Clinical Study Protocol

Protocol Title:	The Sonic Incytes Liver Incyte System, assessment of liver fibrosis and steatosis
Protocol Number:	SI-CLIN-01
Study Sponsor:	Sonic Incytes
Study Sites:	LAIR Centre 750 W Broadway, Vancouver, BC V5Z 1H2, Canada Vancouver Infectious Diseases Centre (VIDC) 1200 Burrard St, Vancouver, BC V6Z 2C7, Canada Beth Israel Deaconess Medical Center 110 Francis St. 4A, Boston, MA. 02215 Pureform Radiology 350 - 600 Crowfoot Crescent NW Calgary, AB T3G 0B4
Principal/ Qualified Investigators:	Dr. Edward Tam, MD FRCPC (LAIR) Dr. Brian Conway, MD FRCPC (VIDC) Dr. Nezam Afdhal, MD, Gastroenterology (Beth Israel) Co-investigator: Dr. Michael Curry, MD, Gastroenterology (Beth Israel) Harmeet Kaur, MD (Pureform Radiology)
Version Number:	1.2
Replaces Previous Version Number:	1.1
Date:	3-25-2019

IRB Approved at the
Protocol Level
Apr 11, 2019
Panel 10

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

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:	<u>Primary</u> 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. <u>Secondary</u> 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 <u>Exploratory</u> 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

	ultrasound system (MDL #94446). MRE (at Beth Israel Deaconess site only), the 3T GE Discovery MR 750 (K163331) with MR-Touch option (K083421). MRE at Canadian sites, the Philips 3T Ingenia Elition MR system with elastography option (MDL #101182) Two populations of participants will be recruited for the study with healthy volunteers (Cohort 2) acting as controls.
Study population:	All sexes, 19-75 years old Cohort 1: patients with treated viral hepatitis or with non-alcoholic steatohepatitis, with a previous FibroScan measurement between 8 kPa and 40 kPa Cohort 2: healthy volunteers with no history of liver disease
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:	Primary 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 Secondary d) Adverse events associated with elasticity measurements using the Liver Incyte system e) User Experience Survey results and Liver Incyte session Questionnaire results Exploratory 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	Primary a) AUROC and 95% CI for Liver Incyte measurement discriminating healthy volunteers from those with liver fibrosis and compared to FibroScan or SWE. Secondary b) Descriptive statistics including frequency, severity and

	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. 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. Exploratory 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