Safety and Effectiveness of Essential Phospholipids Paste in Patients with Non-alcoholic Fatty Liver Disease or Viral Hepatitis

Vladimir T. Ivashkin[1], Igor V. Maev[2], Chavdar S. Pavlov[1], Marina V. Mayevskaya[1], Aleksey A. Samsonov[2], Lyudmila K. Palgova[3], Kirill M. Starostin[4]

[1]*I.M. Sechenov First Moscow State Medical University, Ministry of Health of Russia, Moscow, Russia*
[2]*A.I. Evdokimov Moscow State University of Medicine and Dentistry, Ministry of Health of Russia, Moscow, Russia*
[3]*Clinical Research and Educational Center in Gastroenterology and Hepatology of St Petersburg Universitetskaya Naberezhnaya, Saint Petersburg, Russia*
[4]*Sanofi-Aventis, Moscow, Russia*

Cite this article as: Ivashkin VT, Maev IV, Pavlov CS, *et al*. Safety and effectiveness of essential phospholipids paste in patients with non-alcoholic fatty liver disease or viral hepatitis. *Turk J Gastroenterol*. 2021; 32(9): 750-757.

ABSTRACT

Background: *Essential phospholipids (EPL) are used as adjuvant treatment in people with fatty liver disease and other chronic liver diseases. A new formulation of EPL paste was developed to improve patient compliance. The study was aimed to assess the safety, patient-reported outcomes, and impact on compliance of the new EPL paste formulation in patients with non-alcoholic fatty liver disease (NAFLD) or viral hepatitis.*

Methods: *The study enrolled 147 patients (48.3% male; mean ± standard deviation (SD) age 44.8 ± 10.5 years) in the intention-to-treat population; 72.8% had NAFLD and 27.9% had viral hepatitis B (HBV) or hepatitis C (HCV). Patients received EPL paste (one 600 mg sachet 3 times daily) for 12 weeks, with 4-, 8-, and 12-week scheduled visits and a 13-week follow-up visit. Patient-reported outcomes were evaluated at 4, 8, and 12 weeks compared with baseline using dedicated Likert scales. Compliance was assessed by comparing actual versus prescribed dosing of the EPL.*

Results: *After 12-week treatment with EPL paste, statistically significant improvements were observed in mean ± SD Global Overall Symptom scores (from 4.21 ± 1.09 to 1.87 ± 0.91; P < .01) and overall Gastrointestinal Symptom scores (from 19.91 ± 5.74 to 11.17 ± 3.57; P < .01), compared to baseline scores. Compliance with prescribed essential phospholipid treatment was 99% throughout the 12-week treatment period.*

Conclusion: *Essential phospholipids paste had a favorable safety profile associated with improved gastrointestinal symptoms and with high levels of compliance in patients with NAFLD and viral hepatitis.*

Keywords: *Essential phospholipids, gastrointestinal dysfunction, liver disease, non-alcoholic fatty liver disease, phosphatidylcholine*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common reasons for liver transplantation. The incidence of NAFLD in cryptogenic liver cirrhosis is up to 75%.[1] A diagnosis of NAFLD is associated with a 34-69% increase risk of death of over 15 years,[2] and the prevalence of NAFLD is gradually increasing worldwide.[3] According to the DIREG2 study, the prevalence of NAFLD in Russia in 2015 was more than 37% and had increased by 10% compared with 2007.[4] Fatty liver disease also raises concerns because of its latent evolution and association with other diseases, including type 2 diabetes (T2DM) and obesity.[4] Non-alcoholic fatty liver disease is known to be associated with a 4-fold increase of cardiovascular disease risk and up to a 3-fold increase in risk of cardiovascular death.[5,6] Increasing evidence suggests an association between NAFLD and a higher risk of gastrointestinal disorders, including cholelithiasis, gastroesophageal reflux disease, and hepatocellular carcinoma, as well as an increased risk of breast cancer in women and colorectal cancer in men.[7-9] Severe exacerbation of chronic pancreatitis has also been observed in patients with NAFLD.[10]

The current therapy of NAFLD primarily includes lifestyle changes, weight loss, and treatment of comorbidities.[11] However, no "gold standard" pharmacotherapy for NAFLD currently exists. Several promising molecules have been investigated, and a number of pharmacotherapeutic options have been applied in clinical practice.[12] Among

Corresponding author: ***Kirill M. Starostin****, e-mail:* ***Kirill.Starostin@sanofi.com***
Received: ***August 3, 2020*** *Accepted:* ***January 31, 2021*** *Available Online Date:* ***September 20, 2021***

DOI: 10.5152/tjg.2021.20294

the existing hepatoprotective interventions, essential phospholipids (EPL) are the most studied pharmacologic therapy in NAFLD, especially with regard to their impact on steatosis.[11,13] The efficacy of EPL in reducing steatosis was shown in 6 randomized controlled trials, based on ultrasound, computed tomography (CT), and liver histology assessments.[14-19] Polyenyl phosphatidylcholine (PCH), a key component of EPL, has membranous, antioxidative, and antifibrotic effects and may be characterized as a pathogenetic-based treatment of NAFLD.[13] Furthermore, EPL has a favorable safety profile, with no serious adverse events (AEs) and transient non-serious AEs observed during its use.[13,20] Non-alcoholic fatty liver disease is not characterized by any highly specific symptoms. However, a variety of non-specific systemic and gastrointestinal symptoms may accompany this condition, impairing the patient's quality of life.[21]

Essential phospholipids may also be used as an adjunctive intervention in patients with viral hepatitis.[20] The highest prevalence rate of NAFLD has been reported in patients with hepatitis C (HCV) and hepatitis B (HBV), at 55%, and about 22%, respectively.[22] Viral hepatitis is usually associated with impaired quality of life and non-specific gastroenterology symptoms.[23] Essential phospholipids can be used as part of an appropriate treatment complex because of their contribution to histological improvement in viral hepatitis.[20] Essential phospholipids may help to facilitate recovery and therefore improve patient-reported outcomes, including self-reported symptom intensity.[20] Based on evidence regarding the benefits of EPL in people with viral hepatitis[19,24-26] and on the presence of virus-associated steatosis in patients with viral hepatitis which is expected to exacerbate disease progression and worsen the prognosis,[22,27] essential phospholipids therapy in patients with fatty liver and viral hepatitis may also be valuable from a clinical point of view.

In most studies of patients with NAFLD and viral hepatitis, the therapeutic efficacy of EPL was demonstrated at a daily dose of 1800 mg.[13,20] When considering the active component, the amount of PCH contained in an effective therapeutic dosage of EPL is estimated to be 1368 mg daily. In the Russian Federation, over-the-counter EPL is available as a capsule formulation of 300 mg, which requires patients to take 6 capsules daily (2 capsules 3 times daily) to achieve the recommended dose. Given the required frequency of administration, the patient's adherence to EPL treatment may be reduced.[28] Furthermore, the capsule may be difficult to swallow for certain patient populations, such as the elderly, children, or patients with dysphagia.[29] Generally, up to 40% of adults experience difficulties in swallowing tablet or capsule formulations.[30] Therefore, changing the formulation of the medication may allow for more comfortable and easier administration in these patients.[30] The present study aimed to investigate the safety and effectiveness of a new EPL formulation, a PCH-containing paste, in Russian patients with NAFLD or viral hepatitis. The EPL paste is available in sachets, each containing 600 mg of EPL. Unlike the capsule formulation, and due to the increased dosage compared with the capsule formulation, the EPL paste can be administered as 1 sachet 3 times daily. Although the number of daily doses of EPL remains unchanged, dosing is less complex, which is an important factor affecting treatment adherence and compliance with the dosing regimen.[28] In general, taking 1 pill at a time instead of 2 increases adherence.[31]

Since fatty liver and viral hepatitis are the most common liver diseases, and EPL may be used as adjunctive treatment in both, our primary objective was to achieve the safety of a new form of EPL, and we decided to include both NAFLD and viral hepatitis patients.

MATERIALS AND METHODS

Study Design and Patient Population

This was an open-label, interventional, multicenter, prospective, non-controlled clinical study to evaluate the safety profile of EPL paste and assess patient-reported clinical outcomes in terms of the safety and effectiveness of 600 mg of EPL paste administered orally thrice daily (1800 mg of EPL daily) in patients with NAFLD or viral hepatitis, in the presence of clinical gastrointestinal symptoms.

The study included 8 sites in 6 Russian cities: Moscow, Nizhny Novgorod, Kazan, Arkhangelsk, Saint-Petersburg, and Rostov-on-Don.

The study protocol complied with the recommendations of the Declaration of Helsinki and the International Conference on Harmonization guidelines for good clinical practice. The protocol also complied with all applicable Russian laws, regulations, and guidelines. Ethical approval was granted by the Russian Healthcare Ministry Ethics Committee. All study participants provided written informed consent prior to study inclusion. The study details are disclosed at clinicaltrials.gov (NCT02517385).

From the time a patient entered the study (between August 31, 2015 and June 15, 2016), it took in total

14 weeks, with 5 planned visits (1 week of prescreening, 12 weeks of treatment, and 1 week of follow-up). Physicians and gastroenterologists at the in-patient departments of the study sites carried out the recruitment and all interventions. Eligible patients were aged 18-65 years and had gastrointestinal symptoms in the presence of NAFLD (a diagnosis of NAFLD confirmed on ultrasound) or viral hepatitis (based on appropriate clinical and laboratory assessments), without signs of severe fibrosis or liver failure. Only patients receiving standard therapy for the underlying liver disease were included in the study. The exclusion criteria were: age <18 or >65 years; pregnancy or lactation; hypersensitivity to EPL; congenital α-1 antitrypsin deficiency; other types of hepatitis; liver failure; severe organic gastrointestinal disorders; intake of medicines affecting liver function and not included in the standard treatment of the underlying disease during the 1 month preceding screening; and other severe diseases.

All study participants were prescribed 600 mg of oral EPL paste, 1 sachet thrice daily with meals (1800 mg/day) for 12 weeks, starting on day 1 of enrolment into the study. Additionally, the participants were advised to follow their physician's recommendations as part of their standard therapy for the underlying liver disease (lifestyle changes for NAFLD, antiviral pharmacotherapy for viral hepatitis). All participants were advised to avoid alcohol consumption and to implement dietary and physical exercise recommendations before study participation.

Study Outcomes

The primary outcome was occurrence of AEs associated with the use of the study drug (as per investigator judgment) during the 12-week treatment and 1-week follow-up periods. Secondary safety outcomes were the frequency (number and percent) of AEs not associated with the study drug, and serious AEs based on objective examination, patient interviews, and analysis of their diaries (regardless of the causal relationship with the study drug) during 4, 8, and 12 weeks of treatment. Adherence to the prescribed treatment regimen was assessed after 4, 8, and 12 weeks. The following formula was used to estimate treatment adherence: [(number of sachets administered)/(expected number of sachets administered)] × 100%. A healthcare professional recorded all dosage changes and the number of missed doses (if any) in a registry. A result below 80% was interpreted as low adherence.

Clinical effectiveness was assessed based on changes in overall clinical state, measured as intensity of any symptoms observed after 4, 8, and 12 weeks compared with baseline using a 7-point Global Overall Symptoms (GOS) score, in which 1 = no problem and 7 = very serious problem which is impossible to ignore and impairs daily activities.[32] An improvement of ≥30% from baseline on the GOS scale after 12 weeks of treatment was expected. The intensity of 6 gastrointestinal symptoms was also analyzed on a Gastrointestinal Symptoms (GIS) score. For this purpose, a questionnaire adapted from Veldhuyzen (2006)[32] and Svedlund (1988)[33] was used to measure the intensity of gastrointestinal symptoms on a 7-point Likert scale. The following 6 symptoms were assessed: fatigue; abdominal pain/discomfort; discomfort after meals; sensation of fullness after meals; nausea/vomiting; and eructation/bloating. The overall GIS score and the intensity of each of the 6 gastrointestinal symptoms were assessed separately. The proportion of patients with response to therapy (defined as a reduction in the GOS score to 0 or 1-2 points) was calculated. A response rate of ≥50% was expected.

Statistical Analysis

Descriptive statistics were used for the statistical analysis of demographic data as well as the variables of safety and patient-reported outcomes (effectiveness). The descriptive analysis included calculation of N, and mean, standard deviation (SD), median, Q1 and Q3 quartiles, and minimum and maximum values. The distribution of the variables was tested for normality using the Shapiro–Wilk test and the skewness and kurtosis test; the homogeneity of variances was estimated using Levene's test (critical significance level $P = .05$). For the comparison between time points, the ANOVA method was used (or the Kruskal–Wallis test in the case of nonparametric distribution), followed by a comparison based on Student's *t*-test (or the Mann–Whitney *U*-test, respectively), if necessary, and the paired Student's *t*-test (or Wilcoxon signed-rank test, respectively). Statistical analysis was performed using SAS 9.4 (or above) and NCSS 10.0 (or above) software. The critical level of significance was $P = .05$, and the Bonferroni correction was used for multiple comparisons.

Assuming that the incidence of treatment-related AEs would be about 3.5% of the calculated sample size, an estimated 140 study participants (patients) were needed to achieve 80% power when comparing the proportion of patients with study drug-related AEs, based on Fisher's Exact test with 2-sided α = 5% (compared with a theoretical predetermined 10% incidence). Considering a 5% potential dropout rate, 147 participants were to be included in the study.

The safety analysis was conducted in the intention-to-treat (ITT) population (defined as study participants who received ≥1 dose of the study drug), while the effectiveness analysis was conducted in the per-protocol (PP) population (defined as study participants who completed all study procedures in accordance with the protocol). Adherence to the prescribed regimen was analyzed in a modified ITT (mITT) analysis that included all patients with available data, following a predetermined formula.

RESULTS

Baseline Characteristics

In total, 147 patients were screened and included in the study between August 31, 2015 and June 15, 2016. The ITT population analysis included 147 patients (mean ± SD age 44.8 ± 10.5 years) who received ≥1 dose of the study drug; 48.3% were males. In the study, 5 major protocol deviations were recorded; 4 related to screening procedures at visit 2, specifically assessing exclusion criteria based on a laboratory analysis conducted more than 30 days previously. The other major protocol deviation was a failure to meet one of the inclusion criteria (viral hepatitis was confirmed, but alanine aminotransferase [ALT] levels were not elevated), which was reported after the patient was included and the study drug was dispensed. This patient discontinued the study and was excluded from the PP analysis. In total, 4 patients did not complete the study: 2 discontinued due to the unpleasant taste of the study drug, 1 discontinued for logistical reasons, and 1 was excluded due to an error and failure to meet inclusion criteria (see protocol deviation described above). Thus, 143 patients (97.3%) completed the entire course of therapy and were included in the PP population.

Of the 147 patients in the ITT population, 107 (72.8%) had NAFLD and 41 (27.9%) had viral hepatitis (1 patient was diagnosed with both conditions); most of these patients had HBV, with 1 patient having concurrent HBV and HCV, and another patient having concurrent NAFLD and HCV. At baseline, most patients (n = 105; 73.5%) rated their overall condition as moderate or moderately severe, and only 12 patients (8.4%) reported no issues or overall minimal symptoms. Of the individual gastrointestinal symptoms, the most pronounced were fatigue (mean ± SD score 3.8 ± 1.51), abdominal pain and discomfort (3.72 ± 1.32), eructation, and bloating (3.65 ± 1.48).

At baseline, the most frequent comorbidities were hepatobiliary disorders (77.6%), metabolic and nutritional disorders (38.8%), infections (36.1%), gastrointestinal disorders (31.3%), and cardiovascular disorders (30.6%). In total, 82 patients (55.8%) were receiving concomitant medications for comorbidities.

Safety

During the 12-week treatment and 1-week follow-up periods, 37 drug-related AEs were observed in 22 patients (15.0%). Drug-related AEs primarily included diarrhea (16 cases in 10 patients [6.8%]) and dyspepsia (7 cases in 5 patients [3.4%]). Totally 6 cases of dyspepsia were observed during the 12-week treatment period and 1 case was observed during the 1-week follow-up period. The incidence of all other study drug-related AEs did not exceed 2% (nausea [2.0%], dysgeusia [2.0%], dry mouth [0.7%], thirst [0.7%], and abdominal pain [0.7%]). None of the participants discontinued treatment due to AEs and no deaths or other SAEs occurred.

EFFECTIVENESS AND PATIENT-REPORTED OUTCOMES

GOS Score and Response Rate

At baseline, the mean ± SD GOS score was 4.21 ± 1.09. After 4 weeks of treatment, a significant reduction from baseline in mean ± SD GOS score to 3.01 ± 1.11 points ($P < .01$) was observed (i.e., a 28.4% reduction from baseline). This statistically significant reduction remained consistent during the entire treatment period, with a 43.7% reduction from baseline at 8 weeks (mean ± SD GOS score 2.37 ± 0.87 points; $P < .01$) and a 55.5% reduction from baseline after the full 12-week treatment period (mean ± SD GOS score 1.87 ± 0.91; $P < .01$; Figure 1). After the completion of the 12-week treatment period, the response rate was 81.1%, which exceeded the pre-established threshold of 50% (Figure 1).

GIS Score

Essential phospholipids paste treatment was associated with significant reductions in the severity of gastrointestinal symptoms, and with statistically significant reductions from baseline in mean GIS scores observed after 4, 8, and 12 weeks of treatment (Figure 2). The mean GIS score decreased by 54.3% ($P < .01$) after 12 weeks of treatment, which exceeded the expected reduction of ≥30% (Figures 2 and 3).

Mean ± SD GIS scores decreased from 19.91 ± 5.74 at baseline to 14.48 ± 4.69 at 4 weeks ($P < .01$), 11.17 ± 3.57 at 8 weeks ($P < .01$), and 9.09 ± 3.55 at 12 weeks ($P < .01$). When considering the individual components of the GIS score, a significant reduction in each symptom intensity

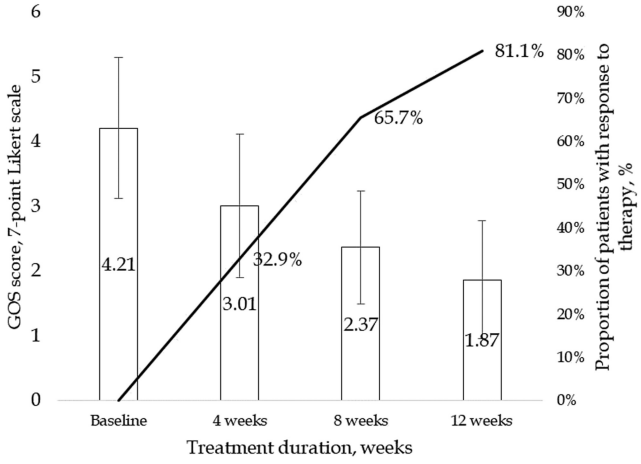

Figure 1. GOS score assessment and clinical status as assessed on a 7-point Likert scale (vertical scale on the left, diagram columns) and the proportion of patients with response to therapy following 4, 8, and 12 weeks of treatment (vertical scale on the right, line on the diagram).

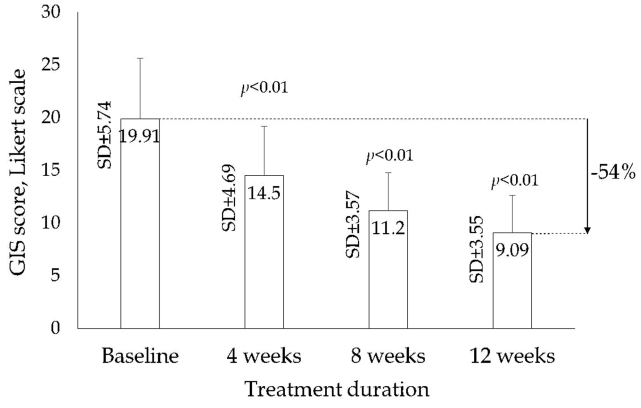

Figure 2. GIS scores as assessed on a 7-point Likert scale.

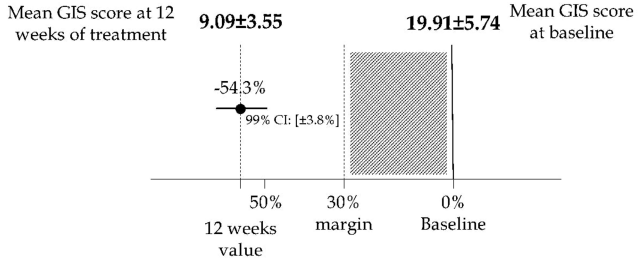

Figure 3. Absolute and relative decrease in mean GIS score after 12 weeks of treatment (54.3%; $P < .01$), which met the expected threshold of ≥30% reduction.

was observed after 4 weeks of treatment and remained significant at 8 and 12 weeks (Table 1).

Adherence to Treatment

Totally 2 patients discontinued the study before visit 3 (week 4), with no data regarding administered dosages; therefore, 145 patients were included in the mITT analysis of treatment adherence at visits 3 and 4 (weeks 4 and 8), and adherence data were available for 143 subjects at visit 5 (week 12). At each visit, treatment adherence was calculated as 99%, meaning that almost all patients received ≥80% of the prescribed treatment as per the study protocol.

DISCUSSION

Our study showed that the new paste formulation of EPL has a favorable safety profile in patients with NAFLD or viral hepatitis and gastrointestinal symptoms, when administered as 1 dose thrice daily with meals, over a period of 12 weeks. The AEs specifically associated with the EPL paste formulation were bitter taste, dyspepsia, and dry mouth. However, the investigators recognized these events as transient and not requiring treatment withdrawal. The EPL paste formulation was associated with statistically significant improvements from baseline in gastrointestinal symptom severity within the first 4 weeks of treatment, that were maintained throughout the 12-week treatment period. The EPL 600 mg paste was also associated with a high level of treatment adherence.

The severity of gastrointestinal symptoms is known to significantly impact health and quality of life.[34] One of the quickest and easiest ways to assess a patient's well-being is with validated questionnaires,[33] which can help to assess the patient's health condition and quality of life. Having analyzed non-specific gastrointestinal symptoms in NAFLD and viral hepatitis, we have chosen the GOS and GIS scores as most relevant to assess patient-reported outcomes through symptoms. Assessment of symptoms was made using GOS and GIS scores based on a 7-point Likert scale, which allows us to perform a more accurate assessment of the symptoms than the standard 4-point scale. This method for determining the severity of symptoms was based on the correlation of both NAFLD progression and liver-related markers in hepatitis with symptoms of impaired gastrointestinal function.[35,36] The GOS and GIS scores showed an improvement in overall gastrointestinal symptom severity within the first month of therapy that was sustained during the entire 12-week

Table 1. Individual GIS Scores at Baseline and After 4, 8, and 12 Weeks of Treatment

	Mean ± SD Score (% Reduction vs Baseline)			
Gastrointestinal Symptom	Baseline	4 Weeks	8 Weeks	12 Weeks
Fatigue	3.8 ± 1.51 (NA)	2.83 ± 1.24 (25.6%)*	2.28 ± 1.07 (40%)*	1.81 ± 0.87 (52.3%)*
Abdominal pain/discomfort	3.72 ± 1.32 (NA)	2.55 ± 1.12 (31.4%)*	1.91 ± 0.88 (48.7%)*	1.56 ± 0.86 (58.1%)*
Eructation/bloating	3.65 ± 1.48 (NA)	2.48 ± 1.16 (32.0%)*	1.91 ± 0.97 (47.7%)*	1.62 ± 0.89 (55.7%)*
Sensation of fullness after meals	3.45 ± 1.42 (NA)	2.52 ± 1.14 (26.8%)*	1.92 ± 0.86 (44.2%)*	1.54 ± 0.77 (55.4%)*
Early satiety	3.01 ± 1.45 (NA)	2.38 ± 1.11 (20.9%)*	1.86 ± 0.83 (38.3%)*	1.43 ± 0.7 (52.7%)*
Nausea/vomiting	2.28 ± 1.34 (NA)	1.71 ± 0.96 (24.8%)*	1.29 ± 0.52 (43.3%)*	1.14 ± 0.39 (50.0%)*

*$P < .01$ versus baseline, Wilcoxon signed-rank test.

treatment period. This observation is consistent with another study, which reported a statistically significant and reliable improvement of biochemical blood parameters (fasting glucose, lipid profile, bilirubin, and several serum enzymes) by the 30th day of treatment with PCH.[37]

It is worth noting that most publications have observed an effect of EPL on steatosis after 3-6 months of treatment.[14-18] According to the available literature, the physical and mental dimensions of the quality of life in patients with NAFLD are lower than those in the general population.[38]

Viral hepatitis treatment includes antiviral drugs as a basic obligatory approach. At the same time, there is accumulated clinical evidence showing that EPL may be added an adjunctive treatment to improve both the objective and subjective outcomes.[19,20,24-26] Both HBV and HCV may be accompanied with non-specific gastrointestinal symptoms which are usually not in primary clinical focus.[36,39] Thus, in this study, we have shown that EPL as adjunctive treatment in viral hepatitis may contribute to the clinical patient-reported improvement in gastrointestinal symptoms based on GOS and GIS scores.

Based on the obtained results, we may conclude that this treatment intervention may improve non-specific gastrointestinal symptoms and quality of life in patients with NAFLD and viral hepatitis. Further well-designed randomized controlled trials, including patient-reported outcomes are needed to confirm our observations.

In recent years, a closer look at the potential clinical signs or symptoms which may be helpful in suspecting NAFLD has shown that this disease may manifest not only with fatigue, the sensation of heaviness in the upper right abdomen, and changes in appetite. Patients with NAFLD may also present with concentration difficulties, memory difficulties, daytime drowsiness, mood changes, and emotional dysphoria.[40-42] Moreover, in addition to mood changes and depression which correlate with the intensity of hepatocyte degeneration and severity of liver damage,[41] cognitive impairment is observed in "pure" steatosis. This cognitive impairment is unrelated to the hyperammonemia-associated encephalopathy that occurs with decompensated liver cirrhosis.[42] Another source of NAFLD suspicion is non-specific gastrointestinal symptoms.[43]

With regard to selecting NAFLD treatment based on evidence-based medicine, and keeping in mind that the first (benign and practically the only fully reversible) "hit" within the pathogenesis of NAFLD is steatosis, we provide the following view. At the earliest stage of the NAFLD—the stage of steatosis—the patient should be encouraged to implement lifestyle modifications and to become more physically active, switch to a healthy diet, and lose weight. However, knowing that patient adherence to non-pharmacologic therapies is often low, addition of pharmacotherapy with a proven effect on liver steatosis and a patient-reported clinical state may be recommended.

Our study has shown the safety and the potential effectiveness of EPL on the clinical state of patients with NAFLD and viral hepatitis, including improving the severity of non-specific gastrointestinal symptoms. Since previous controlled studies showed a positive effect of EPL on the liver structure using objective diagnostic methods, including liver biopsy, the practical value of the present study is its assessment of the impact of EPL on outcomes that matter to patients and are self- reported, which is gaining more importance in clinical practice.[44]

Our research study has some limitations, such as the absence of a comparison (i.e., a control group), masking of subjects and investigators assessing outcomes, and the absence of objective confirmation of changes in the liver structure following treatment. However, the strengths of this study include the use of patient-reported outcomes not previously assessed in NAFLD and viral hepatitis patients receiving EPL. Another merit of the study is the safety assessment of an established drug in a new formulation. Finally, since the study sample included patients with NAFLD and chronic hepatitis, the use of EPL as an adjunctive treatment may improve the condition in these populations.

CONCLUSIONS

The study drug, 600 mg EPL paste, administered thrice daily with meals for 12 weeks in patients with NAFLD or viral hepatitis and gastrointestinal symptoms, showed a favorable safety profile (no serious AEs or deaths; the most common AEs were diarrhea and dyspepsia). Beneficial patient-reported outcomes of EPL paste were confirmed by the significant improvements in general symptoms and gastrointestinal symptoms, which were observed within the first 4 weeks of treatment and maintained at 8 and 12 weeks. Further confirmation of its clinical effectiveness was the high response rate (81.1%), which exceeded the 50% threshold predefined in the study protocol. Furthermore, the study drug showed high levels of treatment adherence. These findings indicate that EPL may be used as a first-line agent in patients with NAFLD, in combination with non-pharmacologic therapies, the relevance and value of which should not be underestimated. The new dosage form of EPL may simplify administration in patients with swallowing difficulties, thereby potentially increasing patient adherence to treatment.

Core Tip: The present clinical study investigated the safety and effectiveness of a new formulation of EPL, a phosphatidylcholine paste, in patients with NAFLD or viral hepatitis. The EPL paste showed a favorable safety profile and provided significant improvements from baseline in scores of Global Overall Symptoms and Gastrointestinal Symptoms. In addition, patients' adherence to this new formulation of EPL remained high. Our data provide clinical support for the use of EPL paste to alleviate symptoms in chronic liver diseases; however, these data should be confirmed in well-designed controlled trials.

Data Availability Statement: Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com/.

Ethics Committee Approval: This study was reviewed and approved by the Ethics Committee of the Ministry of Health of the Russian Federation [CHOLIL06301] No. 20-2-466312/R/ET-Z from December 1, 2014.

Informed Consent: All study participants provided written informed consent prior to study inclusion. Study details are disclosed at clinicaltrials.gov (NCT02517385).

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – V.T.I., I.V.M.; Design – V.T.I., I.V.M.; Supervision - V.T.I., I.V.M.; Resource - V.T.I., I.V.M.; Materials - C.S.P., M.V.M., A.A.S., L.K.P.; Data Collection and/or Processing - All authors; Analysis and/or Interpretation - All authors; Literature search - KMS; Writing – KMS; Critical Reviews – All Authors; Final approval - All Authors.

Acknowledgments: We are grateful to "Atlant Clinical Ltd." for operational management of this trial, data management, and statistical analysis. We would also like to thank Darya Osipova, MD and Kristina Kokoreva, MD, Sanofi Medical Department Specialists who helped us with medical writing and publication processing.

Conflict of Interest: Kirill M. Starostin is an employee of Sanofi. The other authors declare no potential conflicts of interests.

Financial Disclosure: This clinical trial was sponsored by Sanofi.

REFERENCES

1. Pais R, Barritt AS, Calmus Y, et al. NAFLD and liver transplantation: current burden and expected challenges. J Hepatol. 2016;65:1245-1257. [CrossRef]
2. Patel V, Sanyal AJ, Sterling R. Clinical presentation and patient evaluation in non-alcoholic fatty liver disease. Clin Liver Dis. 2016;20:277-292. [CrossRef]
3. Benedict M, Zhang X. Non-alcoholic fatty liver disease: an expanded review. World J Hepatol. 2017;9:715.
4. Ivashkin VT, Drapkina OM, Mayev IV, et al. The prevalence of non-alcoholic fatty liver disease in patients of outpatient practice in the Russian Federation: the results of the study DIREG 2 (Russian). Russ J Gastroenterol Hepatol Coloproctol. 2015;25:31-38.
5. Lazebnik LB, Radchenko VG, Golovanova YV, et al. Non-alcoholic fatty liver disease: clinic, diagnostics, treatment (guidelines for the specialists on internal medicine, 2nd version). Therapy. 2017;3:6-23.
6. Zhou YJ, Li YY, Nie YQ, Huang CM, Cao CY. Natural course of non-alcoholic fatty liver disease in southern China: a prospective cohort study. J Dig Dis. 2012;13:153-160. [CrossRef]
7. Qin JJ, Ding WJ. Nonalcoholic fatty liver disease and its relevant factors increased the risk of gallstone disease: a systematic review and meta-analysis. Int J Clin Exp Med. 2016;9:3009-3016.
8. Yang HJ, Chang Y, Park SK, et al. Non-alcoholic fatty liver disease is associated with increased risk of reflux esophagitis. Dig Dis Sci. 2017;62:3605-3613. [CrossRef]

9. Kim GA, Lee HC, Choe J, et al. Association between non-alcoholic fatty liver disease and cancer incidence rate. J Hepatol. 2017;68:140-146. [CrossRef]
10. Yoon SB, Lee IS, Choi MH, et al. Impact of fatty liver on acute pancreatitis severity. Gastroenterol Res Pract. 2017;2017. [CrossRef]
11. Ivashkin VT, Mayevskaya MV, Pavlov CS, et al. Diagnostics and treatment of non-alcoholic fatty liver disease: clinical guidelines of the Russian Scientific Liver Society and the Russian gastroenterological association (Russian). Russ J Gastroenterol Hepatol Coloproctol. 2016;26:24-42. [CrossRef]
12. Sumida Y, Yoneda M. Current and future pharmacological therapies for NAFLD/NASH. J Gastroenterol. 2018;53:362-376. [CrossRef]
13. Gundermann KJ, Gundermann S, Drozdzik M, Mohan Prasad VG. Essential phospholipids in fatty liver: a scientific update. Clin Exp Gastroenterol. 2016;9:105-117.
14. Gonciarz Z, Besser P, Lelek E, Gundermann KJ, Johannes KJ. Randomised placebo-controlled double blind trial on "essential" phospholipids in the treatment of fatty liver associated with diabetes. Med Chir Dig. 1988;17:61-65.
15. Sas E, Grinevich V, Efimov O, Shcherbina N. 1366 Beneficial influence of polyunsaturated phosphatidylcholine enhances functional liver condition and liver structure in patients with nonalcoholic steatohepatitis. Results of prolonged randomized blinded prospective clinical study. J Hepatol. 2013;58:S549. [CrossRef]
16. Li Z. Efficacy of polyene for diabetes complicated with non-alcoholic fatty liver disease. Inn Mong. J Tradit Chin Med. 2013;31:10-11.
17. Li JH, Chen X-Y, Zhong C-F, Min J. A randomized controlled study of essential phospholipids in the treatment of fatty liver (Chinese). Infect Dis Inf. 2000;13(4):180-181.
18. Sun C, Zheng X, Tan Z, et al. Clinical observation on polyene phosphatidylcholine and metformin in the treatment of type-2 diabetes and non-alcoholic fatty liver disease. Clin Focus. 2008;23:1272-1273.
19. Iliè V, Begic-Janeva A. Treatment of HBsAg positive chronic active hepatitis: efficacy of "essential" phospholipids (German). Med Welt. 1991;42:523-525.
20. Gundermann KJ, Kuenker A, Kuntz E, Drożdzik M. Activity of essential phospholipids (EPL) from soybean in liver diseases. Pharmacol Rep. 2011;63:643-659.
21. Younossi ZM, Stepanova M, Henry L, et al. A disease-specific quality of life instrument for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: CLDQ-NAFLD. Liver Int. 2017;37(8):1209-1218. [CrossRef]
22. Adinolfi LE, Rinaldi L, Guerrera B, et al. NAFLD and NASH in HCV infection: prevalence and significance in hepatic and extrahepatic manifestations. Int J Mol Sci. 2016;17. [CrossRef]
23. Mittal P, S Matreja P, Rao HK, Khanna P. Prevalence and impact of hepatitis on the quality of life of patients. Euroasian J Hepatogastroenterol. 2015;5(2):90-94. [CrossRef]
24. Ghose N, Santra A, Pal A, Mazumdar DN. Role of essential phospholipids (EPL) in acute viral hepatitis. Indian Med Gaz. 1993;6:179-183.
25. Visco G. Polyunsaturated phosphatidylcholine (EPL) in association with vitamin B complex for the treatment of acute viral hepatitis B: results of a randomized double-blind clinical study (Italian). Clin Ter. 1985;114(3):183-188.
26. Jenkins PJ, Portmann BP, Eddleston AL, Williams R. Use of polyunsaturated phosphatidylcholine in HBsAg negative chronic active hepatitis, results of prospective double-blind controlled trial. Liver. 1982;2(2):77-81. [CrossRef]
27. Lim CT, Kumar R. Hepatitis B and concomitant hepatic steatosis. Ann Transl Med. 2017;5:38. [CrossRef]
28. Srivastava K, Arora A, Kataria A, et al. Impact of reducing dosing frequency on adherence to oral therapies: a literature review and meta-analysis. Patient Prefer Adherence. 2013;7:419-434.
29. Liu F, Ranmal S, Batchelor HK, et al. Patient-centred pharmaceutical design to improve acceptability of medicines: similarities and differences in paediatric and geriatric populations. Drugs. 2014;74:1871-1889. [CrossRef]
30. Lau ETL, Steadman KJ, Cichero JAY, Nissen LM. Dosage form modification and oral drug delivery in older people. Adv Drug Deliv Rev. 2018;135:75-84. [CrossRef]
31. Laufs U, Rettig-Ewen V, Böhm M. Strategies to improve drug adherence. Eur Heart J. 2011;32:264-268. [CrossRef]
32. Veldhuyzen van Zanten SJ, Chiba N, Armstrong D, et al. Validation of a 7-point global overall symptom scale to measure the severity of dyspepsia symptoms in clinical trials. Aliment Pharmacol Ther. 2006;23:521-529. [CrossRef]
33. Svedlund J, Sjödin I, Dotevall G. GSRS-A clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988;33. [CrossRef]
34. Bovenschen HJ, Laheij RJF, Tan A, et al. Health-related quality of life of patients with gastrointestinal symptoms. Aliment Pharmacol Ther. 2004;20:311-319. [CrossRef]
35. Reddy SK, Zhan M, Alexander HR, El-Kamary SS. Non-alcoholic fatty liver disease is associated with benign gastrointestinal disorders. World J Gastroenterol. 2013;19:8301-8311.
36. Evon DM, Stewart PW, Amador J, et al. A comprehensive assessment of patient reported symptom burden, medical comorbidities, and functional well being in patients initiating direct acting antiviral therapy for chronic hepatitis C: results from a large US multicenter observational study. PLoS One. 2018;13(8):e0196908. [CrossRef].
37. Padma L, Mukaddam Q, Trailokya A. An observational study of essentiale-L in the treatment of patients with fatty liver disease. Indian J Clin Pract. 2013;23:735-739.
38. David K, Kowdley KV, Unalp A, et al. Quality of life in adults with nonalcoholic fatty liver disease: baseline data from the non-alcoholic steatohepatitis clinical research network. Hepatology. 2009;49(6):1904-1912. [CrossRef]
39. Hann HW, Han SH, Block TM, et al. Symptomatology and health attitudes of chronic hepatitis B patients in the USA. J Viral Hepat. 2008;15(1):42-51. [CrossRef]
40. Peng K, Lin L, Wang Z, et al. Short sleep duration and longer daytime napping are associated with non-alcoholic fatty liver disease in Chinese adults. J Diabetes. 2017;9:827-836. [CrossRef]
41. Youssef NA, Abdelmalek MF, Binks M, et al. Associations of depression, anxiety and antidepressants with histological severity of non-alcoholic fatty liver disease. Liver Int. 2013;33:1062-1070. [CrossRef]
42. Seo SW, Gottesman RF, Clark JM, et al. Non-alcoholic fatty liver disease is associated with cognitive function in adults. Neurology. 2016;86:1136-1142. [CrossRef]
43. Khoonsari M, Azar MMH, Ghavam R, et al. Clinical manifestations and diagnosis of non-alcoholic fatty liver disease. Iran J Pathol. 2017;12(2):99-105. [CrossRef]
44. Deshpande PR, Surulivel R, Sudeepthi BL, Nazir CPA. Patient-reported outcomes: a new era in clinical research. Perspect Clin Res. 2011;2:137-144. [CrossRef]