Efficacy of essential phospholipids in reducing hepatic steatosis in patients with different stages of Metabolic Dysfunction-Associated Steatotic Liver Disease – A phase IV study

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INTRODUCTION

- Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), is strongly associated with obesity, type-2 diabetes mellitus (T2DM) and dyslipidaemia and is the leading chronic liver condition with a global prevalence of 30-32%.[1-3]
- Essential phospholipids (EPLs) are recommended as an adjunctive therapy for managing liver disorders, including MASLD. Though the efficacy of EPLs as a supportive therapy for MASLD is confirmed, its effect on quality of life (QoL) and symptom changes in MASLD patients remain unclear.[4]
- EXCEL is the first randomised controlled clinical trial to assess steatosis reduction and QoL improvement with EPLs (Opella®) using FibroScan® controlled attenuation parameter (CAP) and a validated questionnaire (Chronic Liver Disease Questionnaire [CLDQ]) specific for MASLD, respectively.[4]

OBJECTIVE

To assess the efficacy and safety of EPLs (Opella®), added to standard-of-care (SoC), on hepatic steatosis, compared with placebo, added to SoC, in adult patients with MASLD associated with T2DM and/or hyperlipidaemia and/or obesity.

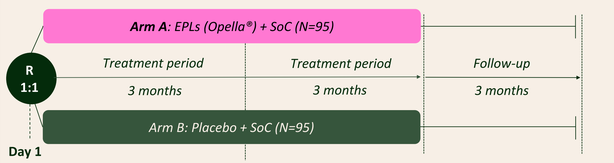
Here we report the results of CAP score, subgroup analysis of CAP score by baseline CAP score, glycated haemoglobin (HbA1c) and exploratory results on metabolomic parameters.

METHODS

Study design

- In this multicentre, double-blind, randomised, placebo-controlled, parallel-group, phase IV clinical trial, patients were randomized (1:1) to receive EPLs (Opella®; 1800 mg/day, orally) or placebo along with SoC.
- The study design and inclusion criteria are detailed below in **Figure 1.**

Figure 1: Study design and inclusion criteria[1]



Eligible criteria:
- Aged 18-70 years
- Suffering from MASLD
- Steatosis score of S1-S3
- Liver fibrosis score of F1-F3
- Confirmed ≥1 of the following: T2DM, hyperlipidaemia, obesity (Body mass index [BMI] ≥30 kg/m²)

Duration of the trial: 10 months

Countries: Germany, Poland

Active ingredient of EPLs (Opella®): 1,2-dilinoleoylphosphatidylcholine (DLPC)[2]

- **Primary endpoint:** Reduction in steatosis measured by CAP score from baseline to 6 months
- **Key secondary endpoints:** Change in QoL measured by the validated CLDQ-MASLD from baseline to 6 months
- **Subgroups analysis:** Change in CAP score from baseline to 6 months was analysed in subgroups categorised by baseline CAP score (<288 dB/m and ≥288 dB/m) and HbA1c (<8% and ≥8%)
- **Exploratory endpoints:** Changes in metabolomic parameters from baseline to 3 and 6 months
- The modified intention-to-treat (mITT*) population is used for analysing results and a mixed-effects model with repeated measures was used for statistical analysis.

RESULTS

Baseline characteristics

- In total, 193 patients (EPLs arm: 97, placebo arm: 96) were included in the study. Of these, the mITT set included 165 patients (EPLs arm: 82, placebo arm: 83).
- The mean age was 53.7 years in the EPLs arm and 52.0 years in placebo arm. Mean BMI was 32.3 and 33.5 kg/m² in the EPLs and placebo arm, respectively. Most patients were obese (EPLs arm: 78%, placebo arm: 85.5%) (**Table 1**).
- The patient demographics and baseline disease characteristics were presented in **Table 1**.

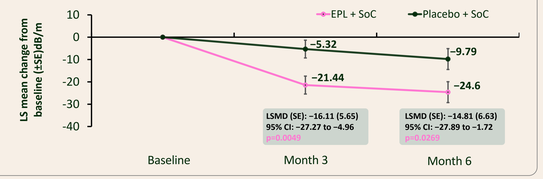
Table 1: Baseline characteristics (mITT population)

Characteristic	EPLs + SoC (N=82)	Placebo + SoC (N=83)	Characteristic	EPLs + SoC (N=82)	Placebo + SoC (N=83)
Age (years), mean (SD)	53.7 (12.13)	52.0 (10.81)	**CAP (dB/m), mean (SD)**	314.6 (34.50)	321.6 (40.08)
Male, n (%)	41 (50.0)	49 (59.0)	**CAP (dB/m), n(%)**		
Country; N (%)			S1: CAP score is ≥248 and <268	6 (7.3)	6 (7.2)
Germany	42 (51.2)	44 (53.0)	S2: CAP score is ≥268 and <280	8 (9.8)	9 (10.8)
Poland	40 (48.8)	39 (47.0)	S3: CAP score is ≥280	68 (82.9)	68 (81.9)
BMI (kg/m²), mean (SD)	32.3 (4.32)	33.5 (4.88)	**LDLC (mmol/L), mean (SD)**	3.85 (2.75)	3.92 (2.43)
MASLD, n (%)			**HDLC (mmol/L), mean (SD)**	1.79 (3.34)	2.27 (4.31)
Type 2 diabetes	14 (17.1)	8 (9.6)	**TG (mmol/L), mean (SD)**	2.20 (1.03)	2.42 (1.59)
Hyperlipidaemia	49 (59.8)	51 (61.4)	**HbA1C (%), mean (SD)**	6.52 (2.88)	6.16 (2.04)
Obesity (BMI ≥30 kg/m²)	64 (78.0)	71 (85.5)			
BMI category (kg/m²), n (%)					
Normal (18.5 to <25)	3 (3.7)	2 (2.4)			
Overweight (25 to <30)	15 (18.3)	10 (12.0)			
Obese (≥30)	64 (78.0)	71 (85.5)			

Significant reduction in CAP score

A **statistically significant reduction** in CAP score at month 3 (**p=0.0049**) and month 6 (**p=0.0269**) was seen in the EPLs + SoC arm compared with the placebo + SoC arm (**Figure 2**).

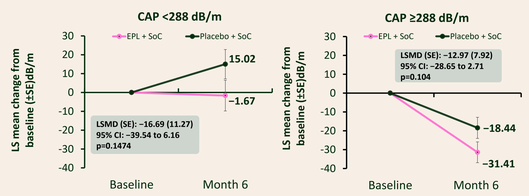
Figure 2: Change in CAP score from baseline to 3 and 6 months



CAP score analysis by subgroups

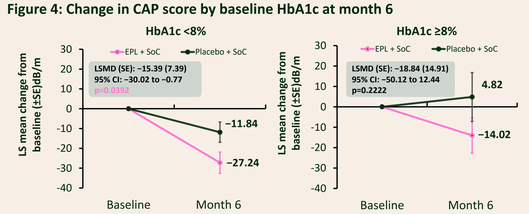
A **numerically higher reduction** in the CAP score was observed at month 6 in the EPLs + SoC arm compared with the placebo + SoC arm in both the subgroups of patients (**Figure 3**).

Figure 3: Change in CAP score by baseline CAP Score at month 6



A **statistically significant** reduction in the CAP score was reported in the EPLs + SoC arm vs placebo + SoC arm **in patients with HbA1c <8.0%** but the reduction was not statistically significant in patients with HbA1c ≥8% (**Figure 4**).

Figure 4: Change in CAP score by baseline HbA1c at month 6



Exploratory efficacy results

- Mean changes from baseline to 3 and 6 months in metabolomic parameters are presented in **Table 2.**
- EPLs significantly reduced HbA1c levels versus placebo at 6 months (**p=0.0069**)
- The mean changes in low-density lipoprotein (LDL) and triglycerides (TG) levels were similar in both treatment arms and were slightly higher for high-density lipoprotein (HDL) in EPLs arm versus placebo at 6 months.

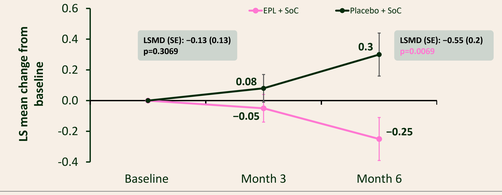
Table 2: Changes in metabolomic parameters from baseline to 3 and 6 months

Parameter	EPLs + SoC vs Placebo + SoC	
	Baseline to 3 months	Baseline to 6 months
HbA1c		
LS mean difference (SE)	−0.13 (0.13)	−0.55 (0.2)
95% CI; p-value	−0.38 to 0.12; 0.3069	−0.95 to −0.15; 0.0069
LDL		
LS mean difference (SE)	−0.33 (0.19)	−0.03 (0.21)
95% CI; p-value	−0.7 to 0.05; 0.0898	−0.45 to 0.39; 0.9051
HDL		
LS mean difference (SE)	0.36 (0.4)	0.22 (0.37)
95% CI; p-value	−0.42 to 1.15; 0.3647	−0.52 to 0.96; 0.5617
TG		
LS mean difference (SE)	−0.17 (0.19)	0.06 (0.14)
95% CI; p-value	−0.54 to 0.2; 0.3579	−0.22 to 0.34; 0.6789
Total cholesterol		
LS mean difference (SE)	−0.4 (0.27)	0.16 (0.25)
95% CI; p-value	−0.94 to 0.13; 0.1372	−0.33 to 0.65; 0.5281

Significant reduction in HbA1c levels

A **statistically significant reduction** in HbA1c levels at month 6 (**p=0.0069**) was seen in the EPLs + SoC arm compared with the placebo + SoC arm (**Figure 5**).

Figure 5: Change from baseline in HbA1c levels at 3 and 6 months



CONCLUSIONS

- EPLs significantly reduced hepatic steatosis when used alongside SoC, with results already visible in just 3 months and kept at 6 months.
- EPLs can help improve glycemia, which is beneficial for patients with MASLD and related impaired metabolic conditions.
- These results suggest a potential role of EPLs as an early intervention alongside SoC in patients with MASLD associated with comorbidities.

*mITT analysis set: All patients from the randomisation set with evaluable CAP scores at baseline and at least one post-baseline CAP measurement and who actually received the randomised treatment (at least 80% of the study drug planned to be given within 6 months).

BMI, body mass index; CAP, controlled attenuation parameter; CLDQ, chronic liver disease questionnaire; CI, confidence interval; EPLs, essential phospholipids; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, least square; LSMD, least squares mean difference; MASLD, metabolic dysfunction-associated steatotic liver disease; mITT, modified intention-to-treat; NAFLD, non-alcoholic fatty liver disease; QoL, quality of life; SE, standard error; SD, standard deviation; SoC, standard-of-care (lifestyle modification [diet and physical activity/exercise]); T2DM, type-2 diabetes mellitus; TG, triglycerides.

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