Clinical trial results:
Double-blind, randomised, placebo-controlled, multi-centre phase III clinical study comparing the combination of ursodeoxycholic acid capsules plus budesonide capsules to ursodeoxycholic acid capsules plus placebo in the treatment of primary biliary cirrhosis

Summary

EudraCT number	2007-004040-70
Trial protocol	DE SE FR AT NL FI ES HU GB LT DK IT PL
Global end of trial date	19 October 2015

Results information

Result version number	v1 (current)
This version publication date	23 December 2018
First version publication date	23 December 2018

Trial information

Trial identification

Sponsor protocol code	BUC-56/PBC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00746486
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Falk Pharma GmbH
Sponsor organisation address	Leinenweberstrasse 5, Freiburg, Germany, 79108
Public contact	Project Management, Dr. Falk Pharma GmbH , +49 7611514199, markus.proels@drfalkpharma.de
Scientific contact	Project Management, Dr. Falk Pharma GmbH , +49 7611514199, markus.proels@drfalkpharma.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2015
Global end of trial reached?	Yes
Global end of trial date	19 October 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- To compare the efficacy and tolerability of a combination therapy with ursodeoxycholic acid (12-16 mg/kg body weight/d) plus budesonide (9 mg/d) vs. ursodeoxycholic acid (12-16 mg/kg body weight/d) plus placebo in the treatment of PBC.

Protection of trial subjects:

Close supervision of subjects by implementing interim visits every 14 days during the first 4 weeks of treatment, every 3 months up to Month 12 and every 6 months up to month 36 to guarantee their safety and wellbeing.
Prior to recruitment of patients all relevant documents of the clinical study were submitted and approved by the Independent Ethics Committees (IECs) responsible for the participating investigators. Written consent documents embodied the elements of informed consent as described in the Declaration of Helsinki, the ICH Guidelines for Good Clinical Practice (GCP) and were in accordance with all applicable laws and regulations. The informed consent form and patient information sheet described the planned and permitted uses, transfers and disclosures of the patient's personal data and personal health information for purposes of conducting the study. The informed consent form and the patient information sheet further explained the nature of the study, its objectives and potential risks and benefits as well as the date informed consent was given. Before being enrolled in the clinical trial, every patient was informed that participation in this trial was voluntary and that he/she could withdraw from the study at any time without giving a reason and without having to fear any loss in his/her medical care. The patient’s consent was obtained in writing before the start of the study. By signing the informed consent, the patient declared that he/she was participating voluntarily and intended to follow the study protocol instructions and the instructions of the investigator and to answer the questions asked during the course of the trial.

Background therapy:

None.

Evidence for comparator:

Ursodeoxycholic acid (Ursofalk®250 mg capsules) is registered for the treatment of cholestatic liver diseases including PBC.

Actual start date of recruitment	21 January 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Sweden: 7

Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Lithuania: 12
Worldwide total number of subjects	62
EEA total number of subjects	61

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	54
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 90 patients were enrolled into the study in Austria, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Lithuania, Netherlands, Poland, Spain and Sweden from February 2009 to Oct 2014.

Pre-assignment

Screening details:

Screening Criteria: 1. Signed Informed Consent 2. Age ≥ 18 years 3. UDCA treatment for at least 6 months prior to baseline exam. 4. Liver biopsy performed.
In total, 90 patients were screened. Thereof 62 patients were randomised and received at least one dose of study medication and were included in the safety set and full analysis set (FAS) .

Pre-assignment period milestones

Number of subjects started	62
Number of subjects completed	62

Period 1

Period 1 title	Treatment Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Conducted with the double-blind design.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

9 mg Budesonide (3 mg capsules TD). 6 mg Budesonide (3 mg capsules BD) are allowed if adjustment according to disease activity is necessary plus 12-16 mg/kg BW/d ursodeoxycholic acid

Arm type	Experimental
Investigational medicinal product name	Budesonide plus ursodeoxycholic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

9 mg Budesonide (3 mg capsules TD). 6 mg Budesonide (3 mg capsules BD) if adjustment according to disease plus 12-16 mg/kg BW/d ursodeoxycholic acid.

Arm title	Arm B

Arm description:

Budesonide Placebo (one Placebo capsule TD) or BD depending on AST values plus 12-16 mg/kg BW/d ursodeoxycholic acid .

Arm type	Placebo

Investigational medicinal product name	Budesonide Placebo (one capsule TD) or BD depending on AST values plus 12-16 mg/kg BW/d ursodeoxycholic acid.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Budesonide Placebo (one capsule TD) or BD depending on AST values plus 12-16 mg/kg BW/d ursodeoxycholic acid.

Number of subjects in period 1	Arm A	Arm B
Started	40	22
Completed	40	22

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Phase (overall period)
Reporting group description:	
90 patients have signed an Informed Consent at Screening. 62 patients were finally randomised in one of the two treatment groups. 28 patients were Screening failures.	

Reporting group values	Treatment Phase (overall period)	Total	
Number of subjects	62	62	
Age categorical			
90 patients have signed the Informed Consent at Screening. 62 patients were finally randomized.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	54	54	
From 65-84 years	8	8	
85 years and over	0	0	
Gender categorical			
Subjects of both sex were recruited into the trial.			
Units: Subjects			
Female	60	60	
Male	2	2	

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
9 mg Budesonide (3 mg capsules TD). 6 mg Budesonide (3 mg capsules BD) are allowed if adjustment according to disease activity is necessary plus 12-16 mg/kg BW/d ursodeoxycholic acid	
Reporting group title	Arm B
Reporting group description:	
Budesonide Placebo (one Placebo capsule TD) or BD depending on AST values plus 12-16 mg/kg BW/d ursodeoxycholic acid .	

Primary: Number of patients with Improvement of liver histology

End point title	Number of patients with Improvement of liver histology
End point description:	
Number of patients with improvement of liver histology with respect to inflammation and no progression of fibrosis.	
End point type	Primary
End point timeframe:	
From Baseline to the last individual patient visit	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	22		
Units: number	11	5		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Statistical analysis description:	
For confirmatory hypothesis testing the Cochran-Mantel-Haenszel test for comparing two rates	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Cochran-Mantel-Haenszel

Secondary: Number of patients presenting with cirrhosis or esophageal varices and/or ascites

End point title	Number of patients presenting with cirrhosis or esophageal varices and/or ascites

End point description:

Number of patients presenting with cirrhosis or esophageal varices and/or ascites at the end of the treatment.

End point type	Secondary

End point timeframe:

At the end of the treatment (from Baseline to the last individual patient visit).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	22		
Units: number	1	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were assessed at all interim visits (Week 2, Week 4, Month 3, Month 6, Month 9, starting from Month 12 (every 6 months) to final study visit of individual patient or Month 36 respectively.

Adverse event reporting additional description:

Treatment-Emergent Adverse Events

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Arm A

Reporting group description:

9 mg Budesonide (3 mg capsules TD). 6 mg Budesonide (3 mg capsules BD) are allowed if adjustment according to disease activity is necessary plus 12-16 mg/kg BW/d ursodeoxycholic acid.

Reporting group title	Arm B

Reporting group description:

Budesonide Placebo (one Placebo capsule TD) or BD depending on AST values plus 12-16 mg/kg BW/d ursodeoxycholic acid

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 40 (62.50%)	14 / 22 (63.64%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gatrointestinal tract adenoma			
subjects affected / exposed	1 / 40 (2.50%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 40 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 40 (2.50%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 40 (2.50%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Biopsy liver	Additional description: Planned hospitalization due to liver biopsy was reported as serious adverse event according to the clinical study protocol in this trial.		
subjects affected / exposed	22 / 40 (55.00%)	11 / 22 (50.00%)	
occurrences causally related to treatment / all	0 / 22	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	1 / 40 (2.50%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 40 (2.50%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Central nervous system lesion			
subjects affected / exposed	1 / 40 (2.50%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 40 (2.50%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 40 (2.50%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Tongue cyst			
subjects affected / exposed	1 / 40 (2.50%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary cirrhosis primary			
subjects affected / exposed	0 / 40 (0.00%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallblader polyp			
subjects affected / exposed	0 / 40 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 40 (2.50%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 40 (97.50%)	21 / 22 (95.45%)	
Investigations			
Blood cortisol			
subjects affected / exposed	6 / 40 (15.00%)	0 / 22 (0.00%)	
occurrences (all)	6	0	
Weight increased			
subjects affected / exposed	5 / 40 (12.50%)	0 / 22 (0.00%)	
occurrences (all)	5	0	
Blood glucose increased			
subjects affected / exposed	2 / 40 (5.00%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 40 (45.00%)	9 / 22 (40.91%)	
occurrences (all)	18	9	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	5 / 40 (12.50%)	4 / 22 (18.18%)	
occurrences (all)	5	4	
Nausea			
subjects affected / exposed	4 / 40 (10.00%)	4 / 22 (18.18%)	
occurrences (all)	4	4	
Diarrhoea			
subjects affected / exposed	3 / 40 (7.50%)	4 / 22 (18.18%)	
occurrences (all)	3	4	
Dyspepsia			
subjects affected / exposed	5 / 40 (12.50%)	1 / 22 (4.55%)	
occurrences (all)	5	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 40 (17.50%)	4 / 22 (18.18%)	
occurrences (all)	7	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2011	Amendment was issued based on an advice from the German competent authority and containing the following elements: • Modification of trial population from "patients at risk of disease progression" to "patients with an incomplete response to UDCA treatment" • Modification of the primary endpoint • Modification of the secondary endpoints • Adjustment of sample size due to modified primary endpoint and trial population
12 February 2015	Termination of recruitment into the study following a recommendation of the Independent Data Monitoring Committee. Patients had to leave the study after at least 1 year of study treatment. The last visit of the last patient who completed the study after at least 1 year of treatment was estimated to occur in August 2015. As a consequence, the number of patient enrolled into the study was 62.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Early termination of the trial by the sponsor based on the recommendation of the IDMC.
IDMC recommendation was to observe the blinded patients recruited until now for one year more was respected.

Notes: