, especially in Alagille syndrome and PFIC. However, following thorough review of the submitted studies, UDCA's efficacy in reducing pruritus is not considered consistent and robust enough as in some studies only 20% of patients reported improvement of pruritus and in some cases even worsening of pruritus was observed. Therefore the rapporteur concluded that the use of UDCA can not be routinely recommended at present for the treatment of pruritus in paediatric cholestatic liver diseases. Issue resolved.

3) Discussion of the evidence available highlighting the long-term efficacy and safety outcome of UDCA treatment of paediatric hepatobiliary disorder associated with cystic fibrosis

MAH 1
Long-term (≥2 years) experience with UDCA in cystic fibrosis associated hepatobiliary disorders (CFAHD)
In a study with 9 patients with long-standing CFAHD in the age range from 10 to 24 years (Reichen et al 1991, Cotting et al. 1992,) UDCA (15 – 24 mg /kg body weight/day, given in four to three divided doses) over a period of at least 2 years not only led to a sustained improvement of serum liver parameters, but also to a significant improvement of a quantitative liver function tests (BSP [sulphobromophthalein] 45 min retention test; ^{14}C-aminopyrine breath test). Elevated levels of serum bilirubin at baseline decreased under treatment with UDCA and albumin, body weight, body mass index and muscle mass (calculated from creatinin excretion) had increased significantly after two years of treatment, respectively. However, steatorrhoea did not improve. The authors of this study compared their results with that of two other studies with UDCA in paediatric CFAHD patients and found that all but one of a total of 48 patients tolerated UDCA very well. One patient in the study by Bittner complained of diarrhoea and vomiting. It was concluded that the use of high-dose UDCA appears quite safe. In another publication of the same study, Reichen et al (1991) stated that all patients felt better while taking UDCA and no side effects were reported.
Feigelson et al (1993) reported on the treatment of 15 cirrhotic CFAHD patients treated with a daily dose of 20 mg/kg body weight UDCA during a period two years (the precise duration of UDCA treatment is not reported). With the exception of one patient, who died of pulmonary failure, serum liver enzyme concentration normalised in all patients. A partial stabilisation of clinical signs and imaging were seen.
In a study with 10 patients with CFAHD (8 - 28 years of age) (Lindblad et al. 1998) no further worsening of hepatobiliary scintigraphy was observed during 24 months of treatment with 10 to 15 mg UDCA/kg body weight/day. 8 patients responded with normalisation of liver function tests and all with decreased serum levels of IgG. In one non-responder the UDCA dose was increased to 20 mg UDCA/kg/d after 12 months of therapy. Blinded evaluation of liver biopsies indicated improved liver morphology with less inflammation and/or bile duct proliferation than before treatment with UDCA in 7 patients. Only 1 patient had signs of progression of clinical liver disease. UDCA was well tolerated and no adverse effects were noted.
A more extensive report on an observational survey of CF patients of the same centre (The West Swedish CF-centre, Queen Silvia Children's Hospital, Gotenburg, Sweden, coordinating investigators: Dr. A. Lindblad, Prof. B. Strandvik) is available as a biometrical report (URC 118/CCF). Even if it is not clearly stated, it can be assumed that cases reported in the publication by Lindblad et al. (1998), as presented above, are included also in this report. CF patients who had serum liver function parameters increased for more than 6 months or

increased echogenecity on ultrasound but without cirrhosis or signs of splenomegaly with portal hypertension at baseline were included. In general, patients received treatment with 20 mg UDCA/kg body weight/d, but from 1989 to 1992 lower doses of UDCA were given; in some patients who did not respond adequately, the UDCA dose was increased up to 30 mg/kg bodyweight/d. The first section of this report concerning biopsy data aimed to show that UDCA treatment can prevent the progression of CFAHD. Biopsies were taken at baseline and after 5 and 10 years of treatment. As only few patients supplied valid biopsy data for the 10-years follow-up this data-point was not statistically analysed. UDCA treatment was to be for at least 5 years. Several biopsy-based parameters were evaluated as endpoints e.g. a fibrosis score, a score for bile duct proliferation of the portal zones, and a score for inflammation in the portal zones. Finally, 50 patients (age at inclusion ranging from 1 to 43 years; mean 13.5 ± 9.8 years) were included into the analysis. Neither the mean fibrosis score nor the mean bile duct proliferation score showed significant changes, while the mean inflammation score showed a small but significant decline, i.e. a slight improvement. Concerning the total fibrosis score and the ultrasound score, a stop of progression of CFAHD was highly significant but other parameters did not indicate a stop of progression. In a further section of the report, hepatological laboratory data (ALT, AST, GGT, ALP) of 63 patients (ranging from 0.07 to 45.5 years of age (mean 13.3 ± 9.9 years) were evaluated. In summary, with exception of ALP, the courses of the liver enzymes showed a very similar course declining significantly from high baseline values to normal values within one year of treatment which was interpreted as a stable normalisation. The decline of ALP was smaller and difficult to interpret as there are age-dependent changes in this parameter in paediatric patients. In this report, safety data were not assessed systematically, but 3 deaths were recorded among the initial 76 patients in the first section of this report. There are no reports about ADRs.

A dramatic improvement in an infant of 9 days of age with severe CFAHD has been reported under treatment with UDCA (initial dose 40 mg, reduced to 30 and later to 22.8 mg/kg body weight/day) (Scher et al. 1997). After 2 years of continuous treatment with UDCA this child was thriving with no evidence of liver or pulmonary diseases. There were no reports on adverse events.

In a prospective, randomised 2-year cross-over trial treatment (one year with placebo, one year UDCA or vice-versa) (Spray et al. 1998, 2000a, 2000b) focusing on histological changes in 21 children with CFAHD, UDCA (20mg/kg body weight daily) proved to significantly reduce the progression of portal fibrosis compared to placebo if UDCA was given in the first year of the trial when CFAHD was less advanced at baseline. There was a suggestion that chemical cholangitis had improved in the group who received UDCA early. At the end of the trial period, progression to cirrhosis was similar in both groups. This was interpreted to be due to the discontinuous treatment with UDCA. No change in nutritional status occurred throughout the trial period. Serum liver transaminases improved during treatment with UDCA deteriorating rapidly when treatment with UDCA was discontinued. It was concluded that UDCA may prevent histological deterioration in portal fibrosis if started early and given without interruption. In an unpublished manuscript of the study (Spray et al. 2000b), it was reported that UDCA treatment was well tolerated and no side effects of UDCA therapy were seen during the study.

Colombo et al. (1999) evaluated the effects of long-term treatment with UDCA in 36 CFAHD patients (mean age 10 years, range 3 – 31 years), and compared patients with a normal (18) and those (18) with delayed time of intestinal visualization (TIV) at baseline hepatobiliary scintigraphy (TIV reflects intra-and extra-hepatic biliary drainage). The mean treatment duration of the treatment period was 4.8 years (range 2 – 8.3 years) in those with normal TIV and 5.3 years (range 0.9 – 8.4 years) in those with delayed TIV. Mean serum concentrations of ALT and GGT decreased significantly in both groups. TIV decreased significantly only in those with initially delayed intestinal visualization. Treatment failure (lack of biochemical response [AST, ALT, GGT] or occurrence of a clinical relevant event [death, liver transplantation, development of major complications or signs of cirrhosis] occurred in 61% of patients with normal TIV and in 22% of the patients with initially delayed TIV. Clinically relevant adverse events developed in

39% of the patients with normal TIV and in 6% of the patients with initially delayed TIV. Treatment with UDCA was followed by improvements of serum liver enzyme levels, which normalised in 54% of the patients with initially abnormal levels. Elevated liver enzymes were present at the final evaluation in 50 % of the patients with initially normal and in 22% of the patients with initially delayed TIV (ns). A sustained biochemical response was associated with a lower risk of developing clinical relevant events or portal hypertension. Patients with normal liver enzymes at baseline did not develop any biochemical alteration during the follow-up. No drug-related adverse event (other than treatment failure) was reported.

Colombo et al. 2001 report on the long-term effects of UDCA in a significant number of CFAHD patients who had been treated for a median period of 6 years. Response to UDCA, defined as complete biochemical normalisation without any evidence of progression of liver disease occurred in 60% of the treated patients. Biochemical response appeared to predict a benign clinical outcome at long-term follow-up. After one year of treatment, liver biochemistry was normal in 36/57 patients, 32 of whom proved to be responders to long-term UDCA treatment, whereas only four were non-responders. In addition, none of the patients with biochemical liver disease who experienced liver-related events achieved biochemical normalisation by end of the first year. Thus, lack of biochemical normalisation on UDCA treatment appeared to be correlated with progression of liver disease. The presence of cirrhosis before starting UDCA therapy was found to be predictive of treatment failure, indicating the importance of starting treatment early in the course of the disease. The only other baseline characteristic associated with treatment failure was the scintigraphic picture of apparently normal biliary drainage. No side effects of UDCA were reported. The data were interpreted in the sense that UDCA treatment may be able to slow, but not to to completely halt the progression of CFAHD. It was concluded that, although larger series of patients and longer follow-up periods are needed to achieve definitive conclusions, in view of the safety and relatively low costs of UDCA, its administration appears justifiable in all CF patients with documented liver disease.

A more extensive report on an observational survey on phases longer than 335 days of treatment with UDCA of CF patients presenting between 1988 and 2007 in the same centre (U.O.C. Centro Fibrosi Cistica, Milano, Italy, coordinating investigator: Prof. C. Colombo) is available as biometrical report (Report URC 117/CCF). Even if it is not stated particularly it can be assumed that cases reported in the publications by Colombo et al., presented above, are included again in this report. Treatment with UDCA was regularly started in patients with CFAHD and all UDCA treated patients with CFAHD at the centre with an appropriate documentation were included in the survey. If a patient had UDCA treatment for several phases, only data of the longest treatment phase were selected for analysis. In addition, periods with concomitant treatment with taurine or with taurine-UDCA were excluded. While laboratory values were assessed at almost every visit, scintigraphic, spirometric and ultrasonic parameters were assessed less frequently. The survey did not specifically aim at safety issues, but adverse drug reactions (ADR) documented in the patient files were registered. Of a total of 101 CF patients, 91 were treated with UDCA (20 mg/kg body weight/day) and 59 patients were included in the efficacy analysis. The mean age at the start of the observed UDCA treatment phase was 9.4 ± 6.5 years; the mean age at the end of the observed treatment phase was 15.6 ± 7.3 years. The mean time under continuous UDCA treatment was 6.2 ± 4.1 years ranging from 1.26 to almost 18 years. The largest and fastest beneficial effects were observed in the liver enzyme parameters (ALAT, ASAT, GGT and AP) declining from pathologically high baseline values to lower follow-up values. Thus, a stable normalisation of liver parameters due to UDCA treatment was observed. The courses of scintigraphic values indicate a discontinuation of disease progression. The pulmonary function parameters showed large interindividual variance but neither a trend towards worsening nor improvement during the first 5 years. 7 deaths were observed within this survey which comprised a total of 101 patients. All deaths occurred in patients who were treated with UDCA. 1 patient committed suicide and 5 patients died due to cystic fibrosis. One patient died because of hepatic failure due to biliary atresia not associated to cystic fibrosis. Hence, no patient who received UDCA treatment died due to CFAHD. No ADRs

of UDCA were recorded in the whole sample. It was concluded that no evidence for doubt in the safety of UDCA was observed in this survey.
Kappler et al. (2001) observed a consistent normalisation of the liver function parameters (AST, ALT, GGT and GLDH) in 53% of a total of 58 patients (mean age 15.4 years, range 1 month – 36 years) with CFAHD after 6.5 years (range 1 – 11.8 years) of treatment with 20 mg UDCA/kg body weight/d . Only one patient who was non-compliant to the treatment with UDCA developed portal hypertension. No side effects with UDCA were reported. The disease course of the UDCA treated patients were compared to a historic cohort of 9 CFAHD patients before the benefits of UDCA therapy in CFAHD became known. Comparing the disease course of the untreated to the UDCA-treated CFAHD patients, the liver protective effects of UDCA become obvious. It was concluded that treatment with UDCA delays severe liver disease with portal hypertension in CFAHD patients. The authors recommend UDCA therapy at least in patients with high risk of liver disease, such as those with meconium ileus or postpartal elevated liver enzymes.
A more extensive report on an observational survey of CF patients of the same centre (Dr. v. Hauner Children's Hospital; University of Munich, Germany, Coordinating investigators: Dr. M. Kappler, Prof. M. Griese) is available as biometrical report (Report URC 116/CCF), Report URC 116/CCF Addendum Lung Function. Even if it is not stated particularly it can be assumed that cases reported in the publication by Kappler et al. (2001), presented above, and are included again in this report. This observational survey reports on a total of 382 CF patients attending a single centre between 1989 and 2006 in whom a continuous treatment with 20 mg UDCA/kg body weight/day was rigorously initiated if one or more serum liver enzymes (GLDH, AST, ALT, GGT) were elevated ≥ 1.5 fold above the upper limit of normal over a period of at least 6 months. 98 patients with CFAHD were included in this survey (safety analysis set), 87 of whom were considered to be compliant to the treatment with UDCA and thus were included in the efficacy analysis set. The age range at the start of the UDCA treatment in patients in the efficacy set was in the range from 0.6 to 36 years (mean 14.46 ± 7.79 years). The patients were under UDCA treatment and under observation for a range of 1 to 17 years (mean 8.43 ± 4.2 years). Efficacy evaluation comprised serum concentrations of liver enzymes, thrombocyte counts, lung function (FEV-1%) and body growth (weight for height) which were assessed during annual routine visits. All serum liver parameters showed very similar courses i.e. a significant decline from pathologically high baseline values to lower follow-up values and a stable normalisation of these parameters due to UDCA treatment could be shown. Thrombocyte counts indicating long persisting liver disease, declined only non-significantly. However, there was a significant evidence for a worsening of lung function after 10 years but not after 5 years. Given that CF is an irreversible, progressing and chronic disease the small decline in FEV-1% observed in patients under UDCA treatment appears to indicate a rather stable lung function according to the authors of the report. A significant increase in weight for height scores was observed under UDCA treatment and in general the patients included in this survey were even slightly higher in weight compared to the healthy normal sample. An additional non-randomised matched pairs comparison with CF patients without hepatobiliary disorders (i.e. without UDCA treatment) indicated that in both groups lung function declined slowly but constantly over time and this progression was not affected by UDCA treatment. The average rate of ADR was 0.0061 per year and patients, i.e. very low. No serious or severe ADR were observed. The results from the biometrical report URC-116/CCF combined with a comparison with a historical cohort of untreated patients were published very recently (Kappler et al., Alimentary Pharmacology and Therapeutic June 2012): The comparison with the untreated cohort showed that overt liver disease developed in only one of 382 patients who were treated with UDCA for increased serum liver enzymes compared to nine patients in the historic control group ($p < 0.05$). Serum liver enzyme levels declined in most patients receiving UDCA treatment during the follow-up. No difference was seen in lung function between subjects with CFAHD and the matched controls without hepatobiliary disorders due to CF. Based on these results it was concluded that regular and systematic screening for liver involvement enables early introduction of UDCA therapy in affected cystic fibrosis patients, reduced the development of severe liver disease and leads to a

significant and persistent improvement in serum liver tests, without impairing long-term pulmonary outcome.

Nousia-Arvanitakis et al. (1998, 2001) describe an observation period of 12 years in patients with CFAHD (2 – 29 years of age). 7 patients with nodular biliary cirrhosis (NBC) were treated with UDCA (20 mg/kg body weight/day) for 10 years. 70 patients, 30 of them with focal biliary cirrhosis (FBC) were also treated with UDCA. During the observation period before the start of the UDCA treatment, the progression rate from FBC to NBC was about one patient per year. In the patients with initial NBC, liver enzymes (GGT, ALT, AST) had returned to normal within 1 year and remained normal throughout the study during treatment with UDCA. No hepatic complication developed during the period of 10 years. The size of liver and spleen decreased, but hepatosplenomegaly persisted. In 30 patients with initial FBC, there was no further progression from FBC to NBC after the start of the treatment with UDCA over the 10-year period. Ultrasound examination of the liver showed an increased number of patients with normal findings and the number of patients with FBC decreased from 30 to 1. 62 of 70 patients with CFAHD had normal hepatic parenchyma on ultrasound examination, normal hepatic function and clinical evidence of liver involvement. One patient having normal hepatic echogenicity demonstrated focal lesions near the completion of the study. The effectiveness of UDCA on his focal lesions was not evaluated. No side effects with UDCA were reported.
A more extensive report of an open-label, non-comparative long-term observational survey of CF patients treated continuously for at least 335 days with UDCA of the same centre (Department of Pediatrics, Aristotetle University of Thessaloniki, Greece, Coordinating investigators: Dr. M. Fotoulaki, Dr. P. Panagopoulou, Prof. S. Nousia-Arvanitakis) is available as biometrical report (Report URC 120/CCF). Even if it is not stated particularly it can be assumed that cases reported in the publications by Nousia-Arvanitakis et al. (1998 and 2001), presented above, are included also in this report. Treatment with 20 mg UDCA/kg body weight/d was regularly started in CF patients with evidence of liver disease according to ultrasonographic examination independent of the serum concentrations of liver parameters (which indeed was within the normal range at baseline in many patients). Serum concentrations of ASAT, ALAT and GGT were the main efficacy parameters and were usually assessed twice a year. Data of 75 patients with CFAHD were captured, 45 of them received UDCA treatment (safety analysis set) and 34 had an evaluable UDCA treatment phase (≥ 335 days) (efficacy analysis set) and 29 were compliant to the treatment. The mean age at the start of UDCA treatment was 12.4 ± 5.9 years, ranging from 0.2 to 27.9 years. The duration of evaluable UDCA treatment phases ranges form 1.2 to 15.8 years (mean 8.3 ± 4.7 years). The decrease from abnormally high ALAT and ASAT values to normal values after UDCA treatment of 1 to 10 years was significant. Changes in GGT were not statistically significant. The efficacy analysis showed statistically more cases of improvement than cases with worsening from baseline to all follow-ups. There was a strong evidence for a beneficial effect of UDCA for the 1- and 2-years follow-ups. Hardly any patients were at risk of worsening of their liver enzyme values. 7 patients died after the initiation of UDCA treatment. No patient died because of CFAHD. Three patients died because of CF. The causes of death of the remaining patients were unknown. No ADRs of UDCA were recorded.
Kapustina (2003) demonstrated in a 2-years study with 25-30 mg UDCA/kg b.w./day a normalisation of the serum alkaline phosphatase (AP) values in 70% of the patients after 1 year of treatment. Further results were the decrease of the ultrasound echogenicity of the biliary tract and of the content of the gallbladder significantly ($p<0.01$) after 1 year in CF patients with liver cirrhosis. In addition, there was a change of the serum phospholipid composition with an increase of the serum phosphatidylcholine and a decrease of the phosphatidylethanolamine concentration which might have an impact on membrane fluidity and cytoprotection. There were no reports on adverse events.
Desmond et al. (2007) describe 22 adult CFAHD patients (mean age at diagnosis of CFAHD: 23 years, range 8-47 years, diagnosis of CFAHD during childhood in 10 pts.), 67% of them with portal hypertension who were treated with a median daily dose of 11.3 mg UDCA/kg body

weight (range 7 – 22 mg/kg, titrated according to symptomatic and/or biochemical responses) for a median duration of 3.6 years. Administration was associated with an improvement in hepatobiliary symptoms including pruritus, fatigue and right upper quadrant pain which were prevalent in 50% of the patients in the pre-UDCA period but persisted only in 4% after the UDCA treatment. In addition, UDCA therapy was associated with a significant reduction in serum liver transaminases and alkaline phosphatase. Concerning safety it was stated that no severe side effects were reported. Two patients described pruritus transiently associated with the introduction of UDCA. This resolved with ongoing use and did not require dose adjustment.

Similar to biometrical reports survey on UDCA treatment in CFAHD patients presented above (URC-116/CCF, URC-117/CCF, URC-118/CCF and URC-120/CCF) there is an additional report on an open-label, non-comparative, long-term observational survey of CFAHD patients treated with UDCA between 1997 and 2007 form the university hospital in Stara Zagora, Bulgaria (coordinating investigator: Prof. K. Kalinova; Report URC-119/CCF). UDCA treatment was regularly started in patients with CFAHD, diagnosed by elevated liver enzymes and/or according to ultrasound examination. Patients were included if they had been treated with a daily dose of 15 – 20 mg UDCA/kg body weight for at least 335 days. Besides standard laboratory parameters, assessed during routine visits (ALAT, ASAT, GGT, AP and bilirubin), pulmonary function (FEV1, FVC) and portal vein enlargement, splenomegaly, hepatomegaly measured by ultrasonography were assessed. This survey did not aim specifically at safety issues, but ADRs documented in patient files could be registered in the study database. 40 CFAHD patients were treated with UDCA and were included in the safety analysis. 37 of them had adequate evaluable treatment phases with UDCA and were included into the efficacy analysis. Mean age at onset of the UDCA treatment was at 13.2 ± 4.0 years. The duration of evaluable UDCA treatment phases varied form 1.2 to 9.3 years (mean 4.3 ± 2.0 years). The most pronounced and fastest beneficial effects of UDCA treatment were observed in liver enzyme parameters. All of them declined significantly from pathologically high levels at baseline to lower values at follow-up visits. ALAT, ASAT and GGT showed ongoing declines during the whole observational period, while bilirubin and AP showed a distinct drop from baseline to significantly lower plateau during the remaining observational period. Results concerning pulmonary functions were inconsistent. FEV1 showed a significant worsening of lung function, while FVC showed no significant changes from baseline up to 2 years follow-up, but a significant improvement from baseline to 5 years follow-up. There was a significant reduction of liver enlargement from baseline to all follow-ups. Two deaths were observed. One patient died because of CF and CFAHD. The cause of the second patients was unknown. 4 cases of ADR were documented (3 cases of vomiting and one case of headache), all occurring in the beginning of the UDCA treatment. In summary, considerable improvement was observed over time under UDCA treatment in all variables related to liver function. Although this was an observational, single arm survey without a control group, the data suggest that the improvements can be attributed largely to the treatment with UDCA.

Reviews on UDCA treatment in CFAHD

In their review on UDCA treatment in CFAHD Colombo et al (2001) state that treatment with UDCA aims at improving biliary secretion in terms of bile viscosity and bile acid composition. Besides liver transplantation, UDCA is the only available therapeutic option in this condition. According to the authors, treatment with UDCA is virtually devoid of serious side-effects. Evidence has been provided of the short-term efficacy of UDCA in CFAHD, in terms of improvement of liver biochemistry, hepatic excretory function and biliary drainage, histology and the status of essential fatty acid. However, the short duration of the randomized controlled trials carried out so far has not allowed a definitive conclusion on the long-term effects of treatment, particularly its ability to improve survival, reduce the need for liver transplantation or to delay development of complications of cirrhosis and portal hypertension.

In a later review on CFAHD performed by the same group of authors (Colombo et al. 2006), the assessment of the role and significance of UDCA in the management of this disorder is

confirmed: Oral bile acid therapy with UDCA is considered to be currently the only available therapeutic approach for CFAHD and it is free of serious side effects. The various well established effects of UDCA treatment are summarised in the table below. However, it is pronounced that its impact on the natural course of CFAHD remains to be defined. The optimal UDCA dose is said to be 20 mg/kg/day. It is recommended that UDCA should be administered on a regular and probably life-long basis in CF patients. Asymptomatic patients with early stage CFAHD are more likely to benefit from UDCA administration. The long-term effectiveness of UDCA treatment on clinically relevant outcomes should be further investigated.

Effects of UDCA in CFAHD

Effect on	Comment	Evidence
Liver biochemistry	Consistently improved	RCT*
Quantitative liver function	Improvement not consistently maintained	Open studies
Biliary drainage	Often normalized	Open studies
Liver histology	Decrease in bile duct proliferation inflammation, fibrosis	RCT*
Fat absorption	No effect	RCT*
Nutritional status	Improvement in severely malnourished patients	Pilot studies
Essential fatty acid status	Improvement in essential fatty acid deficiency	RCT*
Liver transplantation	No data available	
Mortality	No data available	

*Randomized controlled trials

Source: Colombo et al. 2006

Guideline Recommendations on UDCA treatment in CFAHD

With respect to treatment of patients with CFAHD with UDCA the clinical practice guidelines on the management of cholestatic liver diseases by the *European Association for the Study of the Liver (EASL)* the following can be found (excerpt): “No therapy of proven benefit for long-term prognosis of CFAHD exists. UDCA at doses of 20 – 30 mg/kg body weight/d has been shown to consistently improve serum liver tests, to stimulate impaired biliary secretion, to improve histological appearance (over 2 years) and nutritional status. The optimal dose of UDCA and its impact on survival in cystic fibrosis remain to be established. UDCA in a dose of 20 to 30 mg/kg body weight/d is recommended for the improvement of serum liver tests and histological parameters in CFAHD.” There is no restriction to patients in age groups (i.e. to paediatric patients or to adult patients) in these guidelines.

In the most recent *Best Practice Guidance for the Diagnosis and Management of Cystic Fibrosis-associated Liver Disease* (Debray 2011), it is recommended to initiate UDCA therapy as soon as the diagnosis of pre-symptomatic signs of cystic fibrosis associated liver disease during annual screenings is made, with the aim to halt or delay disease progression. An initial daily dose of 20 mg/kg is recommended. A therapeutic schedule based on multiple divided doses (at least twice a day) seems to be advantageous because of incomplete intestinal absorption of larger doses. Evaluation of indices of cholestasis and cytolysis should be performed 3 and 6 months from initiation of therapy to test for the efficacy of UDCA and the dose should be increased if necessary. No significant side effects related to the long-term use have been

reported. Again, there is no recommendation about the duration of treatment with UDCA in this indication.

In summary, the recommendations for the use of UDCA for the treatment of CFAHD in both guidelines presented above do not refer to age groups of patients. It is clear from what is stated in these guidelines, that CFAHD develops primarily (if not exclusively) in paediatric CF patients. Treatment with UDCA should start as soon as hepatobiliary disorders associated with CF are diagnosed, implicating that in most cases UDCA treatment should be started in childhood.

MAH 1's conclusion

UDCA is currently the only medicinal option for the treatment of CFAHD. Continuous treatment with adequate doses of UDCA has shown to result in sustained effects on liver function parameters and biliary drainage is often normalised. There is some evidence that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepato-biliary changes if given in early stage of CFAHD. The most effective initial dose appears to be 20 mg UDCA/kg body weight/day. In patients who do not respond sufficiently with this dose, a trial has shown that a dose increased up to 30 mg UDCA/kg body weight/day was effective in a considerable number of patients who did not respond to the initial dose. From clinical studies there is experience with long-term UDCA treatment for 10 years and more. Experts recommend life-long treatment with UDCA in CFAHD patients although its effects on the natural course of CFAHD, mortality or the need for liver-transplantation need to be further defined. There is no evidence for attenuation of its beneficial effects nor for any specific safety impact with long-term use. Treatment with UDCA should be started as early as first signs for CFAHD are diagnosed. However, based on the experience of the studies presented, the beneficial effects of UDCA treatment in patients with advanced CFAHD and liver cirrhosis may be restricted to improvements of liver function parameters. From the experience of the studies presented above, it appears that the treatment of CFAHD patients with UDCA in the recommended dose range is safe and well tolerated. Side effects are rare and there is no evidence of serious adverse events.

However, MAH 1 concluded that due to the recently reported safety concerns with high-dose long-term UDCA use in PSC patients it is not recommended to use UDCA in doses beyond 20 mg/kg body weight (see response to issue 9, below) as long as this issue is not solved.

MAH 2

Evidence highlighting the long-term use (1 year or more) of UDCA in the pediatric population with cystic fibrosis-liver disease (CFLD) is limited. Evidence comes mainly from studies that have evaluated long-term treatment with UDCA in cystic fibrosis patients with liver disease by including a mixed population of both children and adults so that it is difficult to really assess its long-term effects specifically in children. There are only four (4) published reports of long-term treatment with UDCA in the pediatric population exclusively (< 18 years old). These are summarized in the table below.

Description of studies evaluating long-term UDCA treatment of CF-associated liver disease in children (paediatric patients exclusively)

Reference	Study type	# of pts; age	Inclusion criteria	Dose and duration	Endpoints	Efficacy results	Safety results	Authors' conclusions
Lepage 1997	Prospective, double-blind, placebo-controlled, cross-over plus LT - extension	N=19 (13 M, 6 F); 11.9 ± 0.6 yrs (range 7 – 17 yrs)	Criteria for liver dysfunction : abnormal findings on at least 2 LFTs (ALT, AST, GGT) and abnormal findings on abdominal US and/or liver biopsy	Starting dose of 15 mg/kg/day increased to 30 mg/kg/day in the absence of a 50% decrease of ALT and/or AST within 2 months of treatment; 1 year duration for the DB period (two periods of 6 months each) plus LT extension of 25 months (range 16 to 39 months)	Status of essential fatty acids (EFA) and fat-soluble vitamins	↓ in plasma triglyceride and cholesterol levels after 6 and 25 months of treatment; beneficial effect on EFA status by improving the EFA deficiency index; no change in vitamin E levels but improvement in retinol status	No side effects reported during adminis-tration of UDCA for up to 39 months	UDCA alters lipoprotein metabolism by improving the EFA and retinol status of pediatric patients with CFLD
Scher 1997	Case reports	N=2 (9 days and 6 weeks)	Two (2) severely cholestatic infants with CF and evidence of cholestasis, duct proliferation and portal fibrosis on liver biopsy	Pt 9 days old treated with 40 mg/kg/day and Pt 6 wks old with 30 mg/kg/day on a long-term basis	Not applicable	At 2 and 3 years of age, respectively, the 2 children had no signs of liver disease under constant UDCA treatment	No data provided	UDCA results in functional improvement in infants with CF-associated hepatobiliary disease. Because of its relatively low cost and wide therapeutic index, UDCA treatment should be considered at

Reference	Study type	# of pts; age	Inclusion criteria	Dose and duration	Endpoints	Efficacy results	Safety results	Authors' conclusions
								the earliest sign of CF-associated liver disease.
Spray et al., 2000; and unpublished data provided in Rappor-teur's preliminary assessment report of March 2012	Prospective, randomized, double-blind, placebo-controlled cross-over study	N=18 (11 M, 7 F); mean age 10.3 yr (range 6.3 – 17.1 yr)	Children with hepatomegaly / hepato-splenomegaly and/or abnormal LFTs on 2 occasions over a 6-month period	20 mg/kg/day versus placebo for one year each; Group A (n = 8): Placebo one year, then UDCA one year; Group B: UDCA one year then Placebo one year	Histological changes as measured by liver biopsy at entry, cross-over and completion; cirrhosis noted as well as scores for steatosis, portal fibrosis and cholangitis	4/8 (Group A) and 4/10 (Group B) had cirrhosis at baseline and did not improve during the trial; at 2 yrs, deterioration seen in steatosis and portal fibrosis in patients who had received UDCA late (Group A) compared to those who had received UDCA earlier (Group B) and the treatment effect of UDCA on the progression of portal fibrosis was significant if UDCA was given during the 1st year of the trial (Group B) ; chemical cholangitis improved at 2 yrs in Group B (NS)	No data provided	UDCA may moderate chemical cholangitis, portal fibrosis and steatosis if given early enough in the course of CFLD, but has no effect on progression of cirrhosis
Siano 2010	Retrospec-tive evaluation of patients from a CF Care Center Database	N=26; UDCAe: N = 14 (7 M, 7 F); UDCA d: N = 12 (9 M, 3 F)	Children diagnosed with CF by meconium ileus (MI) at birth	Mean dosage of 15 mg/kg/day; UDCAe treated by UDCA before 2 months of age; UDCAd treated with UDCA only at the onset of liver disease; 23	Prevalence of CFLD defined on the basis of clinical signs (hepato-megaly), abnormal liver	None of the patients treated early developed CFLD during the F/U period, while 33% of the group treated only at the onset of signs and symptoms developed CFLD	No data available	Despite the small number of subjects evaluated in this trial, results suggest that UDCA may slow the

Reference	Study type	# of pts; age	Inclusion criteria	Dose and duration	Endpoints	Efficacy results	Safety results	Authors' conclusions
				patients were strictly monitored until 9 years of age and the 3 others for a mean F/U of 48 months	biochemistry (↑ of at least 2 serum liver enzymes above the ULN) and abnormal ultrasono-graphic findings (↑ echogenicity, nodularity, irregular margin, splenomegaly) recorded on 2 consecutive examinations within a 3-month period			progression of liver disease in the pre-cirrhotic stage; prospective multicenter trials are needed to define the timing for the preventive role of UDCA therapy

The data from these 4 reports suggest that long-term UDCA treatment in children with signs and symptoms of cholestatic liver disease may partially improve nutritional status, and slow or halt the progression of the disease or even reverse it. In infants with meconium ileus, a known predisposing factor for CFLD, it may even prevent the occurrence of the cholestatic liver disease.
The positive results from this limited number of studies in children are in line with those from uncontrolled studies performed in a mixed population of children and adults being treated with UDCA on a long-term basis for at least one year to evaluate the effect on nutritional status: Colombo 1996 (1 year); Cotting 1992 (1 year) or progression of liver disease: Colombo 2001 (1 year); Lindblad 1998 (2 years); Kappler 2001 (6.5 years); Nousia-Arvanitakis 1998 (8 years) and Nousia-Arvanitakis 2001 (10 years). All these studies showed improvement in nutritional status or a beneficial effect on the progression of liver disease with UDCA treatment being free of relevant side effects.
In the study by Colombo (2001), UDCA at a dose of 20 mg/kg/day improved hepatic excretory function and biliary drainage in the majority of patients with the exception of those already presenting with cirrhosis for which treatment with UDCA did not have any effect. Lindblad (1998) reported a decrease in inflammation, bile duct proliferation and fibrosis in patient treated with UDCA at a dose of 10-15 mg/kg/day and Kappler (2001) have shown that UDCA at a dose of 20 mg/kg/day delayed the development of severe liver disease with portal hypertension. Kappler (2001) have also observed a tendency for patients with meconium ileus or postpartal elevated liver enzymes to show continuous liver enzyme elevations significantly earlier in childhood compared to other CF patients developing CFLD.
The most striking results are probably those obtained in by Nousia-Arvanitakis (1998, 2001) where patients with CFLD were treated for 8 to 10 years at a dose of 20 mg/kg/day. In these reports, patients with CFLD were already suffering from focal or nodular biliary cirrhosis at the beginning of UDCA treatment. After the administration of UDCA, the progression of nodular biliary cirrhosis ultrasound changes was arrested, hepatic function was preserved, and no variceal bleeding was observed. No case of focal biliary cirrhosis progressed to nodular biliary cirrhosis. Furthermore, the multifocal, multilobular changes suggestive of focal biliary cirrhosis on ultrasound scan were reversed to normal.

MAH2's conclusion
Larger series of patients would be needed to achieve definitive conclusions, both in children or adults with CFLD. These could not be placebo-controlled trials due to ethical considerations. In view of the safety of UDCA and the life-threatening condition of end-stage liver disease, it seems reasonable to consider long-term treatment with UDCA, especially in view of the promising results demonstrated so far in clinical trials in CFLD. Treatment should be initiated as soon as possible, after diagnosed hepatobiliary disease, in order to try to stop progression of the disease. Further trials should be conducted in children at risk of developing CFLD, such as those with meconium ileus at birth or postpartal elevated liver enzymes, in which cases treatment with UDCA may even prevent the development of hepatobiliary disease.

Rapporteur's Comment
Both MAHs provided a comprehensive summary of the available data on UDCA's long term use (≥2 years) in children with cystic fibrosis. The rapporteur agrees with the MAHs' conclusion that continuous treatment with adequate doses of UDCA was proven to have sustained positive effects on liver function parameters and biliary drainage. In addition, there is some evidence that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepato-biliary changes if given at an early stage of cystic fibrosis associated liver disease (CFLD); however this evidence is not considered robust enough and further studies are deemed necessary. Nevertheless, it can be concluded that treatment with UDCA should be started as soon as CFLD is diagnosed as it appears from the presented studies that if UDCA was started when CFLD has advanced and liver cirrhosis developed, the

beneficial effects may be limited to improvements only in liver function parameters and not in actual histological changes. Based on the above presented data the rapporteur also considers that UDCA was proven to be safe and well tolerated when used long term at a dose of 20-30 mg/kg/day in paediatric patients with cystic fibrosis.

In summary, the rapporteur considers that the currently available evidence supports UDCA's use in children (1 month-18 years) with hepatobiliar disorder associated with cystic fibrosis to improve liver function parameters and biliary drainage. MAH 1's proposal to include the currently available information on UDCA long term effects in the paediatric population in section 5.1 of the SmPC is fully supported. MAH 1's proposed wording is also considered acceptable with minor changes:

5.1 Pharmacodynamic properties
Paediatric population
Cystic fibrosis:
From clinical reports long-term experience up to 10 years and more is available with UDCA treatment in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepato-biliary changes if given ~~in~~at early stage of CFAHD. Treatment with UDCA should be started as soon as the diagnosis of CFAHD is made in order to maximize treatment effectiveness.

Regarding the posology recommendations for children with cystic fibrosis associated hepatobiliary disorders please refer below to point 9.

4) Use of excipients in UDCA suspensions

MAH 1
UDCA 50 mg/ml suspension is a mono-preparation containing ursodeoxycholic acid as the active ingredient. The active ingredient is obtained via a semi-synthetic route and its action is well-known. Since 1998 there is a final monograph on the substance in the European Pharmacopoeia.
MAH 1 provided the following expert statement:
The preparation contains several widely used excipients. The MAH has many years of experience in dealing with products containing bile acids.

Justification of choice of excipients
The aim of the development was to design an alternative UDCA-containing oral formulation that was suitable for those with swallowing difficulties (e.g. the elderly, children) and which would also enable easy and finer adjustment of dosage to the needs of the individual patient. Therefore a multidose container was chosen and a measuring device for individual dosage was added (1.25ml- 2.5ml- 3.75ml- 5ml). As a multidose preparation containing water and sweeteners, the suspension must contain a preservative. Benzoic acid was chosen for this purpose which is known for its good compatibility based on an AD1 (= acceptable daily intake) of 5mg benzoic acid per kg body weight. A very low dosage of 1.5mg benzoic acid/ml suspension was established, for which effectiveness was proven by many stability experiments including challenge tests according to EP performed with drug product at the beginning and end of its shelf life.
A second challenge was to mask the natural bitter taste of the bile acid (UDCA) avoiding sugar, while giving the patient an acceptably tasting product increasing treatment compliance.

Therefore the drug substance was kept in suspension using water as a solvent. Avoiding cariogenic excipients, the sweetener sodium cyclamate was chosen besides the sugar substitute xylitol. Sodium cyclamate has an AD1 of 7mg per kg body weight and is described in an EP monograph.
Finally propylene glycol was used as a solubiliser for the lemon flavouring which contributes as part of the flavouring system in the formulation to the well tolerable taste.
This formulation is on the market for many years starting in June 1999 (Germany, MA number 39200.00.01) since then proving its efficacy and safety. The formulation is covered by a patent of formulation (No. EP 0 640 344) which also includes the specific excipients. Moreover exchanging 3 out of 11 excipients including the preservative would gravely modify the formulation on the level of a major change which may in some countries even trigger an additional bioequivalence study.

Regulatory considerations
Benzoic acid: According to the current EU-Guideline "Excipients in the label and package leaflet of medicinal products for human use" the following warning "May increase the risk of jaundice in newborn babies" has to be given only in the leaflet for parenterally administered drug products. No warning is suggested for orally applied drugs. Although UDCA suspension was just recently registered in some EU countries (e.g. in Ireland in January 2011 and in Cyprus in September 2010) no concern was raised with regard to the content of benzoic acid. Dosage recommendation for children starts at a level of 5 kg in these countries. In children suffering from cystic fibrosis (CF) and weighing ca. 6 kg the recommended daily dose of UDCA suspension would be 0.5 cup per day (= 20mglkglday UDCA), corresponding to 2.5 ml (= 3.75 mg benzoic acid), which corresponds to a daily dose of 0.625 mg/kg/day benzoic acid. This is well below the WHO AD1 of 5mglkglday.

Sodium cyclamate: The current EU-Guideline "Excipients in the label and package leaflet of medicinal products for human use" does not contain any warning with regard to sodium cyclamate. In children suffering from CF and weighing ca. 6 kg the daily dose of UDCA suspension would be 0.5 cup per day, corresponding to 2.5 ml (= 12.5 mg sodium cyclamate), which corresponds to a daily dose of 2 mg/kg sodium cyclamate. This is also below the WHO AD1 of a maximum of 11 mg/kg/day.
Moreover, sodium cyclamate is still listed in FDA's (drug) Inactive Ingredient Database. UDCA suspension (same formulation as in Europe) is at the moment under development in the USA for the indication CF. Up to now the FDA has not raised concerns with regard to the excipients including sodium cyclamate.

Overall sodium content: With regard to the overall sodium content the following information is given in Section 4.4 of the SPC: "One cup (= 5 ml) UDCA suspension contains 0.50 mmol (11.39 mg) sodium. This has to be taken into consideration by patients on a controlled sodium (low sodium chloride) diet."

Propylene glycol: In the current EU-Guideline "Excipients in the label and package leaflet of medicinal products for human use" the following warning "May cause alcohol-like symptoms" is given for orally administered drugs containing 400mg/kg in adults or 200mglkg or more in children. One cup UDCA suspension contains 50 mg propylene glycol. In children suffering from cystic fibrosis (CF) and weighing ca. 6 kg the recommended daily dose of UDCA suspension is 0.5 cup per day (= 20mglkglday UDCA), corresponding to 2.5 ml (= 25 mg propylene glycol), which corresponds to a daily dose of 4.167 mg/kg propylene glycol. This again is far below the dose mentioned in the EU Guideline and well below the WHO AD1 of 25mg/kg/day. Based on these considerations the benefit/risk assessment with respect to the excipients used in UDCA suspension is positive even for young children.

MAH 2
Not applicable. No UDCA marketing authorization in suspension is currently held by MAH 2.

Rapporteur's Comment
MAH 1's expert statement provides sufficient justification for the choice of excipients addressing both quality and regulatory considerations for paediatric use. The amounts of excipients also remain within the recognized paediatric safety margins when doses of 20-30 mg/kg/day are used. The rapporteur shares MAH 1's conclusion that the benefit/risk assessment with respect to the excipients used in UDCA suspension is positive. Issue resolved.

5) Paediatric pharmacokinetic data, if available

MAH 1
A literature research was performed in MedLine (PubMed) with the search profile "Ursodeoxycholic Acid"[Mesh]) AND "Pharmacokinetics"[Mesh], Limits activated: All Child 0-18 years. There was no indication of studies on UDCA pharmacokinetics in paediatric patients. Thus, no pharmacokinetic data on UDCA in paediatric patients are available.

MAH 2
Two studies related to the pharmacokinetics of ursodiol in neonates had been included in the Critical Literature Overview initially provided to the Rapporteur.
The first study (Vuong 2010) aimed to evaluate accelerator mass spectrometry (AMS) as a tool for neonatal PK modelling rather than providing PK information about UDCA. Indeed, the authors stated that "further discussion of the results or any conclusions about the behavior of neonatal biliary systems in response to small ursodiol doses is beyond the scope of this report which serves to introduce the concept of Accelerator Mass Spectroscopy (AMS) tracing ^{14}C compounds in neonates."
In a second trial performed by the same group of investigators (Baillie 2011), the pharmacokinetics of ursodiol was studied in 5 neonates. Subjects did not have cholestasis and caloric intake was parenteral. Non-compartmental analysis showed that the UDCA concentrations were dose-proportional. Compartmental analysis yielded a 3-compartment model with a gall bladder compartment. The apparent Vdist was 145 ± 31 ml; T-half was 20.3 ± 5.5 hr. The model was extended to represent cholestasis and predict changes in bile release. The authors concluded that AMS and PK/PD modeling provide validated, essential tools for neonatal PK and trial design. AMS sensitivity allows a significantly lower tracer dose and much lower sample volumes. Low intra-subject variability indicated that AMS provides useful data supporting modeling and insight into UDCA PK. High inter-subject variability implied significant physiological variability between newborns. Modeling suggested several experiments to reduce the variability. Authors concluded that the PK model constructed from AMS data could be used to study bile flux in cholestatic patients. Unfortunately, this study has only been published as a conference abstract so that only limited data are available. Therefore valuable PK data in neonates cannot be derived solely from this abreviated report. The authors specified that this was the first clinical study of ursodiol PK in neonates and that the clinical trial was still ongoing at the time of presentation at the conference. A search on Pubmed to try to find a full literature report of this study has not given any results. Since this conference presentation occurred in 2011, it is possible that a full literature report is not yet available.

No other data on the pharmacokinetics of UDCA in the pediatric population has been found as a result of further literature searches on Pubmed using the following key words: (Children OR neonates OR pediatric) AND (ursodiol OR UDCA or ursodexoxycholic acid) without any language limits.

Rapporteur's Comment
Based on the submitted evidence, the rapporteur acknowledges that the available PK data on UDCA in paediatric patients is very limited and not fully relevant. It is concluded that an update to section 5.2 is not considered necessary. Issue resolved.

6) Study URU-3/NEO: explanation of weight loss in UDCA group

MAH 1
The Rapporteur noted a steady weight loss from day 30 in the UDCA group, whereas the body weight continued to rise in the placebo group.
MAH 1 states that at study day 30, a comparable number of patients was analyzed both in the UDCA (n=13) and the Placebo group (n=10). After day 30 the arithmetic mean weight decreases in the UDCA group, but it is recognized that at day 39 this weight is based only on 3 patients in the UDCA group and only 1 patient in the Placebo group. It can also be seen that a comparable weight gain is achieved in both treatment groups at the end of study period 3. Finally, the individual patient data listing confirms that no single neonate lost weight during the study but gained weight throughout the study.
In addition, the Rapporteur noted a significant difference in the study duration between the treatment groups (UDCA group 37.4 $\pm$ 10.4 days vs.. Placebo group 50.5 $\pm$ 19.8 days). The MAH states that the duration of each study period was variable and the overall time of exposure to UDCA or Placebo ranged from first day of study medication intake (day 3 of life) until 4 to 6 weeks of life (day 28 to day 42 of life). Therefore the last possible study day is day 39 (42 – 3) but could theoretically be 14 days earlier (in this study the shortest duration was 28 days in both groups). This specific design allowed to analyze the individual time until full enteral nutrition and implicates that patients who achieve the primary endpoint only late or even not at all during the study will stay longer in the study, whereas patients with early response would have stopped the treatment earlier. Consequently, this has also implications on the body weight data when this parameter is analyzed in relation to study date.
In conclusion, the difference between the treatment groups seen in the study duration indirectly confirms the difference in time to full enteral nutrition in favour of the UDCA group.

MAH 2
Not applicable.

Rapporteur's Comment
MAH 1 provided the full study report and a clear explanation for the observed weight loss and difference in study duration between treatment groups. Issue resolved.

7) Review of the MAHs' post-marketing safety database in order to identify any paediatric safety reports since UDCA has been licensed

MAH 1
MAH 1's UDCA capsules were first approved in Germany in November 1979 (EU and international birth date). MAH 1 claims that there is no indication for safety signals of use of UDCA in paediatric patients since the set-up of their post-marketing safety base in 1997. Earlier data are not available.
A line listing has been provided by MAH 1 and described 2 non-serious adverse events.
Case 1 – Teeth stained: 5 year old female with cystic fibrosis. Relation to UDCA was reported as 'not assessable' as several other concomitant drugs were also suspected: tocopherol, retinol, ergocalciferol, phitomenadione, cefuroxime sodium, dornase alfa and pancreatin. Company considered the case 'not related to UDCA'.

Case 2 – Urticaria: 18 year old male with primary sclerosing cholangitis. Dechallange was positive. Relation to UDCA was considered 'probable' by both the reporter and the company.

MAH 2

The paediatric data included in this analysis were retrieved from reports received by MAH 2 between 10-Dec-1997 and 31-Mar-2012 inclusively. In this analysis, 32 cases with 54 events were retrieved from MAH 2's database. Among them, 18 medically confirmed cases and 14 non-medically confirmed cases were reported in the paediatric population. There were 11 cases from USA and 2 cases from France, while the majority of the reported cases came from MAH 2's partners (16 cases from Japan, 1 from Italy and 1 from Portugal). In addition, there was 1 case retrieved from a literature article in Turkey.

1. Seriousness:

Serious	Fourteen (14) cases
Non-serious	Eighteen (18) cases

2. Sources:

Solicited (clinical trials)	No cases
Spontaneous (HCP)	Five (5) cases
Spontaneous (Non-HCP)	Fourteen (14) cases
Spontaneous-literature	Twelve (12) cases
Regulatory authority	One (1) case

3. Causality assessment:

Not related	Twelve (12) cases
Related	Eighteen (18) cases
UNK	Two (2) cases

4. Age groups:

Neonatal (0 to 1 month)	No cases reported in this age group.
Infant (1 month to 2 years)	Twelve (12) cases
Children (2 to 12 years)	Ten (10) cases
Adolescent (12 to 17 years)	Seven (7) cases
Unknown:	Three (3) cases have been reported in paediatric patients without mentioning the patient's age.

5. UDCA strength:

50mg/day	2 cases
100mg/day	1 case
200mg /day	2 cases
250mg/day	2 cases
300mg/day	1 case
500mg/day	1 case
600mg/day	1 case
1000mg/day	1 case
20mg/kg/day*	1 case
Unknown	20 cases

*The weight is not available

6. Indications:

Accidental exposure	Eleven (11) cases
Autoimmune hepatitis	Two (2) cases
Hepatitis X	One (1) case
Hepatitis	One (1) case
Biliary cirrhosis	One (1) case
Cholestasis	Five (5) cases
Ciprofloxacine-induced liver disorder	One (1) case
Wilson disease with cirrhosis	One (1) case
Drug use for unknown indication	Three (3) cases
Sclerosing cholangitis	One (1) case
Idiopathic neonatal hepatitis	One (1) case
Liver disorder	One (1) case
Fatty liver disease	One (1) case
Liver pain and transaminases increased	One (1) case
Progressive familial intrahepatic cholestasis (PFIC) type 2 (due to heterozygous mutation of ABCB11).	One (1) case

7. Time to onset:

Concerning the time to onset, this information was not always available in all reports. However, in some cases it was mentioned as follows:

Case ID	*Treatment duration*	*Time to onset*	*Event*
AXC-2011-187	2 days	2 days	Erythema
URSO-2006-022	15 days	Few days later	Rash, Pruritus, Platelet count decreased * WBC count decreased * RBC count decreased*
AXC-2012-0006	1 month	1 month	Aplastic anaemia *
URSO-2007-224	8 years	8 years	Coagulopathy * Pruritus * Growth retardation *
AXC-2012-077	Unk	Same day	Pruritus

*Serious event

1. Serious cases:

Fourteen (14) cases out of 32 were considered serious, the SOC with the most frequently reported events was ``General disorders and administration site conditions`` (7 cases) in which the `` Drug ineffective for unapproved indication`` was the most frequently reported event, there were also 5 events in each of the following SOCs `` Investigations` and ``Gastrointestinal disorders`` and 4 events in the ``Skin and subcutaneous tissue disorders`` SOC.

The serious cases are detailed below. Five (5) cases were recovered/recovering, in 4 cases the outcome was unknown, in 3 cases the outcome was either fatal (1 case) or not recovered (2 cases). In 2 cases, some of the events recovered while the other continued at the time of the reports.

URSO-2004-020

This medically confirmed report described a case of a 2-year-old female patient who experienced **hypoglycemia** while being treated with UDCA for biliary cirrhosis. She had a medical history of surgery for biliary ducts atresia with sequelae of biliary cirrhosis and portal hypertension. On an unspecified date, enteral nutrition had been stopped and few weeks later, the patient was found unconscious in her bed, pale, with eyes rolled upwards, hypothermia at 35.6° C and severe hypoglycemia at 0.13 g/l. She received glucose 30% serum via perfusion and regained consciousness progressively. She was hospitalized for 48 hours without recurrence of hypoglycemia even after perfusion discontinuation and return to normal feeding. All drugs were continued unchanged. The French Medicine Agency suspected a different medication (Avlocardyl=propranolol) as a causal agent.

URSO-2006-022
This non-medically confirmed case described the occurrence of **rash, itching, low platelets count, low white blood cell count and low red blood cell count** in a 6 year-old male patient who was prescribed Urso 250 mg (UDCA) bd for hepatitis X. Few days after starting Urso, he had severe itching on the soles of his feet and a red rash across his chest. Within a week after starting Urso, WBC count was decreased to 1.0 and RBC count was at 2.44. After that, his platelets count was decreased to 15.000 and his WBC count was at 1.0. Neupogen (filgrastim) was started. The patient was hospitalized and Urso was discontinued, the itching subsided within a few days. His blood count started a gradual recovery later.

URSO-2006-032
This is a medically confirmed report which describes the occurrence of **drug interaction with methotrexate** in a 14-year-old male patient treated with methotrexate for leukaemia who presented with liver pain and increased transaminases. His physician decided to treat chemotherapy adverse effects including liver pain, transaminases increase and jaundice with DELURSAN (UDCA 500 mg/day). A clinical improvement was observed but a drug interaction between methotrexate and DELURSAN was suspected because serum concentration of methotrexate was decreased. Based on the data received, a causal relationship for an interaction between methotrexate and ursodesoxycholic acid **cannot be excluded**.

URSO-2007-224
This is a literature report describing the occurrence of **massive pulmonary and intestinal hemorrhage due to severe coagulopathy, severe pruritus and growth failure** in a 8-year-old male patient treated with UDCA for progressive familial intrahepatic cholestasis (PFIC) type 2. The pruritus persistence and the coagulopathy may be anticipated in patients receiving UDCA treatment, which is not intended to cure the cholestatic disease but to ameliorate the course of the disease. For MAH 2 there was **no reasonable possibility** of a causal relationship between UDCA and the reported events except for the pruritus.

URSO-2008-069
This medically confirmed report described an 8 year-old female patient who received URSO (UDCA) for autoimmune hepatitis, who experienced **direct bilirubin increased, autoimmune hepatitis aggravation (the underlying disease) and gallstones.** The relevant medical history included: hereditary spherocytosis, cardiac murmur, haemolytic anemia, ulcerative colitis and abnormal hepatic function that was diagnosed as autoimmune hepatitis. After gallstones were removed, direct bilirubin gradually decreased. For MAH 2 this was an off-label use of URSO and there was **no reasonable possibility** for a causal relationship between URSO and the events, which are considered due to the progression of the underlying disease.

URSO-2009-152

This medically confirmed report described a case of a male patient with a history of autoimmune hepatitis (AIH) diagnosed around the age of 7 who experienced **unspecific enteritis (manifested as diarrhoea and melaena), oesophageal varices, pancytopenia, primary slerosing cholangitis (manifested as jaundice (due to cholecystitis and cholangitis) and upper abdominal pain), osteoporosis and stage II lower bile duct cancer (right hypochondriac pain, nausea and aggravation of jaundice and hepatic function)** while being treated with Urso (UDCA) For MAH 2 there was **no reasonable possibility** for a causal relationship between Urso and these events that are most likely related to the underlying disease and its complications as well as to the prednisolone treatment (osteoporosis) and azathioprine (pancytopenia) used to treat the condition.

AXC-2010-000289:
This is a medically confirmed case of a 13-year-old female patient with a medical history of Crohn's disease, type 1 diabetes mellitus and autoimmune thyroiditis treated with infliximab, azathioprine, corticosteroids, 5-ASA and Urso (UDCA) (the latter for liver disorder after hospitalization), who **experienced influenza encephalopathy, central line infection, aggravation of diarrhea and rash.** For MAH 2 there was **no reasonable possibility** for a causal relationship between Urso and the reported events.

Three cases were reported in the same literature article (AXC-2011-000025; AXC-2011-000026 and AXC-2011-000027):
AXC-2011-000025
This medically confirmed report describes the **occurrence of drug ineffective for unapproved indication** in a 4 year- old girl who received UDCA for severe pruritus due to cholestatic liver disease Relevant past medical history included Alagille syndrome. Co-suspected medication included Phenobarbital and Rifampin (rifampicin). The patient had previously been treated with UDCA, phenobarbital and Rifampin without improvement. At the hospital, she was treated with intravenous continuous naloxone and was later discharged on oral naltrexone. For 15 months, her itching significantly improved with the exception of mild daytime pruritus. At 12-years of age, the patient was free of pruritus and was taking no medications.

AXC-2011-000026
This medically confirmed report describes the occurrence of **drug ineffective for unapproved indication** in a 9-year-old girl who was treated with UDCA for severe pruritus due to cholestatic liver disease. The patient developed lichenification of both feet secondary to pruritus localized in both lower extremities and excessive scratching. Neither local emollient therapy nor phototherapy was effective. The patient started oral naltrexone. One month later, due to persistent early morning nausea and crampy abdominal pain, the patient discontinued naltrexone and restarted Rifampin (rifampicin). At 18 years of age, patient was free of pruritus and was taking no medications.

AXC-2011-000027
This medically confirmed describes the occurrence of **drug ineffective for unapproved indication and disease progression** in a child female patient who was treated with UDCA for severe pruritus due to cholestatic liver disease. Past medical history included Alagille syndrome. Co-suspected medication included cholestyramine, hydroxyzine and Rifampin (rifampicin). At 3 years of age, the patient underwent liver transplantation for Alagille syndrome. Her post liver transplant course was complicated by portal vein thrombosis, multiple episodes of variceal hemorrhage and the eventual development of chronic liver failure secondary to chronic graft rejection and cholangitis. The patient complained of severe daytime and nighttime pruritus despite therapy with UDCA, cholestyramine, hydroxyzine and Rifampin resulting in tremendous disability. She was treated with oral naltrexone for 3 months with significant improvement

resulting in only daytime pruritus. At age 13, the patient died of liver failure. For Aptalis there was **no reasonable possibility** for a causal relationship between UDCA and the reported events.

AXC-2011-000075
This medically confirmed report described a case of a 16-year-old female patient who experienced **Epstein-Barr virus infection resulting in lymphoproliferative disease** (LPD) while being treated with mesalamine for Crohn's disease and UDCA for Wilson's disease. The patient co-suspected medications included azathioprine, infliximab, trientine and nadalol. For MAH 2, there is **no reasonable possibility** for a causal relationship between UDCA and the reported event due to the lack of biologic plausibility and based on the fact that immunosuppressive agents such as azathiorpine and infliximab may have suppressed patient's immune system which have caused an Epstein-Barr virus infection that lead subsequently to the development of a lymphoproliferative disorder. As per reporter, EBV can induce lymphoproliferative histiocytosis, post-transplant lymphoproliferative disorder, and lymphoma in immunocompromised hosts.

AXC-2011-000369
This literature article reported a case of a 3-month-old female patient with a genetic mutation, who experienced **upper respiratory tract infection, wheezing, rales, otitis media, jaundice, developmental delay, rickets and pruritus** while being treated with UDCA for cholestasis. In this case, in accordance with the reporter's opinion, the underlying cholestasis and the reported genetic mutations have likely determined the occurrence of all the reported adverse events. Therefore, for MAH 2 there was **no reasonable possibility** for a causal relationship between UDCA and the reported events.

AXC-2011-000505
This medically confirmed report was derived from the medical literature[4] and described a case of a 13 year-old female patient who experienced **autoimmune pancreatitis** while being treated with UDCA for granulomatous colitis and sclerosing cholangitis respectively. For MAH 2 considering the other more plausible cause (the underlying Crohn's disease) there is **no reasonable possibility** for a causal relationship between ursodeoxycholic acid and all the reported adverse events.

AXC-2012-000006
This medically confirmed report described a case of a 15 year-old male patient who experienced **severe aplastic anemia associated with pancytopenia** while being treated with UDCA for ciprofloxacin-induced liver disorder. This patient had a background of liver disease, whose nature was not clarified, and which may explain the occurrence of the reported events. Nevertheless, considering the temporal and biological plausibility, the role of UDCA in the origin of the events **cannot be ruled out** in this case.

2. Non serious cases:
There were 18 non-serious cases, most of them were in ``Injury, poisoning and procedural complications`` SOC (Accidental exposure) or in the `` Skin and subcutaneous tissue disorders`` SOC and consisted in Erythema in 1 case, Skin exfoliation in 1 case, Pruritus 2 cases, Pruritus generalized and Erythema in 1 case, Lechenoide keratosis in 1 case.
Ten (10) cases of Accidental exposure have been reported, one of them with an unspecified adverse event. Almost all cases describing an accidental exposure with or without adverse events were received in a line listing from our Japanese partner without further information, there was 1 spontaneous case URSO-2006-038 of accidental exposure received from a school teacher and described the occurrence of inadvertent intake of Urso (UDCA) tablets by a male

child after the reporter dropped one of her Urso 250mg tablet and the child (unspecified age) picked it up, took a bite and spit it out. The child did not experience any adverse outcome following the event.

MAH 2's conclusion

The review of UDCA paediatric data showed that there were 14 serious cases with 36 events and 18 non serious cases with 18 events. Among the serious cases, there were skin reactions (such as rash and pruritus), haematological events (such as pancytopenia and severe anemia) and symptoms of hepatobiliary disorders (such as jaundice, pancreatitis, oesophageal varices, primary slerosing cholangitis and lower bile duct cancer). Confounding factors such as concurrent medical conditions and concomitant medications were present and may have played a role in the occurrence of these events. Cumulatively accidental exposure and skin disorders were the most frequent adverse events reported in paediatric patients. The paediatric data of UDCA are in line with the safety profile of UDCA as described in the MAH 2 Core Data Sheet.

Rapporteur's Comment

Both MAHs provided a line listing of adverse events associated with paediatric use of UDCA.
MAH 1 submitted 2 non-serious cases and MAH 2 summarized 14 serious and 18 non serious cases. Skin disorders (rash, urticaria, pruritus) were reported by both MAHs. The reported ADRs are in line with both MAHs' Core Safety Profile.

A PSUR work-sharing procedure on UDCA (MT/H/PSUR/0001/001) in 2009 also concluded that a significant number of non-serious ADRs fell within SOC: 'Skin and subcutaneous tissue disorders' and requested the MAHs to closely monitor this in the future. Of note, there is an ongoing UDCA PSUR worksharing procedure (MT/H/PSUR/0001/002) which covers the reporting period from 01.12.2008 to 30.11.2011 and will most likely also address the issue of dermatological adverse events.
It has been noted that MAH2 submitted three cases (URSO-2009-152, URSO-2007-224, AXC-2012-000006) where adverse haematological events (coagulopathy, pancytopenia) were reported and in one of these cases association with UDCA was reported as 'can not be ruled out'. Furthermore, the currently approved product information does not contain any relevant information about potential haematological adverse events.
Based on the above presented data, both MAHs are advised to closely monitor dermatological and haematological adverse events in children.
Furthermore, in light of the newly proposed paediatric indication MAHs should be ready to submit a risk management plan (RMP) in accordance with the new pharmacovigilance legislation.

8) Discussion of efficacy and safety in infants with TPN associated cholestasis

MAH 1

As was already set out in the previous Clinical Expert Overview and confirmed in the Rapporteurs Preliminary Assessment Report the evidence for a clear role of UDCA in the treatment of infants with cholestasis due to parenteral nutrition is rather poor.
The available evidence is presented in two recent systematic reviews.
San Luis & Btaiche (2007) reviewed the role of UDCA in parenteral nutrition associated cholestasis. 5 studies and two case reports with paediatric patients and one study in adults were identified and evaluated. The authors concluded that even if there is some evidence that in the

short term UDCA in doses ranging from 10 to 30 mg/kg body weight/day improves biochemical signs and clinical symptoms of liver disease associated with parenteral nutrition the impact of the treatment on the general outcome is not clear. In addition, relevant issues such as dosage and duration of UDCA administration and optimisation of timing are still to be achieved. Moreover UDCA may not be effective in conditions such as short bowel syndrome or in those with resected terminal ileum because of reduced UDCA absorption. A general restriction of the role of UDCA in this condition is that the studies supporting the efficacy of UDCA in the treatment of cholestasis associated with parenteral nutrition are limited by small sample size, absence of randomisation and controls, short duration, and lack of evaluation of confounding variables.

In a more recent systematic review on interventions for the management of intestinal failure and its complications in children, Barclay et al. (2011) included data from 33 original articles, among them - as the only study with UDCA - the retrospective study by Chen et al. 2004 (see Clinical Expert Overview). They conclude that, generally, the evidence base for medical interventions in paediatric intestinal failure is limited and of poor quality.

After the submission of our first Clinical Expert Overview some new evidence on the use of UDCA in paediatric patients with parenteral nutrition-associated cholestatis (PNAC) were published:
A recent publication (Willis et al. 2010) on the “natural course” of PNAC in a series of 66 infants with parenteral nutrition associated cholestasis despite treatment with UDCA reported 10 deaths and one referral for liver transplantation. 40 patients had positive blood cultures among them all fatal and transplant cases. On the other side, in those patients without positive blood cultures, no death or transplantations occurred. The average time from peak bilirubin levels to two-times upper limit of normal levels was 66 ± 7 days (n=49). This case series clearly shows that there is a strong need for treatment options in addition to UDCA in these patients.
Gokmen et al. (2012) conducted a three-armed prospective, randomised double-blind controlled study with 75 pre-term infants (< 32 weeks gestational age) with very low birth weight (< 1500g) who received < 75 ml/kg body weight/day of milk feeds by the 14th day of life and who received total parenteral nutrition for at least 12 days. One group was treated with 125 mg/day erythromycin, another group received 5 mg UDCA every 6 h and the third group received placebo. Primary outcome measures were full enteral feeding or intestinal failure-associated liver disease. Erythromycin- and UDCA-treated infants had higher gestational age and higher birth weight than those in the placebo group. Patients randomised to erythromycin achieved full enteral feeding significantly earlier (median 22.5 days) compared to placebo (27 days) or UDCA (24 days). Increases in serum GGT-levels indicating cholestasis were lowest in the UDCA group (mean from 59 IU/l pre-treatment to 72 IU/l post-treatment) and significantly higher in the placebo group (from 62 IU/l to 121IU/l). The difference remained statistically significant after adjusting for differences in birth weight. 5 patients in the UDCA group, 10 in the erythromycin group and 13 placebo-treated patients had post-treatment GGT levels higher than 120 IU/l. Other parameters (peak serum total or conjugated bilirubin, aminotransferases) did not differ significantly among all three groups. The authors conclude that erythromycin was most effective in facilitating enteral feeding and UDCA was most effective in preventing cholestasis. According to the authors, prophylactic usage of UDCA could be considered in infants with prolonged parenteral nutrition.

MAH 1 concluded that the potential efficacy of UDCA appears to be well known in those concerned with risks for or prevalent complications of PN and TPN. However, there is not enough robust evidence on the effects of UDCA on mortality or morbidity in this indication to support a paediatric recommendation.

MAH 2

The potential beneficial effect of UDCA administration in total parenteral nutrition – associated cholestasis (TPNAC) has been evaluated in many studies whether in premature or very low body weight (VLBW) neonates or in children suffering from intestinal failure due to short bowel syndrome (SBS) or other causes and needing TPN.

Studies in premature or VLBW neonates

In premature or VLBW neonates, the effect of UDCA on biochemical markers of cholestasis has been investigated in seven non-randomized prospective or retropective studies involving small sample size patient populations (Al-Hathlol 2006; Chen 2004; Cocjin 1993, 1994; Garzon 2009; Kowalski 1994; Levine 1999). Some of these trials were not controlled, while in others the lack of treatment with UDCA served as a control group. In these trials, all other causes of cholestasis were eliminated except for the study by Al-Hathlol (2006) which was conducted in VLBW neonates suffering from intractable cholestasis that persisted even while off TPN and already on full enteral feeding (FEF). This advanced disorder was related to additional risk factors in these premature infants such as gastro-intestinal surgery for severe necrotizing enterocolitis, intestinal atresia, prolonged TPN duration and frequent episodes of sepsis.

A consistent beneficial effect on GGT or total bilirubin was observed in all studies while the effect on other liver enzymes (AST, ALT) was not consistent across studies. Cocjin (1994) also reported that no infants treated with UDCA developed gallstones, cholangitis or needed cholecystectomy whereas a large proportion of the untreated infants had an unfavorable outcome. In these trials, UDCA was generally well tolerated and free of side effects at doses ranging between 15 and 30 mg/kg/day, except for mild diarrhea in 3 patients in the study by Al-Hathlol (2006).

Aside from these 7 non-randomized trials, three prospective, double-blind, placebo-controlled trials have been conducted in the same patient population in order to evaluate the safety and efficacy of UDCA in premature neonates receiving TPN (Arslanoglu 2008; Gokmen 2012; Moro 2011[1]) by treating 14, 24 and 15 neonates, respectively. In these studies, infants suffering from TPNAC had to be free of other causes of cholestasis, congenital abnormalities, chromosomal aberrations, congenital infections, proven or suspected necrotizing enterocolitis or severe neonatal diseases. In one trial (Gokmen 2012), neonates on TPN were treated early with UDCA, before any occurrence of cholestasis. Outcome measures were occurrence or treatment of TPNAC, as well as time to achieve full enteral feeding (FEF).

At least one biochemical marker of cholestasis (more consistently GGT) was improved or normalized in all 3 studies. Indeed, GGT has become a widely used parameter in detecting PNAC because it is the earliest and the most persisting marker of cholestasis (Gokmen 2012). However, UDCA did not decrease significantly the time to achieve FEF in any of these 3 studies. In all 3 trials, UDCA was safe and well tolerated.

Aside from their placebo and UDCA groups, Gokmen (2012) also treated a group of neonates on TPN with erythromycin, a macrolide which increases overall motor activity in the stomach and intestine, and could have a positive effect on non-anatomically obstructive gastro-intestinal dysmotility in premature neonates. Their study demonstrated that erythromycin-treated infants were able to attain FEF more quickly as compared to the placebo and UDCA-treated groups. They concluded that erythromycin was most effective in facilitating enteral feeding and UDCA was most effective in preventing TPNAC, since at the end of treatment, the incidence of TPNAC in the placebo group was significantly higher than in the UDCA group.

The results obtained in these 3 placebo-controlled, RCTs are again in favor of a positive effect of UDCA administration on the principal marker of cholestasis (GGT). However, the distinction

between improvement in the severity and/or duration of TPNAC versus prevention of cholestasis would warrant further studies.

Studies in infants with intestinal failure needing TPN

Three non-randomized trials have been conducted in infants with intestinal failure (IF) attributable to different conditions, the most frequently observed ones being SBS and necrotizing enterocolitis (Cowles 2010; De Marco 2006; Immacolata 1996). Periods without treatment or voluntary temporary withdrawal of UDCA therapy or no treatment in some infants served as controls. Cholestasis had to be related to PN and other causes were excluded.

The patient population treated with UDCA was very small in two trials: n = 12 and n= 7 for studies conducted by De Marco (2006) and Immacolata (1996), respectively, whereas Cowles (2010) conducted their investigation in 93 children. In the latter study however, UDCA treatment was not used alone but as part of a rehabiliting program consisting of cycling of PN, limiting lipid infusions, enteral stimulation and UDCA treatment so that the exact contribution of UDCA in this study is difficult to establish. It is noteworthy to point out that this program was successful in reversing intestinal failure – associated liver disease (IFALD) in the majority of children involved in this trial, thereby preventing adverse outcomes of organ transplantation or death.

In both trials by De Marco (2006) and Immacolata (1996), biochemical markers of cholestasis were improved or normalized by UDCA treatment at 30 mg/kg/day. A rebound increase of cholestasis occurred in a small group of patients in which UDCA was temporarily withdrawn and levels returned to normal upon resumption of UDCA treatment.

MAH 2's conclusions

Although only 3 randomized, double-blind, placebo-controlled trials have been performed in premature or VLBW neonates on TPN, many trials have been performed in this patient population, which have given consistent results with regards to improvement or resolution of some biochemical markers of cholestasis. Data presented in these trials do not permit robust evaluation of the possible prophylactic effect of UDCA on the incidence of TPNAC in this patient population. Although they provided favourable results, trials conducted in infants with IFALD treated with UDCA are scarce, especially that in one of these studies, UDCA was administered as part of a rehabilitation program consisting of many other medical interventions.

Kobt (2009) and Tufano (2009) have conducted retrospective analyses of the effect of UDCA in children with neonatal cholestasis of various etiologies. The purpose of these analyses was not to study the effect of UDCA on TPNAC since not all neonates were on TPN (Tufano 2009) or data on TPN were not provided (Kobt 2009). In the study by Tufano (2009), the aetiology of cholestasis was mutifactorial in the vast majority of neonates consisting of prematurity, asphyxia, TPN, chromosomal disorder, infections and/or sepsis, and UDCA treatment had no clinical or biochemical effect on cholestasis in this patient cohort after a 3-week treatment at 30 mg/kg/day. Kobt (2009) also reported an absence of effect of UDCA in neonatal hepatitis, most of these cases being idiopathic, but some being of infectious etiology. In this study, neonates treated with UDCA even suffered lesser successful outcome and more hepatic and extrahepatic complications compared to those who had not received UDCA. In their trial described above and specifically investigating the effect of UDCA on TPNAC, Al-Hathol (2006) have reported 2 episodes of increments in direct bilirubin during UDCA treatment that were associated with severe bacterial and fungal sepsis. The authors concluded that sepsis may have altered the effectiveness of UDCA therapy in these cases, which could be in line with the absence of efficacy of UDCA reported by Kobt (2009) and Tufano (2009) in severely ill neonates.

In the vast majority of cases, TPNAC resolves spontaneously after cessation of TPN and FEF. However, in a few patients with intractable cholestasis, cholestasis does not resolve and may progress to severe hepatobiliary damage and death (Al-Hathol 2006). Alternatively, TPNAC can

also cause gallstones necessitating cholecystectomy (Cocjin 1994). Therefore, in order to improve bile flow and reduce the formation of biliary sludge, UDCA treatment may be advantageous and is in fact currently used in the management of TPNAC (Kelly 2010). UDCA is safe and well tolerated in newborns as well as infants receiving TPN. Evidence towards the efficacy of UDCA in improving biochemical markers of cholestasis has been shown in many studies in premature and/or VLBW neonates otherwise free of other causes of cholestasis. In infants with further causes of cholestasis such as IF, UDCA treatment may also be advantageous, although this has been a bit less documented.

There is barely any information regarding the efficacy and safety of UDCA in cases of TPNAC in infants also suffering from concomitant sepsis or other causes of cholestasis, congenital abnormalities, chromosomal aberrations, congenital infections, or severe neonatal diseases. However, in view of the results obtained by Tufano (2009) and especially those obtained by Kobt (2009), use of UDCA in TPN-associated cholestasis should be restricted to premature and / or VLBW neonates, or alternatively, infants requiring TPN as a result of intestinal failure due to SBS or necrotizing enterocolitis, infants otherwise free of other neonatal diseases or conditions.

Rapporteur's Comment
Both MAHs provided a comprehensive overview of available evidence on UDCA's use for the treatment of total parenteral nutrition induced cholestasis in infants. The above described studies suggest that UDCA may have a positive effect on reducing cholestatic markers (GGT) however it did not decrease significantly the time to achieve full enteral feeding.
In summary, the rapporteur is of the view that the currently available evidence is not robust enough to support UDCA's use in paediatric patients with TPNAC. Issue resolved.

9) Discussion of the recently emerged carcinogenicity safety concerns in adults with PSC

MAH 1
As UDCA has been used for the treatment of primary sclerosing cholangitis (PSC) which is characterised by inflammation, fibrosis and strictures of intra- and extrahepatic bile ducts and which is often associated with ulcerative colitis. In many trials with PSC patients using doses of UDCA of 15 mg/kg body weight/day or higher, elevated liver function parameters decreased but no consistent effect on disease progression or survival could be shown. Clinical trials indicated that compared to the treatment of PBC, higher doses of UDCA might be needed for an efficacious treatment of PSC. In all studies with PSC patients hitherto, as with its use in other indications, UDCA was regarded generally very safe and well tolerated, even when it was used in high doses up to 30 mg/kg body weight/day. Moreover, UCDA was even suggested to reduce the risk of hepatobiliary and colonic carcinomas which is increased in PSC patients (for details see below). Thus, even if the efficacy of UDCA was not clearly established in PSC, it is used in many patients, in most European countries off label.
A recent long-term, randomized, double-blind, placebo-controlled study on the effect of high-dose (28 – 30 mg/kg body weight/day) UDCA in 150 adult patients with PSC was terminated prematurely after 6 years due to futility. Predefined endpoints such as death, liver transplantation, minimal listing criteria for liver transplantation, cirrhosis, esophageal or gastral varices were reached by significantly more patients (30/76) in the UDCA group compared to the placebo group (19/74) although liver function parameters had improved under UDCA treatment (Lindor et al. 2009). However, in the total study population neoplasias i.e. cholangiocarcinoma and colonic dysplasia were not more frequent in the UDCA group (2 cases of cholangiocarcinoma, 3 cases of colonic dysplasia) than in the placebo group (2 cases of cholangiocarcinoma, 5 cases of colonic dysplasia). Serious adverse events, many of them

relating to the development of primary endpoints, were more common in the UDCA group, i.e. the endpoints which were more frequently reached in the UDCA group were considered as serious adverse events of the agent.
However, in a nested cohort study using the data of 56 patients out of a total of 91 patients and out of 65 eligible patients with PSC and concomitant ulcerative colitis (UC) from Lindor et al. (2009) randomised high UDCA dose study, it was shown that the treatment with high-dose UDCA was associated with a significantly higher risk of colorectal neoplasia (defined as low grade dysplasia, high grade dysplasia or colon cancer) in the UDCA group compared to placebo (hazard ratio (HR) 4.44; 95%CI:1.30–20.10;p=0.02) (Eaton et al. 2011). Even after adjusting for known risk factors for colorectal dysplasia such as smoking and duration of the UC, the use of high-dose UDCA was still associated with a higher incidence of colorectal neoplasia (HR: 5.97;95%CI:1.39–41.44; p=0.02). The majority of patients developed colorectal neoplasia at or after 2 years of UDCA use. In the UDCA group, one case of colon cancer, one case of high-grade dysplasia and 7 cases of low-grade dysplasia occurred, whereas in the placebo group each one case of colon cancer, high grade and low grade dysplasia were detected. Thus, the difference in the frequency of colorectal neoplasia relates only to an increased number of cases with low-grade dysplasia in the UDCA group. This finding is of high clinical relevance as in patients with ulcerative colitis low grade dysplasia is associated with a high risk of developing colorectal cancer (Thomas et al. 2007).

Potential reasons to explain the “paradoxical” effects of UDCA which hitherto was accepted as a decidedly safe drug, on reaching the liver- and carcinogeneity endpoints were discussed in the primary and the secondary publications of the study and experience with high dose UDCA from other studies should be considered to potentially resolve the unexpected findings of this study:

- Analysis of the drug supplied for the study failed to disclose any unusual compounds, so general substance-associated toxicity can be excluded.
- UDCA modulates apoptosis (Amaral et al. 2009). It was suspected that the high doses of UDCA prevented apoptosis of activated stellate cells, which continued to be active in fibrogenesis, leading to the advanced liver diseases found in this study. It is not clear if prevention of apoptosis might also have contributed to the increased risk of colorectal neo- or dysplasia.
- Already in the primary publication of the randomised study, it was discussed that toxic bile acids such as lithocholic acid (LCA) which can be generated by the microbiota in the colon from unabsorbed UDCA might have been causative for side effects of high dose UDCA in PSC patients. In a post hoc analysis of serum bile acids at baseline and at the end of the study period of 56 patients found significantly increased levels of LCA at the end of the study period in the UDCA group (Sinakos et al. 2010). Also the serum concentrations of UDCA and total bile acids were significantly increased in the UDCA group but no significant changes were seen for cholic acid, deoxycholic acid or chenodeoxycholic acid. In patients in the UDCA group who reached clinical liver-related endpoints post-treatment total bile acid levels were increased to a greater degree compared to those not reaching these endpoints but this difference was not statistically significant. The failure of significance between patients with endpoint and those without endpoints may be explained by the relatively small number of patients that reached endpoints. Notwithstanding, the authors of the post-hoc analysis of bile acids noted that they do not believe that the data about differences in serum bile acid concentrations are solid enough to support the hypothesis that the adverse effects associated with high-dose UDCA treatment in PSC patients can be explained solely by increases in LCA levels.
Serum bile composition before and after treatment in the randomised study was also available for review in 14 out of a total of 91 and out of 65 eligible PSC patients with concomitant UC who received high-dose UDCA. Four of them had developed a colorectal dysplasia or colorectal carcinoma, 10 did not. The difference in bile acid composition between those who did and those who did not develop colorectal neoplasia was not statistically significant. However, there was a

numerical greater increase in LCA and chenodeoxycholic acid in those who developed colorectal dysplasia or colorectal cancer compared to those who did not (Eaton et al. 2011). As secondary bile acids e.g. LCA have been shown the potential to cause DNA damage in colonic cells *in vitro* (Bernstein 2009 et al.), this may point to a potential underlying cause of the increased incidence of colorectal neoplasia associated with high UDCA doses in patients with PSC and concomitant UC.

- Another potential explanation of the increased incidence of liver-related endpoints in the UDCA group is the interpretation of the side effects as a direct toxic effect of the high doses of UDCA on hepatocytes in patients with advanced PSC who frequently have biliary obstruction due to strictures (Chapman 2010). Similarly, the authors of the post-hoc analysis of the bile acids profile discuss the possibility of an aggravation of bile infarct due to increased bile flow and biliary pressure in the setting of biliary obstruction (Sinakos et al. 2010). However, this hypothesis appears to be not fully compatible with the finding of another post-hoc analysis of the data of the primary study, in that a significant difference in endpoints between the UDCA- and the placebo-group was apparent only in patients with early stage PSC, but not in patients with later stages of PSC (Imam et al. 2011). However, it is not clear if a direct toxic effect of high doses of UDCA might also be involved in the higher incidence of colorectal neoplasia.
- A fact that might have contributed to the finding in the Lindor et al (2009) study and the Eaton cohort study is that 415 of the included patients already had cirrhosis or at least advanced fibrosis at the baseline of the study. Considering the limitations in hepatobiliary bile acid secretory capacity of late stage PSC, this is not an ideal population for a long-term treatment with high-dose UDCA.
- There is some issue which might cast some doubt on the finding of the increase of low grade dysplasia, given that the rates of high grade dysplasia and that of colon carcinoma both of which are easier to diagnose were not different between the UDCA and the placebo group. Low-grade dysplasia is indeed difficult to diagnose moreover in the inflamed colon (Rutter et al. 2004). Therefore it is all the more remarkable that these findings were not validated by a second experienced pathologists, but only by two authors who are clinical gastroenterologists / hepatologists.
- It was even discussed if the unexpected finding of the increased incidence of serious adverse events in the UDCA group may simply be a chance finding, as the number of patients who reached the primary outcome measures of death or liver transplantation was relatively small (Chapman 2010).

Despite additional post-hoc analyses and intensive discussions in the scientific community up to now it appears that there is still no conclusive explanation of the finding of the occurrence of serious side effects such as an increased incidence of colorectal neoplasia with high dose UDCA in PSC patients with or without concomitant UC in this particular study (Chandok et al. 2012).

In the discussion of the main publication of the randomised high dose UDCA study in PSC patients (Lindor et al. 2009), the findings were declared as “quite unanticipated”, also because a previous pilot study with similarly doses (25-30 mg/kg/day) of UDCA in 30 PSC patients had not indicated such deleterious effects of high dose UDCA but in contrast, the treatment with high-dose UDCA for one year significantly improved the mayo risk score for expected survival and was well tolerated with only few side effects such as nausea and diarrhoea (Harnois et al. 2001). Similar to the findings in the randomised trial, serum levels of alkaline phosphatase, total bilirubin and albumin improved. However, it should be taken into consideration that in the pilot study high dose UDCA was given only for one year. In the nested cohort study most cases of colorectal neoplasia were detected only at or after 2 years of treatment with UDCA (Eaton et al. 2011). Therefore, it cannot be excluded that the exposition to UDCA in the study of Harnois et al. (2001) was too short to detect an increased incidence of colorectal neoplasia. In this pilot PSC study with high dose UDCA, two patients underwent evaluation for liver transplantation (at

6 and 9 months) and another patient died from liver-related complications at 3 months. These events were not considered to be related to the treatment with high-dose UDCA.

Other experience on carcinogenicity in UDCA-treated PSC patients

Colorectal carcinoma

Prior to the findings of the study by Lindor et al. (2009) and the subgroup analyses of this study by Eaton et al (2011), UDCA was considered to rather have preventive effects against neoplasia/carcinoma based on preclinical observations. Moreover, from several clinical studies, there is some evidence that this might be clinically relevant.

A multivariate analysis of an early cross-sectional study on 59 PSC patients with ulcerative colitis who underwent colonoscopic surveillance for colonic dysplasia revealed that UDCA was significantly associated with a decreased prevalence of colonic dysplasia (Tung et al. 2001). The control group had an unusually high rate of dysplasia and there were some differences in the characteristics of the patients treated with UDCA or not, raising bias in the study. No significant associations were detected between colonic dysplasia and the use of anti-inflammatory or immunosuppressive drugs. The mean dose and duration of UDCA in those patients without dysplasia was 9.9 mg/kg body weight/day and 3.5 years, respectively. However, the relationship between total cumulative UDCA dose and progression to dysplasia was not significant and even in the group of UDCA-treated patients, 50% developed dysplasia.

Pardi et al. (2003) followed up on 52 PSC patients with concomitant UC from a prior randomised placebo-controlled trial for a total of 355 person-years. PSC patients treated with 13 – 15 mg UDCA/kg/day were found to have a significantly lower risk (74% decreased) for developing dysplasia or colorectal cancer compared to the placebo-treated patients. Other drugs had no influence on the incidence of dysplasias or cancers.

In another cohort study, Ullman et al. (2003) included 50 PSC patients with UC, 32 of them were treated with UDCA, 18 were nor treated with UDCA. Mean follow-up was 59.6 months. Among the UDCA users the incidence of colorectal cancer or dysplasia was numerical but not statistically inferior compared to patients who did not take UDCA.

Wolf et al. (2005) performed a historical cohort study with PSC patients with ulcerative colitis. 28 patients who were treated with UDCA for a mean duration of 3.4 years were compared to 92 historical, untreated patients. The cumulative incidence of colorectal dysplasia or cancer was not significantly different between cases and controls but the cumulative mortality was significantly lower in the UDCA-treated patients.

The four cohort studies on the effect of UDCA on the risk of colorectal cancer in PSC patients presented above were analysed in a recent metaanalysis (Ashraf et al. 2012). In the combined analysis there were 26 cases of adenoma in 130 UDCA users compared to 34 adenomas in 151 patients who were not treated with UDCA (Odds ratio [OR] 0.53; 95% CI 0.19 – 1.48, p=0.23) and 5 cases of colorectal cancer in 89 patients treated with UDCA compared to 19 cases in 133 patients who were not treated with UDCA (OR 0.50; 95%CI: 0.18 – 1.43; p=0.20). All studies included in the metaanalysis for colorectal cancer prevention showed a trend of UDCA to be protective but the number of patients included and/or the number of events was too small to show a statistically significant effect.

In a study by Lindström et al. (2012) 98 PSC patients with concomitant ulcerative colitis from a previous 5-year randomised placebo-controlled trial were followed up for a total time of 760 person-years. UDCA was given in a dose of 17 -23 mg/kg body weight/day. Dysplasia- and cancer-free survival was comparable between the placebo and the UDCA-treated group (16% vs. 13%).

Cholangiocarcinoma.

Brandsaeter et al. (2004) prospectively recorded data from all Scandinavian PSC patients listed for liver transplantation during 1990 – 2001. In a multiple regression analysis, no treatment with UDCA was one of several statistically significant independent predictors of hepatobiliary

malignancies even if the duration of the treatment was not associated with this kind of neoplasia. No information on the doses of UDCA used was given.

Cholangio- and colorectal carcinomas

From 1987 to 2007, a German group performed a long-term prospective observational study on UDCA treatment in 171 PSC patients. Patients with decompensated liver cirrhosis, those foreseen for liver transplantation, and those with a history of neoplastic and/or coexisting hepatic disease were excluded form the study and some patients were lost to follow up for non hepatic reasons. In addition to the treatment with UDCA, in all 97 but one patient with dominant stenoses of the extrahepatic bile ducts endoscopic retrograde cholangiography (ERC) was performed in yearly intervalls (Rudolph et al. 2009). In patients with total or subtotal stenosis of the major bile duct and biochemical evidence of cholestasis stenotic segments of the extrahepatic bile ducts were dilated repeatedly until successful. Up to 1995, UDCA was given in a dose range of 9-15 mg/kg body weight/day which since 1995 was increased to 14-17 mg/kg body weight/day and since 2001 to 18-21 mg/kg body weight/day in three divided doses. In 20 patients, the dose was even increased up to 22-32 mg/kg body weight/day for three months (see also Rost et al. (2004), below). The median duration of UDCA treatment and follow-up was 6.7 years, ranging from 0.3 to 18.7 years. It is reported, that unwanted effects of UDCA were not observed (Rudolph et al 2011). From this study, several publications report particularly on issues concerning carcinogenicity:

Rudolph et al. (2007) describe 150 PSC patients without evidence of cholangiocarcinoma at baseline. The authors reported that the incidence of cholangiocarcinoma was only about half of that reported historically with untreated PSC patients (Burak et al. (2004). Moreover, the incidence of cholangiocarcinoma decreased with the duration of UDCA treatment. Cholangiocarcinoma occurred only in PSC patients with dominant stenoses of the bile ducts.

In another publication of this study, Rudolph et al. (2010) reported that the incidence of carcinomas of the bile ducts and colorectum was only increased in those 67 PSC patients with concomitant IBD and dominant bile duct stenosis (8 carcinomas of the biliary tract, 6 colorectal carcinomas) but neither in 104 PSC patients without dominant stenoses nor in those without IBD (total incidence in these subgroups: 1 colorectal carcinoma, no colorectal carcinomas). Similarly, need for liver transplantation and death were strongly associated with dominant stenoses and concomitant IBD.

Moreover, the same group reported that in the 120 PSC patients with concomitant inflammatory bowel disease, most colon carcinomas developed in the first years after the start of UDCA treatment. However, from 6 years after the start of the UDCA treatment, the rate of carcinomas decreased and after treatment of more than 9 years, no further cases of colorectal carcinoma were observed (Rudolph et al. 2011). This is in line with previous observations showing that in PSC patients with concomitant UC who were not treated with UDCA the incidence of colorectal carcinoma increased steadily with duration of disease (Broome et al. (1995), Claessen et al. (2009)). As in their former publication, Rudolph et al. (2011) confirm that in the subgroup of patients with concomitant PSC and UC in the study the total rate of colorectal carcinomas in their study was considerably lower than reported formerly in patients who were not treated with UDCA. Therefore, it was suggested that UDCA treatment reduces the risk for colorectal carcinomas in PSC patients with ulcerative colitis.

Thackeray et al. (2011) report on a retrospective review of 54 PSC patients with concomitant inflammatory bowel disease and colonic neoplasia. 33 (61%) of the patients were on treatment with UDCA. The mean duration of the follow-up of the patients with PSC and UC was 4.2 years (range 1.0 - 6.4 years). In the total group of patients, i.e. those treated with UDCA and those not treated, the incidence of colorectal neoplasias was similar within the first 2 years and within all 2-year intervals up to 10 years after the recognition of the coexistence of both diseases. In the publication, there is no separate evaluation of the neoplasia incidence of patients treated and those not treated with UDCA. Therefore, it remains speculative if the findings of a constant incidence of colorectal neoplasia in the total group, results from an increasing incidence in the

untreated patients and an decreasing incidence in those treated with UDCA as discussed by Rudolph et al (2011).
In a publication about the clinical course of PSC in France, Garioud et al. (2010) observed 150 PSC patients, 90 of them with associated IBD. All but 9 were treated with UDCA in a mean dose of 13.1 mg/kg/day. 11 cases of various carcinomas (cholangiocarcinoma: n=5, hepatocellular carcinoma: n=2, gallbladder carcinomas: n=2; colorectal cancer: n=1) were reported at the start of the observation and 6 cases (colorectal carcinoma: n=4; cholangiocarcinoma: n=1; gallbladder carcinoma: n=1) occurred during the follow-up (mean 3.9 years). The authors concluded that on the one hand under treatment with standard doses of UDCA, PSC remains a severe disease. On the other hand, the low incidence of cholangiocarcinoma seems compatible with a potential protective effect of UDCA on the development of biliary neoplasia.
In the light of the findings of the randomised, placebo-controlled long-term, high-dose UDCA study in PSC patients (Lindor et al. 2009), the authors of the primary and secondary publications of the study and various commentators recommended not to use high dose UDCA for the treatment of PSC and not to use UDCA at all for the prevention of neoplasia in patients with concomitant PSC and UC.

Other safety experience with high-dose UDCA in PSC
In a dose-finding pilot study, Cullen et al. (2008) randomised 31 PSC patients to treatment with either low dose (10 mg/kg), standard dose (20 mg/kg) or high dose (30 mg/kg) daily of UDCA for 2 years to evaluate if a high level of biliary enrichment of UDCA was tolerated by the patient and might produce additional benefits. According to the patients and the study coordinators UDCA was well tolerated at all doses with tolerability. There were no differences in the incidence and kind of side effects between the three doses of UDCA. Similar to the patients in the lower dose groups, among the patients in the high dose group (n=10) there was each one case with cholangitis and cholecystectomy which however were not considered to be related to the treatment with UDCA. Despite the fact that most of the patients had concomitant ulcerative colitis, only 3 complained of exacerbation of diarrhoea which was considered not to be associated with UDCA. One patient interpreted loss of libido as side effect of UDCA. Upon premature termination of the study partial recovery of libido was reported.
Rost et al (2004) treated 56 PSC patients with different doses of UDCA, among them 8 who received high doses of UDCA (26-32 mg/kg body weight/day) for three months to evaluate UDCA enrichment in bile and its degradation to potential toxic bile acids. These patients were already reported in the publications by Rudolph et al. 2007, 2010 and 2011, discussed above. In addition to the treatment with UDCA, dominant stenoses of major bile ducts were treated by dilatation. Biliary bile acid composition was determined in 56 PSC patients including 30 patients with repeat bile samples treated with various doses of UDCA. There was no increase in toxic hydrophobic bile acids with increasing doses of UDCA. There is no report about side effects associated with UDCA in the publication of the study.
In a recent Cochrane metaanalysis of bile acids for the treatment of PSC (Poropat et al. 2011) eight trials were included, among them the trial published later on by Lindor et al. (2009). However, for the metaanalysis only an abstract of this trial was available. It was concluded that UDCA was safe and well tolerated by PSC patients. There was no statistical significant difference between treatment with UDCA and placebo or no treatment with respect to the number of adverse events reported in the trials. The authors of the metaanalysis reported that they were not able to find the causes of the eight deaths that occurred in the Lindor randomised trial. No deaths were reported in the remaining trials.

MAH1's conclusion
The finding of an increased risk of dysplasia/carcinogenicity associated with high dosed UDCA appears to be restricted to colorectal low grade daysplasias reported in PSC patients with concomitant UC in one single study (Eaton et al. 2011). In contrast, from this study/evaluation there is no evidence of an increased risk of hepatobiliary neoplasia associated with high dose,

long-term UDCA. The finding of an increased incidence of colorectal dysplasia in patients with PSC and UC who were treated with high doses of UDCA is unique to this study/evaluation. There are several other reports on the treatment of patients with PSC with or without IBD and on patients with various other hepatobiliary diseases, none of them indicating an increased neoplasia/carcinogenicity risk associated with UDCA treatment. In contrast, from the results of former studies, UDCA was considered rather to be associated with protective effects against colorectal as well as hepatobiliary neoplasia and cancers, although a definitive conclusion is limited by the quality and heterogeneity of the evidence. One obvious difference between the findings of Eaton et al. and the other studies is that UDCA was given in high doses (28-30 mg/kg body weight/day) and for a long duration (mean 4.01±1.54 years). Studies using similarly high doses of UDCA for shorter duration and studies using lower doses of UDCA but for longer duration did not report on comparable adverse effects. Therefore, the risk might be associated with a high cumulative UDCA dose administered within a certain time in patients with severly limited hepatobiliary secretory capacities. Another point might be that endoscopic treatment and dilatation of dominant bile duct stenoses was not performed in the randomised high dose UDCA study published by Lindor et al. (2009) – at least it is not reported. This is in contrast to the study reported by Rudolph et al. (2010) who particularly showed an increased risk of colorectal cancer associated with dominant stenoses in PSC patients with IBD. If this hypothesis would prove true, high carcinogenicity risk would be associated with and possibly even restricted to diseases with untreated relevant biliary obstructions.
Notwithstanding some indications and hypotheses as those discussed above, up to now, there is no conclusive explanation of the increased carcinogenicity risk and other serious side effects which were found to be associated with high dose, long-term UDCA treatment observed only in the study by Lindor et al. (2009).

MAH 2

Effect on occurrence of cholangiocarcinoma

UDCA at a dose of 10-15 mg/kg per day has consistently improved liver biochemistries in PSC patients in several trials, but did not affect other outcomes related to disease progression, even in the largest randomized, controlled trial consisting in as much as 6 years of follow-up (Lindor 1997). This contrasts with the long-term effects of UDCA in primary biliary cirrhosis (PBC), another chronic cholestatic liver disease with a less erratic course than PSC. The dose of 13-15 mg/kg /day has shown to improve long-term survival in patients with PBC (Poupon 1997).
A number of studies have therefore been conducted in patients with PSC, using larger doses, based on the hypothesis that these higher doses would be necessary to prevent the progression of the disease, usually leading to biliary cirrhosis, portal hypertension and liver failure over a 10 to 15-year period (Lindor 2009). Cholangiocarcinoma also occurs in 5 to 10% of cases with an incidence of 0.6 to 1.5% per year in patients with PSC. A median duration of 12 to 15 years from the time of diagnosis has been observed for patients developing end-stage liver disease.
An open label pilot study evaluated the effect of a high-dose treatment (25-30 mg/kg/day) in 30 PSC patients treated for 1 yr (Harnois 2001). A marked improvement in liver biochemistry was observed as expected. A significant decrease in a surrogate endpoint, the PSC Mayo risk score, was observed, which predicted a significant decline in expected mortality at 4 years. When comparing to the results of a previous study from the same team (Lindor 1997), it appeared that the projected 4-yr mortality was significantly decreased with the high-dose of UDCA (11%) compared to placebo (17%), but not with the low-dose (13%). UDCA was well tolerated in this pilot trial.
Another pilot study, this time a randomized dose-ranging trial, attempted to determine whether further enrichment of the bile acid pool with UDCA would lead to an improvement in outcome for PSC patients (Cullen 2008). Thirty-one (31) patients with PSC were randomised to treatment with either 10 mg/kg (n = 11), 20 mg/kg (n = 11) or 30 mg/kg (n = 9) daily of UDCA for 2 years. Serum liver tests improved in all groups taking UDCA. Survival probability at 1, 2, 3 and 4 years

as evaluated by the Mayo risk score tended to improve for all patients and significantly improved for the high dose group ($p<0.02$). Only 3 (10%) of all patients had a Ludwig score showing histological deterioration over the trial period. UDCA treatment was well tolerated in all patients.
From these pilot studies, it was concluded that high-dose UDCA is well tolerated and is associated with an improvement in survival probability. A trend towards stability/improvement in histological stage was also observed.

Lindor (2009) then conducted a long-term, randomized, double-blind controlled trial of high-dose UDCA (28-30 mg/kg/day) in patients with PSC treated for 5 years. The primary outcome measures were development of cirrhosis, varices, cholangiocarcinoma, liver transplantation, or death. At enrollment, the UDCA (n = 76) and placebo (n = 74) groups were similar with respect to sex, age, duration of disease, serum aspartate aminotransferase and alkaline phosphatase levels, liver histology, and Mayo risk score. During therapy, aspartate aminotransferase and alkaline phosphatase levels decreased more in the UDCA group than the placebo group ($p < 0.01$), but improvements in liver tests were not associated with decreased endpoints. By the end of the study, 30 patients in the UDCA group (39%) versus 19 patients in the placebo group (26%) had reached one of the pre-established clinical endpoints. After adjustment for baseline stratification characteristics, the risk of a primary endpoint was 2.3 times greater for patients on UDCA than for those on placebo ($p < 0.01$) and 2.1 times greater for death, transplantation, or minimal listing criteria ($p = 0.038$). Serious adverse events were more common in the UDCA group than the placebo group (63% versus 37% [$p < 0.01$]). Many of these serious adverse events were related to the development of primary endpoints and no unusual side effects were identified.
Lindor (2009) hypothetized that the use of higher doses of UDCA may have allowed more unabsorbed drug to enter the colon and be modified into hepatoxic bile acids. They also pointed out that, in an animal model, UDCA aggravated bile infarcts and hepatocyte necrosis, in the setting of biliary obstruction and that this may also explain, why the results in PSC, where biliary obstruction occurs, were different than in PBC. Based on these observations, the authors concluded that high doses of UDCA should not be used in PSC patients, despite findings in previous pilot trials.
Despite the fact that previous pilot trials involved a limited number of patients and were not placebo-controlled, it is difficult to explain why treatment with UDCA at similar high doses ranging from 25 to 30 mg/kg/day for 1 or 2 years (Harnois 2001 and Cullen 2008, respectively) in patients with PSC showed favourable outcomes and were well tolerated. In the study by Cullen (2008), the median dose in the high dose group was actually 33.1 mg/kg/day (range 18.9 to 44.1). A possibility is that the progression of the disease at baseline in patients enrolled in the study by Lindor (2009) could have been more advanced compared to that of patients enrolled in the pilot trials. Indeed, seventeen (17) and 18 percent of patients in the UDCA and placebo groups, respectively, were already presenting varices at study entry in the trial conducted by Lindor (2009). Thus, this difference in outcomes could be explained by differences in baseline patient population characteristics. However, not enough details are provided in these literature reports to further analyze this hypothesis.
Nevertheless, in view of the results obtained by Lindor (2009), high-dose UDCA may not be effective in patients suffering from PSC.

Effect on occurrence of colorectal cancer

Nearly 70% of cases of PSC are associated with inflammatory bowel disease, typically ulcerative colitis (UC). Patients with UC have an increased risk for developing colorectal cancer and dysplasia and individuals with concomitant PSC and UC are at a higher risk of developing colorectal cancer than patients with UC alone (Lewis 1999; Marchesa 1999).
Animal and *in vitro* studies have suggested that UDCA may have a role as a chemopreventive agent in the prevention of colorectal neoplasia (Serfaty 2010). Human studies have also investigated the role of UDCA as a chemopreventive agent, but results are conflicting, as some have observed a significant reduction in the occurrence of neoplasia (Pardi 2003; Tung 2001)

whereas in another one, a non-significant trend was observed (Wolf 2005). In the 2 studies where the dose used was mentioned, these were low (ranging from 10 to 15 mg/kg/day). In the third one (Wolf 2005), it is unclear what the mean dose was, but Eaton (2001) suspected that the use of high doses in this trial was very unlikely.

A recent prospective trial, (Rudolph 2011) investigated the annual incidence of colorectal carcinomas after long-term (median time of 6.7 years) UDCA treatment in patients with PSC with or without concomitant inflammatory bowel disease (IBD). Of a total of 171 patients enrolled in this study which started in 1987, 120 had IBD, the majority being UC (n = 108) and the others, Crohn's disease (n = 12). Up to 1995, all patients were treated with UDCA at a dose of 9–15 mg/kg per day. Under the assumption that higher doses may be more effective, starting in 1995, the patients were treated with an increased dose of 14–17 mg/kg per day, and starting from 2001 with 18–21 mg/kg per day. Intermittently, 56 patients participated in a dose-finding study and 20 patients received doses of 22–32 mg/kg per day of UDCA for a period of 3 months. During this very short time, no adverse effects have been observed. The results of these studies suggested that in patients treated with UDCA, the incidence of colonic carcinomas is low, and, after prolonged treatment, does not increase and may even decrease.

Eaton (2011) have retrospectively evaluated the pathology and colonoscopy reports from patients with both PSC and UC enrolled in a previous trial they had conducted (Lindor 2009), looking for the development of low-grade or high-grade dysplasia or colorectal cancer. Serum bile acid composition was also examined. All eligible patients were randomized by computer to study drug or placebo, stratified by histological stage of PSC, Mayo risk score and presence of varices. Fifty-six (56) subjects, among which 25 on UDCA and 31 on placebo had been followed for a total of 235 patient years with a similar mean duration of drug use of 4.0 ± 1.54 years in the UDCA group and 4.35 ± 2.02 years in placebo group. Endoscopic surveillance was balanced between the two groups as well as baseline characteristics (including duration of PSC and UC, medications, patient age, family history of colorectal cancer, and smoking status).

A total of 12 patients developed colorectal neoplasia during follow-up. Nine patients had received high-dose UDCA (1 colon cancer, 1 high-grade dysplasia, and 7 low-grade dysplasia), and 3 patients had received placebo (1 colon cancer, 1 high-grade dysplasia, and 1 low-grade dysplasia). In the UDCA group, the majority (78%) of patients developed colorectal neoplasia after 2 years of treatment. Patients who had received high-dose UDCA had a significantly higher risk of developing colorectal neoplasia (dysplasia and cancer) during the study compared with those who had received placebo (hazard ratio: 4.44, 95% confidence interval: 1.30–20.10, *P*=0.02). After adjusting for smoking, and UC duration, the use of high-dose UDCA was still associated with a higher incidence (HR: 5.97, 95% CI: 1.39– 41.44, *P* = 0.02) of colorectal neoplasia. Serum bile composition before and after treatment was available for review in 14 patients who received high-dose UDCA. Of those, 4 had developed colorectal neoplasia and the other 10 had not. The change in bile acid composition between those who had and had not developed colorectal neoplasia was not statistically significant. However, there was a trend toward a greater increase in lithocholic acid (LCA; 0.6 ± 0.6 vs. 0.2 ± 0.2, *P* = 0.28) and deoxycholic acid (DCA; 0.6±0.8 vs. 0.1±0.3, *P* = 0.22) in those who had developed colorectal neoplasia compared with those who had not.

As was hypothetized by the authors in the study by Lindor (2009), the possibility that higher doses of UDCA may have produced prolonged exposure to increased levels of the more toxic secondary bile acids, such as LCA and DCA, has also been retained in this situation, in view of the fact that *in vitro* studies have suggested a potential carcinogenic potential for these secondary bile acids. The authors concluded that high-dose UDCA should not be used for the prevention of colorectal neoplasia in this patient population suffering from both PSC and UC.

Torres et al. (2011) suggested that in addition to increased levels of secondary bile acids, genetic factors such as chromosome 6p2 can potentially have a role in the increased risk of colon neoplasia in PSC-UC patients.

In summary, only one article described that UDCA does not appear to decrease the risk of colorectal cancer or dysplasia (Wolf 2005). No study other than Dr Lindor's (2009) and their retrospective evaluation (Eaton 2011) has reported a risk of developing colorectal neoplasia with the use of high-dose UDCA.

MAH2's conclusions

Pilot clinical trials have shown that long-term administration of high doses of UDCA can improve surrogate markers of prognosis in children with PSC, such as the Mayo score. This score is however only a surrogate marker for survival, indicating a survival probability that does not necessarily translate into true improvement in survival. Some human studies performed to investigate the effect of low or medium dose UDCA treatment for the prevention of colorectal neoplasia in patients with PSC and IBD have not generated consistent results, providing either statistically significantly favourable outcomes or only trends.

One multicenter, randomized, double-blind, placebo-trial (and a retrospective evaluation of further results from this same trial) has been performed and has provided unexpected results, as long-term administration of UDCA, at a high dose of 28-30 mg/kg/day, seems to accelerate rather than slow down the disease process by increasing, among other complications, the likelihood of developing cholangiocarcinoma in patients with PSC and colorectal cancer in patients with both PSC and UC. It is not clear whether the patients enrolled in this trial could have suffered from more advanced disease as compared to the ones enrolled in the pilot studies investigating the effect of similar doses on survival probability.

Therefore, despite promising results obtained in pilot trials, results of the study by Lindor (2009) and their retrospective evaluation (Eaton 2011) caution against the empiric use of high doses of UDCA in patients with PSC.

Rapporteur's Comment

Both MAHs provided a comprehensive overview of UDCA's use in patients with primary sclerosing cholangitis (PSC). In addition, analyses of the recently emerged safety concerns have been submitted. The MAHs' conclusions are endorsed: although several potential reasons have been discussed, it appears that there is still no conclusive explanation as to why the serious side effects - such as an increased incidence of colorectal neoplasia - occured with high dose UDCA in adult PSC patients with or without concomitant UC in Lindor et al's study (2009). The rapporteur shares the MAHs' views that caution is needed against the empiric long term use of high dose UDCA is patients with PSC.

Following thorough review of the hereby identified safety signal, the rapporteur considers that the above described findings are only relevant to the adult population who have been receiving high dose UDCA long term for the treatment of PSC and therefore the benefit/risk balance of UDCA use in children remains uneffected. As discussed previously, in the proposed paediatric indication (hepatobiliar disorder associated with cystic fibrosis) UDCA was proven to be safe and well tolerated when administered long term (>2 years) and in high doses (20-30 mg/kg/day and above).

In summary, although a potential safety signal has been identified in the adult population, it does not affect the benefit/risk balance for the paediatric population and therefore no action is deemed necessary as part of this paediatric work-sharing procedure. However, the rapporteur identified an ongoing PSUR worksharing procedure (MT/H/PSUR/0001/002) where the identified signal could be appropriately followed up and member states could provide their input. From the paediatric perspective the issue is considered resolved and no regulatory action is deemed necessary.

Dosing

In light of the above discussed safety concerns, MAH 1 considers the use of high doses of UDCA (30 mg/kg/day) critical and therefore does not recommend UDCA to be used in doses beyond 20 mg/kg/day as long as this safety issue is not solved.
The rapporteur does not consider this action necessary as the safety concerns appear to be specific to adult patients with PSC only. Furthermore, there is robust evidence available that long term and high dose UDCA therapy is safe and well tolerated in children with cystic fibrosis (see comments in point 3).
The currently available evidence presented in this report about UDCA's both short- and long term use in children with CF is considered robust enough to justify the safety and efficacy of doses 20 to 30 mg/kg/day in this indication. In fact, it has been reported that at doses below 15 mg/kg/day none or only marginal effects might be seen, especially if given only for a short period of time. Furthermore, several studies demonstrated that if a child is not responding to a lower dose (15-20 mg/kg/day) of UDCA, a further increase of treatment dose (30-40 mg/kg/day) leads to the desired positive effect in most cases (see discussion in section II.3.2.b, page 14).

10) Proposals for paediatric SmPC text in sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2. The proposal should be justified by supporting data from the MAH databases and relevant published data.

MAH 1
MAH1 suggested to include the following additional information in the SmPC of UDCA containing drug products:

4.1 Therapeutic indications
Hepatobiliar disorder associated with cystic fibrosis in children aged 1 month to less than 18 years

4.2 Posology and method of administration
Paediatric population
Children with cystic fibrosis aged 1 month to less than 18 years:
The daily dose depends on body weight, and is ca. 20 mg/kg/day ursodeoxycholic acid in 2-3 divided doses.

4.3 Contraindications
Paediatric population:
Unsuccessful portoenterostomy without recovery of good bile flow in children with biliary atresia.

5.1 Pharmacodynamic properties
Paediatric population
Cystic fibrosis:
From clinical reports long-term experience up to 10 years and more is available with UDCA treatment in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepato-biliary changes if given in early stage of CFAHD. The most effective dose appears to be 20 mg UDCA/kg body weight/day. Treatment with UDCA should be started as soon as the diagnosis of CFAHD is made.

Treatment of pruritus (various forms of intrahepatic cholestatic liver disease)
There is evidence for the efficacy of UDCA in the treatment of pruritus in paediatric patients with various forms of intrahepatic cholestatic liver disease, particularly in those with Byler disease and Alagille syndrome with standard doses of UDCA (15 – 20 mg/kg /day). However, in rare

cases pruritus or deterioration of pruritus seemed to be triggered by UDCA (see Section .4.2 "Posology and method of administration")

Rapporteur's Comment
MAH 1 also provided the following comments (individually addressed by the rapporteur):

4.1
"We understand that changes of adult indications are not part of this procedure. However, it is in our opinion medically not reasonable to stop UDCA treatment at the age of 18 in patients with cystic fibrosis"

The rapporteur is not proposing to add/delete adult indications and considers that a separate 'Paediatric population' subheading in section 4.1 would make a sufficient distinction between UDCA's adult and paediatric use.

4.2
"The additional information suggested in the PAR "…with a further increase to 30mg/kg/day, if necessary" should in our opinion not be included in the dosage recommendation for the following reason: Although the findings with high dose UDCA in the study performed by Lindor et al. 2009 were related to patients suffering from PSC mainly with concomitant ulcerative colitis and the relevance for patients with cystic fibrosis is unclear, Falk does not recommend high dose UDCA treatment in any indication so far."

The rapporteur considers the previously recommended paediatric posology of "20 mg/kg/day in 2-3 divided doses, with a further increase to 30 mg/kg/day if necessary" justified and safe based on the available evidence presented in this report. Therefore MAH 1's proposal not to recommend doses higher than 20 mg/kg/day is not supported.

4.3
A minimal change is recommended to MAH 1's proposed wording in section 4.3:
"Unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia".

5.1
As previously discussed in point 3, MAH 1's proposal to include the available information on UDCA's long term use is fully supported by the rapporteur. MAH 1's proposed wording with a few minor changes is considered acceptable:
Paediatric population
Cystic fibrosis:
From clinical reports long-term experience up to 10 years and more is available with UDCA treatment in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepato-biliary changes if given at early stage of CFAHD. Treatment with UDCA should be started as soon as the diagnosis of CFAHD is made in order to optimize treatment effectiveness.
However, the rapporteur considers that the available evidence is not robust enough to indicate inclusion of information about treatment of pruritus in section 5.1 of the SmPC (see section above point 2).

MAH 2

MAH 2's proposed the following modifications of UDCA 250mg/500mg tablet SmPCs registered in France:

4.1. Therapeutic indications
Paediatric population :
Hepatobiliary disorder associated with cystic fibrosis in children aged 6 years to less than 18 years.

4.2. Dosage and method of administration
Paediatric population
Children with cystic fibrosis aged 6 years to less than 18 years: 20 mg/kg/day in 2-3 divided doses, with a further increase to 30 mg/kg/day if necessary

4.3. Contraindications
Paediatric population
Unsuccessful portoenterostomy or without recovery of good bile flow in children with CF and biliary atresia

Rapporteur's Comment
It is noted that MAH 2 proposed age range in section 4.1 has been altered to 6 years to less than 18 years (rather than 1 month to under 18 years). This is considered acceptable in light of the fact that MAH 2 only markets film coated tablets.

VIII. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Both MAHs' responses to the Rapporteur's and member states request for additional information adequently covered the issues identified in the preliminary assessment of the use of UDCA in the paediatric population and all issues are considered resolved.

In summary, the currently available evidence only supports UDCA's use in hepatobiliar disorder associated with cystic fibrosis in children aged 1 month to less than 18 years. Treatment with UDCA in this paediatric condition is considered to be safe and effective at a dose of 20 mg/kg/day in 2-3 divided doses with an increase up to 30 mg/kg/day if necessary based on clinical response. Although some concerns emerged recently regarding long term high dose UDCA treatment in adults with PSC, this is not considered relevant to the paediatric CF population. Furthermore, the currently available evidence presented in this report about UDCA's long term use in children with CF further justifies the safety and efficacy of doses 20 to 30 mg/kg/day in this indication.
Sufficient evidence has been provided that UDCA is able to improve/normalise hepatic transaminases in children suffering from cystic fibrosis associated hepatobiliar disorders (CFAHD) both when used short- and long term (up to 12 years). Moreover, there is some evidence suggesting that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepato-biliary changes if given at early stage of CFAHD. Treatment with UDCA should be started as soon as the diagnosis of CFAHD is made in order to maximize treatment effectiveness.

Based on the submitted safety data, both MAHs are advised to closely monitor dermatological and haematological adverse events in children. Furthermore, in light of the newly proposed paediatric indication MAHs should be ready to submit a risk management plan (RMP) in

accordance with the new pharmacovigilance legislation at the time of the variations to implement the new indication.

In summary, based on this paediatric work-sharing assessment of the use of ursodeoxycholic acid in children the following information should be included in sections 4.1, 4.2, 4.3 and 5.1 of the SmPC. Of note, the SmPC update recommendations are formulation-specific as MAH 2 does not hold market authorization for a suspension formulation.

a) Suspension

Section 4.1 Therapeutic indications
Paediatric population
Hepatobiliar disorder associated with cystic fibrosis in children aged 1 month to less than 18 years

Section 4.2 Posology and method of administration
Paediatric population
Children with cystic fibrosis aged 1 month to less than 18 years: 20 mg/kg/day in 2-3 divided doses, with a further increase to 30 mg/kg/day if necessary

Section 4.3 Contraindications
Paediatric population
Unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia

Section 5.1 Pharmacodynamic properties
Paediatric population
Cystic fibrosis
From clinical reports long-term experience up to 10 years and more is available with UDCA treatment in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepato-biliary changes if given at early stage of CFAHD. Treatment with UDCA should be started as soon as the diagnosis of CFAHD is made in order to optimize treatment effectiveness.

b) Tablets, Capsules

Section 4.1 Therapeutic indications
Paediatric population
Hepatobiliar disorder associated with cystic fibrosis in children aged 6 years to less than 18 years

Section 4.2 Posology and method of administration
Paediatric population
Children with cystic fibrosis aged 6 years to less than 18 years: 20 mg/kg/day in 2-3 divided doses, with a further increase to 30 mg/kg/day if necessary

Section 4.3 Contraindications
Paediatric population
Unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia

Section 5.1 Pharmacodynamic properties

Paediatric population

Cystic fibrosis

From clinical reports long-term experience up to 10 years and more is available with UDCA treatment in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepato-biliary changes if given at early stage of CFAHD. Treatment with UDCA should be started as soon as the diagnosis of CFAHD is made in order to optimize treatment effectiveness.

The applicants are therefore requested to submit a Type IB variation to update the SmPCs and PILs of products containing ursodeoxycholic acid in line with the above work-sharing recommendations.

Furthermore, in light of the new paediatric indication, the MAHs are requested to submit a Risk Management Plan (RMP) to address the identified risks for the paediatric population in accordance with the new pharmacovigilance legislation at the time of the variations to implement the new paediatric indication. This has to be done in line with the current CMDh advice, which can be found at the following link
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Pharmacovigilance_Legislation/CMDh-257-2012-Rev2-2012_07.pdf

IX. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Active Substance	Product name	MAH
Ursodeoxycholic acid (UDCA)	DELURSAN 250 mg, film-coated tablet	AXCAN PHARMA SAS
Ursodeoxycholic acid (UDCA)	DELURSAN 500 mg, scored, film-coated tablet	AXCAN PHARMA SAS
Ursodeoxycholic acid (UDCA)	Ursofalk 250mg hard capsules	Codali SA
Ursodeoxycholic acid (UDCA)	Ursofalk 250mg hard gelatin capsules	Dr Falk Pharma
Ursodeoxycholic acid (UDCA)	Ursofalk 250mg/5ml oral suspension	Dr Falk Pharma
Ursodeoxycholic acid (UDCA)	Ursofalk 50mg/ml oral suspension	Dr Falk Pharma
Ursodeoxycholic acid (UDCA)	Ursofalk 250mg film-coated tablets	Dr. Falk Pharma GmbH
Ursodeoxycholic acid (UDCA)	URSOFALK 250mg hard capsule	GALENICA A.E
Ursodeoxycholic acid (UDCA)	URSOFALK 250 mg/5 ml oral suspension	GALENICA A.E
Ursodeoxycholic acid (UDCA)	Ursofalk 250 mg Kapseln	Merck GmbH
Ursodeoxycholic acid (UDCA)	Ursofalk 250mg orale Suspension	Merck GmbH
Ursodeoxycholic acid (UDCA)	Ursofalk 250 mg hard capsule	SALUS, Ljubljana, d.d.

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