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Pilot Study of On-Cart Liver Fat Quantification (LFQ) Feature to Assess Correlation with Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) Results

Short Title: LFQ Phase 2 Pilot Study
CTMS Protocol ID: US-GIS-Liver Fat Quantification Phase 2-2018-10481

Clinical Study Protocol Version 2.0

Date: May 31, 2019

Document Revision History

Version	Amendment	Version Date	Summary of Changes
1.0	N/A	March 25, 2019	Initial release
2.0	N/A	May 31, 2019	Minor revisions in the “Clinical Study Participation Risks” section

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Investigators, Clinical Study Sites, and Reviewing IRB Information

Principal Investigators	This information is maintained separately in the Trial Master File (TMF) for *US-GIS-Liver Fat Quantification Phase 2-2018-10481*
Co/Sub-Investigators	
Clinical Study Sites	
Reviewing IRBs	

Note: Signed Investigator Agreements are maintained separately from the Sponsor Approvals provided above. The blank Investigator Agreement is provided in Section 22 of this Clinical Study Protocol.

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Sponsor Approvals

Pilot Study of On-Cart Liver Fat Quantification (LFQ) Feature to Assess Correlation with Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) Results

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Jessica Parsons — 15 Sep 2019

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Clinical Study Synopsis – Multicenter LFQ Phase 2 Pilot Study

Study Title	Pilot Study of On-Cart Liver Fat Quantification (LFQ) Feature to Assess Correlation with Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) Results
Short Title	LFQ Phase 2 Pilot Study
Protocol ID	US-GIS-Liver Fat Quantification Phase 2-2018-10481 (short ID: 10481)
Country/Region	All clinical sites in the USA
Regulatory Path	Non-significant risk device and study per 21 CFR 812.3(m)
Investigational Device	Philips EPIQ Ultrasound System with C5-1 imaging transducer and investigational LFQ software (on-cart)
Study Design	Multi-center single-arm pilot study
Enrollment	Up to 150 subjects across all investigational sites No more than 50% of total enrollment expected from a single site
Primary Objective	To assess the correlation between each of several quantitative ultrasound biomarkers derived from the investigational LFQ feature and the known liver fat percentage obtained from MRI-PDFF, in order to identify which ultrasound biomarkers can best estimate the liver fat content.
Secondary Objectives	To evaluate the robustness of the investigational LFQ feature in the clinical environment by determining same-day inter-operator variability in quantitative ultrasound biomarker measurements and the overall data acquisition failure rate (i.e., percentage of subjects who have unacceptable image quality due to technical limitations).
Study-Related Procedures	Study-related procedures will consist of two (2) ultrasound imaging examinations conducted on the same day with the Philips EPIQ Ultrasound System with investigational LFQ software. In addition, one (1) standard MRI-PDFF examination is also required, unless MRI-PDFF is performed prior to enrollment as part of standard of care at the clinical site. No other procedures are required. All imaging procedures (investigational LFQ ultrasound exams and MRI-PDFF exam) must be completed within an 8-week window (+ 5 days).
Study Duration	Approximately 1 year from first subject enrollment to last subject visit
Subject's Participation	Up to 8 weeks from enrollment to completion of all study-related procedures
Primary Performance Endpoints	The primary performance endpoints are measurements of the quantitative ultrasound biomarkers that are believed to be correlated with liver fat content and/or liver stiffness. The following specific biomarkers may be measured, though not all are required to be reported for every subject: • Hepatorenal Index (HRI) (unitless) • Acoustic attenuation (dB/cm/MHz) • Nakagami parameter (unitless) • Tissue viscosity (Pa·s) (or viscosity-related metric) • Speed of sound (m/s) • Tissue stiffness (kPa) Performance of these endpoints will be evaluated by assessing their correlation with known liver fat percentages reported from MRI-PDFF.

Secondary Performance Endpoints	• Same-day inter-operator variability as measured by the difference in quantitative ultrasound biomarker measurements acquired from the same subject on the same day by two different operators who have undergone standardized training for LFQ data acquisition • Data acquisition failure rate as measured by percentage of subjects who have unacceptable image quality due to inadequate acoustic scanning windows, motion artifacts, or other technical limitations
Primary Safety Endpoints	Number and seriousness of any Adverse Device Effects reported
Subject Population	Subjects will be identified from a population suspected of having or diagnosed with NAFLD/NASH and who are eligible to undergo standard abdominal ultrasound imaging and MRI-PDFF.
Inclusion Criteria	• Must be at least 18 years old and able to provide written informed consent. • Must attest to absent or minimal alcohol consumption (i.e. < 2 alcoholic beverages per day for women and < 3 alcoholic beverages per day for men, where an alcoholic beverage is defined as 12 oz. of regular beer, 5 oz. of wine, or 1.5 oz. of distilled spirits[1]). • Must be eligible for a standard abdominal ultrasound examination and standard non-contrast MRI examination. In addition, <u>at least one</u> of the following criteria must also be met: • Overweight or obese (BMI ≥ 25). • Diagnosed with Type 2 diabetes per standard clinical guidelines. • Diagnosed with hypercholesterolemia per standard clinical guidelines. • Diagnosed with or clinically suspected of having NAFLD/NASH based on previous medical record, medical imaging, liver biopsy, and/or laboratory testing.

Exclusion Criteria	• Evidence of moderate/heavy/binge alcohol consumption exceeding the thresholds above.
	• Evidence of hepatotoxicity.
	• History of chronic liver disease (e.g., viral, cholestatic, or autoimmune).
	• Use of drugs associated with hepatic steatosis:
	  ○ Amiodarone
	  ○ Methotrexate
	  ○ Nucleoside reverse transcriptase inhibitors (didanosine, stavudine)
	  ○ Valproic acid
	  ○ Dexamethasone
	  ○ Tamoxifen
	  ○ 5-FU-based adjuvant chemotherapy
	  ○ Apo-B inhibitors (mipomersen, lomitapide)

[1] National Institute on Alcohol Abuse and Alcoholism. URL: https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink.

	○ Tetracycline exceeding 2 g/day ○ Acetylsalicylic acid exceeding 150 mg/kg • Hepatic lesions that cannot be excluded from the imaging field during ultrasound LFQ data acquisition. • Subjects anticipated or planned to undergo any diagnostic or therapeutic intervention during enrollment period that, at discretion of the Investigator, may affect liver fat content (e.g., bariatric surgery, chemotherapy). • History of previous liver surgery or hepatic implants that, at the discretion of the Investigator, may adversely impact ultrasound or MRI image quality or the subject's eligibility to undergo ultrasound or MRI.
Follow-up Assessments	None – subject participation ends at time of imaging procedure completion
Data Shared with Sponsor	De-identified ultrasound imaging data (biomarker measurements, DICOM files of static images and cineloops, raw radiofrequency data), de-identified MRI-PDFF imaging data (DICOM files), radiology reports of MRI-PDFF studies including fat percentage results, and pertinent health records including laboratory test results related to liver function (if available) and liver biopsy reports (if available) may be shared with Philips as part of the study, following appropriate privacy protections. All Protected Heath Information (PHI) will be removed before sharing.

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Table of Contents

1. List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
AUROC	Area Under Receiver Operating Characteristic
CAP	Controlled Attenuation Parameter (EchoSens Fibroscan)
CFR	United States Code of Federal Regulation
CRF	Case Report Form
CRO	Contract Research Organization
CTMS	Clinical Trial Management System
DDE	Direct Data Entry
DICOM	Digital Imaging and Communications in Medicine (format standard)
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption (FDA)
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intention-to-Treat subject population
LFQ	Liver Fat Quantification
MRI-PDFF	Magnetic Resonance Imaging - Proton Density Fat Fraction
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NPO	Nil per os (nothing by mouth)
PHI	Protected Health Information
PP	Per-Protocol subject population
PP-ODA	Per-Protocol with Optimal Data Acquisition subject population
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SoS	Speed of sound
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VCTE	Vibration-Controlled Transient Elastography (EchoSens Fibroscan)

2. Introduction

2.1 *Overview and Purpose of Clinical Study*

Philips Ultrasound is developing an investigational ultrasound-based Liver Fat Quantification (LFQ) software feature intended to provide a noninvasive imaging solution for detection, staging, and longitudinal monitoring of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) in the at-risk population. This investigational LFQ feature is designed to integrate with the Philips EPIQ Ultrasound System and the C5-1 imaging transducer, both of which are already commercially available, in order to expand the range of clinical imaging-based biomarkers for detecting, staging, and monitoring NAFLD.

The current benchmark for noninvasive imaging-based LFQ is Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF), which can provide sensitive quantitative assessments of steatosis for diagnosis and disease staging; however, MRI-PDFF is cost-prohibitive when repeated measurements are necessary for monitoring therapeutic response or disease progression. The goal of the Philips investigational LFQ feature is to enable rapid noninvasive ultrasound-based measurements of steatosis with reduced cost and capital equipment complexity compared to MRI-PDFF. The investigational LFQ feature is intended to complement Philips' currently available ElastQ™ shear wave imaging solution to provide a comprehensive set of ultrasound-based liver assessment tools to evaluate both steatosis and fibrosis. This approach will give the health care provider a complete suite of noninvasive tools to assess disease severity and monitor the effectiveness of any prescribed interventions (*e.g.,* pharmaceutical therapy, diet restrictions, and/or other lifestyle modifications).

This clinical study will involve performing a series of medical imaging procedures of the abdomen using both ultrasound and MRI modalities in subjects at risk for or already diagnosed with NAFLD. The primary objective of this clinical study is to assess the correlation between each of several quantitative ultrasound biomarkers derived from the investigational LFQ feature and the known liver fat percentage obtained from MRI-PDFF, in order to identify which ultrasound biomarkers can best estimate the liver fat content. This correlation assessment will enable final product development of the Philips ultrasound-based LFQ feature.

2.2 *Context of Study in Clinical Development Plan*

The clinical study described in this protocol represents the first pilot study in which the investigational LFQ feature will be installed on the Philips EPIQ Ultrasound System ('on-cart') and deployed in real-time during abdominal ultrasound examinations. Earlier studies of the investigational LFQ feature were 'off-cart' and were limited to off-line processing of ultrasound data. Transitioning to this on-cart pilot study is an important step that will enable the LFQ algorithm to be evaluated under real-world clinical conditions. The evidence obtained from this pilot study will be used to complete development of the investigational LFQ algorithm and inform future product claims, which will then be validated in the setting of a subsequent confirmatory study.

2.3 *Intended Population and Indications*

Participants in this clinical study will be drawn from the male and female adult population in the United States suspected of having or diagnosed with liver disease on the NAFLD spectrum, including non-alcoholic steatohepatitis (NASH). Complete inclusion/exclusion criteria are specified in Section 5.

2.4 *Description of Investigational Device*

As described in Table 1, the investigational device that is the subject of this clinical study is manufactured by Philips Ultrasound and consists of three main components: (1) the FDA-cleared Philips EPIQ Ultrasound System with the ElastQ™ shear wave imaging feature, (2) the FDA-cleared C5-1 ultrasound imaging transducer, and (3) the investigational LFQ software package, which is currently under development by Philips and does not yet have regulatory clearance. The investigational LFQ software will be installed on the EPIQ Ultrasound System when this study is performed. These components are summarized in Table 1.

Table 1. Identification of Manufacturer and Investigational Device Components

Device Manufacturer		
Philips Ultrasound 22100 Bothell Everett Highway Bothell, WA 98021 (888) 744-5477		
Device Component	**Investigational Status**	**Regulatory Clearance**
Philips EPIQ Ultrasound System with ElastQ™	FDA cleared, marketed in US	510(k): K172607
Philips C5-1 imaging transducer	FDA cleared, marketed in US	510(k): K172607
Philips LFQ software package	Investigational: not cleared for commercial use in USA	n/a

2.4.1 Philips EPIQ Ultrasound System and C5-1 Imaging Transducer

The intended use of the Philips EPIQ Ultrasound System is for diagnostic ultrasound imaging and fluid flow analysis of the human body. When coupled with the C5-1 imaging transducer, the cleared indications for use are abdominal, gynecologic, fetal echo, pediatric GI (Abdomen, Neonatal Head), obstetrical, and urological imaging applications. The only portion of the device that comes in contact with the subject under normal use is the surface of the C5-1 imaging transducer, which has been tested for compliance with applicable biological safety standards (see Table 3). The EPIQ Ultrasound System and C5-1 imaging transducer are shown in Figure 1 below.

Figure 1. Philips EPIQ Ultrasound System. ① Monitor ② On/Off Switch ③ Control Module ④ Transducer receptacle locks ⑤ Transducer receptacles ⑥ side panel ⑦ brake/steering lock pedal ⑧ touch screen ⑨ peripheral bays ⑩ Philips C5-1 Imaging Transducer (curvilinear, 5 – 1 MHz frequency).

2.4.2 Philips Investigational LFQ Feature: Ultrasound Biomarkers for NAFLD/NASH

The investigational LFQ feature is a software package under development intended for use with certain Philips ultrasound imaging systems including the EPIQ Ultrasound System. The LFQ feature works in conjunction with standard Philips ultrasound system hardware and transducers to collect acoustic signals from the liver for analysis during abdominal ultrasound examinations. These acoustic signals are processed via a series of specialized algorithms to measure several quantitative ultrasound biomarkers that are believed to correlate with liver fat content and may therefore provide relevant information for NAFLD/NASH diagnosis and staging.

There are multiple candidate quantitative ultrasound biomarkers derived from these acoustic signals that are currently being evaluated in the Philips investigational LFQ feature, though additional biomarkers may be identified during ongoing development. Some of these biomarkers may be measured in real-time during the investigational LFQ exam, while others will be calculated from offline processing. In addition, an established biomarker measured using the cleared Philips ElastQ™ shear wave imaging feature, tissue stiffness, is used to assess the degree of tissue fibrosis to determine whether a patient's NAFLD may have progressed to NASH. These various quantitative ultrasound biomarkers are described in Table 2.

Table 2. Candidate Quantitative Ultrasound Biomarkers for Assessing NAFLD/NASH

Biomarker	Units	Qualitative Correlation with NAFLD/NASH
Hepatorenal Index (HRI) (echogenicity) (source: investigational LFQ)	unitless	Increased steatosis is associated with *increased* liver echogenicity, manifested as an *increased* HRI value (ratio of the echogenicity ('brightness') of the liver parenchyma relative to that of the adjacent renal cortex).
Acoustic attenuation (source: investigational LFQ)	dB/cm/MHz	Increased steatosis is associated with an *increased* acoustic attenuation value in the liver.
Nakagami parameter (backscatter statistics) (source: investigational LFQ)	unitless	Increased steatosis is associated with an *increased* Nakagami parameter, which represents a shift in the ultrasound backscatter distribution.
Tissue Viscosity (source: investigational LFQ)	Pa·s	Increased steatosis and/or liver inflammation may be associated with *increased* tissue viscosity in the liver.
Speed of sound (source: investigational LFQ)	m/s	Increased steatosis may be associated with a *decreased* speed of sound (SoS) in the liver.
Tissue stiffness (source: cleared ElastQ™ shear wave elastography)	kPa	Increased fibrosis is associated with *increased* tissue stiffness and *increased* shear wave velocity in the liver.

These represent the known candidate quantitative ultrasound biomarkers under consideration presently, and this list may evolve over time. As a result, not all of these biomarkers are required to be measured in every subject, and it is possible that additional candidates may be added.

2.4.3 Physiological Basis for Correlation of Ultrasound Biomarkers with Disease State

These ultrasound biomarkers are leveraged in the investigational LFQ feature and the ElastQ™ shear wave imaging feature because each is directly influenced by the physiology of the NAFLD disease process. Brief overviews of the physiological basis of these biomarkers are described below:

a. *Hepatorenal Index (HRI) / Liver Echogenicity:* As a biological tissue, fatty tissue characteristically has a lower acoustic impedance than other soft tissue types. As a result, as lipid content increases in the liver, the difference between the acoustic impedance of the liver and that of the surrounding abdominal tissues will increase accordingly. This increased impedance mismatch causes larger acoustic reflections to occur during standard B-mode ultrasound imaging, resulting in an increased liver echogenicity ('brightness') compared to that of surrounding tissues. When the echogenicity of the liver is referenced against that of the adjacent renal cortex, fatty liver will therefore result in an increased HRI that can be readily detected. For example, HRI cutoff values of 1.49, 1.86 and 2.23 have be reported to predict 5%, 25% and 60% steatosis, respectively (Webb et al. 2009).

b. *Acoustic Attenuation:* The presence of fatty tissue will increase the attenuation of the ultrasound beam as it propagates through the tissue, due in part to acoustic absorption being higher for fatty tissues than in other soft tissue types. For example, Yasutomo et al. (2002) reported that attenuation coefficient values were 0.59 ± 0.10 dB/cm/MHz in normal livers vs. 0.80 ± 0.12 dB/cm/MHz in fatty livers (P<.0001). Regions of high fat content in the liver may therefore have elevated acoustic attenuation coefficients.

c. *Nakagami Parameter (Backscatter Statistics):* The large vacuoles of triglycerides that accumulate in hepatocytes when steatosis is present alter the arrangement of scatterers within the tissue, thereby affecting the underlying statistics of the backscattered ultrasound signals. The Nakagami parameter considers the envelope of the backscattered signal to detect shifts in the distribution of scatterers. For example, Wan et al. (2015) reported an increase in Nakagami parameter from 0.62 ± 0.11 to 1.02 ± 0.07 in two groups of patients with normal and severe steatosis, respectively. Regions of high fat content in the liver may therefore demonstrate an increased Nakagami parameter.

d. *Tissue Viscosity (or viscosity-related metric)*: The change in liver tissue composition that occurs during NAFLD due to excessive deposition of viscous triglycerides and associated inflammatory responses in hepatocytes may result in an increase in tissue viscosity. For example, Sugimoto et al. (2018) explored the possibility that viscosity may be increased in steatotic patients with liver necroinflammation and found a correlation, whereby higher viscosity was indicative of greater inflammation. Other alternative metrics related to tissue viscosity may also be explored as part of the investigational LFQ feature.

e. *Speed of Sound:* Fatty tissue has a decreased speed of sound (acoustic velocity) compared to most other biological tissue types, due to its reduced density relative to predominantly water-bearing tissues. In a preliminary clinical trial (Imbault et al. 2017), speed of sound results were found to be highly correlated with MRI-PDFF (R^2 = 0.69) and biopsy (AUROC = 0.952) results. Regions of high fat content in the liver may therefore demonstrate lower speed of sound measurements.

f. *Tissue Stiffness and Shear Wave Velocity:* As NAFLD progresses into NASH and/or cirrhosis, the ensuing chronic inflammation results in widespread parenchymal fibrosis and scarring within the liver. This global fibrotic process increases the elasticity of the liver and causes it to lose compliance, resulting in increased tissue stiffness that can be detected using ultrasound elastography techniques. The Philips LFQ feature will complement the commercially available ElastQ™ Shear Wave Elastography feature, which remotely induces shear waves and monitors the velocity of their propagation through the liver to obtain measurements of tissue stiffness. The liver stiffness and shear wave velocity measurements can then be used as a surrogate marker for fibrosis to monitor the progression of NAFLD to NASH.

3. Rationale for Conducting Clinical Study

Justification for conducting this clinical study in human subjects is based on the low risk profile of the investigational device and the study design, the clear evidence of a clinical unmet need that the Philips investigational LFQ feature intends to address, and the comprehensive preclinical product testing that has been performed to demonstrate subject and user safety. These aspects are discussed individually in the following sections.

3.1 *Risks and Benefits of the Investigational Device and Clinical Study*

3.1.1 Statement of Risk Level

This clinical study is expected to be an IDE-exempt Non-Significant Risk Study, as defined in 21 CFR 812.3(m), because the only study-related procedures required are two abdominal ultrasound examinations using the investigational LFQ software and a commercially available MRI-PDFF examination, if not performed prior to enrollment. No additional risk to subjects is expected beyond that associated with any standard diagnostic abdominal ultrasound imaging or MRI procedure. Due to the overall low risk profile of this study, it is expected that only IRB/EC approval will be needed.

3.1.2 Anticipated Clinical Benefits

There are no direct health benefits to the subject for participating in this study because no treatment or diagnosis is being provided by study-related procedures. The ultrasound examinations performed using the investigational LFQ software will not provide any diagnostic or health-related information to the subject or the clinician. However, for those subjects who will undergo MRI-PDFF as a study-related procedure, this examination may provide additional information regarding their health that they would not otherwise receive.

3.1.3 Anticipated Adverse Device Effects

There are no significant Anticipated Adverse Events and Anticipated Adverse Device Effects associated with this clinical study because the investigational procedure is limited to noninvasive diagnostic ultrasound imaging of the abdomen using the investigational LFQ software. The Philips EPIQ Ultrasound System with investigational LFQ software and the C5-1 imaging transducer have been verified to comply with harmonized safety standards governing all diagnostic ultrasound imaging devices (e.g., IEC 60601-1-2 and IEC 60601-2-37, see Table 3) and therefore pose no additional risk to subjects beyond that associated with any other diagnostic ultrasound imaging procedure of the abdomen. Only nonserious ADEs, if any, are therefore anticipated; these may include:

- potential discomfort during the ultrasound examination due to body positioning
- potential discomfort during the ultrasound examination due to pressure exerted by the ultrasound transducer when it is pressed against the abdominal skin

3.1.4 Clinical Study Participation Risks

Beyond the risks associated with the Anticipated Adverse Device Effects listed above, participation in this clinical study includes other types of risks. These include standard risks associated with the MRI-PDFF examination, if that procedure is conducted as a study-related procedure. MRI-PDFF-associated risks include anxiety due to claustrophobic feeling while in the MRI machine and the potential for injury if the subject has undisclosed contraindications to MRI (e.g., implantable devices including pacemakers, certain

types of artificial joints, etc.). These contraindications will be fully discussed during the subject's informed consent discussion for the MRI-PDFF procedure. Moreover, the MRI makes loud banging noises as it takes images which might be uncomfortable for the patient, for which earphone will be used. The MRI also has the potential to cause localized warming of the skin and the underlying tissues. The patient may also experience dizziness or rarely nausea, which in most cases only last a short time. No case of permanent problems is known.

3.1.5 Interactions from Concomitant Medications or Treatments

There are no safety risks expected due to interactions with any concomitant medications or treatments, since this clinical study involves medical imaging procedures only.

3.1.6 Risk Mitigations

Risks will be mitigated by using standard clinical sonography techniques during all LFQ ultrasound examinations to minimize subject discomfort. Furthermore, Philips' risk management activities are compliant with EN-ISO 14971:2012 (*Medical devices: Application of risk management to medical devices*), which ensures that all risks are identified, assessed, and mitigated to acceptable levels.

Risks of MRI-PDFF will be mitigated through standard-of-care informed consent procedures that will disclose all contraindications and known risks of MRI to the subject before the procedure is performed.

3.1.7 Risk to Benefit Ratio

Based on consideration of the above information, this clinical study generally has a low risk profile but may provide valuable information to enable product development of a noninvasive NAFLD screening and staging tool. While there is no immediate or direct benefit to subjects for participating in this study, the general body of medical knowledge related to metabolic liver disease will be advanced by providing new information regarding noninvasive ultrasound biomarkers for NAFLD and NASH.

3.2 *Disease State and Clinical Unmet Need*

Hepatic steatosis is the abnormal and excessive intracellular accumulation of triglycerides within hepatocytes, which causes oxidative stress and inflammation over time (Idilman *et al.* 2013). Nonalcoholic fatty liver disease (NAFLD) is a spectrum of disorders that range from simple steatosis to more severe manifestations including nonalcoholic steatohepatitis (NASH) and cirrhosis. A hallmark of NAFLD is that it is not precipitated by alcohol consumption but is instead a hepatic manifestation of metabolic syndrome, which is associated with obesity, insulin resistance, Type 2 diabetes mellitus, hypertension, hyperlipidemia, and cardiovascular disease. NAFLD is currently estimated to affect 30-40% of all US adults, including 70% of Type 2 diabetics and obese adults.[2] Approximately 20% of patients with NAFLD will progress to develop NASH and the attendant risks of cirrhosis, hepatocellular carcinoma, and liver-related morbidity and mortality. Moreover, NAFLD is often asymptomatic until its later stages, so there is a pressing clinical need for cost-effective screening and diagnostic techniques.

For comprehensive liver assessment, clinicians need information about fibrosis, steatosis, and inflammatory processes occurring within the liver. Currently, liver biopsy and MRI-PDFF are the generally accepted techniques available for definitive liver fat quantification and serve as reference methods to accurately diagnose and stage hepatic steatosis. However, liver biopsies are invasive procedures that carry risk of

[2] National Institute of Diabetes and Digestive and Kidney Diseases. URL: https://www.niddk.nih.gov

bleeding and perforation, and they are limited by spatial sampling bias. While MRI-PDFF provides accurate measurements of steatosis, it is cost-prohibitive for longitudinal monitoring and cannot be deployed in real-time. A third option known as CAP (Controlled Attenuation Parameter) is available using the Fibroscan product (EchoSens, Paris, France). When used together, Fibroscan's CAP and Vibration-Controlled Transient Elastography (VCTE™) can provide simultaneous liver steatosis and fibrosis assessment. However, the Fibroscan product has been associated with rates of unreliable results on the order of 15% (Myers et al. 2011) due to frequent invalid measurements in patients with high body mass index (BMI) or central obesity, which are comorbidities often encountered in NAFLD patients. The Fibroscan product also fails on patients with liver ascites and liver masses. Additionally, because the Fibroscan product lacks a fully integrated conventional ultrasound imaging capability, clinicians have no visual guidance to ensure that the VCTE™ measurement is performed in a uniform region of the liver.

The investigational LFQ feature under development for the Philips EPIQ Ultrasound System is intended to overcome some of these practical limitations associated with other clinically available methods for NAFLD/NASH diagnosis and staging. By integrating a LFQ capability into the Philips EPIQ Ultrasound System to provide complementary information to Philips' existing Shear Wave Elastography (SWE) imaging capabilities, 2D imaging, and flow assessment, a state-of-the-art imaging-based solution is envisioned to noninvasively detect and monitor both liver steatosis and fibrosis in real-time.

3.3 *Compliance with Medical Device Safety Standards and Good Clinical Practice Standards*

The Philips EPIQ Ultrasound System used with on-cart investigational LFQ software and the commercially-available C5-1 ultrasound imaging transducer are considered safe for use in human subjects in this clinical study because extensive safety testing has been conducted to confirm the safety profile and all hardware is FDA-cleared via 510(k) as per Table 1. Furthermore, the only portion of the device that contacts the subject's body is the commercially available C5-1 imaging transducer.

The Philips EPIQ Ultrasound System with investigational LFQ software and the C5-1 imaging transducer comply with the following medical device safety standards listed in Table 3. In addition, this clinical study is designed to comply with the Good Clinical Practice standard listed in Table 3. Compliance with these standards confirms that adequate evidence of safety and human subject protection has been established to justify use of the investigational device on human subjects.

Table 3: Compliance with Medical Device Safety and Good Clinical Practice Standards

	Standard Name and Description
Electrical Safety	**EN/IEC 60601-1:2006 + A1:2013** – *Medical electrical equipment – Part 1: General requirements for basic safety and essential performance.* The Philips EPIQ System with investigational LFQ software and the C5-1 imaging transducer have been designed and verified to comply with the electrical safety requirements of this standard, including requirements for electrical ground bond, leakage current, and dielectric withstand.
Electromagnetic Compatibility	**EN/IEC 60601-1-2:2007** – *Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic compatibility – Requirements and tests.* The Philips EPIQ System with investigational LFQ software and the C5-1 imaging transducer have been designed and verified to comply with the radiated and conducted emission requirements of this standard.

	Standard Name and Description
Usability	**EN/IEC 60601-1-6:2010** – *Medical electrical equipment – Part 1-6: General requirements for basic safety and essential performance – Collateral standard: Usability.* The Philips EPIQ System with investigational LFQ software and the C5-1 imaging transducer have been designed and verified to comply with the usability requirements of this standard.
Diagnostic Ultrasound Imaging	**EN/IEC 60601-2-37:2007** – *Medical electrical equipment – Part 2-37: Particular requirements for basic safety and essential performance of ultrasonic medical diagnostic and monitoring equipment.* The Philips EPIQ System with investigational LFQ software and the C5-1 imaging transducer have been designed and verified to comply with the diagnostic ultrasound imaging requirements of this standard.
Biological Safety	**EN/ISO 10993-1:2009** – *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process.* The patient contact surface of the C5-1 imaging transducer has been designed and verified to comply with the biological safety requirements of this standard and FDA Memorandum G95-1:1995. The evaluations included cytotoxicity, sensitization, and intracutaneous reactivity testing for surface devices with limited-duration skin contact.
Risk Management	**EN/ISO 14971:2012** – *Medical devices: Application of risk management to medical devices.* The risk assessment and mitigation procedures for Philips EPIQ System with investigational LFQ software and C5-1 imaging transducer have been conducted in compliance with the requirements of this standard.
Clinical Investigation	**EN/ISO 14155:2011** – *Clinical investigation of medical devices for human subjects: Good clinical practice.* This clinical study of the Philips EPIQ System with investigational LFQ software and C5-1 imaging transducer is designed and conducted to comply with the content and human protections requirements of this standard. This compliance ensures that clinical investigations adhere to current Good Clinical Practice (GCP) guidelines.
Device Labeling	**EN/ISO 15223-1:2016** – *Symbols to be used with medical device labels, labeling, and information to be supplied – Part 1: General requirements.* The labelling associated with the Philips EPIQ System with investigational LFQ software and C5-1 imaging transducer has been designed and verified to comply with the requirements of this standard.

4. Clinical Study Design: Objectives and Endpoints

4.1 *Overview of Study Design Attributes*

This clinical study will be conducted in the United States under the approval of one or more recognized IRBs and in compliance with GCP guidelines defined in ISO 14155:2011, the Declaration of Helsinki, and all applicable federal and local laws and regulations. This study is a prospective multi-center single-arm pilot study intended to gather data to support final product development of the investigational LFQ feature. No specific *a priori* performance claims are being validated during this study, though data from this study are intended to inform future claims regarding the performance of the LFQ feature.

Subject data from all clinical sites are intended to be pooled for analysis. Separate analysis tiers are planned as described in Section 7 (*Data Analysis and Statistical Considerations*) for the Intention-to-Treat (ITT), Per Protocol (PP), and Per-Protocol with Optimal Data Acquisition (PP-ODA) groups. Though all data are intended to be pooled, it is possible that sub-analyses may be conducted in which subjects from each clinical site are evaluated as a cohort due to variations in the standard MRI-PDFF imaging protocol that may exist among the clinical sites. Also, it is possible that sub-analyses may be conducted depending on subjects' medical histories (e.g., presence of concomitant disease(s)).

4.2 *Study Aims and Objectives*

4.2.1 Overall Aim

The overall aim of this clinical study is to demonstrate that the investigational LFQ feature on the Philips EPIQ Ultrasound System is a viable solution to the clinical unmet need for a noninvasive and cost-effective liver fat quantification tool that clinicians can deploy in real-time. In order to be considered a viable solution, the quantitative ultrasound biomarkers measured by the investigational LFQ feature need to demonstrate correlation with the liver fat percentage provided by the current noninvasive imaging-based benchmark, MRI-PDFF. In addition, the investigational LFQ feature needs to demonstrate robustness in the clinical environment. These aims are addressed in the primary and secondary objectives below.

4.2.2 Primary Objective

The primary objective of this clinical study is to assess the correlation between each of several quantitative ultrasound biomarkers derived from the investigational LFQ feature and the known liver fat percentage obtained from MRI-PDFF, in order to identify which ultrasound biomarkers can best estimate liver fat content. Quantitative liver fat percentages will be obtained from each subject's MRI-PDFF examination to serve as the baseline reference ('ground truth') for a given subject. The correlation between ultrasound biomarkers and MRI-PDFF liver fat percentage will be measured per the considerations included in Section 7 (*Data Analysis and Statistical Considerations*).

4.2.3 Secondary Objective

The secondary objective of this study is to evaluate the robustness of the investigational LFQ feature in the clinical environment. Robustness will be assessed by determining same-day inter-operator variability in quantitative ultrasound biomarker measurements and the overall data acquisition failure rate (i.e., percentage of subjects who have unacceptable image quality due to technical limitations).

4.3 *Study Endpoints*

4.3.1 Primary Safety Endpoints

The primary safety endpoints assessed in this study will be the number and seriousness of any Adverse Device Effects reported during the study, which will be recorded for each subject. As described in Section 15.2 below, due to the nature of this clinical study in which only routine medical imaging procedures are performed, there are no significant Adverse Device Effects anticipated.

4.3.2 Primary Performance Endpoints

The primary performance endpoints are measurements of the quantitative ultrasound biomarkers that are believed to be correlated with liver fat content and/or liver stiffness. As described in Section 2.4.2 above, the following specific biomarkers may be measured either in real-time during the investigational LFQ ultrasound exam or during offline processing after the ultrasound exam is complete:

- Hepatorenal Index (HRI) (unitless)
- Acoustic attenuation (dB/cm/MHz)
- Nakagami parameter (unitless)
- Tissue viscosity (Pa·s) (or viscosity-related metric)
- Speed of sound (m/s)
- Tissue stiffness (kPa)

These candidate quantitative ultrasound biomarkers may evolve over time and, consequently, not all of these endpoints are required to be measured in every subject. Performance of these endpoints will be evaluated by assessing their correlation with known liver fat percentages reported from MRI-PDFF per the considerations included in Section 7 (*Data Analysis and Statistical Considerations).*

4.3.3 Secondary Performance Endpoints

Secondary performance endpoints will include the following:

- Same-day inter-operator variability: difference in quantitative ultrasound biomarker measurements acquired from the same subject on the same day by two different operators who have undergone standardized training for LFQ data acquisition. These operators will be unaware of each other's impressions/findings during the investigational LFQ ultrasound exam (see Section 4.4).

- Data acquisition failure rate: percentage of subjects who have unacceptable image quality due to inadequate acoustic scanning windows, motion artifacts, or other technical limitations. Whether or not image quality is acceptable in each case will be determined by Philips personnel in consultation with investigators.

4.4 *Measures to Minimize Bias*

The following measures will be taken to minimize and/or avoid bias in this clinical study:

- Standardized product training materials will be developed and distributed to all clinical sites to ensure that the investigational LFQ feature is deployed by all operators in a consistent manner in all subjects. This will help to ensure that data of uniform quality are obtained from all subjects.
- A process will be instituted at each clinical site to ensure that the two operators who perform a subject's LFQ ultrasound examinations do not discuss each other's impressions/findings in order to avoid influencing the imaging technique or outcome of the second exam.
- Standardized clinical instructions will be communicated to each subject to ensure uniformity in their preparation for their study-related ultrasound examination (for example, all subjects will be asked to abstain from eating or drinking for 6 hours before their ultrasound examinations, as described in Section 6.4 below).
- The Philips EPIQ Ultrasound System and the C5-1 imaging transducer are highly regulated medical devices that have been calibrated to provide known and reproducible acoustic output. Therefore, the ultrasound data obtained from each subject will be elicited in a controlled manner using standardized equipment.

5. Study Subjects

In general, subjects for this study will be drawn from the adult population at risk for, or already diagnosed with, disease on the NAFLD spectrum, up to and including NASH. Subjects must meet all of the following specific inclusion and exclusion criteria to qualify for enrollment.

5.1 *Inclusion Criteria*

All of the following inclusion criteria must be met at the time of screening before the subject can be enrolled into the study:

- Must be at least 18 years old and able to provide written informed consent to participate.
- Must attest to absent or minimal alcohol consumption (i.e. < 2 alcoholic beverages per day for women and < 3 alcoholic beverages per day for men, where an alcoholic beverage is defined as 12 oz. of regular beer, 5 oz. of wine, or 1.5 oz. of distilled spirits[3]).
- Must be eligible for a standard abdominal ultrasound examination and standard non-contrast MRI examination.

In addition to the above criteria, at least one of the following criteria must also be met at the time of screening:

- Overweight or obese (BMI ≥ 25).
- Diagnosed with Type 2 diabetes per standard clinical guidelines.
- Diagnosed with hypercholesterolemia per standard clinical guidelines.
- Diagnosed with or clinically suspected of having NAFLD/NASH based on previous medical record, medical imaging, liver biopsy, and/or laboratory testing.

5.2 *Exclusion Criteria*

Subjects are not eligible for enrollment if any of the following criteria are met:

- Evidence of moderate/heavy/binge alcohol consumption exceeding the thresholds above.
- Evidence of hepatotoxicity.
- History of chronic liver disease (e.g., viral, cholestatic, or autoimmune).
- Use of drugs associated with hepatic steatosis[4]
  - Amiodarone
  - Methotrexate
  - Nucleoside reverse transcriptase inhibitors (didanosine, stavudine)

[3] National Institute on Alcohol Abuse and Alcoholism. URL: https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink.

[4] List of drugs associated with hepatic steatosis obtained from *Amacher DE and Chalasani N. Drug-Induced Hepatic Steatosis. Semin Liver Dis 34: 205-214 (2014).*

- Valproic acid
- Dexamethasone
- Tamoxifen
- 5-FU-based adjuvant chemotherapy
- Apo-B inhibitors (mipomersen, lomitapide)
- Tetracycline exceeding 2 g/day
- Acetylsalicylic acid exceeding 150 mg/kg

- Hepatic lesions that cannot be excluded from the imaging field during ultrasound LFQ data acquisition.
- Subjects anticipated or planned to undergo any diagnostic or therapeutic intervention during enrollment period that, at discretion of the Investigator, may affect liver fat content (e.g., bariatric surgery, chemotherapy).
- History of previous liver surgery or hepatic implants that, at the discretion of the Investigator, may adversely impact ultrasound or MRI image quality or the subject's eligibility to undergo ultrasound or MRI.

5.3 *Point of Enrollment*

Subjects who sign the Informed Consent Form are screened for eligibility at Visit 1. Subjects meeting all inclusion/exclusion criteria will then be enrolled into the study.

5.4 *Withdrawal or Discontinuation Criteria*

Study participation is voluntary. Subjects may refuse to consent or may withdraw from the study at any time without penalty or loss of benefits to which he/she is otherwise entitled. Subjects may withdraw from the study in person, in writing (including via email), or via telephone communication with any study personnel. The Investigator may discontinue a subject's participation in this study without his/her consent if significant non-compliance is noted or if, in the opinion of the Investigator, the health or safety of a subject is affected adversely by participation in the study.

Because this study does not involve long-term longitudinal follow-up, new subjects can be enrolled to replace any subjects who withdraw their consent or are removed by the Investigator, up to the point at which the maximum enrollment limit is reached. There is no required follow-up for withdrawn subjects due to the non-therapeutic nature of this study, in which only medical imaging data are being collected and no treatment intervention is involved.

5.5 *Number of Subjects*

This study will enroll up to a maximum of 150 subjects across all clinical sites combined. Each site is expected to enroll at least 20 subjects, though additional subjects may be enrolled at a given site within the overall limit of this investigational protocol. No more than 50% of the total enrollment is expected from a single site.

The number of subjects enrolled will affect the statistical confidence in the correlation level observed between each quantitative ultrasound biomarker and the liver fat percentage measured by MRI-PDFF. This sample size effect is discussed in Section 7 below (*Data Analysis and Statistical Considerations*).

5.6 *Study Duration*

5.6.1 Study Duration - Global

This clinical study is expected to last for up to 1 year, from the first subject's enrollment to completion of the last subject's involvement. After all subjects have exited the study, post-enrollment activities will be undertaken for a period of approximately 6 months (monitoring, data analysis, data review/querying, database lock, final report generation, publication generation if appropriate, etc.)

5.6.2 Study Duration – Individual Subject

The duration of each subject's participation in this study is expected to be no more than approximately 8 weeks, from the time of initial enrollment to completion of all visits for imaging procedures (ultrasound and MRI). There is no follow-up period for this study, except for any continued follow-up in the event of an Adverse Event as specified in Section 15.

5.7 *Enrollment Period*

The study's entire enrollment period is expected to last for up to 1 year, consistent with the global study duration listed above.

5.8 *Subject Reimbursement and Compensation*

Subjects enrolled in this study will be reimbursed for any parking fees incurred at the clinical site and may receive additional compensation within clinical site guidelines in acknowledgment of their time needed to complete all study-related procedures during one or more study visits. If more than one visit is required to complete study-related procedures, subjects may receive reimbursement for parking fees and additional compensation on a per-visit basis or a lump sum basis, according to the clinical site's standard procedure.

6. Study Procedures

6.1 *Investigational LFQ Ultrasound Exams*

All subjects enrolled in this study will undergo two abdominal ultrasound examinations using the investigational LFQ feature on the Philips EPIQ Ultrasound System and the C5-1 imaging transducer. These exams will be performed on a single day during the same visit. See Section 6.4 for details.

6.2 *MRI-PDFF Exams*

Additionally, all subjects enrolled in this study will also undergo one standard MRI-PDFF examination, unless this procedure has been performed as part of the subject's clinical standard of care prior to study enrollment within an acceptable time window defined in Section 6.3. Therefore, because the MRI-PDFF examination may or may not be performed as a study-related procedure, the number and nature of required study visits is expected to vary among the clinical sites (see Section 6.4 for details).

6.3 *Time Interval for All Imaging Procedures*

All investigational LFQ ultrasound and MRI-PDFF imaging procedures (clinically-scheduled or study-related) must be completed within a 8-week interval (+ 5 days). Therefore, in order for a clinically-scheduled MRI-PDFF examination performed prior to enrollment to be considered valid for the purposes of this study, it must have been completed no more than 8 weeks (+ 5 days) prior to completion of the subject's investigational LFQ ultrasound examinations. This restriction is intended to ensure that the subject's liver fat status does not change significantly during the time between the MRI-PDFF and investigational LFQ ultrasound examinations.

6.4 *Schedule and Description of Study Procedures*

As a result of the above considerations, subjects enrolled in this study will have at least one study visit and may have up to three study visits, depending on the scheduling of their ultrasound and MRI-PDFF examinations at each clinical site. Individual study visits and their specific procedures will consist of the events described below.

6.4.1 Visit 1: Screening, Enrollment, Investigational LFQ Ultrasound Exams, and MRI-PDFF Exam

Visit 1 consists of screening and enrollment activities and may also include both investigational LFQ ultrasound examinations and/or the MRI-PDFF exam, if being performed as a study-related procedure. However, the LFQ ultrasound exams and/or MRI-PDFF exam may be performed during one or more subsequent visits, depending on Investigator preference or scheduling constraints. If subjects are to undergo investigational LFQ ultrasound exams during Visit 1, they will be asked to fast (NPO) for at least 6 hours prior to arrival.

Visit 1 will consist of the following procedures:

Table 4: Study Procedures during Visit 1 (Screening, Enrollment, LFQ Ultrasound, and/or MRI-PDFF)

Procedure	Description
Informed Consent	The potential subject will be given the most current IRB/EC-approved Informed Consent Form (ICF) to read. He/she will be provided ample time for review and an opportunity to ask questions about the study. If the subject agrees to participate, they will sign the ICF and be given a copy of the signed document for their records. All components of the consent process will be documented. Only after informed consent has been obtained may the remaining study procedures begin. A detailed description of the consent process is provided in Section 14.
Assessment of Eligibility	The Investigator will assess the subject's eligibility for this study per the inclusion and exclusion criteria listed in Section 5.1 – 5.2 and will document the outcome of the eligibility assessment. If the subject qualifies, he or she will then undergo the study-related LFQ ultrasound examinations described below.
Study-Related LFQ Ultrasound Examinations *(Note: may be conducted in a subsequent visit)*	Adherence to the 6-hour NPO request will be verified; any deviations will be noted in the subject's records. The subject will be placed in the supine or lateral decubitus position, depending on which provides the optimal scanning window. The subject's shirt will be lifted or removed and standard ultrasound imaging gel will be applied to the skin in the appropriate region. The EPIQ ultrasound system with the cleared ElastQ™ feature, the investigational LFQ software, and the C5-1 imaging transducer will be used to conduct the first abdominal ultrasound exam using standard sonographic techniques. The entire ultrasound exam is expected to last approximately 15 minutes. The subject may be placed in multiple positions during this time to assess various imaging angles. Study staff will monitor for any Adverse Events (AEs) during or after the ultrasound exam and will document any AEs appropriately (see Section 15). The ultrasound exam will then be repeated by a different operator to obtain data on inter-operator variability in the ultrasound biomarker measurements. This second ultrasound exam can occur immediately after the first and must be completed while the subject is still under fasting conditions.
Study-Related MRI-PDFF Exam *(Note: may be conducted in a subsequent visit)*	If the subject does not already have MRI-PDFF data available from a clinical standard of care exam within the prior 8 weeks (+ 5 days), the subject will undergo a non-contrast abdominal MRI examination using the clinical site's standard PDFF acquisition protocol and procedure. Study staff will monitor for any Adverse Events (AEs) during or after the MRI-PDFF exam and will document any AEs appropriately (see Section 15).
Data Collection and Transmittal	During the study-related ultrasound exams, real-time biomarker measurements will be collected. In addition, DICOM images, cineloops, and raw ultrasound radiofrequency (RF) data may also be collected for offline post-processing by Sponsor personnel. These datasets will be captured and transmitted to the Sponsor using appropriate de-identification procedures and privacy protections via the methods listed in Section 9.3. Data from the MRI-PDFF exam, including DICOM images and radiology reports including fat percentage results, will be transmitted to the Sponsor using appropriate de-identification procedures and privacy protections via the methods listed in Section 9.3.

6.4.2 Visit 2 (Optional: Investigational LFQ Ultrasound Exams (if not already performed)

If the investigational LFQ ultrasound examinations are not performed during the screening and enrollment visit due to Investigator preference or scheduling constraints, they may be conducted during a subsequent visit. This visit must occur within the 8-week window (+ 5 days) specified for all imaging procedures in Section 6.3 above. If subjects are to undergo ultrasound exams during Visit 2, they will be asked to fast (NPO) for at least 6 hours prior to arrival.

If conducted, Visit 2 will consist of the following events:

Table 5: Study Procedures during Optional Visit 2 (LFQ Ultrasound Exams if not already performed)

Procedure	Description
Concomitant Medications /Procedures	A concomitant medications/procedures assessment will be performed to ensure than the subject has not begun taking any prohibited medications (Section 5.2) or undergone any prohibited procedures during the interval between the most recent study visit and the current visit.
Study-Related LFQ Ultrasound Examinations *(if not performed during Visit 1)*	Adherence to the 6-hour NPO request will be verified; any deviations will be noted in the subject's records. The subject will be placed in the supine or lateral decubitus position, depending on which provides the optimal scanning window. The subject's shirt will be lifted or removed and standard ultrasound imaging gel will be applied to the skin in the appropriate region. The EPIQ ultrasound system with the cleared ElastQ™ feature, the investigational LFQ software, and the C5-1 imaging transducer will be used to conduct the abdominal ultrasound exam using standard sonographic techniques. The entire ultrasound exam is expected to last approximately 15 minutes. The subject may be placed in multiple positions during this time to assess various imaging angles. Study staff will monitor for any Adverse Events (AEs) during or after the ultrasound exam and will document any AEs appropriately (see Section 15). The ultrasound exam will then be repeated by a different operator to obtain data on inter-operator variability in the ultrasound biomarker measurements. This second ultrasound exam can occur immediately after the first and must be completed while the subject is still under fasting conditions.
Data Collection and Transmittal	During the study-related ultrasound exams, real-time biomarker measurements will be collected. In addition, DICOM images, cineloops, and raw ultrasound radiofrequency (RF) data may also be collected for offline post-processing by Sponsor personnel. These datasets will be captured and transmitted to the Sponsor using appropriate de-identification procedures and privacy protections via the methods listed in Section 9.3.

6.4.3 Visit 3 (Optional): Study-Related MRI-PDFF Exam (if not already performed)

Some subjects may have had a MRI-PDFF examination performed as part of their clinical standard of care prior to enrollment; in that case, no additional MRI-PDFF examination is required unless the prior examination was conducted more than 8 weeks (+ 5 days) prior to the investigational LFQ ultrasound examinations as specified in Section 6.3 above.

For subjects undergoing MRI-PDFF as a study-related procedure, the MRI-PDFF examination may be combined with any of the other visits as scheduling permits, and therefore there may not be a separate visit required for this procedure. There is no required sequence for the MRI-PDFF examination with respect to the investigational LFQ ultrasound examinations, and it can occur either prior to or after the ultrasound examinations. However, the MRI-PDFF examination must be completed within the 8-week window (+ 5 days) specified for all imaging procedures in Section 6.3.

If a separate visit is conducted for the MRI-PDFF exam, Visit 3 will consist of the following events:

Table 6: Study Procedures during Optional Visit 3 (MRI-PDFF Exam if not already performed)

Procedure	Description
Concomitant Medications /Procedures	A concomitant medications/procedures assessment will be performed to ensure than the subject has not begun taking any prohibited medications (Section 5.2) or undergone any prohibited procedures during the interval between the most recent study visit and the current visit.
Study-Related MRI-PDFF Exam *(if not performed during Visit 1 or 2)*	The subject will undergo a non-contrast abdominal MRI examination using the clinical site's standard PDFF acquisition protocol and procedure. Study staff will monitor for any Adverse Events (AEs) during or after the MRI-PDFF exam and will document any AEs appropriately (see Section 15).
Data Collection and Transmittal	Data from the MRI-PDFF exam, including DICOM images and radiology reports including fat percentage results, will be transmitted to the Sponsor using appropriate de-identification procedures and privacy protections via the methods listed in Section 9.3.

6.4.4 Study Exit

Once the subject has completed the last scheduled imaging procedure (LFQ ultrasound exams or MRI-PDFF exam), he/she will exit from the study. There is no follow-up period for this study, except for any continued follow-up necessary in the event of an unresolved Adverse Event as specified in Section 15.

6.5 *Diagrams of Study Procedures*

6.5.1 Cases where MRI-PDFF is Performed Prior to Enrollment

Figure 2 provides an overview of study procedures per visit for subjects undergoing clinically-scheduled MRI-PDFF prior to enrollment. Subjects in this group will have up to 2 study visits.

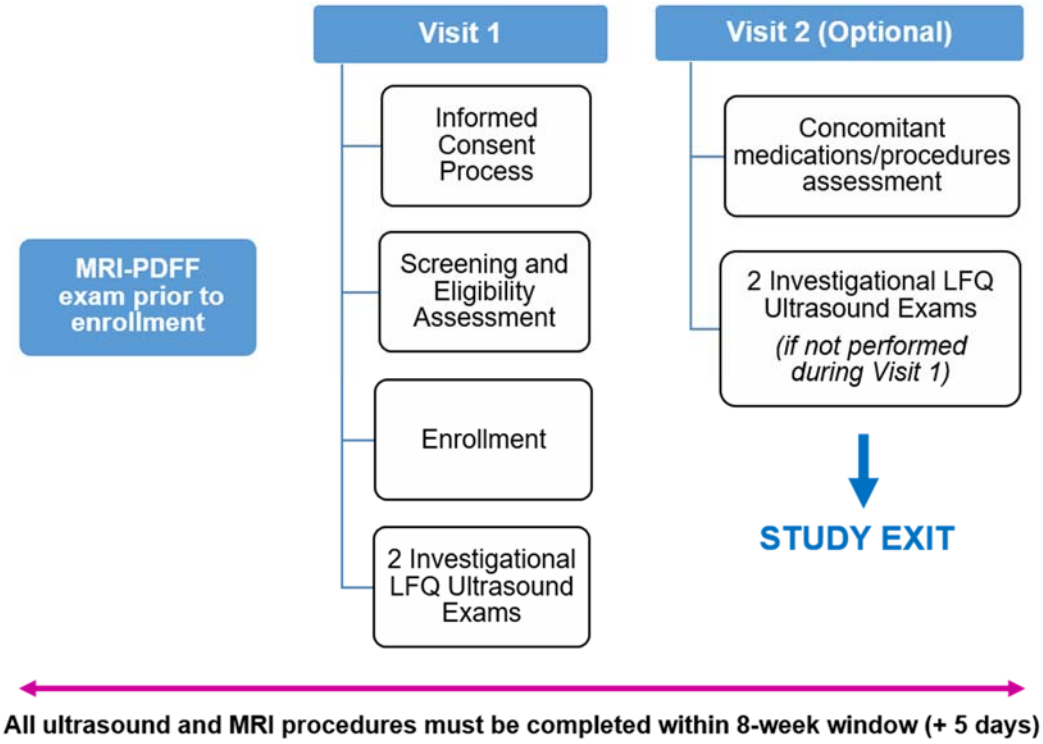

Figure 2. Study diagram for subjects undergoing clinically-scheduled MRI-PDFF prior to study enrollment. Up to two study visits are required, and all LFQ ultrasound and MRI procedures must be completed within an 8-week window (+ 5 days). Both LFQ ultrasound exams will be completed during the same visit.

6.5.2 Cases where MRI-PDFF is Performed as a Study-Related Procedure after Enrollment

Figure 3 provides an overview of study procedures per visit for subjects undergoing MRI-PDFF as a study-related procedure after enrollment. Subjects in this group will have up to 3 study visits.

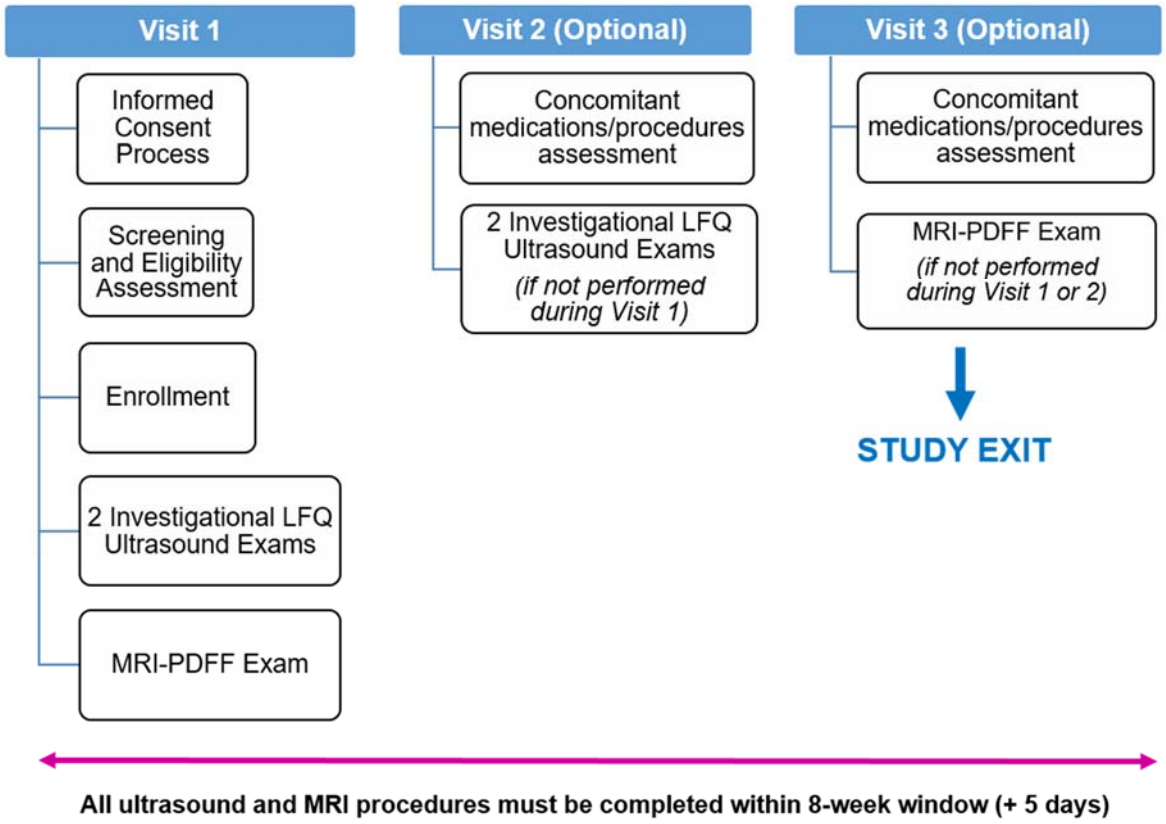

Figure 3. Study diagram for subjects undergoing MRI-PDFF as a study-related procedure after enrollment. Up to three study visits are required, and all LFQ ultrasound and MRI procedures must be completed within an 8-week window (+ 5 days). Both LFQ ultrasound exams will be completed during the same visit. The MRI-PDFF exam can be performed during the same visit as well, or can be scheduled for a different visit.

6.6 *Unscheduled Visits*

All unscheduled visits or procedures occurring during the subject's participation in this study will be recorded in the subject's study record with the following elements noted:

- Date
- Reason for visit/procedure
- Follow-up
- Signature or initials of study staff and date(s)

Any reportable Adverse Events, concomitant medication changes, and/or Clinical Study Protocol deviations will be reported in the subject's study record. Any significant Adverse Events and/or deviations must be reported to the Sponsor upon discovery (see Sections 11.1 and 15.3 for details).

6.7 *Procedures Performed by Sponsor Representatives*

None of the study procedures described above that involve direct interaction with the subject will be completed by Philips personnel; however, offline processing of investigational LFQ ultrasound data will be completed by Philips representatives on an ongoing basis.

6.8 *Types of Data Collected and Shared with Sponsor*

The following types of data may be collected and shared with Philips during the course of this study. All data, regardless of type, will be de-identified before being shared with Philips and will comply with Philips privacy protection policies and HIPAA Privacy Rule requirements as described in Section 9. All records will be codified with a unique study subject identification number and will not contain any Protected Health Information (PHI).

- Ultrasound biomarker measurements for those biomarkers that are measured in real-time during the investigational LFQ ultrasound exam(s)
- Ultrasound biomarker measurements for those biomarkers that are calculated offline after the investigational LFQ ultrasound exam(s)
- Raw ultrasound data (e.g., radiofrequency (RF) data) from investigational LFQ ultrasound exam(s)
- DICOM images and cineloops from the investigational LFQ ultrasound exam(s) and the MRI-PDFF exam
- Subject health record information directly related to liver status, including laboratory reports for bloodwork relevant to liver function, radiology reports from the MRI-PDFF exam including liver fat percentage results, and pathology reports from prior liver biopsy (if available).

7. Data Analysis and Statistical Considerations

7.1 *Plan for Interim Analyses*

Because this is a pilot study, *ad hoc* interim analyses are expected to be conducted as data become available in order to enable prioritization of quantitative ultrasound biomarker development during the course of the study. Interim analyses will be conducted by Philips personnel on an as-needed basis to evaluate ongoing biomarker performance.

7.2 *Analysis Groups*

Separate analysis tiers are planned for the Intention-to-Treat (ITT), Per Protocol (PP), and Per-Protocol with Optimal Data Acquisition (PP-ODA) groups. The term 'ITT' is used herein due to convention, even though no treatment of any sort is being administered during this study. Correlation levels will be assessed between quantitative ultrasound biomarkers and MRI-PDFF fat percentages for the following sub-groups.

7.2.1 Intention-to-Treat Group

This is the full population of 'all-comers' consisting of all enrolled subjects who have any amount of investigational LFQ ultrasound data and MRI-PDFF data available, regardless of the quality of the imaging data received, whether any protocol deviations occurred, or the presence of other confounding effects that may result in outliers. The correlation level between the ultrasound biomarkers and MRI-PDFF fat percentage is expected to be lowest among the full ITT group.

7.2.2 Per-Protocol Group

This is the subset of the full ITT group who underwent all investigational ultrasound procedures in compliance with this protocol, including those who adhered to the NPO restrictions, had no evidence of eligibility deviations at the time of imaging, etc. The PP group may have variations in ultrasound image quality due to different data acquisition conditions that may be present at the time of scanning, including suboptimal scanning windows due to rib impingement, artifacts from subject motion, etc. The correlation level between the ultrasound biomarkers and MRI-PDFF fat percentage is expected to be higher in the PP group than the ITT group.

7.2.3 Per-Protocol with Optimal Data Acquisition Group

This is the subset of the PP group who underwent investigational ultrasound procedures under optimal data acquisition conditions, including those who had optimal scanning windows due to minimal or absent rib shadowing, who had no motion artifacts from breathing, etc. Subjects in this PP-ODA group will be identified by Philips personnel in collaboration with the PIs at each site, upon review of the data. The correlation level between the ultrasound biomarkers and MRI-PDFF fat percentage is expected to be highest in this PP-ODA group.

7.3 *Data Poolability*

Subject data from all clinical sites are intended to be pooled for analysis to broaden demographic representation; however, it is possible that sub-analyses may be conducted in which subjects from each clinical site are evaluated as a cohort if clinically significant variations in standard MRI-PDFF imaging protocols exist among the investigational sites. Also, it is possible that sub-analyses may be conducted depending on subjects' medical histories (e.g., presence of one or more concomitant diseases).

7.4 *Sample Size Considerations*

The primary performance endpoints listed in Section 4.3 (quantitative ultrasound biomarkers) will be evaluated by assessing their correlation with known liver fat percentages reported from MRI-PDFF. The following biomarkers may be assessed for correlation:

- Hepatorenal Index (HRI) (unitless)
- Acoustic attenuation (dB/cm/MHz)
- Nakagami parameter (unitless)
- Tissue viscosity (Pa·s) (or viscosity-related metric)
- Speed of sound (m/s)
- Tissue stiffness (kPa)

Each biomarker's correlation with the fat percentage reported from MRI-PDFF is considered to be an independent variable and will be analyzed independently.

The sample size achieved during this study will affect statistical confidence in the correlation level observed between a given quantitative ultrasound biomarker and the MRI-PDFF-derived fat percentage. For illustrative purposes, Table 7 below shows the effect of various sample sizes on the lower bound of the 95% confidence interval (CI) around two example targeted correlation levels consistent with those observed in preliminary data. In the case of a targeted Pearson's product-moment correlation of 0.75, a sample size of 90 subjects provides a two-sided 95% CI around this targeted correlation with a lower bound of approximately 0.64. If the targeted Pearson's correlation increases to 0.80, this same sample size would result in a two-sided 95% CI with a lower bound of 0.71. Correspondingly, these lower bounds increase with increasing sample size, up to the maximum enrollment of 150 subjects.

Table 7: Lower Bound of 95% Confidence Interval for Targeted Pearson's Correlations

	Targeted Correlation = 0.75	**Targeted Correlation = 0.80**
Sample Size	**Lower Bound of 95% CI**	**Lower Bound of 95% CI**
150	0.670	0.734
140	0.667	0.731
130	0.663	0.728
120	0.659	0.725
110	0.655	0.721
100	0.649	0.716
90	0.643	0.711

If a Pearson's correlation of 0.80 is observed for a given quantitative ultrasound biomarker and MRI-PDFF ground truth in at least 90 subjects, there is >95% confidence that the true correlation exceeds 0.7, which is taken to indicate a technically meaningful association between the two variables.

7.5 *Additional Statistical Analysis Plan*

Additional statistical analysis considerations may be described in a separate Statistical Analysis Plan (SAP) for this study, consistent with ISO 14155:2011 guidance and Philips Ultrasound's internal study management procedures (9060-0623, *Clinical Study Statistical Analysis and Data Management*). This separate SAP may include provisions for sensitivity/specificity analyses to evaluate the investigational LFQ feature's ability to discriminate among various steatosis stages or groupings of stages.

8. Monitoring Plan

8.1 *Overview*

This study will be monitored using a risk-based monitoring approach, consistent with the FDA guidance *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* (2013) and Philips Ultrasound's clinical study monitoring procedures (9060-0588 and 9060-0589). Monitoring will ensure that documents used to originally record subject data (source documents) are maintained, and to verify that transcribed data are accurately reflected on the study electronic Case Report Forms (eCRFs). See the associated Monitoring Plan for the nature, timing and intensity of planned monitoring, based on risks and critical data. It will detail any planned remote monitoring, source data verification, Site Regulatory File review, and Informed Consent Form review, distinguishing between remote and on-site monitoring. It will also specify the monitoring team and required training. The Monitoring Plan will be maintained in the Trial Master File.

8.2 *Source Documentation Access, Subject Privacy, and Subject Confidentiality*

A unique source record will be available for each study subject including completed Informed Consent Forms, other documentation of the consent process, medical history, concomitant medication review, and all records related to use of the investigational device on the subject. See Section 9.1 for a detailed description of source documentation.

Subject study information will remain confidential. Subjects enrolled on study will be assigned a study ID code. All data will then be reported per the unique Subject ID, ensuring all subject identifiers have been redacted before transmission to Sponsor, thus providing the Sponsor a 'coded' data set. Only authorized personnel associated with the conduct and/or review of the study and the resultant data will have access to information that links subject identifiers to the corresponding assigned study code. Documentation of privacy and confidentiality training (e.g., data privacy, data protection laws, HIPAA, etc.), to site study team members will be maintained in the Site Regulatory File (SRF) or a centralized site record, accessible to sponsor and external monitors and/or auditors.

The subject source record as well as other source documentation (e.g., completion of protocol study procedures, procedure findings, essential documents in the Site Regulatory File, copies of completed case report forms, etc.) must be made available for review by Philips or its designees, auditors, IRB/EC, and regulatory authorities. All efforts must be made by all parties involved to ensure protection of subject confidentiality at all times throughout the clinical study. Because of the need for study site(s) to release information to these parties, absolute confidentiality cannot be guaranteed. Disclosure of subject information to personnel other than those permitted by Philips, its designees or representatives, or appropriate regulatory agencies is prohibited.

Study records will be kept in a secure area, protecting subject and overall study confidentiality. The results of this research project may be presented at meetings or in publications; however, subject identity will not be disclosed in such publications.

9. Data Management, Quality Assurance, and Confidentiality Standards

9.1 *Source Documentation, Reporting, and Maintenance*

Source Documentation is the original (first) collection of subject/study data. If source data are captured more than once at different time points, the later collection serves as corroborating source documentation. Source documents must have adequate study and subject identifiers and must be legible.

For this study, source data may be captured manually in hard copy (on paper) as well as directly recorded into electronic case report forms (eCRFs), as described in the Electronic Data Capture System section below, at the time of procedure completion. If source data are entered manually in hard copy form, a blue or black pen should be used. Any eligibility metrics that will be directly recorded in eCRFs will be identified and reported to the Sponsor prior to study start.

Source documentation must be maintained in a secure area. Study-specific source documentation will have limited access to Investigator-delegated study staff.

9.2 *Electronic Data Capture System*

The DATATRAK electronic data capture (EDC) system is a secure, validated, US CFR Part 11 compliant EDC program provided by the Sponsor to facilitate data entry and storage for this study (DATATRAK, Mayfield Heights, OH). It is an internet-based EDC system for reporting clinical data to the Sponsor via electronic Case Report Forms (eCRFs). All subjects who consent to participate will be registered in the EDC system.

Access to the EDC system will be protected by login identification and password. The Sponsor will train delegated Site personnel on procedures for data entry into the web-based system. Following training, delegated staff will be provided ID codes and passwords unique to each team member's delegated study role. They will be trained on Philips guidelines for maintenance of electronic ID codes and passwords. A staff member's ID code/password will never be shared or used by another staff member, in any circumstance. If prior training has already been delivered for other Philips-sponsored studies of similar design, this training may be reinforced via teleconference prior to study commencement as appropriate.

9.3 *Data Reporting to Sponsor*

Subject data will be reported to Philips via electronic Case Report Forms (eCRFs) using the DATATRAK electronic data capture (EDC) system described in Section 9.2. Only staff that have been delegated by the Principal Investigator(s) will be able to enter or make changes to data in the case report forms. Additional anonymized data (DICOM images, cineloops, and raw ultrasound radiofrequency (RF) data) may be captured and transmitted via a qualified third-party image transfer service (AG Mednet, Boston, MA) with which Philips has contracted for this purpose. No central laboratories or radiology services are planned to be used during this study.

9.4 *Data Review, Cleaning, and Query Resolution*

After study data are recorded and submitted to the EDC system, automated edit checks, programmed to ensure the collection of consistent and complete data, may be raised. In addition, after data submission, Philips (or contracted) Clinical Monitors, Statisticians, and/or the Philips Clinical Data Management group may remotely review data listings generated at different time points during the study. Data queries will be generated to resolve any discrepancies or concerns.

Any data transcribed to eCRFs will be verified against source documents by the Sponsor or its designee(s) on a percentage of the subject population, per a risk-based monitoring approach as described in the Monitoring Plan associated with this study and maintained in the Trial Master File. Data queries will be generated to resolve any discrepancies or concerns.

Designees will be trained on the query issue and resolution process. It is the responsibility of the designated personnel at each clinical site to respond to all edits checks and queries generated. Submitted data as well as all modifications to submitted data will be documented by the EDC system and available in audit trails.

9.5 *Data Retention and Duration*

Upon conclusion of the study, after all eCRFs are marked as complete and all discrepancies are resolved, the Principal Investigator will be notified to review and provide electronic signatures. Subsequently, a member of the Philips Clinical Data Management team will lock the database and deactivate the system. The final data set will be transferred to SAS for analysis at Philips.

All study documentation (e.g., source documentation, completed Informed Consent Forms, Site Regulatory File documents, copies of completed eCRFs, etc.) will be securely retained until receipt of written authorization from Philips is given to destroy records. At a minimum, the retention period will be two years after study completion, consistent with 21 CFR 812.140(d). Philips may require that records are maintained for longer than this two year period; if so, the site will be notified accordingly.

9.6 *Study Confidentiality Standards*

This Clinical Study Protocol, its associated methodologies, study devices, study-generated data, and the data management system contain confidential and proprietary information. Release of such information outside the scope of planned study operation is prohibited. All federal and local laws regarding protection of patient confidentiality will be followed, as well as any additional site-specific requirements that may be required.

10. Amendments to the Clinical Study Protocol

Any changes necessary to the Clinical Study Protocol after full execution are documented as protocol amendments. Prior to execution at investigational sites, each protocol amendment must be:

- submitted and approved by the applicable IRB/EC(s)
- agreed to and signed by the Investigator(s)

If the protocol amendment introduces any new information that affects Informed Consent, the Informed Consent Form will also be amended and submitted to the applicable IRB/EC for approval. All records related to protocol amendments will be added to the Site Regulatory File and Trial Master File.

11. Deviations from the Clinical Study Protocol

The Investigator(s) are not allowed to deviate from the Clinical Study Protocol, except for emergency circumstances (see ISO 14155 4.5.4b)).

11.1 *Deviation Recording, Reporting, and Analysis*

Completion of study-related procedures will be source documented. A copy of eCRFs will be provided to study staff to serve as source document templates for documenting procedure completion and findings. Sites may use their own templates for source documentation as well.

Compliance and potential deviations will be assessed by study site designees. At the beginning of each study visit, clinical site personnel will interview subjects for compliance to pre-study visit instructions (if any) and to assess whether any relevant concomitant medications have been taken by subjects that would affect their eligibility (see Section 5.2).

Any deviations from this Study Protocol will be documented upon discovery and reported in the subject's eCRFs. Significant deviations (marked below with an asterisk) need to be reported immediately to the Sponsor (see Section 15.5). Examples of non-compliance, including significant deviations, include but are not limited to:

- failure to obtain informed consent prior to performing any study-related procedures*
- enrollment of ineligible subject*
- failure to complete any study-related procedure*
- usage of prohibited medication or performance of any prohibited procedure during enrollment period (see Section 5.2)
- failure to conduct any study-related procedure within specified time window (see Section 6.3)
- failure to maintain specified fasting time prior to ultrasound examination (see Section 6.4)

** = significant deviation that needs to be reported immediately to the Sponsor per Section 15.5*

11.2 *Deviation Escalation and Notifications*

Site personnel associated with the conduct of this study must report any significant deviations from Good Clinical Practice or significant deviations from this Clinical Study Protocol to the Philips Clinical Study Manager. Any deviations that affect subject's rights, safety and well-being, or the scientific integrity of the clinical study must be reported to the approving IRB/EC and the Sponsor within 3 days.

11.3 *Interventions and Medications Prohibited during Study*

During each subject's enrollment period (the time between when he or she is first enrolled and when all required imaging procedures are completed), usage of any of the medications listed in Section 5.2 is prohibited due to their association with drug-induced hepatic steatosis. Performance of any therapeutic intervention that may affect the liver fat content during the enrollment period is also prohibited as listed in Section 5.2.

While the potential for these confounding events is low due to the short enrollment period of each subject, it is nevertheless critical that the subject does not begin taking any of the prohibited medications or undergo a prohibited procedure until his or her participation has completed. If any such events occur during the subject's enrollment, the subject will need to be withdrawn from the study and a Study Protocol Deviation will need to be reported accordingly.

All other interventions, treatments, and medications that do not affect the subject's ongoing eligibility are allowed during study participation.

11.4 *Corrective and Preventive Actions*

Prior to study initiation at each clinical site, delegated site staff will be trained to the Clinical Study Protocol at a Site Initiation Visit to ensure comprehensive understanding of study procedures and to optimize compliance to the protocol and Good Clinical Practice.

Compliance and proper deviation reporting will be monitored periodically during remote and/or on-site monitoring visits for any required corrective actions, escalations (e.g., significant deviations), and/or notifications. If non-compliance events are observed, corrective actions may include supplemental protocol training and discussions with the Investigator(s) and study staff to implement activities to prevent future recurrence. Ongoing significant non-compliance may result in study discontinuation at the clinical site involved.

12. Investigator and Site Qualifications

Philips must ensure that Investigators selected to conduct this clinical study are appropriately credentialed and experienced in the medical field associated with this study. Toward that end, each Investigator will provide a signed, accurate, non-misleading, and current copy of his or her curriculum vitae to Philips that demonstrates his or her qualifications to conduct this study and, if requested, will provide a list of sub-Investigators or health professionals who are assisting in the conduct of this study and similar documentation of their qualifications.

Persons debarred from conducting or working in clinical studies by any court or regulatory agency will not be allowed to conduct or work on this study. The Investigator will immediately disclose to Philips in writing if any person who is involved in conducting the study is debarred, or to the best of the Investigator's knowledge, if any proceeding for debarment is pending or threatened. The Investigator attests that he or she has not been personally debarred and will not use as an assistant any person who is debarred from participation in clinical studies under any provision of federal law (e.g., 21 CFR § 312.70). If such a debarment proceeding should occur, involving the Investigator or any assistant involved in the study, the Investigator will promptly inform Philips. Further, the Investigator attests that he/she, as well as any other person or entity affiliated with the Investigator or under the Investigator's supervision as part of this study, is not excluded from participation in a Federal Health Care Program as defined in 42 U.S.C. § 1320a.
The Investigator attests that the facilities where he/she will conduct this study have the necessary patient population and resources to properly conduct the study.

13. Product Labelling and Accountability

Access to the study device will be controlled to prevent unauthorized use. Further, the study device will be used only in this clinical study according to the procedures specified in this protocol.

13.1 *Sponsor Responsibilities*

13.1.1 Product Labeling

The Philips EPIQ Ultrasound System with the on-cart LFQ feature is an investigational device. The system will be labeled with an easily seen, clearly marked warning label stating 'CAUTION – Investigational device. Limited by Federal (or United States) laws to investigational use.'

13.1.2 Accountability Documentation

Philips will keep records documenting accountability for the investigational device from shipment to the clinical sites until return or disposal. Records will be maintained in the Trial Master File (TMF). Required information regarding shipping will be documented as specified in the Master Device Accountability Log at each Clinical Site.

13.1.3 Monitoring

Accountability will be monitored by Philips personnel on an ongoing basis via on-site and/or remote monitoring, as designated in the Monitoring Plan for this clinical study. Monitoring will ensure:

- adequate supply of study devices
- proper security of subject records and study devices
- compliance to storage requirements
- usage compliance
- reconciliation

Any discrepancies will be raised with study personnel upon discovery. Discrepancy management and resolution will be documented and filed with the Accountability Log in the Site Regulatory File and Trial Master File.

13.2 *Site Responsibilities*

Upon receipt, product shipments will be inventoried and accountability documented in the provided Product Accountability Log. Once subjects are enrolled, product usage tracking will be documented at the subject level. At the conclusion of the study, all investigational products will be reconciled and accounted for prior to return to the Sponsor.

13.2.1 Accountability Documentation

Study Investigator(s) or authorized designee(s) will keep records documenting study product accountability from receipt until return to the Sponsor. Records will be maintained in the Site Regulatory File (SRF). The following will be documented on the provided Product Accountability Log
Product Receipt by Clinical Site

- Study product names

- Quantities received
- Receipt dates
- Product IDs (e.g., lot or batch numbers, serial numbers and/or unique codes, as applicable)
- Name of person who processed product receipt

Product Usage at Clinical Site

- Device usage dates (by subject IDs)

Product Return to Sponsor

- Study product names
- Quantities returned
- Return dates
- Product IDs (e.g., lot or batch numbers, serial numbers and/or unique codes, as applicable)
- Name of person(s) who reconciled study product

13.2.2 Accountability Reporting

Once received product has been inventoried, a copy of the completed Accountability Log will be provided to the Sponsor for confirmation purposes. Subject-specific product accountability will be reported in the subject's (e)CRFs.

13.2.3 Study Product Return

The Philips EPIQ Ultrasound System, C5-1 imaging transducer(s), and all accessories will be returned at the end of this study. Once all returnable products are reconciled and accounted for on the Accountability Log, they will be returned to Philips using a Philips-specified shipping service per instructions that will be provided at the time of device return.

14. Informed Consent

14.1 *Process for Obtaining Informed Consent*

Study participation is voluntary. In order for potential subjects to decide whether they would like to participate, an informed consent discussion will be conducted according to the process described in ISO 14155: 2011. Potential subjects, and/or their legal representatives, will be given the most current IRB/EC-approved Informed Consent Form to read. They will be provided ample time for review and an opportunity to ask questions about the study. If they agree to participate, they will sign the Informed Consent Form and be given a copy of the signed document for their records. Each of these actions/steps will be documented. Only after informed consent has been obtained may study-related procedures begin.

14.2 *Availability of New Information*

Any new information about the study that may affect a consented subject's decision to be in the study (e.g., changed procedures, safety, etc.), will be communicated in a timely manner. Depending on the nature of the new information, subjects who have completed the study may or may not be informed, documenting the decision and justification as well as any activities for informing completed subjects. Additionally, the approving IRB/EC and/or regulatory authority will also be informed. The currently

approved Informed Consent Form will be updated and submitted to the approving IRB/EC and/or regulatory authority for review and approval. Active subjects will be re-consented, following the above process, with the newly-approved consent form.

14.3 *Inability to Provide Consent*

For this study, eligible subjects must be willing and physically/mentally able to give their informed consent to participate. If potential subjects are unable to provide consent, they may not participate.

15. Safety Events: Definitions, Reporting, and Follow-up

Subject safety will be monitored to detect any product deficiencies or risks from the time of consent until conclusion of the study or, if applicable, resolution of a safety event. This will include monitoring for Adverse Events and Adverse Device Effects, as defined in ISO 14155:2011.

15.1 *Safety Event Definitions*

The following definitions are adopted from ISO 14155:2011:

Adverse Event (AE): Any untoward medial occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device/product.

Serious Adverse Event (SAE): Any Adverse Event that leads to any of the following:

- Death
- Serious deterioration in the health of the subject that results in any of the following:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Fetal distress, fetal death or a congenital abnormality or birth defect

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the study protocol, without serious deterioration in health is not considered a Serious Adverse Event.

Adverse Device Effect (ADE): An Adverse Event related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, installation, or operation, or from any malfunction of the investigational medical device. This definition also includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Device Effect (SADE): An Adverse Device Effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

Unanticipated Adverse Device Effect (UADE): An Adverse Device Effect that does not meet the definition of SADE but which by its nature, incidence, severity, or outcome has not been identified in this Clinical Study Protocol or the current version of the device's Risk Analysis Report.

Unanticipated Serious Adverse Device Effect (USADE): A Serious Adverse Device Effect which by its nature, incidence, severity, or outcome has not been identified in this Clinical Study Protocol or the current version of the device's Risk Analysis Report.

Device Deficiency: Any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device Deficiencies include malfunctions, use errors, and inadequate labeling (including instructions for use).

15.2 *Foreseeable Safety Events*

There are no significant foreseeable safety events associated with this study. As discussed in Section 3.1 above, no significant ADEs are anticipated during this study because the investigational procedure is limited to noninvasive diagnostic ultrasound imaging of the abdomen using the investigational LFQ software. The Philips EPIQ Ultrasound System with investigational LFQ software and the C5-1 imaging transducer have been verified to comply with harmonized safety standards governing all diagnostic ultrasound imaging devices (e.g., IEC 60601-1-2 and IEC 60601-2-37, see Table 3) and therefore pose no additional risk to subjects beyond that associated with any other abdominal ultrasound imaging procedure. Only the following nonserious ADEs are therefore anticipated to occur:

- potential discomfort during the ultrasound examination due to body positioning
- potential discomfort during the ultrasound examination due to pressure exerted by the ultrasound transducer when it is pressed against the abdominal skin.

15.3 *Safety Event Reporting*

All Adverse Events, Adverse Device Effects, and Device Deficiencies will be collected at the time of reporting by the subject or detection by the Investigator. They will be source documented and maintained as part of the study record and reported in the (e)CRFs.

An assessment of the following metrics will be made by the Investigator for each Adverse Event:

- severity,
- seriousness,
- anticipated or unanticipated,
- relation to study participation or investigational device,
- action taken,
- outcome (resolution, sequelae, etc.)

The following will be reported in the eCRFs for each Device Deficiency that occurs:

- device ID,
- device event description,
- date of deficiency,
- whether the deficiency caused or could have caused an Adverse Device Effect to occur.

The disposition of all safety events, assignment of relatedness, and determination of seriousness is the responsibility of the Investigator.

The following adverse changes from baseline require reporting to Philips:

- any Unanticipated Adverse Device Effect (UADE) that is either possibly related or related to the investigational device and which is not specified in Section 15.2 above.
- any Serious Adverse Device Effect
- any Serious Adverse Event, whether or not it is related to the investigational device

The following Device Deficiencies require reporting to Philips:

- All Device Deficiencies related to the quality, durability, reliability, safety, or performance of the investigational medical device, including user or use errors and equipment failures.
- Any Device Deficiency that could have potentially led to a SADE if:
    - suitable action had not been taken,
    - timely intervention had not been made, or
    - circumstances had been less fortunate.

Any other Adverse Event or Device Deficiency that does not meet any of the above criteria does not require reporting to the Sponsor, unless the approving IRB/EC requires reporting. An Investigator may always opt to report any safety event even if it does not meet any of the above criteria. Examples of Adverse Events that do not need to be reported to Philips include instances such as:

- Broken bone from a car accident
- A seasonal head cold
- Headache, if it isn't at least possibly related to the investigational device or study procedure
- Infection, if it isn't at least possibly related to the investigational device or study procedure

All Adverse Events will be reported in the final Clinical Study Report for this study.

15.4 *Concomitant Medications*

At Visit 1, baseline concomitant medications will be source documented and reviewed by the Investigator or clinical staff against the eligibility criteria. Only changes to baseline medications (i.e., changes to amount, frequency, etc.) or the addition of new medications require reporting in the eCRFs. Changes in baseline medications will be reviewed with the Investigator to determine whether they may constitute Adverse Events or safety concerns.

15.5 *Expedited Reporting Requirements*

Any SAE, SADE, or Device Deficiency that could have led to a SADE must be immediately reported to the Philips Clinical Study Manager within 24 hours of the Investigator learning of the event.

Promptly following such a report, the Investigator will provide a detailed written report of the event. Additionally, upon Philips' request, the Investigator will provide any additional information related to the safety reporting of a particular event. The Investigator is responsible for reporting the event to the approving IRB/EC as dictated by the guidelines defined by the IRB/EC and, if applicable, regulatory authorities. Additionally, the Investigator will report to regulatory authorities as required by national regulations.

15.6 *Safety Monitoring Time Period*

Subject safety will be monitored to detect any changes in health status present at enrollment. Subject safety will be monitored from the time each subject signs the Informed Consent Form until conclusion of study participation. An Adverse Event that is present at the time of study completion is to be designated as ongoing on the eCRF (e.g., 'Recovering/Resolving' or 'Not Recovered/Not Resolved'). However, all ongoing events that require expedited reporting, as described in Section 15.5, or other important medical findings in the opinion of the Investigator, are to be followed until resolution.

15.7 *Data Monitoring Committee*

There is no Data Monitoring Committee planned for this pilot study.

15.8 *Sponsor Monitoring and Reporting of Safety Events*

Philips will monitor the Investigator's documentation, assessment, and reporting of all safety events occurring during this clinical study. The timing and frequency of safety monitoring will be outlined in the associated Monitoring Plan. Subsequent to monitoring of site records and reports, Philips will review and classify Adverse Events and ensure ongoing safety evaluation of the clinical study as described in ISO 14155:2011. In cases of disagreements with Investigator assessments, Philips will communicate both opinions to concerned parties (IRB/EC and regulatory authorities as applicable).

Philips will inform all Investigators in writing of all SADEs at all clinical sites that have been reported to Philips and ensure reporting to their IRBs/ECs, if required by national regulations or the IRB/EC, whichever is more stringent. Philips will ensure that all IRBs/ECs and the applicable regulatory authorities are informed of significant new information about the clinical study.

Lastly, in case of SADEs and Device Deficiencies that could have led to SADEs, Philips will determine whether the device's Risk Management File needs to updated and will assess whether corrective or preventive action is required.

15.9 *Methods for Assessing Safety Events*

Adverse Events and Adverse Device Effects may be identified through direct observation of the subject by the Investigator or other clinical staff during health assessments or physical examinations, in response to open-ended questioning by the Investigator or other clinical staff during study visits, or by unsolicited reports from subjects themselves.

16. Vulnerable Populations

According to ISO 14155:2011, a vulnerable subject is an individual whose willingness to volunteer in a clinical study could be unduly influenced by the expectation, whether justified or not, of benefits

associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. This study will not enroll participants from any identified vulnerable population.

17. Suspension or Premature Termination of the Clinical Study

This clinical study may be terminated by Philips immediately upon notice to the Investigator if any of the following conditions occur:

- Authorization and approval to conduct the study is withdrawn by any authorized regulatory agency or IRB or the study is placed on clinical hold.
- New preclinical or clinical data from this or other studies emerge which supports early termination.
- Any Adverse Device Effect emerges in this or other studies that is of such magnitude or incidence, in the opinion of Philips or one or more Investigators, to support termination.
- Philips may also terminate the study for any internal business reasons at any time, at its sole discretion.

In addition, participation at an individual clinical site may be terminated in cases of repeated or ongoing non-compliance with this clinical study protocol or ethical standards specified by Good Clinical Practice (e.g., ISO 14155:2011).

In the event of suspension or premature termination of this clinical study for any of the reasons specified above, no follow-up of study subjects is required unless there is an ongoing Adverse Device Effect that has not resolved at the time of study suspension or termination. In that case, the affected subject will be followed until Adverse Device Effect resolution is documented.

18. Publication Policy

The results of this clinical study may be submitted for publication to clinical or medical journals or to congresses or conferences for podium presentations. The rights for publication of results from this study remain with Philips. The Investigator must request permission from Philips prior to initiating any publication. Permission must be requested and received in writing. Review and approval by Philips of any data, abstract, or manuscript is required. Philips reserves the right to delay publication to review the presentation of study methodology, data collection, data analysis, interpretation of data, proprietary information or patented technology. A request for delay and the reason(s) will be communicated by Philips to the Investigator in writing. Philips ultimately reserves the right to deny any request to publish.

19. Registration on Publically-Accessible Clinical Study Registry

This clinical study does not meet the criteria to be considered an “Applicable Clinical Trial” (ACT) under 42 CFR 11.22(b); therefore, there is no mandatory requirement to register this study on the publically-accessible federal clinical trial registry maintained by the National Institutes of Health, *ClinicalTrials.gov*.

However, the International Committee of Medical Journal Editors (ICMJE), which represents many academic and clinical journals that may be considered for publication of results generated during this study, typically requires prospective clinical study registration as a condition of publication. Because Philips or the Investigator(s) may pursue publication of results from this study, Philips intends to register this study on *ClinicalTrials.gov* and submit results to the registry upon study completion. Philips Ultrasound’s study registration procedure (9020-0542, *Registration and Disclosure of Clinical Studies*)

will be followed to document justification for this registration decision. Per federal regulations, study registration will be completed within 21 days of first subject enrollment in this study.

20. Statements of Compliance

The ethical principles for the treatment of human subjects in this clinical study have their origin in the Declaration of Helsinki. This study will be conducted according to the IRB/EC-approved Clinical Study Protocol, any other additional stipulations imposed by the IRB/EC as a condition of approval, and all national regulatory requirements in the United States. This study will also be conducted in compliance with Good Clinical Practice as described in ISO 14155:2011 – *Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice.* This Clinical Study Protocol complies with the content requirements of ISO 14155:2011.

21. Referenced Documents

The following Philips Ultrasound Clinical Affairs procedures are referenced in this protocol.

Document ID	Document Title
9060-0617	Clinical Study Protocol Development and Approval Procedure
9060-0623	Clinical Study Statistical Analysis and Data Management
9020-0542	Registration and Disclosure of Clinical Studies
9060-0588	Clinical Study Monitoring Global Procedure
9060-0589	Clinical Study Monitoring Plan Procedure

22. Investigator Agreement

I agree to conduct this study as specified in this Clinical Study Protocol in accordance with the Sponsor's guidelines, other applicable FDA regulations, Good Clinical Practice, and any conditions of approval imposed by the reviewing IRB/EC. The Sponsor's guidelines include, but are not limited to, the Investigator performing the following duties:

- Submit this Clinical Study Protocol and the Informed Consent Form to an IRB/EC and ensure approval from the IRB/EC is secured prior to initiating the study.
- Ensure that properly executed written informed consent is obtained from each subject prior to the use of any study device or performance of any study-related procedures.
- Provide Philips with a current curriculum vitae and documentation of current medical licensure.
- Provide comprehensive financial disclosure information to allow Philips to make an accurate disclosure statement as required under 21 CFR Part 54 for the course of the investigation and for up to one year after its completion.
- Provide supervision of and restricted access to all investigational study devices used with human subjects.
- Permit Philips and/or regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures subject confidentiality. If this study is to be inspected by a regulatory agency, Philips is to be notified as soon as possible.
- Submit any proposed change in or significant deviation from this Clinical Study Protocol to the IRB/EC using a signed formal amendment document prepared by the Sponsor. Any proposed changes or deviations from this Clinical Study Protocol require that the Informed Consent Form also reflects such changes or deviations and that the revised Informed Consent Form be approved by an IRB/EC.
- Document and report any individual Clinical Study Protocol deviations and violations and provide full explanations of such deviations and/or violations.
- Submit reports of Adverse Events and other safety-related information to the Sponsor and IRB/EC as outlined in this Clinical Study Protocol.
- If applicable, submit timely progress reports to the IRB/EC and Sponsor at appropriate intervals on a schedule determined by the IRB/EC or Sponsor.
- Record keeping: Maintain adequate and accurate records for each subject enrolled to document completion of all study procedures, related observations, and other key data (such as safety, compliance, and product accountability) pertinent to the study. The investigator must maintain these records for a period as specified by Philips following completion of the study.

I agree that all information provided to me by the Sponsor including pre-clinical data, study protocols, electronic databases, CRFs, and verbal and written information will be kept strictly confidential and confined to the clinical personnel involved in conduct of the study. It is recognized that this information may be related in confidence to the IRB/EC. I also understand that reports or information about the study or its progress will not be provided to anyone not involved in the trial other than the Sponsor or other legally constituted authority.

_____ _____

Investigator's Signature **Date**

_____ _____

Investigator's Printed Name **Investigator's Institution**

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