A placebo-controlled randomised trial of budesonide for PBC following an insufficient response to UDCA

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Supplementary Methods

Patient population

Further exclusion criteria included ascites or history of ascites, signs of portal hypertension, hepatic encephalopathy or history of hepatic encephalopathy, albumin < 36 g/L, prothrombin time < 70% (or prothrombin ratio (INR) out of normal range and clinically significant), platelet count < 135.000/mm^3, treatment with corticosteroids (except inhalative corticosteroids) and immuno-suppressants within the last 2 months prior to baseline and treatment with ketoconazole or other CYP3A inhibitors within the last 4 weeks before baseline (rifampicin (up to 600 mg/d) was allowed to treat pruritus until baseline).

Liver biopsy evaluation

The samples were evaluated by a second central pathologist. The histological evaluation of one central pathologist was sufficient for patient exclusion based on the presence of cirrhosis. Results of both evaluations had to be consistent in the staging according to Ludwig[1] for the assessment of cirrhosis as secondary endpoint. The histological evaluations of both central pathologists regarding the absence or presence of inflammatory activity needed to be consistent before enrolment. The histological evaluations of the follow up biopsy samples needed to be consistent as well.

Procedures

Bone specific AP, N-terminal midfragment (N-MID) osteocalcin was assessed at baseline, at the interim visits in Month 12 and 24 and at the EOT/withdrawal visit. Bone mineral density was assessed at baseline, at the interim visit in Month 12 and at the EOT/withdrawal visit by dual x-ray absorptiometry (DXA) of the femoral neck and lumbar spine. Suppression of adrenal

function was determined at baseline, at the interim visits in Month 12 and 24 and at the EOT/withdrawal visit by measuring serum cortisol.

Pruritus was assessed by VAS (Visual Analogue Scale) at the interim visits in Month 3, 6, 9, 12, 18, 24 and 30 as well as at the EOT/withdrawal visit. Fatigue and Quality of Life were assessed with the PBC-40 Quality of Life questionnaire at baseline, at the interim visits in Month 12 and 24 and at the EOT/withdrawal visit. The investigator's and patient's assessment of efficacy was documented at the interim visits in Month 3, 6, 9, 12, 18, 24 and 30 as well as at the EOT/withdrawal visit. The severity of the liver disease was assessed using an adapted Mayo Risk Score for PBC[2] at baseline, at the interim visits in Month 12 and 24 and at the EOT/withdrawal visit. The original Mayo Risk Score requests information about variceal bleeding.[2] This was not available at the final visit in this study. Therefore, the presence of varices at the final visit was used (instead of variceal bleeding) and the Mayo Risk Score was be adapted as follows: = 0.0295 × (age in years) + 0.5373 × $\log_e$ (total bilirubin in mg/dL) - 0.8389 × (serum albumin in g/dL) + 0.5380 × $\log_e$ (AST in IU/L) + 1.2426 × (points for presence of varices). Patient age at initiation of UDCA therapy is part of the original GLOBE score[3]. This was not known in every case for this study. Therefore the globe score was calculated with the patients age at baseline and at the EOT/withdrawal visit (modified globe score) as follows: 0.044378 × (age in years) + 0.93982 × $\log_e$ (bilirubin times the upper limit of normal (ULN)) + (0.335648 × $\log_e$ (alkaline phosphatase times the ULN) – 2.266708 × (albumin level times the lower limit of normal (LLN)) – 0.002581 × (platelet count per 109/L) + 1.216865. Concomitant medications and adverse events (AEs) were documented at every visit. The patients had to return unused study medication at every visit. The trial investigators documented treatment adherence by counting the unused study medication at the visits

Statistics

In the patient population selected for this study, the response rate of the standard treatment arm was estimated at approximately 15%. It was assumed that in the combination therapy the percentage of patients with improvement in liver histology as defined in the primary efficacy variable would be 40%. Under these assumptions, the power was 80% if the sample size was 114 patients (one-sided $\alpha = 0.025$) and a total number of 144 patients if it is assumed that 20% of the patients were not providing an assessment of the primary efficacy variable, e.g. they did not consent to performing a liver biopsy at their individual last visit within the study. The study was performed according to a 2-stage group-sequential adaptive design with possible sample size adjustment after the planned interim analysis. The interim analysis was planned after observation of 42 evaluable patients of the ITT-population (approximately 28 patients in the budesonide group and 14 patients in the placebo group) and conducted with 43 patients (27 patients treated with budesonide and 16 patients with placebo). Superiority of budesonide compared to placebo could not be demonstrated at this interim analysis. The IDMC assessed these efficacy results as positive but smaller than expected.

For sample size recalculation the normal approximation test for comparing two rates based on the unstratified overall response was used ($\alpha = 0.025$, one-sided). A sample size of $n = 167$ (placebo) and $n = 334$ (budesonide) would have been necessary to achieve conditional power 80% for the subsequent stage of the study.

As there were no concerns regarding safety, the overall recommendation of the IDMC was to continue the study with the planned sample size of 501 patients in the second stage. Due to very insufficient recruitment, the sponsor decided to stop the study, but followed the IDMC recommendation to continue patients already recruited for up to one year of treatment. Early termination of this study resulted in a lack of power.

Table S1: Cortisol and Bone Health.

		Mean (SD)	
		Budesonide (n = 40)	**Placebo (n = 22)**
Cortisol [µg/dl]	Baseline	13.8 (6.2) n=40	13.8 (6.4) n=22
	LOCF	9.2 (6.3) n=40	13.2 (4.0) n=22
Bone-specific alkaline phosphatase [µg/l]	Baseline	45 (30) n=40	47 (36) n=22
	LOCF	31 (23) n=40	44 (42) n=22
N-MID Osteocalcin [ng/ml]	Baseline	18.7 (6.8) n=40	16.0 (6.6) n=22
	LOCF	14.0 (5.9) n=40	14.6 (5.9) n=22
T-Score of femoral neck	Baseline	-0.9 (0.9) n=40	-0.5 (0.8) n=21
	LOCF	-1.3 (0.8) n=40	-0.6 (0.8) n=22
T-Score of lumbar spine	Baseline	-1.0 (1.1) n=40	-0.7 (0.9) n=22
	LOCF	-1.2 (0.9) n=40	-0.7 (0.9) n=22

LOCF, last observation carried forward.

References:

[1] Ludwig J. The nomenclature of chronic active hepatitis: An obituary. Gastroenterology 1993;105:274-278.

[2] Angulo P, Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Kamath PS, et al. Utilization of the Mayo risk score in patients with primary biliary cirrhosis receiving ursodeoxycholic acid. Liver 1999;19:115-121.

[3] Lammers WJ, Hirschfield GM, Corpechot C, Nevens F, Lindor KD, Janssen HL, et al. Development and Validation of a Scoring System to Predict Outcomes of Patients With Primary Biliary Cirrhosis Receiving Ursodeoxycholic Acid Therapy. Gastroenterology 2015;149:1804-1812 e1804.