

# Therapeutic Equivalence of Ursodeoxycholic Acid Tablets and Ursodeoxycholic Acid Capsules for the Treatment of Primary Biliary Cirrhosis

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## Keywords

cholestasis, clinical study, efficacy, liver enzymes, primary biliary cirrhosis, quality of life, ursodeoxycholic acid

Primary biliary cirrhosis (PBC) is a chronic cholestatic, progressive inflammatory liver disease with a suspected autoimmune pathogenesis.<sup>1</sup> The disease is typically diagnosed in women at an age between 30 and 65 years and has a prevalence of up to 1 in 1000 women over the age of 40.<sup>2</sup> The only approved medical therapy for PBC is ursodeoxycholic acid (UDCA) in a recommended dose of 13–15 mg/kg/day.<sup>3</sup>

UDCA is a hydrophilic dihydroxy bile acid (3 $\alpha$ ,7 $\beta$ -dihydroxy-5 $\beta$ -cholanoic acid). In humans, UDCA accounts for up to 4% of the bile acid pool. Following oral administration, approximately 30–60% of UDCA is absorbed in the gut.<sup>4</sup> After intestinal absorption, UDCA enters the portal circulation and is then taken up by the hepatocytes via specific bile acid transporters.<sup>5</sup> Within the hepatocyte, UDCA is conjugated to glycine or taurine and is subsequently transported into the bile ducts by the bile salt export pump (BSEP). In bile, UDCA concentration peaks 1  $\pm$  3 h following oral administration.<sup>6</sup> In humans, the biological half-life of UDCA is 3.5–5.8 days and the predominant route of elimination is by feces.<sup>7</sup>

UDCA exerts its beneficial effects at the level of hepatocytes and cholangiocytes. It stimulates hepatocyte secretion by mostly post-transcriptional mechanisms, including insertion of transporters like BSEP and the anion exchanger AE2.<sup>5</sup> In addition, UDCA exerts antiapoptotic effects in hepatocytes and protects cholangiocytes against endogenous toxic bile acids by modifying micelle formation.<sup>3,5</sup> UDCA consistently improves the biochemical parameters of cholestasis, delays the histological progression and the time to liver transplantation in patients suffering from PBC.<sup>8–11</sup>

Both, UDCA 250 mg capsules and UDCA 500 mg tablets (“Ursofalk<sup>®</sup>”), are registered in Germany and other European countries for the treatment of PBC.

UDCA 500 mg tablets were developed to facilitate medication intake compared to the standard UDCA 250 mg capsule preparations. Tablets are considerably smaller, but contain twice as much active pharmaceutical ingredient compared to the capsule preparation, which might improve the compliance of patients and thereby increase its therapeutic efficacy. Ursofalk tablets were registered in Germany on the basis of bioequivalence studies comparing  $t_{max}$ ,  $C_{max}$ , and AUC values of UDCA between capsules and tablets.  $C_{max}$  values of UDCA in plasma are probably of only limited clinical relevance for the efficacy and safety of UDCA.<sup>12</sup>

Aim of this trial was to assess if the therapeutic efficacy of UDCA 500 mg tablets is equivalent to that of UDCA 250 mg capsules (both at 14  $\pm$  2 mg/kg BW/day once daily) in patients with PBC. Therapeutic efficacy was measured by comparing the liver enzyme parameters alkaline phosphatase (AP),  $\gamma$ -glutamyl transferase ( $\gamma$ GT), and alanine aminotransferase (ALT) under both treatments. The secondary objectives were to assess the safety

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and tolerability, to examine patients' preference of drug formulations and to assess patients' quality of life.

## Materials and Methods

### Study Design

This was a double-blind, double-dummy, randomized (1:1), cross-over, multicenter, Phase IV clinical trial performed according to a two-stage group sequential adaptive design with one interim analysis allowed for sample size adaptation. It was conducted in eight centers in Germany and one in The Netherlands. In this trial, two different UDCA formulations (tablets and capsules) were tested. There were two consecutive phases (Phase 1 and Phase 2, each 12 weeks). Within 24 weeks, six visits were performed. The laboratory parameters were analyzed by a central laboratory.

Patients  $\geq 18$  years of age with PBC who provided written informed consent were considered eligible for the study, when the following major inclusion criteria were met:<sup>1</sup> PBC was diagnosed when at least two of the following three criteria were fulfilled: (i) histologically proven early-stage PBC, (ii) positive AMA (titer  $\geq 1:40$ ), (iii) serum AP  $> 1.5$  times upper limit of normal at any time since diagnosis.<sup>2</sup> Patients had to be on UDCA ( $\geq 10$  mg/kg/body weight/day) for at least 6 months prior to inclusion and responsive to this treatment (normalization or reduction of AP  $\geq 40\%$  after onset of UDCA) according to Pares et al.<sup>10</sup>

Histologically proven cirrhosis, other co-existing liver diseases, pregnancy, known intolerance to the study drugs, acute inflammation of the gallbladder or the biliary tract, occlusion of the biliary tract, concomitant medication interacting with UDCA (such as colestyramine) and concomitant immunosuppressive therapy were the main exclusion criteria. Compliance was assessed by counting the study medication returned at all visits.

The human medical ethics committees of the participating centers in Germany and in The Netherlands approved the study, the trial was registered at <http://www.clinicaltrials.gov> NCT0151086) and was performed according to the Declaration of Helsinki and ICH-GCP guidelines.

### Randomization and Treatment

A randomization list was generated using the software RANCODE Version 3.6 (idv-Datenanalyse und Versuchsplanung, Gauting, Germany). The study was composed of two consecutive phases (Phase 1 and Phase 2, each 12 weeks) with two different formulations of UDCA. To guarantee the double-blinding, the study was conducted using the double-dummy technique with patients receiving verum UDCA tablets together with placebo capsules or verum UDCA capsules together with placebo tablets.

The individual dose of UDCA tablets and capsules depended on the particular body weight (daily dose:  $14 \pm 2$  mg UDCA/kg body weight/day in the evening). In sequence Group 1, patients received in the first 12-week treatment phase UDCA tablets plus placebo capsules (treatment 1, test), and in the second 12-week treatment phase UDCA capsules plus placebo tablets (treatment 2, reference). In sequence Group 2, patients received in the first 12-week treatment phase UDCA capsules plus placebo tablets (treatment 2, reference), and in the second 12-week treatment phase UDCA tablets plus placebo capsules.

### Study Endpoints

The primary aim was to determine if the therapeutic efficacy of UDCA 500 mg tablets is equivalent to that of UDCA 250 mg capsules in patients with PBC. This was assessed by the relative differences (measured in percent) of AP,  $\gamma$ GT, and ALT between the end of the treatment period with UDCA 250 mg capsules and the end of the treatment period with UDCA 500 mg tablets. The therapeutic equivalence margin for mean relative differences (%) was defined as  $\Delta = 15\%$  absolute. The secondary objectives were to assess the safety and tolerability, to examine patients' preference of drug formulations and to assess patients' quality of life as determined by the PBC-40 questionnaire.<sup>13</sup> This questionnaire was completed by the patients at the baseline visit, at visit 4 (after 12 weeks) and at the termination visit. The preference for a drug formulation was assessed at the termination visit.

For the efficacy analysis, two data sets were determined, the intention-to-treat (ITT) analysis set and the per-protocol (PP) analysis set. The ITT analysis set included all patients of the safety analysis set who had diagnosed PBC at baseline. The PP analysis set included all patients of the ITT analysis set, who did not have major protocol violations. Efficacy evaluation was performed based on the ITT and the PP analysis set, the PP analysis was considered primarily decisive for confirmatory conclusions. The safety analysis set included all randomized patients who received at least one dose of study medication.

### Measurement of Serum Liver Enzymes

The serum liver enzymes AP,  $\gamma$ GT, ALT, and bilirubin were measured in a central laboratory using commercially available Cobas<sup>®</sup> test kits (Roche Diagnostics, Mannheim, Germany).

### Sample Size and Statistical Methods

The study was conducted using a group-sequential adaptive Pocock design with one interim analysis which allowed for sample size adaptation. The inverse normal method was used to combine *P*-values across analysis

stages, the information rates which determined the weights for the combination were prospectively set at 0.65 and 1.

Initial sample size calculations were performed using nQuery Advisor 6.01 (Statistical Solutions Ltd., Cork, Ireland) and simulation tools of ADDPLAN 4.0 (ADDPLAN GmbH, Cologne, Germany). A power of 80% was targeted, the overall one-sided level of significance was 0.025, the non-inferiority margin was 15% absolute, and a standard deviation of 25% was assumed. An interim analysis was performed when the data of 26 evaluable patients were available. Based on the interim analysis it was then planned to randomize a total of 64 patients. The relative differences were within-patient differences and were expressed in percent of the patient's value after 12 weeks of treatment with capsules.

The main hypothesis of therapeutic equivalence consisted of three single hypotheses for the liver enzyme parameters AP,  $\gamma$ GT, and ALT. To avoid an inflation of  $\alpha$ -error the hypotheses were hierarchically ordered, that is, only if all higher order hypotheses were statistically significant, the next hypothesis could be used for confirmative testing. One-sided Wilcoxon-signed rank tests were used to test if mean relative differences (pooled for both sequence groups) were significantly smaller than the 15% margin. For the PBC-40, absolute differences (which were calculated between treatments within each patient) were tested using two-sided Wilcoxon-signed rank tests.

## Results

### Study Population

In total, 65 patients were recruited and randomized into the study. The first patient was enrolled in November 2008, the last visit occurred in July 2010. After randomization, only one patient declined treatment (withdrawal of consent) and was therefore not included into any statistical analysis, thus 64 patients were available for the ITT analysis. Eleven patients were excluded from the PP analysis because of major protocol violations, thus the PP analysis set included 53 patients.

Baseline characteristics of the 64 patients which comprised the safety analysis set and the ITT analysis set are summarized in Table 1. As expected, most patients were female (93.8%). All patients were of Caucasian/Oriental race and 21.9% were smoking. The mean age at baseline was 57 years and ranged between 32 and 79 years. About half of the patients (46.9%) suffered from PBC symptoms present at baseline. The most frequent symptoms were fatigue (35.9%) and pruritus (31.3%), while lethargy was only reported by 7.8%. At baseline, the mean AP value was 123 U/L and the mean  $\gamma$ GT value 72 U/L, both higher than the upper limit of normal. These and all other baseline demographics and general

anamnestic characteristics did not show relevant differences between the sequence groups.

The mean  $\pm$  SD daily dose per kg body weight of UDCA before inclusion into the study was  $14 \pm 3.3$  mg/kg, that is, pre-study treatment was on average very close to the targeted daily dose of  $14 \pm 2$  mg/kg UDCA. There were no relevant differences between sequence groups regarding daily dose and frequency of UDCA formulations applied before inclusion into the study.

Of the 64 patients who were treated with study medication, 6 terminated the trial prematurely. The reasons for the termination were as follows: Two patients with withdrawal of consent, one patient with lack of compliance, one patient with major violation of enrolment criteria and two patients with prohibited medication due to an adverse event (AE).

### Therapeutic Efficacy

The mean and median relative differences in AP and  $\gamma$ GT between capsules and tablets after 12 weeks of treatment with each formulation were very small, close to zero, respectively (Fig. 1). At the interim analysis ( $n = 27$ ), the adjusted overall  $P$ -values for AP and  $\gamma$ GT were below the one-sided significance level of  $\alpha = 0.025$  in the ITT as well as in the PP analysis, but this was not the case for ALT. At the final analysis the adjusted overall  $P$ -values of ALT fell below the one-sided significance level of  $\alpha = 0.025$  in both analyses sets as well.

Hence, therapeutic equivalence could be concluded for AP and GGT at the interim as well as final analysis and for ALT after the final analysis ( $P < .001$  for AP,  $P = .002$  for GGT and  $P = .006$  for ALT in the PP analysis set; and  $P < .001$  for AP,  $P < .001$  for GGT and  $P < .001$  for ALT in the ITT analysis set; non-inferiority margin  $\Delta = 15\%$ ). Thus, the rejection of the null hypotheses concerning AP and  $\gamma$ GT was stable over the whole sample. In addition to (adjusted)  $P$ -values of the Wilcoxon-signed rank test repeated confidence intervals (RCI) were determined assuming normally distributed data which were equivalent to those from the primary evaluation based. Hence, therapeutic equivalence of UDCA tablets compared to UDCA capsules concerning AP, GGT and ALT could be concluded from the evaluation of 95%-RCIs as well.

### Quality of Life and Preference of Drug Formulation

Quality of life was assessed with the PBC40-questionnaire at the baseline and at the final visit of each treatment phase. The absolute differences in PBC-40 scores calculated between treatment phases for each patient were always small and according to the  $P$ -values of the Wilcoxon-signed rank tests not significantly different from zero.

The patients' acceptance and preference of study medication was assessed at the final visit of the study. A

**Table 1.** Patient Characteristics at Baseline

		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%)
Age at baseline [years]	Mean (SD)	57 (10.7)	59 (10.5)	54 (10.6)
Time since diagnosis, mean (SD)	Years (SD)	5 (4.7)	5 (4.7)	5 (4.7)
Stage of PBC (at time of diagnosis, 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%)
AP at baseline	[U/L] Mean (SD)	123 (56.8)	128 (58.5)	118 (55.4)
γGT at baseline	[U/L] Mean (SD)	72 (100.5)	83 (129.5)	60 (59.0)
ALT at baseline	[U/L] Mean (SD)	31. (17.8)	29 (13.7)	34 (20.9)
AST at baseline	[U/L] Mean (SD)	33(11.2)	32 (8.2)	34 (13.6)
Bilirubin at baseline	[mg/dL] Mean (SD)	0.5 (0.16)	0.5 (0.16)	0.5 (0.16)
Present symptoms of PBC				
Lethargy	n (%)	30 (46.9%)	15 (46.9%)	15 (46.9%)
Pruritus	n (%)	5 (7.8%)	2 (6.3%)	3 (9.4%)
Fatigue	n (%)	20 (31.3%)	13 (40.6%)	7 (21.9%)
Associated autoimmune disease	n (%)	23 (35.9%)	11 (34.4%)	12 (37.5%)
Associated autoimmune disease				
Fatigue	n (%)	9 (14.1%)	5 (15.6%)	4 (12.5%)
PBC-40 at baseline				
Total (possible range: 40–200)	Mean (SD)	70 (21.2), n = 63	69 (22.7), n = 31	71 (19.9), n = 32
Itch (possible range: 3–15)	Mean (SD)	4 (1.8), n = 62	4 (2.1), n = 30	4 (1.6), n = 32
Fatigue (possible range: 11–55)	Mean (SD)	23 (9.6), n = 63	22 (10.1), n = 31	24 (9.1), n = 32

high proportion (29/64, 45.3%) of patients in the ITT analysis set judged UDCA tablets as “more convenient to take,” while only 10 patients (15.6%) preferred UDCA capsules. Twenty-one of the remaining patients (32.8%) did not express a preference for one of the formulations, and four patients did not answer the question. The most important factor for the decision about the convenience level of intake was the amount of tablets/capsules to be taken, that is, 29 patients (45.3%) ticked “fewer tablets,” while 22 patients (34.4%) ticked “texture of the tablets/capsules surface” and 11 patients (17.2%) ticked “size of the tablets/capsules” (multiple answers were possible). So the findings from all secondary efficacy endpoints, including assessments of health-related quality of life, supported the conclusion of therapeutic equivalence of UDCA tablets compared to UDCA capsules.

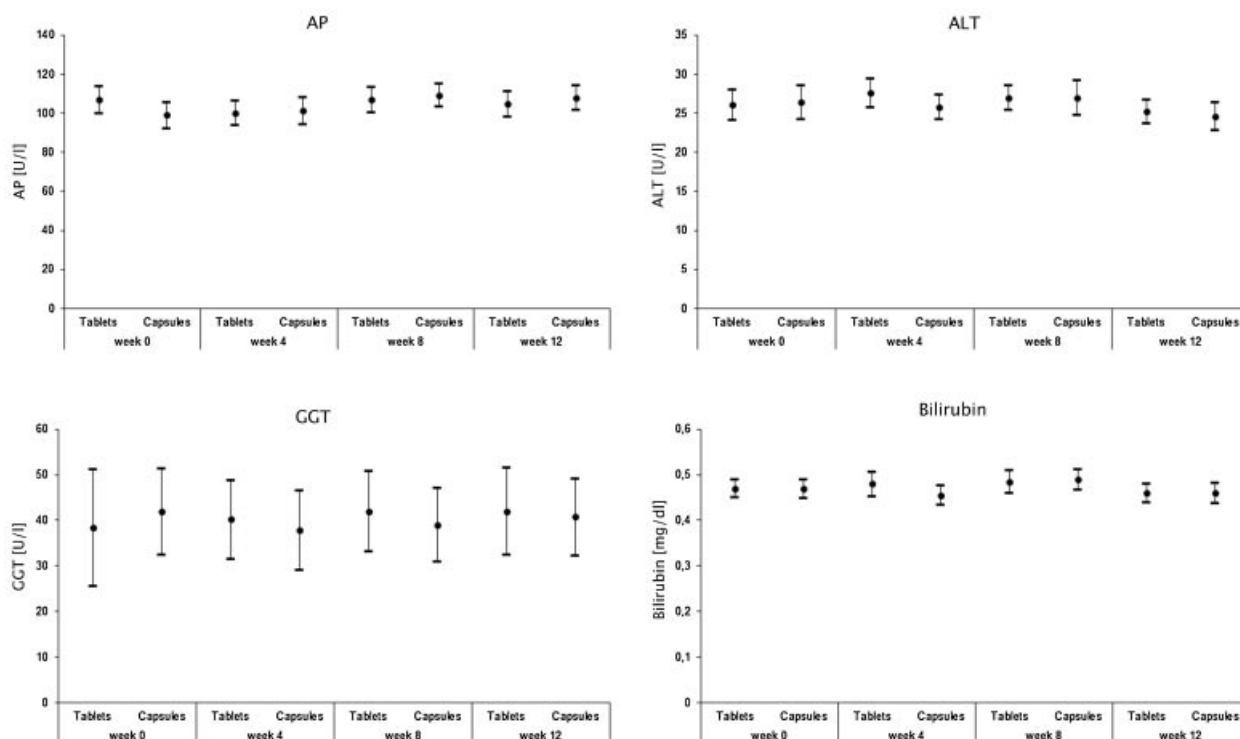
### Safety

A total of 98 AEs were reported in 43/64 (67.2%) patients. The overall incidence of treatment-emergent AEs during treatment with UDCA tablets was very similar to treatment with UDCA capsules: in 28/62 (45.2%) patients at least one AE occurred newly during tablet treatment

compared to 29/61 (47.5%) patients for who an AE newly occurred during treatment with capsules. Most AEs for which the relationship was assessed as at least possibly related with UDCA (adverse drug reactions, ADR) were gastrointestinal disorders (abdominal pain upper, eructation, abdominal distension, nausea, vomiting). The number of potential ADRs with onset during the tablet phase was comparable with the corresponding number during the capsules phase. No death occurred during the study. Two serious adverse events (SAEs) due to hospitalization were reported. One patient had a nasal septum operation and one patient a replacement of the aortic valve due to stenosis, both were assessed as not related to UDCA therapy. In conclusion, both formulations were well tolerated, and the safety analyses showed a comparable safety profile of UDCA tablets and UDCA capsules.

### Discussion

In this study, we could demonstrate therapeutic equivalence of UDCA tablets and UDCA capsules in the treatment of PBC. Due to the cross-over design, within-



**Figure 1.** Serum liver tests during the 12-week study period. The arithmetic mean ( $\pm$ SE) values of alkaline phosphatase (AP),  $\gamma$ -glutamyl-transferase (GGT), alanine aminotransferase (ALT), and bilirubin at each of the study visits (Weeks 0, 4, 8, and 12) during treatment with either ursodeoxycholic acid (UDCA) 500 mg tablets or UDCA 250 mg capsules are shown ( $n = 64$  patients in each group).

patient comparisons could be made to reduce the impact of inter-individual variability. Patients had to be pre-treated with UDCA and the duration of each treatment period in the study was 12 weeks.

In general, the maximal effect of UDCA on liver function parameters is observed within 8 weeks.<sup>14,15</sup> If 3.5–5.8 days are considered as the biological half-life of UDCA,<sup>7</sup> a 12-week treatment phase appears appropriate to obtain reliable measurements on liver function parameters at a steady state level under treatment without a carry-over-effect of any possible pre-treatment. This is in line with the study of Verma et al.,<sup>14</sup> which determined the optimum UDCA dose during a dose-finding study in an 8-week treatment period interrupted by a 4-week washout period. Three clinically relevant parameters were chosen in our study to assess therapeutic efficacy (AP, GGT, and ALT). AP was ordered first because it is regarded as the most reliable surrogate marker for effective PBC treatment that correlates with survival<sup>10</sup> and liver histology.<sup>16</sup> Therapeutic equivalence of UDCA 500 mg tablets was shown with respect to AP and GGT already at the interim analysis and this result was then confirmed at the final analysis. In addition, the final analysis showed that the therapeutic equivalence of UDCA 500 mg tablets compared to UDCA 250 mg capsules was also statistically significant with respect to ALT.

Clinical efficacy of UDCA 500 mg tablets as shown in the present study is further supported by findings of a recent pharmacokinetic study in patients with PBC in which a mean biliary enrichment of 42.8% under treatment with UDCA 500 mg tablets at a daily dose of 15 mg/kg body weight during 3 weeks was shown.<sup>17</sup> In this study, the pharmacokinetic parameters in serum of healthy subjects were AUC  $49.8 \pm 19.0$  h  $\mu$ mol/L (0–24 h) and  $C_{max}$   $15.2 \pm 7.6$   $\mu$ mol/L.<sup>17</sup> The extent of biliary enrichment is able to facilitate clinical efficacy.<sup>17,18</sup> Indeed, biliary enrichment of UDCA correlated with AUC over the dosing interval of UDCA in plasma but not with  $C_{max}$  of UDCA in plasma, and therefore, AUC is considered to be the most reliable pharmacokinetic parameter in plasma for bioequivalence assessment.

Findings from all secondary efficacy endpoints, including assessments of health-related quality of life, supported the conclusion of therapeutic equivalence. Both UDCA formulations were well tolerated and the safety analyses showed a comparable safety profile of tablets and capsules. One secondary endpoint assessed patients' preference of UDCA formulations. It could be shown that nearly three times as many patients preferred tablets (45.3%) compared to only 15.6% of patients preferring capsules.

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## Declaration of Conflicting Interests

Heinz Hartmann, Holger Hinrichsen, Marc Eisold, and Christian Rust have served as speakers for Dr. Falk Pharma GmbH. Roland Greinwald and Renate Grieshaber are full-time employees of Dr. Falk Pharma GmbH. Corinna Hopf has nothing to disclose.

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