SYNOPSIS

Name of Sponsor/Company **Dr. Falk Pharma GmbH**	*Individual Study Table Referring to Part of the Dossier*	*(For National Authority Use only)*
Name of Finished Product: **Ursofalk® 500 mg Tablets**	*Volume:*	
Name of Active Ingredient: **Ursodeoxycholic acid**	*Page:*	

Title of Study:
Double-blind, double-dummy, randomised, cross-over, multicentre phase IV clinical study comparing the effect of Ursofalk® 500 mg tablets OD versus Ursofalk® 250 mg capsules OD on liver enzyme parameters in the treatment of primary biliary cirrhosis

Investigators:

Germany
PD Dr. Christian Rust, München
Prof. Dr. Heinz Hartmann, Herne
Dr. Hans-Jörg Cordes, Frankfurt/Main
PD Dr. Holger Hinrichsen, Kiel
Prof. Dr. Martin Rössle, Freiburg
Dr. Marc Eisold, Mössingen
Dr. Johannes Wiegand, Leipzig
PD Dr. Kurt Grüngreiff, Magdeburg

The Netherlands
Prof. Dr. Ulrich Beuers, Amsterdam

Study Centres:
Nine centres enrolled patients: Eight centres in Germany and one centre in the Netherlands.

Publications:
None

Study Period:		**Phase of Development:**
First patient enrolled:	10 Nov 2008	IV
Last patient completed:	14 Jul 2010	

Objectives:
Primary Objective:
- To compare the efficacy of Ursofalk® 500 mg tablets [(14 ± 2 mg/kg body weight (BW)/d)] vs. Ursofalk® 250 mg capsules [(14 ± 2 mg/kg body weight (BW)/d)] in the treatment of primary biliary cirrhosis (PBC).

Secondary Objectives:
- To assess the safety and tolerability in the form of adverse events and laboratory parameters,
- To examine patients' preference of study drug,
- To assess patients' quality of life.

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Methodology:
This was a double-blind, double-dummy, randomised, cross-over, multicentre, phase IV clinical trial. In this trial, two different formulations (tablets and capsules) were tested. There were two consecutive phases (Phase 1 and Phase 2, each 12 weeks) with two different treatments. The sequence of the treatments (Treatment 1 and Treatment 2) was according to the particular sequence group. To maintain double-blinding, the study was conducted using the double-dummy technique. This means that patients received verum Ursofalk® tablets together with placebo capsules or verum Ursofalk® capsules together with placebo tablets.

Treatment 1 (test): Ursofalk® 500 mg tablets 14 ± 2 mg/kg BW/d OD in the evening + Placebo capsules

Treatment 2 (reference): Ursofalk® 250 mg capsules 14 ± 2 mg/kg BW/d OD in the evening + Placebo tablets

The patients were assigned to one of the two following sequence groups in conformity with a randomisation list:

Sequence Group 1: Treatment 1 (week 1 – week 12) + Treatment 2 (week 13 – week 24)
Sequence Group 2: Treatment 2 (week 1 – week 12) + Treatment 1 (week 13 – week 24)

The individual dose of Ursofalk® tablets and capsules (and corresponding number of placebo tablets and capsules) was calculated based on the particular body weight and followed the Summary of Product Characteristics (SmPC).

Number of Patients (Planned and Analysed):
A 2-step group-sequential adaptive design with one interim analysis, which allowed for sample size adaptation, was used. The interim analysis was planned to be performed when the data of 26 evaluable patients were available. Because the interim analysis could have led to successful rejection of null-hypotheses, the lower limit of sample size was 26 patients. Based on the interim analysis, which actually included the first 27 randomised patients, it was planned to randomise 64 patients in order to achieve at least 56 patients with evaluable primary endpoints in the intent-to-treat analysis set. Overall, 65 patients were randomised (27 patients in stage 1, 38 patients in stage 2). One patient did not use study medication and was excluded from the safety analysis set. The safety analysis set and the intent-to-treat analysis set included 64 patients, the per-protocol analysis set included 53 patients.

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Analysed in the Final Analysis:

Number of patients	Total	Sequence Group 1 (Tablets => Capsules)	Sequence Group 2 (Capsules => Tablets)
Randomised	65	32	33
Safety	64	32	32
ITT	64	32	32
PP	53	26	27

Diagnosis and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

- Signed informed consent,
- Male or female patients of ≥ 18 years of age,
- Ursodeoxycholic acid (UDCA) ≥ 10 mg/kg body weight/d treatment for at least 6 months prior to inclusion and responsive (Normalisation of alkaline phosphatase (AP) or reduction of AP ≥ 40% after onset of UDCA),
- At least 2 out of the following 3 criteria:
  - Histologically proven non-cirrhotic liver disease compatible with early-stage PBC (stage I + II),
  - Positive AMA (anti-mitochondrial antibody) testing (titre ≥ 1:40),
  - Serum alkaline phosphatase > 1,5 times upper limit of normal at any time since diagnosis,
- Negative pregnancy test at baseline visit in female patients of childbearing potential,
- Women of child-bearing potential had to apply appropriate contraceptive methods, e.g. hormonal contraception, intra-uterine device (IUD), double-barrier method of contraception (e.g. use of condom and spermicide), sexual abstinence, partner had undergone vasectomy and subject was in a monogamous relationship. The investigator was responsible for determining whether the subject had adequate birth control for study participation.

Exclusion Criteria:

- Histologically proven cirrhosis, PBC stage III + IV - Histology not mandatory,
- Positive Test for HBsAg (hepatitis B surface antigen) and HCV (hepatitis C virus) antibodies,
- Positive HIV (human immunodeficiency virus) serology,
- Features suggestive of other coexistent liver diseases, including hemochromatosis, primary sclerosing cholangitis (PSC), alcohol liver disease, Wilson's disease, α-antitrypsin-deficiency,
- Hepatic encephalopathy or history of hepatic encephalopathy,
- Suspected non-compliance of the patient (suspected difficulties to comply with the study period of 6 months),
- Severe co-morbidity substantially reducing life expectancy,
- Known intolerance/hypersensitivity/resistance to study drugs or drugs of similar chemical structure or pharmacological profile,
- Existing or intended pregnancy or breast-feeding,
- Participation in another clinical trial within the last 30 days, simultaneous participation in another clinical trial, or previous participation in this trial,
- Concomitant medication interacting with Ursofalk®, like cholestyramine, colestipol, and aluminium hydroxide,
- Acute inflammation of the gall bladder or biliary tract,
- Occlusion of the biliary tract (occlusion of the common bile duct or cystic duct),
- Concomitant immunosuppressive therapy (e.g. steroids, azathioprine).

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Duration of Treatment:
24 weeks (2 treatment phases of 12 weeks with cross-over between the two phases from test drug to reference drug or vice versa depending on the patient's sequence group)

Test Drug, Dose and Mode of Administration, Batch Number:
Ursodeoxycholic acid 14 ± 2 mg/kg body weight (BW)/d (Ursofalk® 500 mg tablets) once daily (OD).
Due to the double-dummy design, during Treatment 1 patients were to administer orally:
- Individual number of Ursofalk® 500 mg tablets once daily,
- Individual number of placebo capsules once daily.

Batch Numbers:
Verum tablets: 07H08060L (fictitious batch no. UT151107) Expiry date: 08/2011
Placebo capsules: 0711979001 (fictitious batch no. UT151207) Expiry date: 10/2012
Only one batch each was used for all patients.

Reference Drug, Dose and Mode of Administration, Batch Number:
Ursodeoxycholic acid 14 ± 2 mg/kg body weight (BW)/d (Ursofalk® 250 mg capsules) once daily (OD).
Due to the double-dummy design, during Treatment 2 patients were to administer orally:
- Individual number of Ursofalk® 250 mg capsules once daily,
- Individual number of placebo tablets once daily.

Batch Numbers:
Verum capsules: 07J22467L (fictitious batch no. UT151207) Expiry date: 10/2012
Placebo tablets: 0250733 (fictitious batch no. UT151107) Expiry date: 08/2011
Only one batch each was used for all patients.

Criteria for Evaluation:
Primary Efficacy Endpoint:
- Relative differences (called relative changes in the protocol) of AP (alkaline phosphatase), GGT (γ-glutamyl transferase) and ALT (alanine aminotransferase) between the end of the treatment-period with Ursofalk® 250 mg capsules and the end of the treatment-period with Ursofalk® 500 mg tablets.

Secondary Efficacy Endpoints:
- Liver function measured by liver enzymes,
- Quality of life, measured with PBC-40,
- Global assessment of efficacy by patient and investigator,
- Patient's acceptance and preference of study drug.

Safety:
- Adverse events (AEs),
- Blood count, serum chemistry,
- Vital signs (blood pressure, heart rate),
- Abnormal findings from physical examination,
- Assessment of tolerability by investigator and patient.

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Statistical Methods:

Primary Efficacy Evaluation:	
Relative differences of AP, GGT and ALT between the end of the treatment-period with Ursofalk® 250 mg capsules and the end of the treatment-period with Ursofalk® 500 mg tablets	Two-stage group-sequential adaptive Pocock design; one-sided Wilcoxon signed rank tests (overall $\alpha = 0.025$) to test if mean differences (pooled for both sequence groups) were significantly smaller than the non-inferiority margin $\Delta = 15\%$. Three hierarchically ordered hypotheses (1st AP, 2nd GGT, 3rd ALT)
Subgroup Analyses:	Relative differences in AP, GGT and ALT between the end of the treatment-period with Ursofalk® capsules and Ursofalk® tablets by • country, • centre, • type of previous UDCA treatment, • age at baseline and • AP at baseline.
Secondary Efficacy Evaluation:	
• Liver function measured by liver enzymes (AP, GGT, ALT, total bilirubin, AST)	Summary statistics including 95%-confidence intervals (95%-CIs) for relative and absolute differences between the end of the treatment-period with Ursofalk® capsules and Ursofalk® tablets, liver function at visits, change of liver function within treatment phases.
• Quality of life (measured with PBC-40)	Summary statistics including 95%-CIs and two-sided Wilcoxon signed rank tests for absolute differences in PBC-40 Total score and PBC-40 domain scores between the end of the treatment-period with Ursofalk® capsules and Ursofalk® tablets.
• Global assessment of efficacy by patient and investigator	Absolute and relative frequencies (including cross tabulation regarding treatments), risk differences and McNemar tests.
• Patient's acceptance and preference of study drug	Absolute and relative frequencies of patients' answers, sign test comparing treatments regarding the patients' answers to question 1 (Which medication do you find easier and more convenient to take?).

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Safety Evaluation:	
• Adverse events (AEs)	Absolute and relative frequencies.
• Blood count, serum chemistry	Summary statistics including 95%- CIs for laboratory values at visits, change within treatment phases and absolute and relative frequencies of deviations from the normal range and of investigators' assessments.
• Vital signs (blood pressure, heart rate)	Summary statistics including 95%- CIs for vital signs values at visits.
• Abnormal findings from physical examination	Absolute and relative frequencies.
• Assessment of tolerability by investigator and patient	Absolute and relative frequencies.
Others (e.g. Baseline Characteristics):	
Categorical variables	Absolute and relative frequencies
Continuous variables	Summary statistics

Summary statistics include mean, standard deviation, minimum, maximum, upper and lower quartile, median.

Summary:

Patient Disposition

In total, 65 patients were recruited and randomised into the study. Only one patient did not take any study medication and was therefore not included into any statistical analysis.

Out of the 64 patients who were treated with study medication, 6 terminated the trial prematurely (sequence group 1 [tablets → capsules]: 3/32 patients [9.4%], all during treatment with Ursofalk® tablets; sequence group 2 [capsules → tablets]: 3/32 patients [9.4%], 2 during treatment with Ursofalk® capsules and 1 during treatment with Ursofalk® tablets).

Withdrawal of consent was mentioned twice in sequence group 1 and lack of compliance and major violation of enrolment criteria were mentioned in sequence group 2. "Other reasons" were mentioned in both sequence groups each with one patient. The "other reasons" for withdrawal were need for prohibited medication due to an adverse event for both patients.

Allocation to analysis sets:

	Number of patients		
	Total	**Sequence group 1 Tablets → Capsules**	**Sequence group 2 Capsules → Tablets**
Randomised	65	32	33
Safety	64	32	32
ITT	64	32	32
PP	53	26	27

The safety as well as the ITT analysis set included 64 of 65 randomised patients. Eleven patients were excluded from the PP analysis because of major protocol violations, thus the PP analysis set included 53 patients.

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Key demographic and baseline characteristics (ITT analysis set):

		Total (n=64)	Sequence group 1 Tablets → Capsules (n=32)	Sequence group 2 Capsules → Tablets (n=32)
Sex				
Male	n (%)	4 (6.3%)	3 (9.4%)	1 (3.1%)
Female	n (%)	60 (93.8%)	29 (90.6%)	31 (96.9%)
Race				
Caucasian/oriental	n (%)	64 (100%)	32 (100%)	32 (100%)
Other	n (%)	--	--	--
Smoking behaviour				
Yes	n (%)	14 (21.9%)	6 (18.8%)	8 (25.0%)
No	n (%)	50 (78.1%)	26 (81.3%)	24 (75.0%)
Age at baseline [years]	Mean (SD)	57 (10.7)	59 (10.5)	54 (10.6)
BMI at baseline [kg/m²]	Mean (SD)	25 (4.9)	26 (5.3)	25 (4.4)
Duration of disease [years]				
Time since 1st symptoms	Mean (SD)	7 (5.1) n=63	7 (5.2) n=32	7 (5.2) n=31
Present symptoms of PBC	n (%)	30 (46.9%)	15 (46.9%)	15 (46.9%)
- lethargy	n (%)	5 (7.8%)	2 (6.3%)	3 (9.4%)
- pruritus	n (%)	20 (31.3%)	13 (40.6%)	7 (21.9%)
- fatigue	n (%)	23 (35.9%)	11 (34.4%)	12 (37.5%)
Stage of PBC (according to histology)				
stage I	n (%)	35 (54.7%)	16 (50.0%)	19 (59.4%)
stage II	n (%)	19 (29.7%)	11 (34.4%)	8 (25.0%)
stage III or IV	n (%)	1 (1.6%)	-- (--%)	1 (3.1%)
unknown stage	n (%)	1 (1.6%)	-- (--%)	1 (3.1%)
missing (no histology)	n (%)	8 (12.5%)	5 (15.6%)	3 (9.4%)

Most patients were female (93.8%), all patients were of Caucasian/Oriental race and about a quarter was smoking. The mean age at baseline was 57 years and ranged between 32 and 79 years.
The first symptoms of PBC occurred on average 7 years before baseline. For 56 of 64 patients (87.5%) the diagnosis of PBC was confirmed histologically and the PBC stage was assessed correspondingly: 54 of 64 patients (84.4%) had confirmed PBC stage I or II and one patient had PBC stage III.
These and all other baseline demographics and anamnestic characteristics did not show relevant differences between sequence groups.

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Efficacy results:

Primary Efficacy Evaluation:

Relative differences [%] in AP, GGT and ALT between Ursofalk® 250 mg capsules and Ursofalk® 500 mg tablets at final visits of treatment phases:

		AP	GGT	ALT
ITT analysis set				
Relative difference at week 12 of treatments [LOCF] [%]				
Pooled Stage 1 + 2 (valid n=59; N=64)	Mean (SD)	0.8 (9.95)	4.5 (19.67)	0.7 (31.57)
Stage 1 (valid n=25; N=27)	Mean (SD)	2.4 (7.51)	3.4 (14.41)	3.3 (30.14)
Stage 2 (valid n=34; N=37)	Mean (SD)	-0.4 (11.39)	5.3 (22.96)	-1.3 (32.88)
PP analysis set				
Relative difference at week 12 of treatments [%]				
Pooled Stage 1 + 2 (valid n= 53; N=53)	Mean (SD)	1.4 (10.09)	6.1 (19.47)	2.8 (32.00)
Stage 1 (valid n=23; N=23)	Mean (SD)	3.2 (7.19)	4.5 (14.50)	6.0 (29.90)
Stage 2 (valid n=30; N=30)	Mean (SD)	-0.1 (11.77)	7.3 (22.73)	0.4 (33.83)

Adjusted overall 1-sided p-values (Wilcoxon signed rank test) testing the non-inferiority (Δ = 15%) of Ursofalk® tablets compared to capsules regarding the relative differences in AP, GGT and ALT, and 95%-repeated confidence intervals (RCIs) for relative differences:

Relative difference at week 12 of treatments			**ITT analysis (with LOCF)**	**PP analysis**
1st order hypothesis: AP	after stage 1 (interim analysis)	p-value	**< 0.001**	**< 0.001**
		RCI	**[-1.03; 5.83]**	**[-0.248; 6.65]**
	after stage 2 (final analysis)	p-value	< 0.001	< 0.001
		RCI	[-1.33; 4.04]	[-0.775; 4.84]
2nd order hypothesis: GGT	after stage 1 (interim analysis)	p-value	**< 0.001**	**0.002**
		RCI	**[-3.18; 9.98]**	**[-2.44; 11.4]**
	after stage 2 (final analysis)	p-value	< 0.001	< 0.001
		RCI	[-1.1; 9.27]	[0.0396; 11]
3rd order hypothesis: ALT	after stage 1 (interim analysis)	p-value	0.052	0.121
		RCI	[-10.4; 17]	[-8.32; 20.3]
	after stage 2 (final analysis)	p-value	**< 0.001**	**0.006**
		RCI	**[-8.06; 10.6]**	**[-6.35; 13.5]**

All p-values are "overall" p-values derived by the inverse-normal method and adjusted for the adaptive group-sequential design. 95%-RCIs correspond to a 1-sample t-test which is a parametric analogue to the non-parametric Wilcoxon signed rank test. They are adjusted for the respective stage of the adaptive group-sequential design.
The decisive overall p-values within the adaptive group-sequential testing strategy and the respective RCIs are underlined.

Non-inferiority could be concluded for AP and GGT after stage 1 and for ALT after stage 2 in the ITT as well as in the PP analysis set (non-inferiority margin Δ = 15%).

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The results from the evaluation of 95%-RCIs were equivalent to the primary evaluation based on the Wilcoxon signed rank tests: At stage 1 the 95%-RCIs were completely below the non-inferiority margin $\Delta = 15\%$ for the relative differences in AP and GGT but not for the relative differences in ALT, and after stage 2 the 95%-RCIs for the relative differences in all primary efficacy variables were below the non-inferiority margin.

Secondary Efficacy Evaluation (ITT analysis set):
Findings from all secondary efficacy endpoints, including assessments of health-related quality of life, did not show any relevant or statistically significant differences between Ursofalk® tablets and Ursofalk® capsules and thus supported the conclusion of non-inferiority.

Safety results:
A total of 98 AEs were reported. 97 of these were treatment-emergent events, one event occurred post-treatment. The 97 treatment-emergent AEs were observed in 43/64 (67.2%) patients. The overall incidence of treatment-emergent AEs during treatment with Ursofalk® tablets was very similar to the overall incidence during treatment with Ursofalk® capsules: 28/62 (45.2%) patients experienced at least one treatment-emergent AE during tablet treatment compared to 29/61 (47.5%) patients experiencing treatment-emergent AEs during treatment with capsules.

	Number (%) of patients		
	Total	**Ursofalk® Tablets**	**Ursofalk® Capsules**
Patients	64	62	61
Treatment-emergent adverse events			
Number of AEs	97	44	53
Number (%) of patients with AEs	43 (67.2%)	28 (45.2%)	29 (47.5%)
Number of potential ADRs	10	4	6
Number (%) of patients with potential ADRs	7 (10.9%)	2 (3.2%)	5 (8.2%)
Number of SAEs	2	2	--
Number (%) of patients with SAEs	1 (1.6%)	1 (1.6%)	-- (--%)

No death occurred during the study.
Two SAEs were reported for one patient during the second treatment phase, which was the tablet treatment phase. The causality was assessed as not related for both serious events.
The four System Organ Classes (SOCs) with the highest AE incidences were 'Gastrointestinal disorders' (32.8%), 'Infections and infestations' (23.4%), 'General disorders and administration site conditions' and 'Musculoskeletal and connective tissue disorders' (both 10.9%). Incidences during the tablets phase were comparable with incidences during the capsules phase for each SOC.
Seven patients experienced a total of 10 potential ADRs (relationship was assessed as at least possible), four of which occurred during treatment with Ursofalk® tablets and six during treatment with Ursofalk® capsules.
Overall, laboratory results after 12 weeks of treatment with tablets were comparable to results after 12

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weeks of treatment with capsules. No relevant trends were observed during the course of the study. No abnormality of any laboratory parameter was assessed at any time as 'clinically significant and suspected causal relationship with study medication'.
Vital signs remained virtually unchanged throughout the study. There were no relevant differences between Ursofalk® tablets and capsules.
No striking differences were observed in frequencies of findings from physical examination between results after treatment with tablets and results after treatment with capsules.
The majority of patients and investigators assessed the tolerability as 'very good' or 'good' after both, treatment with tablets as well as after treatment with capsules, respectively.

Conclusions:
A 12-week treatment with Ursofalk® 500 mg tablets (14 ± 2 mg/kg BW/d) was therapeutically non-inferior to a 12-week treatment with Ursofalk®250 mg capsules (14 ± 2 mg/kg BW/d) in controlling liver enzyme values of AP, GGT and ALT in patients with PBC.
Non-inferiority was statistically significant (pre-defined non-inferiority margin 15% and one-sided significance level 0.025) based on the pre-specified primary efficacy endpoints relative differences of AP, GGT and ALT between the end of the 12-week treatment-phase with Ursofalk® 250 mg capsules and the end of the 12-week treatment-phase with Ursofalk® 500 mg tablets.
Findings from all secondary efficacy endpoints, including assessments of health-related quality of life, supported the conclusion of non-inferiority.
Both formulations were well tolerated, and the safety analyses showed a comparable safety profile of Ursofalk® 500 mg tablets and Ursofalk® 250 mg capsules.

Date of the report:	15 Dec 2010