

Clinical Study Protocol

Protocol Title: The Sonic Incytes Liver Incyte System, assessment of liver fibrosis and steatosis

Protocol Number: SI-CLIN-01

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Confidentiality Statement:

This clinical study protocol contains information which is of a confidential, trade-secret or proprietary nature. The protocol is for the use of Sonic Incytes and its designated representatives participating in the investigational trial. It is not to be disclosed to any other person or party without the prior written approval of Sonic Incytes.

Revisions:

Version 1.2

- 1) Expand the BMI range to 40
- 2) Add the multiple user sub study to healthy volunteers
- 3) Removed HIV testing requirement
- 4) Add Philips SWE as control device.
- 5) Add commercial MRE at UBC hospital for subjects in Vancouver

Table of Contents

List of Acronyms and Abbreviations	6
Investigator Agreement	7
Protocol Synopsis	8
1. Introduction	11
2. Study Objectives	13
2.1 Primary Objectives	13
2.2 Secondary Objectives	13
2.3 Exploratory Objectives	13
3. Study Design.....	13
4. Selection and Enrollment of Participants	14
4.1 Inclusion Criteria – Cohort 1: Patients with hepatitis/steatohepatitis	14
4.2 Exclusion Criteria – Cohort 1: Patients with hepatitis/steatohepatitis	14
4.3 Inclusion Criteria – Cohort 2: Healthy volunteers	14
4.4 Exclusion Criteria – Cohort 2: Healthy volunteers	15
5. Withdrawal of Participants	15
5.1 Reasons for Withdrawal and Termination	15
5.2 Procedure for Discontinuation	15
6. Concomitant Medications.....	15
7. Overview of Investigational Device.....	16
7.1 Component Description	16
7.2 Liver Incyte Imaging Procedure	19
8. Randomization and Blinding	20
9. Control Devices and Study Supplies.....	20
10. Study Procedures	21
10.1 Schedule of Events	21
10.2 Screening Procedures (-4 to 1 weeks)	22
10.3 Visit 1 (Day 1, Week 1)	22
10.4 Visit 2 (Day 5 ± 4, Week 1)	23
10.5 User Experience Survey	23
11. Assessment of Performance	24
12. Assessment of Safety	25

12.1	Definitions	25
12.2	Severity and Causality	25
12.3	Recording	26
12.4	Follow-up	26
12.5	Reporting	26
13.	User Experience	27
14.	Statistical Considerations	28
14.1	General Considerations	28
14.2	Sample size justification	28
14.3	Analysis population	28
14.4	Analyses Supporting Primary Objectives	29
14.4.1	Feasibility	29
14.4.2	Discriminant Ability	29
14.5	Analyses Supporting Secondary Objectives	30
14.5.1	Safety and Tolerability	30
14.5.2	User Survey	30
14.6	Analyses Supporting Exploratory Objectives	30
14.6.1	Liver Incyte Model A versus Model B Comparison	30
14.6.2	Comparison to MRE	30
14.6.3	Attenuation Comparison to Fibroscan and MRI	31
14.6.4	Association with Fibrosis Score	31
14.7	Analysis of Demographics	31
15.	Study Ethical Considerations	31
15.1	Ethical Conduct of the Study	32
15.2	Informed Consent	32
15.3	Confidentiality	32
15.4	Research Ethics Board	32
16.	General Trial Conduct Considerations	32
16.1	Adherence to Study Protocol	32
16.2	Study Monitoring	33
16.3	Early Termination of the Study	33
16.4	Data Collection and Evaluation	33
16.5	Record Retention	33

17.	References	33
18.	Appendices.....	35
	Appendix A: User Experience Survey	35
	Appendix B: Liver Incyte Session Questionnaire.....	35

List of Acronyms and Abbreviations

Acronym / Abbreviation	Definition
ADE	Adverse Device Effect
AUROC	Area Under the curve of the Receiver Operating Characteristic
AE	Adverse Events
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
EOT	End of Treatment
HBsAg	Surface antigen of the hepatitis B virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IFN	Interferon
MRE	Magnetic Resonance Elastography
MRI	Magnetic Resonance Imaging
mSUS	modified System Usability Scale
NASH	Non-Alcoholic Steato-hepatitis
PDFF	Proton Density Fat Fraction
SAE	Serious Adverse Event
S-WAVE	Shear Wave Absolute Vibro Elastography
SWE	Shear Wave Elastography
SVR	Sustained Viral Response
SVR12	Sustained Viral Response at 12 weeks after EOT
SVR24	Sustained Viral Response at 24 weeks after EOT
TE	Transient Elastography
VE	VibroElastography

Investigator Agreement

This clinical trial will be conducted according to the principles of Good Clinical Practices set out in ISO 14155 - Clinical investigation of medical devices for human subjects, and will follow the principles of and the Declaration of Helsinki and Tri-Council Policy Statement (2nd Edition): Ethical Conduct for Research Involving Humans (2010).

With the exception of a change intended to eliminate an immediate hazard to subjects, the clinical trial shall be conducted as described in the approved protocol.

I agree to the terms of this clinical trial protocol. I will conduct the trial according to the procedures specified herein and according to principles of Good Clinical Practice and local regulations and requirements.

Investigator Name and Signature

Date

Protocol Synopsis

Protocol Title:	The Sonic Incytes Liver Incyte System, assessment of liver fibrosis and steatosis
Protocol Number:	SI-CLIN-01
Sponsor:	Sonic Incytes
Number of Centres:	3
Study Design:	Open-label, non-randomized, prospective feasibility study
Study Objectives:	<p><u>Primary</u></p> <ul style="list-style-type: none"> a) Evaluate the feasibility of the Liver Incyte system for liver elasticity measurement in healthy volunteers and patients with liver fibrosis b) To evaluate the discriminatory ability of elasticity measurements generated by Liver Incyte for healthy volunteers versus patients with liver fibrosis in comparison to FibroScan or SWE measurements. <p><u>Secondary</u></p> <ul style="list-style-type: none"> c) Evaluate the safety and tolerability of the Liver Incyte system for liver elasticity measurement in healthy volunteers and patients with liver fibrosis d) Evaluate the user experience of Liver Incyte Model A and Model B <p><u>Exploratory</u></p> <ul style="list-style-type: none"> e) Evaluate the elasticity measurements generated from Liver Incyte Model A versus Model B f) Evaluate the relationship between Liver Incyte elasticity and attenuation measurements and the results from MRI elasticity and Proton Density Fat Fraction measurements. g) Evaluate the discriminatory ability of the Liver Incyte system and investigate cutoffs for different stages of liver disease progression h) Evaluate the inter-operator variability by scanning a subset of subjects with multiple users
Sample Size:	N = 200 (Cohort 1: 150, Cohort 2: 50) Approximately 125 in Canada, 75 in the USA.
Investigational Device:	Liver Incyte, Model A Liver Incyte, Model B
Control:	The following devices will be used as control, the FibroScan (FibroScan (Model 502 Touch or Model 530 Compact, MDL #80129, K160524) with both M and XL probes (MDL # 90025). For SWE, Philips Affiniti 70

	<p>ultrasound system (MDL #94446).</p> <p>MRE (at Beth Israel Deaconess site only), the 3T GE Discovery MR 750 (K163331) with MR-Touch option (K083421).</p> <p>MRE at Canadian sites, the Philips 3T Ingenia Elition MR system with elastography option (MDL #101182)</p> <p>Two populations of participants will be recruited for the study with healthy volunteers (Cohort 2) acting as controls.</p>
Study population:	<p>All sexes, 19-75 years old</p> <p>Cohort 1: patients with treated viral hepatitis or with non-alcoholic steatohepatitis, with a previous FibroScan measurement between 8 kPa and 40 kPa</p> <p>Cohort 2: healthy volunteers with no history of liver disease</p>
Randomization:	None; participants are enrolled in each cohort based on eligibility criteria
Duration of study:	Single visit (optional visit at Day 2), no follow up required
Outcome measures:	<p>Primary</p> <ul style="list-style-type: none"> a) Elasticity measurements from the Liver Incyte system and the elasticity measurements from FibroScan or SWE. b) Examine whether satisfactory waves are transmitted through the activation unit and into the participant c) Device deficiencies and failures <p>Secondary</p> <ul style="list-style-type: none"> d) Adverse events associated with elasticity measurements using the Liver Incyte system e) User Experience Survey results and Liver Incyte session Questionnaire results <p>Exploratory</p> <ul style="list-style-type: none"> f) Elasticity measurements from Model A and Model B g) Elasticity measurements MRE h) Steatosis measurements obtained using the FibroScan CAP, Liver Incyte ultrasound attenuation and MRI PDFF i) Elasticity measurements and fibrosis score as determined by FibroScan assessment or SWE measurements. j) The inter-observer variability will be calculated using the elasticity and attenuation measurements of several users
Statistical Analysis	<p>Primary</p> <ul style="list-style-type: none"> a) AUROC and 95% CI for Liver Incyte measurement discriminating healthy volunteers from those with liver fibrosis and compared to FibroScan or SWE. <p>Secondary</p> <ul style="list-style-type: none"> b) Descriptive statistics including frequency, severity and

	<p>association of all adverse events and all adverse device effects with the Liver Incyte device and associated 95% confidence intervals. Aggregated and broken out by healthy/fibrotic individuals.</p> <ul style="list-style-type: none"> c) Descriptive statistics such as N, proportion, mean, median, SD, and range will be calculated for the composite score of the User Survey d) Descriptive statistics such as N, proportion, mean, median, SD, and range will be calculated for each question in the Liver Incyte Session User Questionnaire. <p>Exploratory</p> <ul style="list-style-type: none"> e) Concordance correlation coefficient comparing elasticity measurements from Model A and Model B; linearity test (ie: slope and intercept) on aggregate and separately for healthy volunteers and fibrotic patients f) Concordance correlation coefficient and 95% CIs between MRE and Liver Incyte measurements g) Concordance correlation coefficient and 95% CIs between FibroScan CAP, ultrasound attenuation and MRE PDFF h) For each stage of fibrosis as determined by FibroScan assessment or SWE, an ROC curve will be constructed using the corresponding Liver Incyte measurements, from the AUC and the Liver Incyte values that maximizes the sum of sensitivity and specificity will be determined. Liver Incyte elasticity scores and 95% confidence intervals for mean and sample within each category will be calculated. i) The inter-observer variability will be calculated as the coefficient of variation (CV) for both elasticity and attenuation measurements
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