Informed Consent Form to Participate in the Clinical Study

Study Title:

Multi-Center, randomized, control, phase IV trial to compare the efficacy & safety of Ursoplus® capsules (UDCA 250mg & Silymarin 140mg) versus UDCA alone versus Placebo among Compensated Chronic Liver Diseased Patients

Researchers:

Priniciple investigator.: Dr. Gamal Esmat (Professor Of Tropical Disease and Hepatology)
DR: Ahmed Cordie Abdelhamid
Dr.: Saeed Samy Abdel Sattar

Sponsor: Minapharm Pharmacueticals

Study Objectives:

Primary Objective:

- To assess the efficacy of Ursoplus® capsules (UDCA 250mg & Silymarin 140mg) versus UDCA 250 mg alone and versus Placebo in the reduction of total serum bilirubin, Direct serum bilirubin and elevated liver Enzymes from baseline to End of Treatment (EOT)

Secondary Objectives:

- To assess the efficacy of Ursoplus® capsules (UDCA 250mg & Silymarin 140mg) versus UDCA 250 mg alone and versus Placebo in reducing the degree of steatosis as measured by Vibration-controlled transient elastography with Controlled Attenuation Parameter (CAP)
- To assess the safety of Ursoplus® capsules (UDCA 250mg & Silymarin 140mg) versus UDCA 250 mg alone and versus Placebo among compensated Chronic Liver Diseased Patients
- To describe improvement in quality of life for patients after treatment

Study Procedures to be performed on the patient:

Your health status will be examined, and if found eligible in accordance with the inclusion/exclusion criteria of the protocol and you are willing to participate in the study; the Sponsor will be responsible for providing the medicinal drugs; either Ursoplus® capsules, Ursofalk® capsules, or Placebo to the patient in a quantity enough to be used till the end of the study in addition to sponsoring all the required study procedures (Lab tests, Abdominal Ultrasound, and Vibration-controlled transient elastography with CAP).

Blood samples will be collected and tested, Abdominal Ultrasound and Vibration-controlled transient elastography with CAP will be done in addition to be sure that prescribing the study medications will be beneficial to the patient and will not worsen the patient's status.

Study Visits:

This study consists of: Screening & treatment initiation visit (Visit 1 - Day 0), 5 follow up visits for 5 months of treatment, and the end of the study visit (after 6th month of treatment)

Visit 1 (Screening & treatment initiation visit - Day 0):

During this visit: you will be informed about the study. If you are a woman of childbearing potential, you will be informed that you must use the highly effective contraception other than oral contraceptive pills to avoid pregnancy during the study period.

If you are willing to participate in the study, you will sign the written Informed Consent or finger print and a witness will sign that you are willing to participate in the study. You will be evaluated for study eligibility according to the inclusion and exclusion criteria.

- Screening Assessments will include: physical examination (presence of jaundice, abdomen for liver, spleen and presence or absence of ascites), vital signs, Weight, Height, demographic data (age & sex), medical history, and concomitant medications

- Lab results to be checked for: Blood Chemistry (ALT, AST, ALP, GGT, Total Bilirubin, direct bilirubin, and Serum Albumin), coagulation tests (PT), Hepatitis B surface Antigen (HBsAg), HbA1c for diabetic patients, and Serum β-HCG for females of child bearing potential only.

- PCR test will be performed if not done in the past 6 months

- Abdominal Ultrasound (For detection of any abnormalities in Liver, spleen, and gall bladder such as liver masses, portal hypertension, etc), and Vibration-controlled transient elastography with CAP will be performed.

- Assessment for QoL, using the RAND 36-Item Health Survey will be done.

- You will be instructed how to contact your Investigator immediately if any medical problem or emergency occurred. All concomitant medications and any AEs whether serious or non-serious and whether it is related to the study drug or not will be recorded.

The study population consists of 297 patients with compensated chronic liver disease will be randomized according to Vibration-controlled transient elastography with CAP in screening visit into 2 groups:

- Group 1: with non-cirrhosis, F0, F1 and F2.
- Group 2: with advanced fibrosis and cirrhosis, F3 and F4

Subjects will be randomized into the 3 treatment groups with a balanced ratio of 1:1:1:

1. Group A, who will receive Ursoplus® capsules (99 patients)
2. Group B, who will receive Ursofalk® capsules (99 patients)
3. Group C, who will receive Placebo (99 patients)

- Ursoplus® capsules (UDCA 250mg & Silymarin 140mg), Ursofalk® capsules (UDCA 250mg) or Placebo will be given to you according to your body weight. Sufficient medications will be given to you for the next 30 days and it could be kept in room temperature (max 30˚C).

- Study products sufficient for the next 30 to 90 days will be supplied, and storage conditions will be explained. Study products supplied will be recorded.

- Subjects will be asked to come after 30 or 90 days and bring empty blisters of medication received, with a window of 7 days.

From Visit 2 (Follow Up 1) to Visit 6 (Follow Up 5):

The following procedures will be done during each visit:

- You will undergo through general physical examination (presence of jaundice, abdomen for liver, spleen and presence or absence of ascites), weight, and Vital signs.

- Checking if any AE or SAEs happened and recording them in their separate forms. Any changes in concomitant medication, illness and treatment will be recorded.

- During visit 4 (after 3 months of treatment), assessment for QoL, using the RAND 36-Item Health Survey will be done.

- During visit 6 (after 5 months of treatment), a new lab request will be provided to you with the required lab tests for the next visit to be done 3 days before the visit.
- You will be administered Ursoplus® capsules (UDCA 250mg & Silymarin 140mg), Ursofalk® capsules (UDCA 250mg) or Placebo; with sufficient quantity for the next 30 days and it could be kept in room temperature (max 30˚C).
- Study products sufficient for the next 30 to 90 days will be supplied, and storage conditions will be explained. Study products supplied will be recorded.

- Subjects will be asked to come after 30 or 90 days and bring empty blisters of medication received, with a window of 7 days.

End of Study visit:

The following procedures will be done during this visit:

- You will undergo thorough general physical examination and vital signs

- Assessment for QoL, using the RAND 36-Item Health Survey will be done

- Lab results to be checked for: Blood Chemistry (ALT, AST, ALP, GGT, Total Bilirubin, direct bilirubin), and HbA1c for diabetic patients.

- Vibration-controlled transient elastography with CAP will be performed.

- Checking if any AE or SAEs happened and recording them in their separate forms. Any changes in concomitant medication, illness and treatment will be recorded.

- The study completion form will be completed.

- Serum β-HCG test for females with child bearing potential only

Requested from the Patient:

1- To understand and agree to comply with the prescribed dosing regimens and procedures, report for regularly scheduled study visits, and reliably communicate.
2- To store the study drugs at room temperature up to 30 degrees C, to keep them in the original containers and to store away from heat, moisture, light and children.
3- You should come to the site every 30 days till the end of study visit; with a window of 7 days before/after the date of visit and should bring all the empty and/or partially used blisters that were taken in the previous visit.
4- You should inform the investigator about any untoward or unusual event that occurred since last visit, whether you believe it is related to the study drug or not
5- You should inform the investigator if he/she had taken any concomitant medications between the visits

Total duration of the study/ subject:

- Total duration of the study will be approximately 6 months for treatment and follow-up visits including the screening visit.

- End of Study visit will be after 6 months from start of medications.

Study Population:

297 Egyptian patients with compensated chronic liver disease to be enrolled from ٢ sites:
1- The Research Center of Air Force Specialized Hospital

2- Helwan University Hospital

Expected Risks and side effects:

The most common reported side effects of Ursoplus capsule are diarrhea, indigestion, loose motion, bloating, urge to vomit, stomach pain, and loss of appetite.
Regarding UDCA, animals' studies proved evidence of teratogenic effects during the early phase of gestation. Also, there is insufficient data on the passage of UDCA into breast milk. So, it should be avoided in the first trimester of pregnancy and lactation period, in humans.

Benefits of participating in the study:

The combined power of UDCA & Silymarin makes Ursoplus more beneficial product in the symptomatic treatment of Primary Biliary Cirrhosis (PBC) and it also acts as liver support that improves the hepatic functions in chronic liver disease, provided that there is high incidence rate of deaths from chronic liver disease in Egypt.

Personal Benefit for the participant:

The patient's status will be examined, and if found eligible to the study in accordance with the inclusion and exclusion criteria; the Sponsor will be responsible for providing the medicinal drugs to the patient in a quantity enough to be used till the end of the study, in addition to sponsoring all the required study procedures (Lab tests, Abdominal Ultrasound and Vibration-controlled transient elastography with CAP).

Privacy of the Participant and data confidentiality: Yes

Voluntary Participation:

This Informed Consent Form is to be signed and dated by all patients. In case the patient can't read or write, he/she will finger print in the presence of a witness who'll also sign prior undertaking any study related procedures.

The patient should sign/agree to participate without any pressure or unduly influence from the treating doctor or the witness.

In case the patient refused to participate, there will not be any penalty, and he/she will have the right to complete your treatment as you used to.

Compensation:

There is no financial reward or compensation for your participation in the study. In case of trial related injuries or harms, patients will complete their treatment as they used to in the site and could be supported by insurance certificate provided to all patients.

The right of withdrawal:

The patient has the right to withdraw from the study at any time.

In Case the patient refused to participate:

Patient shall have the right to complete their treatment as they used to in the site

Signing this document will not prevent you to get any of your legal rights, and also it doesn't give the right to the sponsor or the participating physicians to leave their responsibilities

- **For more information regarding the study you can contact:**

Dr Gamal Esmat Tel: 01222455468

Dr.: Ahmed Cordie Abdelhamid **Tel:** 01018183555

- **In case you had any health problems as a result of participating in the study, you can contact:**

  Dr.: Saeed Samy Abdel Sattar **Tel:** 01111544861

Or, you can go directly go to (site)

- **In case you have any other complain, please contact the Ethics Committee office:**

  Tel: 01275555979/ 02-26176981

If you are willing to participate in this study, please make a sign in the appropriate place below:

___ All information in this agreement has been explained.

___ I have read and understood all the information mentioned in this agreement.

Name of the Participant_____

Participant's signature:_____

Date:_____

Witness for the agreement procedures:_____

Witness Signature:_____

Investigator's Signature:_____

Date:_____

This document will not be approved unless it has the stamp of the Ethics Committee.

Valid from: - / - / 202- till - / - / 202-

A copy of the informed consent to be given to the participant and the original to be kept with the Principle investigator.