CONFIDENTIAL

Case Report Form

Clinical Trial Protocol No. URSO – 003

Version 2, dated 17 August 2022

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

Please use a ball point Blue pen

Investigator's Name and Address:

Center Nº: | | |

Patient's Nº: | | | | |

Patient's Initials: | | | |

Patient's Nº:					Patient's Initials:			

General instructions:

1- A CRF must be completed for each study participant who is successfully enrolled (successfully screened)

2- Please write legibly upper case/capital letter is preferred e.g. CASE REPORT FORM

3- . All entries must be made preferably in blue ballpoint pen

4- Do not leave any question unanswered.

If the answer to a question is unknown/ for missing information.

Please enter:

NA - if data is not applicable or not available.

NK - if information is unknown.

ND - if procedure not done

5- If you make an error, please strike through original entry (e. g. ORIGINAL), re- enter the data immediately above the old entry, and initial and date the correction. However, If you make an error on the description for adverse event or medication / non – drug therapy, please strike through original entry. Re-enter the data in the space below the start date, and initial and date the correction. Please do not use white – out or obliterate information.

6- Patient should be identified by patient number and initials in the CRF. If reports or clinic /hospital records are attached to the CRF, the patient name must be blocked over completely with a black marker and the patient number and initials entered.

7- Use leading "0's" to complete entire field.

8- All CRF pages must be reviewed and signed by the investigator participating in the study.

9- All text and explanatory comments should be brief

10-Answer every question explicitly; do not use ditto marks

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the study was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the study.

Investigator's Signature: Date of signature:

Numeric fields

1- **Enter** only 1 digit in each box, with a leading 0 when necessary

2- Record all values in the unites indicated on the CRF

Confidentiality

Patients must only be identified by the subject identification ID (Center number, Patient number

Adverse Event Log/Concomitant Medication Log

If additional pages of adverse event and / or concomitant medication log are required, please make a photocopy of a blank adverse Event log / concomitant medication log and complete the information. The original page will be sent to data management and a photocopy retained at Minapharm and investigator site

Dates

1- All dates are to be reported in the format DD/MMM/YYYY

2- The month is to be reported as the first three characters of the month, e.g. 01/AUG/2012 the month abbreviations are as follows:

January	=	Jan	May	=	May	September	=	Sep
February	=	Feb	June	=	Jun	October	=	Oct
March	=	Mar	July	=	Jul	November	=	Nov
April	=	Apr	August	=	Aug	December	=	Dec

3- In the absence of a precise date for an event or therapy that precedes the participant's inclusion into the study, a partial date may be recorded by recording "NK" in the fields that are unknown e.g. where the day and month are not clear, the following may be entered into the CRF:

0	0	M	A	R	2	0	0	9
DD		MMM			YYYY			

Center Numbering:

Enter the center number (2 digits),

- Research Center of Air Force Specialized Hospital = 01
- Helwan University Hospital = 02

e.g.

Center Nº:	0	1

Patient's Nº:					Patient's Initials:				Screening Visit / Initiation Visit

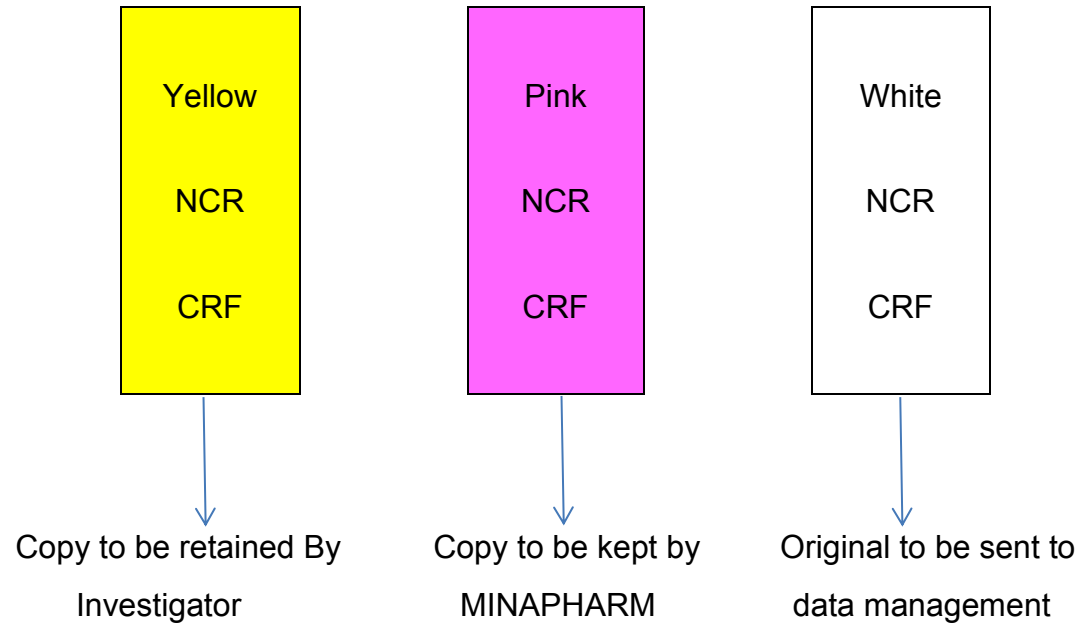
Patients' Numbering;

Enter Patients' Group (A, B, or C), then patient's number (from 001 to 297), e.g.

Patient's Nº	A	0	0	5

No Carbon Required (NCR) CRF

The White original and the pink NCR CRF Will be retrieved by Minapharm personnel during his / her visit to the center. The yellow NCR card will be retained by investigator folder at the site



A study population of 297 patients with compensated chronic Liver Disease, will be randomized according to fibroscan 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

- Group A (Experimental group), will receive Ursoplus® capsules (UDCA 250mg & Silymarin 140mg) = 99 subjects
- Group B (Control group 1), will receive Ursofalk® capsules (UDCA 250mg) = 99 subjects
- Group C (Control group 2), will receive Placebo = 99 subjects

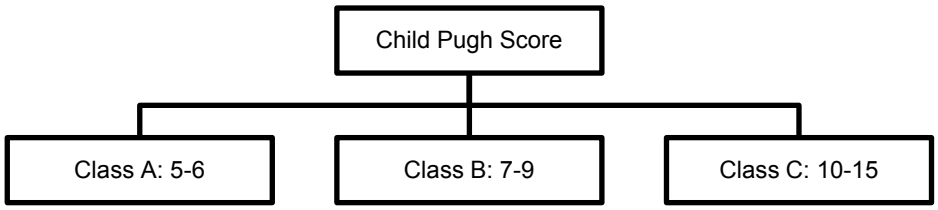
Child-Pugh Score Calculation:

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

Measure	1 point	2 points	3 points
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
Prothrombin time prolongation (secs)	<4.0	4.0-6.0	> 6.0
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

In primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC), the bilirubin references are changed to reflect the fact that these diseases feature high conjugated bilirubin levels. The upper limit for 1 point is 68 µmol/l (4 mg/dl) and the upper limit for 2 points is 170 µmol/l (10 mg/dl).

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above.



Patient's Nº:					Patient's Initials:				Screening Visit / Initiation Visit

Screening Visit

Date of Screening: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Informed Consent:	
Date patient signed written consent form:	__ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Inclusion/ Exclusion Criteria

Inclusion Criteria **The following criteria MUST be answered YES for participant to be included in the trial:**		**Yes**	**No**
1.	Male or female patient aged ≥ 18	☐	☐
2.	Subjects with Compensated Chronic Liver Disease, defined as child 5-7.	☐	☐
3.	Patients with mild disturbance of liver biochemical profile (Elevated Total Serum Bilirubin ≤ 3 mg/dl, or elevated Direct Serum Bilirubin ≤ 2 mg/dl, or elevated one or more of liver enzymes up to 3 times of the normal level (Alanine Transaminase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP) & Gamma Glutamyl Transpeptidase (GGT)).	☐	☐
4.	Non-diabetic subjects and subjects with Co ntrolled DM-type 1 and 2 patients, HbA1C up to 7.5%	☐	☐
5.	Non-pregnant or lactating female patients	☐	☐
6.	Subjects who are willing to sign Informed Consent Form and ready to comply with the protocol for the duration of the study	☐	☐

Exclusion Criteria **The following criteria MUST be answered NO for participant to be included in the trial:**		**Yes**	**No**
1.	Subjects with a history of hypersensitivity to any of the ingredients of the medication being studied	☐	☐
2.	Subjects with positive PCR in the past 6 months	☐	☐
3.	Subjects with positive Hepatitis B surface antigen (HBsAg)	☐	☐

4.	Subjects with elevated liver enzymes more than 3 times of the normal level (Alanine Transaminase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP) & Gamma Glutamyl Transpeptidase (GGT)).	☐	☐
5	Subjects with Primary Biliary Cirrhosis (PBC) and Primary Sclerosing Cholangitis (PSC)	☐	☐
6	Subjects with Child Pugh Score more than 7	☐	☐
7	Subjects with history of bleeding varices	☐	☐
8.	Subjects having uncontrolled Diabetes (HbA1c above 7.5 %)	☐	☐
9.	Subjects with any medical condition require the usage of medication may interfere with the absorption, distribution, metabolism or excretion of the drugs such as: 1- Bile acid sequestering agents such as cholestyramine and colestipol, 2- Antacids containing aluminum hydroxide. 3- Drugs affecting lipid metabolism such as estrogens, oral and hormonal contraceptives, and clofibrate (and perhaps other lipid-lowering drugs)	☐	☐
10.	Subjects who are receiving other liver support drugs (including drugs of the study), 1 month before study initiation.	☐	☐
11	Subjects with auto immune liver disease taking corticosteroid or immune suppressant	☐	☐
12.	Pregnant or breast-feeding women	☐	☐
13	Use of oral contraceptives in child bearing ladies	☐	☐

Demographic Data & Vital Signs

Patient Demography & Vital Signs:
Gender: Male ☐ Female ☐
Birthdate: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)
Weight: ____ ___ ___ Kg **Height:** ____ ___ ___ cm
Blood Pressure (Systolic/Diastolic): ___ ___ ___ / ___ ___ ___ mmHg

Habits

Smoking Habits:		
Does the subject smoke or use tobacco products?	☐ **Yes**	☐ **No**
How many cigarettes per day?		
Others, specify: ……		

Alcohol Consumption:		
Does the subject consume alcohol?	☐ **Yes**	☐ **No**
If yes, how many units per week?		

Physical Examination

*Please fill the relevant forms of adverse events in case any abnormal or untoward event is noticed

Physical Examination	**Normal**	☐	**Abnormal**	☐
Findings	…… …… …… ……			

Medical History

Has the patient had any relevant medical history?	☐ **No**	☐ **Yes,** Complete below

Patient's Nº:					Patient's Initials:				Screening Visit / Initiation Visit

Condition / illness /surgical procedure	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Or tick if ongoing ?
	___/_____/___	___/_____/_____	☐
	___/_____/___	___/_____/_____	☐
	___/_____/___	___/_____/_____	☐

Is the participant taking any concomitant medications?	☐ **No** ☐ **Yes** **If Yes:** Complete Concomitant Medication Page 26

Abdominal Ultrasound

Date of Ultrasound: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Liver	**Normal**	☐	**Abnormal**	☐
If abnormal, findings:	…… ……			
	Portal Vein Diameter: ……mm (N. up to 14mm) **Ascites: ☐ No ☐ Yes If yes, Amount: ……**			
Spleen	**Normal**	☐	**Abnormal**	☐
If abnormal, findings:	…… ……			
	Splenic Vein Diameter:……mm			
Gall Bladder	**Normal**	☐	**Abnormal**	☐
If abnormal, findings:	…… ……			
	Common Bile Duct (CBD) Diameter: ……mm (N. up to 6mm)			

Patient's Nº:					Patient's Initials:				Screening Visit / Initiation Visit

Vibration-controlled transient elastography with CAP (Fibroscan)

Date of Fibroscan: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

	Liver stiffness measurement	Fibroscan score
Liver		☐ F0/F1 ☐ F2 ☐ F3 ☐ F4
If abnormal, findings:	…… ……	

Safety Laboratory Tests

Date of Laboratory Tests: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Laboratory Parameter	Value	Unit	If parameter indicated as out of normal range on report, please check if clinically significant:
ALT			☐ **No** ☐ **Yes**
AST			☐ **No** ☐ **Yes**
Alkaline Phosphatase (ALP)			☐ **No** ☐ **Yes**
Gamma-GT			☐ **No** ☐ **Yes**
Total Bilirubin			☐ **No** ☐ **Yes**
Direct bilirubin			☐ **No** ☐ **Yes**
S Albumin			☐ **No** ☐ **Yes**
PT			☐ **No** ☐ **Yes**
HbA1c for diabetic patients			☐ **No** ☐ **Yes**
PCR/ Antibody for hepatitis C			☐ **No** ☐ **Yes**
HBs Ag			☐ **No** ☐ **Yes**
Serum *β*-HCG (for Females in child bearing period)			☐ **No** ☐ **Yes**

Patient's Nº:					Patient's Initials:				Screening Visit / Initiation Visit

Assessment for quality of life (The RAND 36-Item Health Survey)			
Completed	☐	**Not Completed**	☐

End of Screening Visit

End of Screening Visit Checklist:		**Yes**	**No**
1.	**Does the participant meet the inclusion and exclusion criteria to date?**	☐	☐
2.	**Have all Screening Visit procedures been completed?**	☐	☐
3.	**Have the Medical History and Concomitant Medication pages been completed?**	☐	☐

Participant's eligibility:
Is the participant eligible to take part in the Clinical Study? ☐ Yes ☐ No, Please give reason for screen failure below
Reason(s) for screen failure:
1.
2.
Investigator Sign-Off
Investigator's Name: _____ **Investigator's Signature**: _____ **Date** : __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Patient's Nº:					Patient's Initials:				Screening Visit / Initiation Visit

Randomization

Group A ☐	Group B ☐	Group C ☐

Drug Dispense

Date of Drug Dispense: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Drugs are dispensed for the patient to be sufficient for 30 days of treatment
The subject is asked to take the treatment daily and come next visit with the empty blisters after 30 days, with a window of 7 days.

Drug Dispense	Number of Capsules	Number of Blisters
Drug A, B, or C		

Investigator's Name: _____

Investigator's Signature: _____ **Date**: __ __ / __ __ __ / __ __ __ __

(DD / MMM / YYYY)

Patient's Nº:					Patient's Initials:				Visit 2 (Week 4) Follow Up Visit 1

Visit 2 (Week 4) (may be done by phone call)

Date of Visit 2: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Vital Signs

Vital Signs & Weight:
Weight: ____ ___ ___ Kg
Blood Pressure (Systolic/Diastolic): ___ ___ ___ / ___ ___ ___ mmHg

Physical Examination

*Please fill the relevant forms of adverse events in case any untoward or unusual event that occurred since last visit, whether it is believed to be related to the study drug or not.

Physical Examination	**Normal**	☐	**Abnormal**	☐
Findings	…… …… …… ……			

Drug Dispense

Date of Drug Dispense: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Drug Dispense	Number of Capsules	Number of Blisters
Drug A, B, or C		

Patient's Nº:					Patient's Initials:				Visit 2 (Week 4) Follow Up Visit 1

Drugs are dispensed for the patient to be sufficient for 30 days of treatment
The subject is asked to take the treatment daily and come next visit with the empty blisters after 30 days, with a window of 7 days.

Is the participant taking any concomitant medications?	☐ **No** ☐ **Yes** **If Yes:** Complete Concomitant Medication Page 26

Is the participant had any Adverse Events

The investigator shall ask probing questions, allowing the patient to tell about any untoward or unusual event that occurred since the last visit, whether he/she (the patient) believes it is related to the study drug or not? (including abnormal physical examination/ laboratory results)	☐ **No** ☐ **Yes** **If Yes:** Complete Page 30

I have updated the AEs on page …….. And have assessed them for seriousness, causality, severity and outcome and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant**:**

Investigator's Name: _____

Investigator's Signature: _____ Date: __ __ / __ __ __ / __ __ __ __

(DD / MMM / YYYY)

Visit 3 (Week 8) (may be done by phone call)

Date of Visit 3: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Vital Signs

Vital Signs & Weight:
Weight: ____ ___ ___ Kg
Blood Pressure (Systolic/Diastolic): ___ ___ ___ / ___ ___ ___ mmHg

Physical Examination

*Please fill the relevant forms of adverse events in case any untoward or unusual event that occurred since last visit, whether it is believed to be related to the study drug or not.

Physical Examination	**Normal**	☐	**Abnormal**	☐
Findings	…… …… …… ……			

Drug Dispense

Date of Drug Dispense: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Drug Dispense	Number of Capsules	Number of Blisters
Drug A, B, or C		

Patient's Nº:					Patient's Initials:				Visit 3 (Week 8) Follow Up Visit 2

Drugs are dispensed for the patient to be sufficient for 30 days of treatment
The subject is asked to take the treatment daily and come next visit with the empty blisters after 30 days, with a window of 7 days.

Is the participant taking any concomitant medications?	☐ **No** ☐ **Yes** **If Yes:** Complete Concomitant Medication Page 26

Is the participant had any Adverse Events

The investigator shall ask probing questions, allowing the patient to tell about any untoward or unusual event that occurred since the last visit, whether he/she (the patient) believes it is related to the study drug or not? (including abnormal physical examination/ laboratory results)	☐ **No** ☐ **Yes** **If Yes:** Complete Page 30

I have updated the AEs on page …….. And have assessed them for seriousness, causality, severity and outcome and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant**:**

Investigator's Name: _____

Investigator's Signature: _____ Date: __ __ / __ __ __ / __ __ __ __

(DD / MMM / YYYY)

Patient's Nº:					Patient's Initials:				Visit 4 (Week 12) Follow Up Visit 3

Visit 4 (Week 12)

Date of Visit 4: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Vital Signs

Vital Signs & Weight:
Weight: ____ ___ ___ Kg
Blood Pressure (Systolic/Diastolic): ___ ___ ___ / ___ ___ ___ mmHg

Physical Examination

*Please fill the relevant forms of adverse events in case any untoward or unusual event that occurred since last visit, whether it is believed to be related to the study drug or not.

Physical Examination	**Normal**	☐	**Abnormal**	☐
Findings	…… …… …… …… ……			

Assessment for quality of life

The RAND 36-Item Health Survey			
Completed	☐	**Not Completed**	☐

Patient's Nº:		Patient's Initials:		Visit 4 (Week 12) Follow Up Visit 3

Drug Dispense

Date of Drug Dispense: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Drug Dispense	Number of Capsules	Number of Blisters
Drug A, B, or C		

Drugs are dispensed for the patient to be sufficient for 30 days of treatment
The subject is asked to take the treatment daily and come next visit with the empty blisters after 30 days, with a window of 7 days.

Is the participant taking any concomitant medications?	☐ **No** ☐ **Yes** **If Yes:** Complete Concomitant Medication Page 26

Is the participant had any Adverse Events

The investigator shall ask probing questions, allowing the patient to tell about any untoward or unusual event that occurred since the last visit, whether he/she (the patient) believes it is related to the study drug or not? (including abnormal physical examination/ laboratory results)	☐ **No** ☐ **Yes** **If Yes:** Complete Page 30

I have updated the AEs on page …….. And have assessed them for seriousness, causality, severity and outcome and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant**:**

Investigator's Name: _____

Investigator's Signature: _____ Date: __ __ / __ __ __ / __ __ __ __

(DD / MMM / YYYY)

Visit 5 (Week 16) (may be done by phone call)

Date of Visit 5: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Vital Signs

Vital Signs & Weight:
Weight: ____ ___ ___ Kg
Blood Pressure (Systolic/Diastolic): ___ ___ ___ / ___ ___ ___ mmHg

Physical Examination

*Please fill the relevant forms of adverse events in case any untoward or unusual event that occurred since last visit, whether it is believed to be related to the study drug or not.

Physical Examination	**Normal**	☐	**Abnormal**	☐
Findings	.....			

Drug Dispense

Date of Drug Dispense: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Drug Dispense	Number of Capsules	Number of Blisters
Drug A, B, or C		

Patient's Nº:					Patient's Initials:				Visit 5 (Week 16) Follow Up Visit 4

Drugs are dispensed for the patient to be sufficient for 30 days of treatment
The subject is asked to take the treatment daily and come next visit with the empty blisters after 30 days, with a window of 7 days.

Is the participant taking any concomitant medications?	☐ **No** ☐ **Yes** **If Yes:** Complete Concomitant Medication Page 26

Is the participant had any Adverse Events

The investigator shall ask probing questions, allowing the patient to tell about any untoward or unusual event that occurred since the last visit, whether he/she (the patient) believes it is related to the study drug or not? (including abnormal physical examination/ laboratory results)	☐ **No** ☐ **Yes** **If Yes:** Complete Page 30

I have updated the AEs on page …….. And have assessed them for seriousness, causality, severity and outcome and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant**:**

Investigator's Name: _____

Investigator's Signature: _____ Date: __ __ / __ __ __ / __ __ __ __

(DD / MMM / YYYY)

Visit 6 (Week 20) (may be done by phone call)

Date of Visit 6: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Vital Signs

Vital Signs & Weight:
Weight: ____ ___ ___ Kg
Blood Pressure (Systolic/Diastolic): ___ ___ ___ / ___ ___ ___ mmHg

Physical Examination

*Please fill the relevant forms of adverse events in case any untoward or unusual event that occurred since last visit, whether it is believed to be related to the study drug or not.

Physical Examination	**Normal**	☐	**Abnormal**	☐
Findings	…… …… …… ……			

Drug Dispense

Date of Drug Dispense: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Drug Dispense	Number of Capsules	Number of Blisters
Drug A, B, or C		

Patient's Nº:					Patient's Initials:				Visit 6 (Week 20) Follow Up Visit 5

Drugs are dispensed for the patient to be sufficient for 30 days of treatment
The subject is asked to take the treatment daily and come next visit with the empty blisters after 30 days, with a window of 7 days.

Is the participant taking any concomitant medications?	☐ **No** ☐ **Yes** **If Yes:** Complete Concomitant Medication Page 26

Is the participant had any Adverse Events

The investigator shall ask probing questions, allowing the patient to tell about any untoward or unusual event that occurred since the last visit, whether he/she (the patient) believes it is related to the study drug or not? (including abnormal physical examination/ laboratory results)	☐ **No** ☐ **Yes** **If Yes:** Complete Page 30

I have updated the AEs on page …….. And have assessed them for seriousness, causality, severity and outcome and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant**:**

Investigator's Name: _____

Investigator's Signature: _____ Date: __ __ / __ __ __ / __ __ __ __
(DD / MMM / YYYY)

Patient's Nº:					Patient's Initials:				End of Study Visit (Week 24)

End of study

Date of End of study visit: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Vital Signs

Vital Signs & Weight:
Weight: ____ ___ ___ Kg
Blood Pressure (Systolic/Diastolic): ___ ___ ___ / ___ ___ ___ mmHg

Physical Examination

*Please fill the relevant forms of adverse events in case any untoward or unusual event that occurred since last visit, whether it is believed to be related to the study drug or not.

Physical Examination	**Normal**	☐	**Abnormal**	☐
Findings	.....			

Assessment for quality of life

The RAND 36-Item Health Survey			
Completed	☐	**Not Completed**	☐

Patient's Nº:					Patient's Initials:				End of Study Visit (Week 24)

Safety Laboratory Tests

Date of Laboratory Tests: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Laboratory Parameter	Value	Unit	If parameter indicated as out of normal range on report, please check if clinically significant:
ALT			☐ **No** ☐ **Yes**
AST			☐ **No** ☐ **Yes**
Alkaline Phosphatse (ALP)			☐ **No** ☐ **Yes**
Gamma-GT			☐ **No** ☐ **Yes**
S.Albumin			☐ **No** ☐ **Yes**
Total Bilirubin			☐ **No** ☐ **Yes**
Direct bilirubin			☐ **No** ☐ **Yes**
Serum *β*-HCG (for Females with child bearing potential only)			☐ **No** ☐ **Yes**

Vibration-controlled transient elastography with CAP (Fibroscan)

Date of Fibroscan: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

	Liver stiffness measurement	Fibroscan score
Liver		☐ F0/F1 ☐ F2 ☐ F3 ☐ F4
If abnormal, findings:	…….. …….. ……..	

Is the participant taking any concomitant medications?	☐ **No** ☐ **Yes**

Patient's Nº:					Patient's Initials:				End of Study Visit (Week 24)

	If Yes: Complete Concomitant Medication Page 26

Is the participant had any Adverse Events

The investigator shall ask probing questions, allowing the patient to tell about any untoward or unusual event that occurred since the last visit, whether he/she (the patient) believes it is related to the study drug or not? (including abnormal physical examination/ laboratory results)	☐ **No** ☐ **Yes** **If Yes:** Complete Page 30

I have updated the AEs on page …….. And have assessed them for seriousness, causality, severity and outcome and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant**:**

Investigator's Name: _____

Investigator's Signature: _____ Date: __ __ / __ __ __ / __ __ __ __

(DD / MMM / YYYY

Patient's Nº: | | | | | **Patient's Initials:** | | |

Concomitant Medication Form

Medication (Record Generic or trade name)	**Reason for use** (Medical History diagnosis or other reason, e.g. Prophylaxis)	Dose and units	**Frequency**	**Route**	**Start Date** (DD/MMM/YYYY)	**Stop Date** (DD//MMM/YYY)	**Or tick if ongoing**
1.					___/____/____	___/____/____	☐
2.					___/____/____	___/____/____	☐
3.					___/____/____	___/____/____	☐
4.					___/____/____	___/____/____	☐
5.					___/____/____	___/____/____	☐
6.					___/____/____	___/____/____	☐
7.					___/____/____	___/____/____	☐

PI signature _____ _____ **Date:** _____

Adverse Events (1/2)

AE No	Event Name (Please give Diagnosis if known)	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Serious?	Con-comitant Medication given	Severity 0 - Mild 1- Mode-rate 2 - Severe	Study Drug Action 0 - None 1 - Temporarily Interrupted 2 - permanently withdrawn	Outcome 1- Death related to AE 2- Not resolved/Not recovered 3- Resolved/ Recovered 4- Resolved/ Recovered with Sequelae 5- Resolving/ Recovering 6- Unknown	Relationship to Study Drug 0 - Certain 1 – Probable/Likely 2 - Possible 3 - Unlikely 4 – Conditional/ Unclassified 5 - Un-assessable/ Unclassifiable
1		____/____/____	____/_____/____	☐ No ☐ Yes	☐ No ☐ Yes				
2		____/_____/____	____/_____/____	☐ No ☐ Yes	☐ No ☐ Yes				
3		____/_____/____	____/_____/____	☐ No ☐ Yes	☐ No ☐ Yes				
4		____/_____/____	____/_____/____	☐ No ☐ Yes	☐ No ☐ Yes				
5		____/_____/____	____/_____/____	☐ No ☐ Yes	☐ No ☐ Yes				

I have reviewed the AEs on this page and have assessed them for seriousness, causality, severity and outcome and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant**:**

PI signature _____ _____ **Date:** _____

Adverse Events (2/2)

AE No	Event Name (Please give Diagnosis if known)	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Serious?	Con-comitant Medication given	Severity 0 - Mild 1- Mode-rate 2 - Severe	Study Drug Action 0 - None 1 - Temporarily Interrupted 2 - permanently withdrawn	Outcome 1- Death related to AE 2- Not resolved/Not recovered 3- Resolved/ Recovered 4- Resolved/ Recovered with Sequelae 5- Resolving/ Recovering 6- Unknown	Relationship to Study Drug 0 - Certain 1 – Probable/Likely 2 - Possible 3 - Unlikely 4 – Conditional/ Unclassified 5 - Un-assessable/ Unclassifiable
1		___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
2		___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
3		___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
4		___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
5		___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				

I have reviewed the AEs on this page and have assessed them for seriousness, causality, severity and outcome and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant:

PI signature _____ _____ **Date:** _____

Patient's Nº:					Patient's Initials:				Unscheduled Visit

Unscheduled Visit

Date of Unscheduled Visit: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Vital Signs

Vital Signs & Weight:
Weight: ____ ___ ___ Kg
Blood Pressure (Systolic/Diastolic): ___ ___ ___ / ___ ___ ___ mmHg

Physical Examination

*Please fill the relevant forms of adverse events in case any untoward or unusual event that occurred since last visit, whether it is believed to be related to the study drug or not.

Physical Examination	**Normal**	☐	**Abnormal**	☐
Findings	…… …… ……			

Is the participant taking any concomitant medications?	☐ **No** ☐ **Yes** **If Yes:** Complete Concomitant Medication Page 26

Is the participant had any Adverse Events

The investigator shall ask probing questions, allowing the patient to tell about any untoward or unusual event that occurred since the last visit, whether he/she (the patient) believes it is related to the study drug or not? (including abnormal physical examination/ laboratory results)	☐ **No** ☐ **Yes** **If Yes:** Complete Page 30

I have updated the AEs on page …….. And have assessed them for seriousness, causality, severity and outcome and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant**:**

Investigator's Name: _____

Investigator's Signature: _____ Date: __ __ / __ __ __ / __ __ __ __

(DD / MMM / YYYY)

Study Completion

Did participant complete the trial?

☐ **Yes,** Please provide **date of last day**:

__ __ / __ __ __ / 2 0 __ __ (DD / MMM / YYYY)

☐ **No,** Please provide **date of withdrawal** and complete below:

__ __ / __ __ __ / 2 0 __ __ (DD / MMM / YYYY)

Early Withdrawal: please tick most appropriate reason for participant not completing the trial:

☐ **Adverse Events related:** please state related AE: _____ (add details to AE page)

☐ **Participant's decision, specify: _____**

☐ **Investigator's decision, specify: _____**

☐ **Sponsor's decision**

☐ **Lost to follow up**

☐ **Patient deceased**

☐ **Ineligibility (either arising during the study or retrospective having been overlooked at screening)**

☐ **Significant protocol deviation**

☐ **Significant non-compliance with treatment regimen or study requirements**

☐ **Disease progression which requires discontinuation of the study medication or results in inability to continue to comply with study procedures**

☐ **Consent withdrawn.**

☐ **Pregnancy or discontinuation of contraception**

☐ **Other, specify: _____**

Investigator Sign off

Investigator's Name: _____

Investigator's Signature: _____ **Date** : __ __ / __ __ __ / __ __ __ __
(DD / MMM / YYYY)