SYNOPSIS

NAME OF SPONSOR The University of Adelaide **NAME OF FINISHED PRODUCT** Rifadin, Rimapen, Rimactin **NAME OF ACTIVE INGREDIENT(S)** Rifampicin	**INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD** Not applicable, this drug has Marketing Authority in all countries contributing to the study	**(FOR NATIONAL AUTHORITY USE ONLY)**

Title of Study	A randomised Trial of URsodeoxycholic acid versus RIFampicin in severe early onset Intrahepatic Cholestasis of pregnancy: the TURRIFIC study		
Investigator(s) and study centres ACTIVE	Professor Bill Hague, Robinson Research Institute, The University of Adelaide, North Adelaide, SA, AUS Professor Michael Stark, Women's and Children's Hospital, North Adelaide, SA, AUS Dr Jessica Gehlert, Flinders Medical Centre, Bedford Park, SA, AUS Dr Melissa Whalan, Lyell McEwin Hospital, Elizabeth Vale, SA, AUS Assoc. Professor Raiyomand Dalal, Campbelltown Hospital, Campbelltown, NSW, AUS Professor Angela Makris, Liverpool Hospital, Liverpool, NSW, AUS Dr Antonia Shand, Royal Hospital for Women, Randwick, NSW, AUS Professor Susan Walker, Mercy Hospital for Women, VIC, Heidelberg, AUS Professor Kirsten Palmer, Monash Medical Centre, Clayton, VIC, AUS and Jessie McPherson Private Hospital, Clayton, VIC, AUS Dr Sarah Price and A/Prof Stefan Kane, Royal Women's Hospital, Parkville, VIC, AUS Professor Michael Peek, Nepean Hospital, Kingswood, NSW, AUS Dr Dorothy Graham, King Edward Memorial Hospital, Subiaco, WA, AUS Professor Kate Walker, Nottingham University Hospitals, NHS Trust, Nottingham, UK Professor Catherine Williamson, Imperial College Hospital NHS Trust (Queen Charlotte's and Chelsea Hospital, Hammersmith, London, UK Professor Catherine Nelson-Piercy, Guy's and St Thomas' Hospital NHS Foundation Trust, London, UK		
Investigator(s) and study centres CLOSED 31 Dec 2024	Assoc. Professor Gunilla Ajne, Karolinska University Hospital, Huddinge, SWE Assoc. Professor Ylva Carlsson, Sahlgrenska University Hospital, Gothenburg, SWE Professor Oskari Heikinheimo and Dr Laura Lampio, Helsinki University Hospital, Meilahti, FIN		
Publication	N/A		
Study period	From: 16 July 2019 To: Ongoing	Phase of development	Phase IIIb
Objectives	Primary Objective To test whether Rifampicin (RIF) compared with Ursodeoxycholic acid (UDCA) treatment of women with severe early onset ICP reduces the degree of pruritus. Secondary Objective To test whether RIF compared with UDCA improves short-term outcomes for both mother and infant in severe early onset ICP, including the length of gestation and the incidence of caesarean section and preterm birth.		
Methodology	Randomized, comparator-controlled (UDCA), open-label, multicentre, parallel-group trial		
Number of patients	Planned: 108 Completed: 62, 2 withdrawn		

Diagnosis and main criteria for inclusion	Diagnosis of ICP: Pregnant women with serum bile acids (BA) equal to or greater than 40 µmol/L and with itch and gestational age between 14^{+0} and 34^{+6} weeks' gestation (weeks') are eligible to be included in the study
Test product, dose and mode of administration	Rifampicin, 300 mg twice daily, oral
Duration of treatment	Between 0 to 26 weeks. This is determined by the participant's gestation when she joins the study and when the baby is born.
Criteria for evaluation	**Primary:** Pruritus defined as worst itch in the previous 24 hours assessed on a patient-recorded visual analogue scale. Pruritus will be evaluated at one week after trial entry and then on a monthly basis to 28 weeks', and then weekly to delivery **Secondary** (maternal): serum concentrations of BA, bilirubin (total), alanine transaminase (ALT), gamma glutamyl transferase (GGT), pruritogens including autotaxin, lysophosphatidic acid and progesterone sulphated metabolites; peak serum concentration (between randomisation and delivery) of BA; urinary glucuronidated 6α-hydroxylated BA concentrations 7 days after commencing/changing therapy; serial changes in the maternal gut microbiota and metabolome from randomisation to 6 weeks after delivery; assessment of the placental and amniotic fluid microbiota at delivery; assessment of the maternal exome and virome at trial entry; maximum dose of trial medications required, and days of such medications; days from randomisation to birth, and from 36^{+0} weeks' to birth; days to resolution/amelioration of symptoms; need for added treatment with UDCA or RIF as appropriate after 7 days of the randomly-allocated drug therapy; need for additional therapy at maximum trial dosage (e.g., antihistamines, cholestyramine, therapeutic plasma exchange, other); incidence of gestational diabetes mellitus (GDM) (WHO criteria) and its treatment (diet, metformin, insulin), and of gestational hypertension/pre-eclampsia (ISSHP criteria); mode of onset of labour and gestation at onset; length of labour; presence of meconium in the liquor; mode of birth, classified as spontaneous vaginal, instrumental vaginal or caesarean section; reason for induction or pre-labour caesarean section; estimated blood loss at birth; time for resolution of symptoms after birth. **Secondary** (neonatal): miscarriage (fetal death before 20^{+0} weeks'), Stillbirth (fetal death $\geq 20^{+0}$ weeks' or birthweight >400g if gestation unknown), and neonatal death in hospital up to 7 days after birth (excluding death due to congenital anomalies); neonatal unit (NNU) admissions until infant discharge home from hospital; number of nights in each category of care (intensive, high dependency, special, transitional and normal) and total number of nights in hospital; birthweight (g), and customised/ population birthweight centile; gestational age at delivery; placental weight (untrimmed and trimmed) at birth, and placental histology, compared with the next placenta delivered from a woman of similar gestation, but without ICP; Apgar scores at 1 and 5 minutes after birth; umbilical arterial and venous pH and base excess at birth; cord blood BA; assessment of the neonatal gut microbiota and metabolome in amniotic fluid and meconium at birth and in stool samples at 1 and 6 weeks after birth; need for supplementary oxygen prior to discharge, and number of days when such oxygen is required; need for ventilation support (CPAP/high flow/endotracheal ventilation); pneumothorax (confirmed on chest X-ray); need for phototherapy; abnormal cerebral ultrasound scan; confirmed sepsis (positive blood or cerebrospinal fluid cultures); necrotising enterocolitis (Bell's stage 2 and 3); seizures (confirmed by EEG or requiring anticonvulsant therapy); encephalopathy grade (worst at any time: mild, moderate, severe); hypoglycaemia (blood glucose <2.6 mmol/l on two or more occasions); severe hypoglycaemia (blood glucose <1.8 mmol/l on two or more occasions); other indications and main diagnoses resulting in NNU admission; exclusively breast-fed at discharge from the NNU.
Statistical methods	All analyses will follow the intention to treat principle, i.e., all randomised women and babies will be analysed according to the treatment they were allocated to, irrespective of the treatment they received or whether they received any treatment at all. Demographic and clinical data will be summarised with counts and percentages for categorical variables, means (with standard deviations) for normally distributed

	continuous variables and medians (with interquartile or simple ranges) for other continuous variables. For the primary outcome, the effectiveness of the interventions will be assessed by calculating the differences in mean itch score with 95% confidence intervals (95%CI), determined with a linear regression model using generalised estimating equations (GEEs). All comparative analyses will be performed adjusting for stratification variables and baseline measures of the outcome where relevant. Binary outcomes will be analysed using log binomial regression models. Results will be presented as adjusted risk ratios and 95%CI. If the model is unstable, log Poisson regression models with robust variance estimation will be used. Continuous outcomes will be analysed using linear regression models and results will be presented as adjusted differences in means (with 95%CI). Analysis of outcomes that are measured repeatedly over time (severity of itch and biochemistry measures) will use repeated measures analysis techniques, including generalised estimating equations (GEEs) and/or random effects.

Both the study drug, Rifampicin, and the comparator, Ursodeoxycholic acid, have marketing authority in all countries where this study is being conducted. For this reason, sites use the supply locally available, no manufacturer/brand being specified for use.

SUMMARY CONCLUSIONS
As the study is still ongoing, there has been no analysis of data and no conclusions drawn.

EFFICACY RESULTS
Not applicable.

SAFETY RESULTS
Not applicable

CONCLUSION
Not applicable

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Signed: Date: 25 / 12 / 2025

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