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Essential phospholipids efficacy in improving hepatic steatosis in patients with MASLD associated with type 2 diabetes mellitus and/or hyperlipidemia and/or obesity - *A randomized and controlled, double-blind, phase IV study*

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INTRODUCTION

- Metabolic dysfunction-associated steatotic liver disease (MASLD), previously non-alcoholic fatty liver disease, is associated with comorbidities like obesity, diabetes, and dyslipidemia, increasing the risk of cirrhosis, liver cancer, cardiovascular diseases, and extrahepatic cancers.[1,2]
- While essential phospholipids (EPL) are used as hepatoprotectors in treatment of MASLD,[3] their efficacy when combined with the standard of care (SoC) has not been extensively studied.
- This study (EXCEL trial), conducted in Europe, is the first study to leverage controlled attenuation parameter (CAP) as a key parameter for evaluating EPL (Opella®) efficacy in reducing liver steatosis, while seamlessly integrating personalized SoC recommendations for optimal patient management. It is the first randomized controlled trial to use the recently approved Chronic Liver Disease Questionnaire (CLDQ) to assess the impact on quality of life (QoL) in patients with MASLD.

OBJECTIVE

To evaluate the efficacy of EPL added to SoC for reducing steatosis and improving QoL in patients with MASLD associated with type 2 diabetes mellitus (T2DM) and/or hyperlipidemia and/or obesity.

RESULTS

Baseline Characteristics

- Out of 237 patients screened from 7 (Germany) and 8 (Poland) trial sites, 193 patients were enrolled for the study (EPL arm: 97, placebo arm: 96). Among these patients the modified intention to treat (mITT) set included 82 (EPL arm) and 83 (placebo arm) patients.
- The mean ages were 53.7 (EPL arm) and 52.0 (placebo arm) years. Mean BMI were 32.3 and 33.5 kg/m^2 in the EPL and placebo arm, respectively (**Table 1**).
- Most patients were obese (EPL arm: 78%, placebo arm: 85.5%) followed by hyperlipidemia in nearly half of both groups. Majority of the patients had CAP scores ≥280 dB/m (EPL arm: 82.9%, placebo arm: 81.9%; **Table 1**) and mild fibrosis (Liver Stiffness Measurement [LSM] F1 (5-7 kPa), EPL arm: 61%, placebo arm: 62.7%; F2 (7.1–8.8 kPa), EPL: 22%, placebo: 22.9%; F3 (8.9–11.6 kPa), EPL: 8.5%, placebo: 13.3%; F4* (>11.6 kPa), EPL: 8.5%, placebo: 1.2%). About 90% (EPL arm) and 95% (placebo arm) patients took at least one concomitant medication.

METHOD

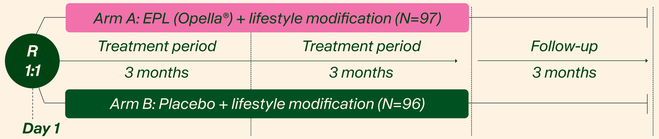
- In this multicenter, phase IV clinical trial, eligible patients were randomized (1:1) to receive EPL (Opella®; 1800 mg/day orally) or placebo along with SoC including lifestyle modification.[4] The study design, inclusion criteria and the endpoints are detailed below in **Figure 1**.[4] A mixed-effects model with repeated measures was used for statistical analysis.

Figure 1: Study design and endpoints

Primary endpoint:
Change in steatosis measured by CAP score from baseline to 6 months.

Secondary endpoint:
Change in QoL [measured by the validated Chronic Liver Disease Questionnaire (CLDQ-MASLD/MASH)] from baseline to 6 months.

Exploratory endpoints:
- CAP score change from baseline to 3 and 9 months.
- Safety.



Active ingredient of EPL (Opella®): 1,2-dilinoleoylphosphatidylcholine (DLPC)[3]

Duration of the trial: 10 months

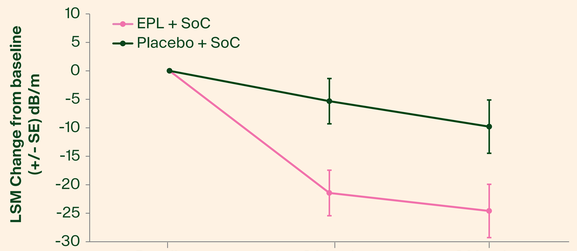
Eligible patients:
- Aged 18-70 years
- Suffering from MASLD
- Steatosis score of S1-S3
- Liver fibrosis score of F1-F3
- Confirmed at least one of the following: T2DM, hyperlipidemia, obesity (BMI ≥30 kg/m^2)

Table 1: Baseline characteristics in mITT population#

Characteristics	EPL + SoC (N=82)	Placebo + SoC (N=83)
Age (years), Mean (SD)	53.7 (12.13)	52.0 (10.81)
Sex, n (%)		
Male	41 (50.0)	49 (59.0)
Country; N (%)		
Germany	42 (51.2)	44 (53.0)
Poland	40 (48.8)	39 (47.0)
Body mass index (BMI) (kg/m^2)		
Mean (SD)	32.3 (4.32)	33.5 (4.88)
MASLD, n (%)		
Type 2 diabetes	14 (17.1)	8 (9.6)
Hyperlipidemia	49 (59.8)	51 (61.4)
Obesity (BMI ≥30 kg/m^2)	64 (78.0)	71 (85.5)
BMI category (kg/m^2), 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)
CAP (dB/m), mean (SD)	314.6 (34.50)	321.6 (40.08)
CAP (dB/m), n (%)		
S0: CAP score is <248	0	0
S1: CAP score is ≥248 and <268	6 (7.3)	6 (7.2)
S2: CAP score is ≥268 and <280	8 (9.8)	9 (10.8)
S3: CAP score is ≥280	68 (82.9)	68 (81.9)

CAP, controlled attenuation parameter; MASLD, Metabolic dysfunction-associated steatotic liver disease; SD, standard deviation; SoC, standard of care

Figure 2: Change in CAP score from baseline at 3 and 6 months in mITT population#



	Baseline	3 Months	6 Months
EPL + SoC	0	-21.44	-24.6
Placebo + SoC	0	-5.32	-9.79

Table 2: Change in CAP score from baseline for EPL vs placebo at 3, 6 and 9 months

Change from baseline (EPL vs Placebo)	LSMD (SE)	95% CI	p value
3 months	-16.11 (5.65)	-27.27 to -4.96	**0.0049**
6 months	-14.81 (6.63)	-27.89 to -1.72	**0.0269**
9 months	-15.19 (6.64)	-28.29 to -2.09	**0.0234**

CAP, controlled attenuation parameter; CI, confidence interval; EPL, Essential phospholipid; LSM, least-squares means; LSMD, least-square mean difference; SD, standard deviation; SE, standard error; SoC, standard of care

*As the study allowed inclusion of F1-F3 (defined as liver stiffness measurement [LSM]) of 5-13 kPa), statistical analysis was done to include F4 based on another specific threshold.
#mITT analysis set: All patients from the randomization set with evaluable CAP scores at baseline and at least one post-baseline CAP measurement and who actually received the randomized treatment (at least 80% of the study drug planned to be given within 6 months).

RESULTS (Cont..)

Primary endpoint

- A **statistically significant reduction** in CAP scores at month 6 was seen in EPL group with least-square mean (LSM) value of -24.6 vs -9.79 for the placebo group, yielding a least-square mean difference (LSMD) of -14.81 (95% CI, -27.89 to -1.72; **p=0.0269**) (**Figure 2, Table 2**).

Secondary endpoint

- Overall, CLDQ-MASLD/MASH score was numerically improved in EPL group compared to placebo (LSM: 0.44 vs 0.28; LSMD: 0.17; p=0.2445)

Exploratory endpoints

- At shorter treatment duration of 3 months steatosis **improved with statistical significance** in the EPL group compared to placebo (LSM: -21.44 vs -5.32; LSMD: -16.11; 95% CI, -27.27 to -4.96; **p=0.0049**). This improvement persisted at the 9-month follow-up (LSM: -22.72 vs -7.53; LSMD: -15.19; 95% CI, -28.29 to -2.09; **p=0.0234**) (**Table 2**).
- CLDQ-MASLD/MASH fatigue subscore improved significantly with EPL than placebo at month 6 (LSM: 0.58 vs 0.27; LSMD: 0.31; **p=0.0229**).
- **Safety analysis**: Serious treatment-emergent adverse events were reported in 5 and 3 patients treated with EPL and placebo, respectively, with no deaths in either group.

CONCLUSIONS

- Treatment with **EPL (Opella®) demonstrated larger efficacy** compared to placebo in **reducing hepatic steatosis in patients with MASLD**. This improvement was shown at 3 months and maintained for 9 months post-treatment, demonstrating **long-term efficacy when combined with SoC.**
- The treatment was well tolerated with no safety concern, making EPL a promising option for **early intervention in MASLD management**.

REFERENCES : 1. Targher G, et al. *Gut*. 2024;73(4):691-702; 2. Tacke F, et al. *J Hepatol*. 2024;81(3):492-542; 3. Gundermann KJ, et al. *Clin Exp Gastroenterol*. 2016;9:105-117; 4. Stefan N, et al. *Trials*. 2024;25(1):374.

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