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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi **Drug substance(s):** Phosphatidyl choline	**Study Identifiers:** U1111-1131-0460, NCT02517385 **Study code:** CHOLIL06301

Title of the study: Multicenter, phase III, open label, prospective, uncontrolled, non-comparative, interventional trial to evaluate safety and effectiveness of phosphatidylcholine paste 600mg in patients with gastrointestinal symptoms due to acute or chronic liver diseases during a 12-week course of treatment

Study center(s): 8 study centers in Russia

Study period:

Date first patient enrolled: 31/Aug/2015

Date last patient completed: 15/Jun/2016

Phase of development: Phase III

Objectives:

The primary objective:

- To assess the safety of the dosing of phosphatidylcholine paste 600 mg three times a day for 12 weeks in patients with acute or chronic liver diseases and symptoms of dysfunction of the gastrointestinal tract.

Secondary objectives:

- To assess effectiveness on symptomatic improvement in patients with gastrointestinal symptoms in acute or chronic liver diseases.
- To assess the compliance with the prescribed regimen of a study drug.

Methodology:

The study was a multicenter, prospective, uncontrolled, non-comparative, open label, interventional Phase III clinical trial.

The duration of study for each subject will be 13 weeks: 1 week prescreening, 12 weeks of treatment. Selection of patients enrolled in the study (prescreening) will be performed within 7 days. During the screening visit, patients will be assigned to treatment with phosphatidylcholine paste 600 mg for 12 weeks. Total planned visits 5: Prescreening visit – Day-7, Screening visit Day 0 (the visit of enrollment and start of study treatment) and visits at 4, 8 and 12 weeks after the start of study treatment). During scheduled visits, patients will visit the hospital.

Determination of sample size according to the protocol: 140 patients eligible for the analysis were required to achieve 80% power for comparison of the percentage of patients with adverse events related to the IP with a specified bond of 10% using Fisher's exact test for two-sided alpha level of 5% suggesting that the observed rate of patients with adverse events associated with treatment is 3.5%. Considering about 5% dropout rate, it was necessary to screen 147 patients.

Number of patients**:** Planned: 147

Screened: 147 (randomization was not intended)

Treated: 147

Evaluated:

Effectiveness: 143 (PP population)

Safety: 147 (ITT population)

Diagnosis and criteria for inclusion:

Male and female patients ≥ 18 and <66 years old, with diagnosed and being treated with standard therapy for at least one acute or chronic liver disease (non-alcoholic fatty liver disease [diagnosed with ultrasound] or viral hepatitis [based on clinical and laboratory signs]), accompanied with gastrointestinal symptoms (fatigue, abdominal pain/discomfort, early satiety, fullness discomfort after meal, nausea/vomiting, belching/abdominal distension, at least one rated as "Moderate Problem" or higher severity at screening visit), and with signed informed consent and without exclusions criteria.

Study treatments

Investigational medicinal product(s): Essentiale®

Formulation: Essential phospholipids derived from soya beans, containing 76% of (3-sn-phosphatidyl)-choline (Paste 600 mg)

Route(s) of administration: Oral

Dose regimen: 600 mg orally 3 times a day with meal

Noninvestigational medicinal product(s): Standard therapy for acute or chronic liver disease (predetermined by the study Investigator)

Formulation: N/A

Route(s) of administration: N/A

Dose regimen: N/A

Duration of treatment: 12 weeks

Duration of observation: 13 weeks

Criteria for evaluation:

Primary endpoint – Safety:

- Frequency (number and percentage) of Adverse Events (AEs) related to study drug over 12-week treatment period.

Secondary endpoints – Safety:

- Adverse events frequency (number and percentage) based on an analysis of all adverse events reports irrespective of a causal relationship to study drug intake according to investigator's decision for 4, 8 and 12 weeks of treatment.
- AE and SAE frequency (number and percentage) related and unrelated to study treatment.

Secondary endpoints – Compliance:

- Compliance with the prescribed treatment regimen after 4, 8 and 12 weeks of treatment.

Secondary endpoints – Effectiveness:

- The percentage change in overall evaluation score of patient's existing symptoms after 4, 8 and 12 weeks of treatment compared with the baseline assessment by 7-point Likert scale.
  - It's expected at least 50% of patients show improvement on global overall symptoms (Responders patients) after 12 weeks of treatment compared with the baseline
- The percentage change in gastrointestinal symptoms score (fatigue, abdominal pain / abdominal discomfort, rapid feeling of satiety, the feeling of fullness after eating, nausea / vomiting, belching / abdominal distension by 7-point Likert scale each symptom) after 4, 8 and 12 weeks of treatment compared with the baseline assessment. Gastrointestinal symptoms score was adapted based on score applied in Veldhuyzen et al. Aliment Pharmacol Ther 2006;23, 521–529 and Svedlund J et al GSRS Dig Dis Sci. 1988 Feb;33(2):129-34.
  - It's expected at least 30% improvement global overall symptoms score after 12 weeks of treatment compared with the baseline.

Statistical methods:

Analysis in accordance with the primary end-point was carried out in the Intent-to-treat (ITT) population, percentage and number of AEs related to study drug was determined. Analysis in accordance with the secondary safety end-points was carried out also in the ITT population, all collected AEs and investigational medicinal product compliance were evaluated using descriptive statistics. Analysis in accordance with secondary effectiveness end-points was carried out in the Per protocol (PP) population, changes in global overall symptoms score and individual gastrointestinal symptom scores from baseline were assessed at 3 time points using Bonferroni corrected paired t-test with significance level set as 0.017. Demographics and other population characteristics were analyzed using descriptive statistical methods.

Summary:

Population characteristics: Intent-to-treat (ITT) population (all enrolled patients who received at least one dose of the study drug, and for whom there were any data from at least one visit after Visit 2) comprised of 147 patients. Proportion of male subjects was 48.3%, all patients belonged to the Caucasian race. Mean age of patients was 44.84 years (SD ± 10.45), mean height was 170.59 (SD ± 7,92), mean BMI was 28.90 (SD ± 4,73), majority of population (75.5%) had never consume alcohol, 10.2% stopped to consume alcohol and 14.3% were current alcohol consumers. None of patients had a history of drug abuse.

All patients in the ITT population had at least one ongoing liver disease, 107 (72.8%) patients had non-alcoholic fatty liver disease (NAFLD) and 42 (28.6%) patients had viral hepatitis. Notice that 1 patient had both hepatitis B and hepatitis C and 1 patient had both NAFLD and hepatitis C. Majority of concurrent conditions fell into *Metabolism and nutrition disorders* (71 medical conditions in 57 (38.8%) patients), and *Vascular disorders* (49 medical conditions in 45 (30.6%) patients).

82 (55,8%) patients in the ITT population received at least one concomitant medication apart from investigational product during the study. Thus, standard therapy of existing liver disease is recognized here as concomitant therapy. In case of NAFLD, standard care could also involve diet and physical exercise without pharmacotherapy. 161 Anatomical Therapeutic Chemical (ATC) codes in total were documented, most of them falling into *Alimentary tract and metabolism and Cardiovascular system* classes almost in equal shares (65 in 40 (27.2%) and 65 in 42 (28.6%) patients respectively).

Per Protocol (PP) population (patients who completed the study in accordance with the study protocol) comprised of 143 patients. Four patients were excluded from analysis due to premature study discontinuation (3 patients decided to discontinue study due to unpleasant taste of the study drug (2) and inability to conduct the last visit due to logistical issue (1), one patient was excluded from the study due to inconsistency concerning inclusion criteria).

Safety results:

Primary endpoint: Frequency (number and percentage) of Adverse Events (AEs) related to study drug over 12-week treatment period+1 week follow-up.

Table: Summary data on study drug related AEs.

Study drug related AE	# AE	# subjects reported	% subjects of total sample (ITT, n=147)
Diarrhea	16	10	6,8%
Dyspepsia	7	5	3,4%
Nausea	6	3	2,0%
Dysgeusia	5	3	2,0%
Dry mouth	1	1	0,7%
Thirst	1	1	0,7%
Abdominal pain	1	1	0,7%
Total	37	22	15,0%

The percentage of patients with drug-related AEs was 15% mainly due to diarrhea (16 cases in 10 patients constituting 6,8% of ITT population) and dyspepsia (7 cases in 5 patients constituting 3,4% of ITT population). Considering dyspepsia, 6 cases occurred within 12 week treatment period and 1 case was reported in follow-up period (within 1 week after completion of study treatment). Other AEs did not exceed 2% frequency.

Secondary endpoints:

- Adverse events frequency (number and percentage) based on an analysis of all adverse events reports irrespective of a causal relationship to study drug intake according to investigator's decision for 4, 8 and 12 weeks of treatment.
- AE and SAE frequency (number and percentage) related and unrelated to study treatment

AE appearance through 12 treatment weeks +1 week follow-up was as follows (see table below):

Table: AE appearance through 12 treatment weeks+1week follow-up:

Period	Patients reported IP related AE, n (%), # AE	Patients reported AE not related to IP, n (%), # AE	Total # (%) Patients reported AE, # AE
0-4 weeks (Visit 2-Visit 3)	21 (14,3%) patients, 29 AE	12 (8,2%) patients, 14 AE	33 (22,4%) patients, 43 AE
4-8 weeks (Visit 3-Visit 4)	2 (1,4%) patients, 7 AE	14 (9,5%) patients, 19 AE	15 (10,2%) patients, 26 AE
8-12 weeks (Visit 4-Visit 5)	0 (0%) patients, 0 AE	11 (7,5%), 12 AE	11 (7,5%), 12 AE
12-13 weeks (Follow-up)	1 (0,7%) patient, 1 AE	0 (0%) patients, 0 AE	1 (0,7%) patient, 1 AE
In frame of study totally	22 (15,0%) patients, 37 AE	32 (21,8%) patients, 45 AE	51 (34,7%) patients, 82 AE

No deaths or SAEs were reported during the whole study period. No discontinuation due to AEs was documented.

The majority of drug related adverse events occurred during first 4 weeks of treatment (29 AEs reported), while within 9 following weeks (4-12 treatment weeks and follow-up week) only 8 AEs were reported. Considering AE not related to study drug its distribution was relatively homogenous across 12 study treatment (14 AE in 0-4 weeks, 19 AEs in 4-8 weeks, 12 AE in 8-12 weeks), whereas no AE not related to study drug was reported within follow-up week.

Effectiveness results:

Secondary endpoints:

1. Evaluation of patient's existing symptoms was performed using a 7-points Likert scale after 4, 8 and 12 weeks of treatment. Rating was performed according to the following categories: 1 - no problem, 2 - minimal problem (can be easily ignored), 3 – mild problem (can be ignored with effort), 4 – moderate problem – (cannot be ignored, but does not influence daily activity), 5 – medium-severe problem (cannot be ignored and occasionally influences daily activity), 6 – severe problem (cannot be ignored and markedly limits daily activity), 7 – very severe problem (cannot be ignored, markedly limits daily activity and requires medication or rest). At baseline most of patients in the PP population (73.5%) scored their overall symptoms as "moderate" and "medium-severe", only 8.4% of patients estimated overall symptoms as "no" or "minimal problem". After 12 weeks of treatment, 81.1% of PP patients were rated as responders, meaning their overall symptom score was rated as "no" or "minimal problem". Mean overall symptoms score (min-max score: 1-7) was 4.21±1.09 at baseline, declined to 3.01±1.11 (- 28.4% from baseline, $p<0.01$) after 4 weeks of treatment, to 2.37±0.87 (- 43.7% from baseline, $p<0.01$) after 8 weeks of treatment, and to 1.87±0.91 (- 55.5% from baseline, $p<0.01$) after 12 weeks of treatment. The gradual decline of the mean overall symptom score by the end of each 4-week treatment period was statistically significant.

2. Mean calculated for the sample based on of summarized gastrointestinal symptoms score (fatigue, abdominal pain/discomfort, early satiety, fullness discomfort after meal, nausea/vomiting, belching/abdominal distension, min-max score: 6-42) decreased from 19,9±5.74 at baseline to 14.5±4.69 (- 27.3%, p<0.01) after 4 weeks of treatment, to 11.2±3.57 (- 43.9%, p<0.01) after 8 weeks of treatment, to 9.1±3.55 (- 54.3%, p<0.01) after 12 weeks of treatment.

Compliance:

Compliance was analyzed in mITT population due to the following reasons: As 2 patients dropped out from the study before Visit 3 they were excluded from compliance calculation. 2 patients stopped taking study drug between Visit 4 and Visit 5, therefore analysis of compliance for 0-12 weeks period included their data for period of their participation only. Percentage of compliance for a patient for a specified period was defined as the number of doses administered divided by the number of doses to be taken according to the treatment scheme. Compliance with the prescribed treatment regimen after 4, 8 and 12 weeks of treatment was the following (mean ± SD): 99.2% ± 2.7%; 99.3% ±1.8%; 99.4% ± 1.3% respectively, (n = 145).

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