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Abbreviations and Definitions

BMD	bone mineral density
CD	compact disc
DICOM	Digital Imaging and Communications in Medicine—standard method for transmitting medical images and associated information originated by the American College of Radiology and National Electrical Manufacturers Assoc.
DTF	Data Transmittal Form
DVD	digital video disc
DXA	dual-energy x-ray absorptiometry
GCP	Good Clinical Practice
GE	General Electric
HIPAA	Health Insurance Portability and Accountability Act
Hz	Hertz
IA	interim analysis
ICON	ICON Medical Imaging
IP	in-phase
KHz	kilohertz
kPa	kilopascals
mg	milligram
MINFULL	minimum full
mm	millimeter
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging-proton density fat fraction
ms	millisecond
NA	not applicable
NASH	nonalcoholic steatohepatitis
NORM	normalization filter
PDF	Portable Document Format
PDFF	proton density fat fraction
Px	pixel

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RF	radio frequency
ROI	region of interest
SENSE	Sensitivity Encoding
SFTP	Secure File Transfer Protocol
SIV	Site Initiation Visit
S/I	superior/inferior
SQUARE	Site Query Assessment & Resolution Environment
TE	echo time
TR	repetition time

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1 Overview

1.1 Purpose

ICON's Medical Imaging group (ICON) has published this Imaging Manual to instruct study imaging centers (sites) in the following areas:

- Protocol-specific image acquisition requirements
- Image data transfer instructions and the associated documentation (Imaging Data Transmittal Forms [DTFs])
- Image data submission and archiving instructions
- Query resolution process for any clerical discrepancies and/or non-compliance to the imaging protocol as described within this Imaging Manual.

Your site will receive an electronic copy of this Imaging Manual, as well as an ICON Study Team Contact Information list, as a Portable Document Format (PDF) email attachment. The study team contact list may be updated during the course of the study if required.

Please note that reading this Imaging Manual is not a substitute for the formal training of site personnel provided by ICON.

1.2 Study Design

This is a multicenter, double-blind, randomized, placebo-controlled study. Patients who qualify for study inclusion will be randomized in a 1:1:1 manner to receive MGL-3196 100 mg, MGL-3196 80 mg, or matching placebo given orally once daily in the morning for up to 54 months. The randomization will be stratified by Baseline type-2 diabetes status (presence/absence) and fibrosis stage (1, 2, or 3). There will be liver biopsies for all patients at Screening, 52 weeks, and 54 months after starting treatment.

There will be a sub-set of sites and subjects performing Magnetic Resonance Elastography (MRE) for the study. Sites must confirm site capability and agreement to perform MREs for the study within the site questionnaire distributed by ICON.

There will be a Week 52 Primary Analysis to assess NASH Resolution Response (resolution of NASH associated with an at least 2-point reduction in NAS and without worsening of fibrosis).

1.3 Imaging Requirements

1.3.1 Prior to obtaining and submitting magnetic resonance imaging-proton density fat fraction (MRI-PDFF) sequences and MRE sequences (if

applicable) for any screening scans or enrolled subjects, acquire phantom scans (as outlined in Section 2) and submit them to ICON for acceptance. Each magnet used for the Madrigal study must be approved.

1.3.2 Acquire and submit Lumbar Spine and Hip dual-energy x-ray absorptiometry (DXA) according to the instructions outlined in this section. Acquire images using the same DXA machine, scan mode based on subject's weight and size, and technique at all imaging visits for a given subject.

1.3.3 If the MRI phantom scans are acceptable, your site will receive approval from ICON to allow scanning subjects for the study.

1.3.4 Submit MRI-PDFF screening scans to ICON to confirm that a subject is eligible to enroll in the study, and that the scanning technique is adequate. ICON will notify your site of the screening results and any imaging areas that need to be addressed.

1.3.5 Acquire and submit the MRI and MRE (if applicable) sequences according to the image acquisition schedule in Table 1.

1.3.6 Use consistent acquisition parameters, subject positioning, and plane orientations throughout the study.

Table 1: MRE and MRI-PDFF Acquisition Schedule

Imaging Visits	Descriptions
Screening	Within 56 days prior to the first dose of study drug (ie, up to -8 wk.)
Treatment Period	Week 16 (+/- 3 days), Week 52 (-10 days), and Month 54 (-10 days)
Early Termination	Only performed if Early Termination is within the first year of the study; (i.e., patients who completed a Week 52 MRI-PDFF and MRE do not need to be re-assessed at Early Termination); Imaging should be performed before the biopsy and may be up to 10 days before the biopsy.

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Table 2: DXA Acquisition Schedule

Imaging Visits	Descriptions
Screening	Within 56 days prior to the first dose of study drug (ie, up to -8 wk.) and up to 7 days post randomization date
Treatment Period	Week 52 (-10 days) and Month 54 (-10 days)
Early Termination	Upon early termination from study

1.4 Submission Requirements

1.4.1 The preferred method for securely transmitting study images and the DTF from your site to ICON is the web-based software application called AG Mednet (Refer to Section 9.3). Please note that all MRI-PDFF, MRE and on study DXA data should be submitted via AG Mednet.

1.4.2 If the use of AG Mednet is not possible, the use of Secure File Transfer Protocol (SFTP) is encouraged to transfer image data electronically to ICON. SFTP is a network protocol that provides file access, file transfer, and file management functionalities over any reliable data stream (Refer to Section 9.4).

1.4.3 If your site is unable to transfer image data electronically, the use of certified courier is acceptable (Refer to Section 9.5). Courier air bills and media labels will be provided upon request.

1.4.4 DXA Phantom plat reports are required to be submitted via the Site Query Assessment & Resolution Environment (SQUARE; Refer to Section 9.7).

1.5 Subject Confidentiality Requirements in Image Submission

Image data submitted via AG Mednet will automatically undergo de-identification of subject information as the data are uploaded to the system.

Note: DXA will require the subject's **month and year of birth** (but not the actual day of birth), as well as the subject's gender, height, weight and ethnicity to enable calculation of the required Z-score and analysis. Submit the actual scan date; not an anonymized date.

For submissions via SFTP or courier, follow your local privacy practices to de-identify (ie, redact) all subject information (name, medical record number, etc.) prior to submitting images to ICON. Upon receipt, ICON will verify that this information has been completely redacted.

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2 MRI-PDFF and MRE Phantom Data Acquisition and Submission

Prior to your Site Initiation Visit (SIV) or acquiring screening scans for this study, acquire phantom scans as outlined below and submit them to ICON for review and approval. Additionally, if a scanner has a major upgrade, a new phantom may be required. Please contact ICON when a scanner is upgraded for guidance.

2.1 Phantom Procedure

The purpose of the phantom scan is to ensure that the required sequences and scan parameters can be acquired on the scanner that will be designated for the Madrigal study. This MRI can be obtained from a volunteer or patient scanned for prior study, within the last 3 months, subject to the guidelines of the site's Institutional Review Board. If that is not possible, please scan with the phantom utilized for routine site QA/QC and ensure to scan MRE sequence using driver set at 60 Hz.

Please note that the use of a water bottle for phantom acquisition is acceptable. If the phantom scan is performed on an inert phantom, the MRE should be performed as though on a human, so please ensure the paddle is attached and turned on. The phantom will be assessed for wave transmission and will not be passes if evidence of wave transmission is not demonstrated.

2.1.1 Acquire phantom scans

Perform the scans according to the sequences listed in Table 3 and the parameters listed in the tables for the appropriate scanner strength and brand in Section 5.1. Submit the phantom scans to ICON with a completed Phantom DTF. Volunteer scans or prior studies that are being used for phantom submission should also be submitted with a Phantom DTF. If using a volunteer for the scan, please ensure all identifying information is anonymized.

Table 3: Phantom Scans Protocol

3-plane localizer
Coronal SSFSE
Axial SSFSE
Multi-echo (ME) with one 6-echo sequence
Axial 3D T1w GRE
Magnetic resonance elastography (MRE) (if applicable for your site)

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2.1.2 Submit the phantom scans to ICON with a completed Phantom DTF

Refer to Section 6 of this Imaging Manual for information on DTF completion and submission.

2.2 Results Notification

2.2.1 ICON Imaging Specialists in collaboration with the Bashir Lab for Liver Imaging Research at Duke University will review the image data to confirm the following:

- Images are free of artifacts that could prevent accurate image interpretation (eg, motion, wrap, etc.)
- All sequences and scan parameters for the Phantom data were followed according to the requirements in Table 3

2.2.2 Your site will receive an email notification regarding the phantom scan review within 5 business days of receipt of image data at ICON.

- If phantom/test scan is approved – retain the approval email in your study records.
- If phantom/test scan is not approved – ICON will provide recommendations for a re-scan. You must re-acquire and submit a second phantom for review.

2.2.3 ICON will notify qualifying sites that the scanner has been approved for image acquisition in this study.

- If your site does not qualify, an ICON Imaging Specialist will contact the site representative to discuss the issue(s) found.
- If equipment or technique is inadequate, the Imaging Specialist will work with your site to resolve the error and bring your site's scanner into compliance.
- If compliance cannot be met, the scanner cannot be used to scan subjects participating in this study.
- For image quality issues, the Imaging Specialist will provide sites with proper guidance for optimizing the imaging procedure to improve image quality.

2.2.4 Once the phantom scans are approved, the same scanner and scan parameters must be used for all scans performed throughout the study. Store the MRI and MRE (if applicable) protocol parameters in your approved scanner.

3 Scan Submission and Confirmation of Eligibility

3.1 Requirements

All imaging data collected at Baseline must be submitted to ICON **within 24 hours of acquisition.** All subsequent timepoints should be submitted within 3 days of acquisition.

Sites will be notified by ICON if submitted scans are of poor quality and not able to be analyzed. In such cases subjects should have repeat scans resubmitted to ICON as soon as possible and not more than 14 days of the original scan. (Note that sponsor approval is required prior to repeat scanning if the repeat scan is to be performed outside of the 14-day window at any timepoint.) Be sure to check the re-scan box on the DTF.

Before randomizing a subject into the MGL-3196-11 study, it must be confirmed that the subject meets the following radiological inclusion criteria:

- Baseline MRI-PDFF with ≥ 8 % steatosis

3.2 Notification of Eligibility Results

ICON Imaging Specialists and the Bashir Lab for Liver Imaging Research at Duke University will review the image data to confirm the adequacy of the imaging quality and radiologic eligibility according to the protocol inclusion criteria.

- Your site will receive email notification within 3 business days from receipt of query free data indicating the MRI-PDFF value for the screened subject. Provide these results to the principal investigator and retain a copy of the email in your study records.
- If the imaging quality of the screening scan is deemed to be inadequate ICON may recommend a re-scan, in which case acquisition and submission of a second set of screening scans will be requested. Please see Section 3.1 for policy on re-scans.

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4 MRI Examination Protocol

Prior to undergoing MRI, patients should complete a safety assessment. Patients should be dressed in MRI-compatible clothing and empty their bladders prior to MRI. Breathing instructions should be explained to the patient's satisfaction prior to MRI. The patient should be positioned supine with pillows/blankets etc. in order to maintain comfort for the examination.

The MRI pulse sequences should be performed in the order below, although it is permissible to reorder or repeat sequences as the needs of the individual patient and examination dictate (for example in order to obtain adequate coverage or rescan due to motion). All sequences should be obtained using at least one set of anterior and posterior phased array coils. For the MRE sequence (if applicable), the MRE driver should be positioned appropriately relative to the phased array coil. For patient comfort, the MRE driver and associated apparatus may be removed while other pulse sequences are obtained.

4.1 General Sequence Guidelines

All pulse sequences should be acquired with respiration suspended at end-inspiration. The field-of-view should be prescribed in order to include the entire peritoneal cavity and abdominal wall on every image, with no phase wrap; partial phase field-of-views are allowed. For sequences that are repeated (e.g. multi-echo fat quant to ensure full liver coverage), number the sequences sequentially (e.g. Multi-echo fat quant 1, Multi-echo fat quant 2, etc.). No fat suppression should be used for any of the pulse sequences. Please do NOT use any in-plane interpolation techniques. Partial Fourier/partial NEX is allowed. For all pulse sequences, parallel acceleration factors up to 2 are allowed.

MRI Scan Protocol

- 3-plane localizer
- Coronal SSFSE liver
- Axial SSFSE liver
- Multi-echo fat quant
- 3D T1w GRE
- MR elastography

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Table 4: Specific Pulse Sequence Parameters

Sequence Name	Plane	Coverage	Flip Angle (°)	TR (ms)	TE (ms)	Base Matrix	Slice Thickness (Gap)
Coronal SSFSE liver	Coronal	Whole liver	90	Min	Min	256 x 128-192	8 (0)
Axial SSFSE liver	Axial	Whole liver	90	Min	Min	256 x 128-192	10 (0)
Multi-echo fat quant	Axial	Whole liver	10-15	175	Six TEs	192 x 96	10 (0)
3D T1w GRE	Axial	Abdomen and Pelvis	10-15	Min TR	Min TE	256 x 192	5 (0)

- Hyperechoes/variable flip angles for reduction of the specific adsorption rate are allowed on SSFSE sequences.

- Multi-echo fat quant sequences must include at least one slice above the liver and at least one slice below the liver. Pulse sequences should be performed in 2D mode without fat suppression:

    - Siemens systems: FLASH sequence (fl2d6)
    - GE systems: StarMap is preferred; multi-echo fgre or mgre sequences are acceptable if StarMap is not available (MERGE)
    - Philips systems: multi-echo Fast Field Echo sequence (mFFE)

    - Multi-echo fat quant

        - At 3T: 10 degrees

        - At 1.5T: 15 degrees

- Multi-echo fat quant - Six echo times:

    At 3T: TEs = 1.19, 2.38, 3.57, 4.76, 5.95, and 7.14 ms.

    At 1.5T: TEs = 2.38, 4.76, 7.14, 9.52, 11.9, and 14.28 ms.

Note that it may not be possible to precisely match the above echo times, particularly with the StarMap sequence. After setting up the rest of the sequence parameters, the receiver bandwidth should be manipulated to provide a range of six evenly spaced echo times between 0-8 ms at 3T, or 0-16 ms at 1.5T.

4.2 Other Technical Guidelines

For the **Coronal and Axial SSFSE liver** sequences:

- Ensure that the entire liver is imaged. If multiple series are needed to cover the liver, ensure at least 2 cm of overlap between each series.
- For the coronal sequences, ensure that at least one image is obtained in front of the liver, and at least one is obtained behind the liver
- For the axial sequences, ensure that at least one image is obtained above the liver, and at least one is obtained below the liver.

For the **Multi-echo fat quant** sequence(s):

- Ensure that the entire liver is imaged. If multiple series are needed to cover the liver, ensure at least 2 cm of overlap between each series.
- Ensure that at least one image is obtained above the liver, and at least one is obtained below the liver.

For the **3D T1w GRE** sequences(s):

- Ensure that the entire abdomen and pelvis is imaged. Do not use FatSat. If phased array coils are not integrated into MR table, and the subject would need to be re-positioned for pelvic coil coverage, the pelvis may be acquired without a coil (using the inherent magnet coil). Parallel imaging would need to be turned off and scan would be done as free breathing.

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5 MR Elastography Pulse Sequence Parameters - Liver

5.1 MRE Scanner Parameters

For MR elastography, please use the vendor-supplied pulse sequence to obtain four slices of 8-10 mm thickness with a 5-10 mm gap through the thickest portions of the right hepatic lobe. Set the shear wave frequency to 60 Hz. Submit source phase and magnitude images.

Generate and submit the grayscale Stiffness Maps with 95% confidence intervals. Submit original wave images and confidence maps. Do not place ROIs on maps. PHI must be removed from all images. DICOM tags (0028, 1052) Rescale Intercept and (0028, 1053) Rescale Slope must be present in DICOM header. Submit source phase and magnitude images.

Table 5: MRE Pulse Sequence Parameters

Plane	Coverage	Shear Wave Frequency	Thickness	Gap	Number of slices
Axial	Thickest portion of right hepatic lobe	60 Hz	8-10 mm	5-10 mm	4

- When acquiring the MRE images for a subject, use the same sequence and same scanner for both MR visits
- Ensure that the passive driver is correctly positioned and secured over the liver.
- Ensure that a representative sample through the thickest portion of the right hepatic lobe is imaged. All four image levels of the MRE acquisition should pass through a substantial portion of the liver.
- Review the confidence maps generated by the MRI system to ensure that at least a 5x5 cm region of the liver on at least two slices is contained within the > 95% confidence region (no cross-hatching on the imaging). If such no such regions were generated, please adjust the system as appropriate and repeat the acquisition.
- For the subsequent examinations after the baseline MRI, please ensure that the same portion of the liver is prescribed as was imaged on the baseline examination.

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6 DXA Lumbar Spine and Hip Regions Requirements

ICON only accepts data files from Hologic and GE DXA scanners. Acquire images using the same DXA machine, scan mode based on subject's weight and size, and technique at all imaging visits for a given subject.

A brief image analysis should be performed by the operator immediately after scan acquisition (with subject still in the room) to ensure accurate scan parameters were used. Include comments on the DTF for sub-optimal or missing scans.

Submit the actual DXA image files to ICON. Submit the native DXA files – **not DICOM or other formats**.

Note: For DXA, follow the example below regarding on-site anonymization. However, maintain the date of birth to perform the required Z-scores:

- Protocol/Study number = Site number
- Protocol Subject number = Site/subject number
- Ethnicity: Correct Ethnicity
- Subject Date of Birth: MM/YYYY

  (Data files must reflect correct subject's MM/YYYY)
- Scan Mode: Hologic=Array/GE= default
- Scan date: Must record actual scan date. Do not de-idendify the scan date
- Height and Weight: Accurate values are required for correct analysis.

Actual scan date must be recorded on the data files

6.1 Lumbar Spine Region for BMD

For this study, all patient will have the spine scanned in the supine position to ensure the most comfort for the patient. In an effort to standardize how the spine scans will be obtained, place the positioning block under patients' legs with hands down at the side per manufacturer's guidelines.

Follow up scans are required to be consistent with baseline scan.

- Same anatomical regions in the same position
- Use the same scan mode (Hologic =Array/GE= default)

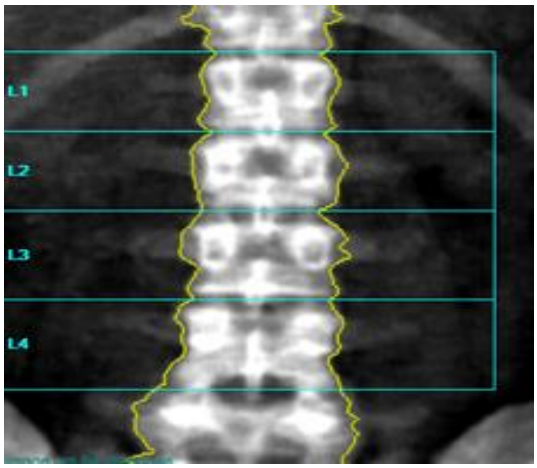
Note: Use the comparison option to match the ROI's to the baseline scan.

Lumbar Spine Positioning

- The spine is centered in scan window with even amounts for soft tissue on each side.

- Anatomy should include at least 1 inch below iliac crest and extend to include mid T-12.
- Ensure all L1-L4 Vertebra are visualized in the scan window for analysis.
- Ensure correct scan mode is being utilized for optimal image.
- It is recommended to review the scan prior to having the patient move from the table. If incorrect positioning is seen Figure 1, please rescan the patient.

Figure 1: Lumbar Spine Analysis



6.2 Hip Region for BMD

For this study, all patients will have the hip scanned in the supine position to ensure the most comfort for the patient. In an effort to standardize how the Hip scans will be obtained, place the manufacturer's positioning device per manufacturer's guidelines.

Follow up scans are required to be consistent with baseline scan.

- Same side hip(Left preferred)
- Same anatomical regions in the same position
- Use the same scan mode (Hologic =Array/GE= default)

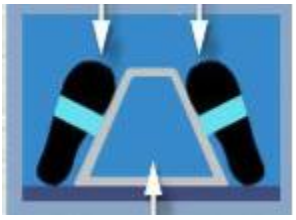
Note: Use the comparison option to match the ROI's to the baseline scan.

Subject Positioning:

- Subject is supine and centered on the table.
- Ensure the legs are flat with feet rotated internally at 15-25 degrees using manufacturer's leg positioning device. (Figure 2).

Note: A small or missing lesser trochanter on the scan image indicates proper hip rotation.

Figure 2: Subject Positioning



- Position the Laser light approximately 7-8-cm (3 inches) below the greater trochanter and 2.5 cm (1 inch) medial to the femoral shaft.
- Entire Femoral Head, greater trochanter and the proximal end of the femoral shaft at least 2.5 cm (1 inch) below the lesser trochanter is visible in the scan window.
- It is important to stress that the entire leg should be rotated not just the foot or lower leg.

  It is recommended to review the scan prior to having the patient move from the table. If incorrect positioning is seen, please rescan the patient.

ROI Positioning

Figure 3: Hologic ROI Positioning

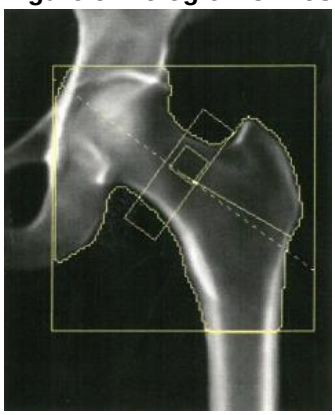
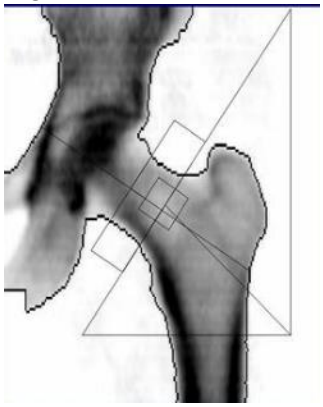


Figure 4: GE ROI Positioning



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7 DXA Phantom Requirements

Submission of DXA phantom data to ICON is not required for the study. However, ICON recommends the use of the Hologic Spine phantom for Hologic DXA scanners or the Black QA Phantom from GE Lunar for phantom acquisition at your site.

Phantom measurements should be performed every day there is a study subject and at least 3 times a week even if the scanner is not being used for subject scans.

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8 Imaging Data Transmittal Forms

Imaging DTFs are required for all MRI and DXA on study data submissions and data resubmission. Use a single DTF with information for only **one subject at only one modality scan date**.

DTFs are treated as source documents; source documents are auditable by regulatory authorities and must be maintained by the site.

8.1 Submissions via AG Mednet

Complete the electronic DTF when you upload image data to AG Mednet. The system will guide you through each required field of the DTF. Refer to Section 9.3 for additional information on the use of AG Mednet.

8.1.1 Complete the required fields carefully in English. Required fields are denoted with a **red** border. The recorded information must be accurate.

8.1.2 Click on the “Save” button to save the file to the AG Mednet system.

8.1.3 Upon successful transfer, you will receive an auto-notification email with a PDF attachment of the completed DTF. Retain the PDF copy of the DTF in the regulatory study files at your site.

8.2 Submissions via SFTP or Courier

Submissions via SFTP or courier require the use of the hard copy version of the DTF that is provided in the Appendix (Section 12 of this Imaging Manual).

When submitting images via SFTP or courier, a separate DTF will be used for the phantom scans and subject scan images:

- PHANTOM DTF (for submission of phantom scans)
- IMAGING DTF (for all subject scan submissions)

8.2.1 Print the page from Section 12 of this Imaging Manual that contains the appropriate blank DTFs.

8.2.2 Complete the correct DTF carefully in English, either immediately prior to or after scanning the subject. The recorded information must be accurate.

8.2.3 Refer to Table 6, Table 7 and Table 8 for specific DTF field instructions that correspond to the PHANTOM DTF and Imaging DTF respectively, as well as the samples that follow in Figure 5, Figure 6, and Figure 7.

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8.2.4 Complete DTFs using a black ball point pen; all entries must be legible. If any fields do not apply, enter "NA" for *Not Applicable*. **Do not leave any fields blank.**

8.2.5 Do not erase or write over errors; do not use correction fluid. Follow the International Council for Harmonisation E6 Good Clinical Practice (GCP) guidelines to correct errors:

- Cross out error with a single line (but do not obliterate)
- Insert correction
- Initial and date change

8.2.6 Ensure that the DTF is signed by the authorized personnel who completed the form. The signature will indicate that a thorough review of all recorded information has been performed.

8.2.7 For SFTP submission: Refer to Section 9.3.

8.2.8 For courier submission: Make a copy of the completed DTF and return the **copy** to ICON with the image data. Retain the **original** of the form in the regulatory study files at your site.

8.2.9 Refer to the sample DTFs or contact an ICON team member for assistance Monday – Friday, 0800 to 1700 (Eastern Time USA) if you have questions about completing the form. An ICON Study Team Contact Information list, containing specific personnel names, roles, responsibilities, and contact information, is provided along with this manual for reference.

Table 6: PHANTOM DTF Field Instructions

General Information	
Site Number	Record the 4-digit site number in the boxes provided.
Scanner Info	Provide the manufacturer/model as well as Tesla strength of the scanner
Scan Date	Record the date that images were acquired in alphanumeric format as follows: ddMMMyyyy (eg, 01JAN2017).
Image Data	
Comments	Record reasons for any protocol variance or system or subject items of interest. *Note:* **Do not record any subject identifying information.** If not recording comments, check box to indicate that comments are not applicable.
Submission	

Submission Method	Check the box that indicates the method used to send images to ICON. If you check “Other,” record the transfer method used.
Completion/Signoff	
Printed Name	Record the printed name of person completing the DTF.
Signature	Record the signature of person completing the DTF.
Date	Record the date that DTF was completed in alphanumeric format as follows: dd-MMM-yyyy (eg, 01-JAN-2017).

Table 7: MRI Imaging DTF Field Instructions

General Information	
Site Number	Record the 4-digit site number in the boxes provided.
Subject Number	Record the 4-digit subject number
Subject Year of Birth	Record the subject’s year of birth in the spaces provided.
Scan Date	Record the date that images were acquired in alphanumeric format as follows: ddMMMyyyy (eg, 01JAN2019).
Visit	Check the appropriate option that corresponds to the imaging visit.
Re-scan	Check the re-scan box if a rescan of screening is being submitted
Image Data	
Modality	The required modality is should be selected (MRI-PDFF or MRE).
Anatomy	The required anatomy should be selected (coverage of entire liver for MRI-PDFF and MRE). If “Other” is selected, the anatomy must be specified.
Comments	Record reasons for any protocol variance or system or subject items of interest. ***Note:*** **Do not record any subject identifying information.** If not recording comments, check box to indicate that comments are not applicable.
Submission	
Submission Method	Check the box that indicates the method used to send images to ICON. If you check “Other,” record the transfer method used.
Completion/Signoff	

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Printed Name	Record the printed name of person completing the DTF.
Signature	Record the signature of person completing the DTF.
Date	Record the date that DTF was completed in alphanumeric format as follows: dd-MMM-yyyy (eg, 01-JAN-2019).

Table 8: DXA Imaging DTF Field Instructions

General Information	
Site Number	Record the 4-digit site number in the boxes provided.
Subject Number	Record the 4-digit subject number
Subject Year of Birth	Record the subject's month and year of birth in the spaces provided.
Scan Date	Record the date that images were acquired in alphanumeric format as follows: ddMMMyyyy (eg, 01JAN2019).
Visit	Check the appropriate option that corresponds to the imaging visit.
Re-scan	Check the re-scan box if a rescan of screening is being submitted
Image Data	
Modality	The required modality DXA should be selected.
Anatomy	The required anatomy should be selected (coverage of lumbar spine and hip for DXA).
Comments	Record reasons for any protocol variance or system or subject items of interest. ***Note:*** **Do not record any subject identifying information.** If not recording comments, check box to indicate that comments are not applicable.
Submission	
Submission Method	Check the box that indicates the method used to send images to ICON. If you check "Other," record the transfer method used.
Completion/Signoff	
Printed Name	Record the printed name of person completing the DTF.
Signature	Record the signature of person completing the DTF.
Date	Record the date that DTF was completed in alphanumeric format as follows: dd-MMM-yyyy (eg, 01-JAN-2019).

Figure 5: Sample PHANTOM DTF

MADRIGAL PHARMACEUTICALS, INC. **PHANTOM MRI Data Transmittal Form (DTF)** **Protocol-MGL 3196-11**

1 2 3 4	Siemens 3T	3 1 J A N 2 0 2 0
Site #	Manufacturer/Model & TESLA	Scan Date (d d M M M y y y y)

☑ Check box if comments are not applicable.

Comments:

SAMPLE

Note: Electronic Transfer is the preferred method of data submission.

Submission Method:	☑ Electronic Transfer (SFTP) ☐ CD/DVD ☐ Other - Specify:				
Printed Name:	Emma Jean Tek, RT	Signature:	Emma Jean Tek	Date:	31-JAN-2020

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Figure 6: Sample MRI Imaging DTF

Madrigal Pharmaceuticals, Inc. **MRI Imaging Data Transmittal Form** **Protocol MGL-3196-11**

1 2 3 4	5 6 7 8	1 9 8 5	3 1 J A N 2 0 2 0
Site #	Subject#	Participant Year of Birth (y y y y)	Scan Date (d d M M M y y y Y)

☑ Baseline ☐ Week 16 ☐ Week 52 ☐ Month 54 ☐ Early Termination

Visit

Is the submission a re-scan? ☐ Yes ☑ No

Please submit one DTF per participant and modality scan date.

Modality *(check all that apply)*	☐ MRE ☑ MRI-PDFF

Anatomy (Scan Coverage) *(Check all that apply)*	**Required:**	☑ Liver
	Optional:	☐ Other - specify:

☑ Check box if comments are not applicable.

Comments:

SAMPLE

Submission Method:	☑ Electronic Transfer (SFTP) ☐ CD/DVD ☐ Other - specify: _____				
Printed Name:	*Emma Jean Tek, RT*	**Signature:**	*Emma Jean Tek*	**Date:**	*31-JAN-2020*

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Figure 7: Sample DXA Imaging DTF

Madrigal Pharmaceuticals, Inc. **DXA Imaging Data Transmittal Form** **Protocol MGL-3196-11**

1 2 3 4	5 6 7 8	A P R 1 9 8 5	3 1 J A N 2 0 2 0
Site #	Subject#	M M M y y y y Participant Month and Year of Birth	d d M M M y y y Y Scan Date

☑ Baseline ☐ Week 52 ☐ Month 54 ☐ Early Termination
Visit

Is the submission a re-scan? ☐ Yes ☑ No

Please submit one DTF per participant and modality scan date.

Modality *(check all that apply)*	☑ DXA	
Anatomy (Scan Coverage) *(Check all that apply)*	**Required:**	☑ Whole Body

☑ Check box if comments are not applicable.
Comments:

SAMPLE

Submission Method:	☑ Electronic Transfer (SFTP) ☐ CD/DVD ☐ Other - specify: _____				
Printed Name:	*Emma Jean Tek, RT*	**Signature:**	*Emma Jean Tek*	**Date:**	*31-JAN-2020*

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9 Image Data Archiving and Submission

9.1 Archiving Instructions

9.1.1 Maintain an onsite archive of all study imaging data in the same format that is submitted to ICON per ICH E6 GCP guidelines or your local requirements, whichever are a higher standard.

9.1.2 Submit a set of the imaging data to ICON.

9.2 Submission Requirements

9.2.1 Send baseline MRI-PDFF scans **within 24 hours** after image acquisition.

9.2.2 Send scans acquired from enrolled subject on-treatment **within 3 days of image acquisition**.

9.2.3 De-identifying options within AG Mednet. Exam date and Patient date of birth must be de-selected.

9.3 Image Data Submission via AG Mednet

AG Mednet is the preferred method for submitting data as it is the most efficient means of transmitting data from your site to ICON. You may contact the ICON Project Team to assist you in setting up the AG Mednet Desktop Agent.

You can access the Desktop Agent website from the following link:

https://portal.agmednet.net/Desktop-Agent/

To open the program, click “launch” or double-click the AG Mednet icon on your desktop.

For support, call AG Mednet at the appropriate number below or send email to **support@agmednet.com**. AG Mednet support is available 24 hours a day, 7 days a week.

Australia: +61.2.800.64624
Austria: +1-617-674-8135
Belgium: +32-0800-265-03
Canada: +1.617.674.8135
France: +33-0805-080250
Germany: +49-0800-183-0754
Hungary: +36-170-08579
Israel: +1-617-674-8135
Italy: +39-800-581-482
Spain: +34-900-838241
United Kingdom: +44.20.3287.5246
United States: +1.888.924.6336

Additional information on the use of AG Mednet will be provided during site training.

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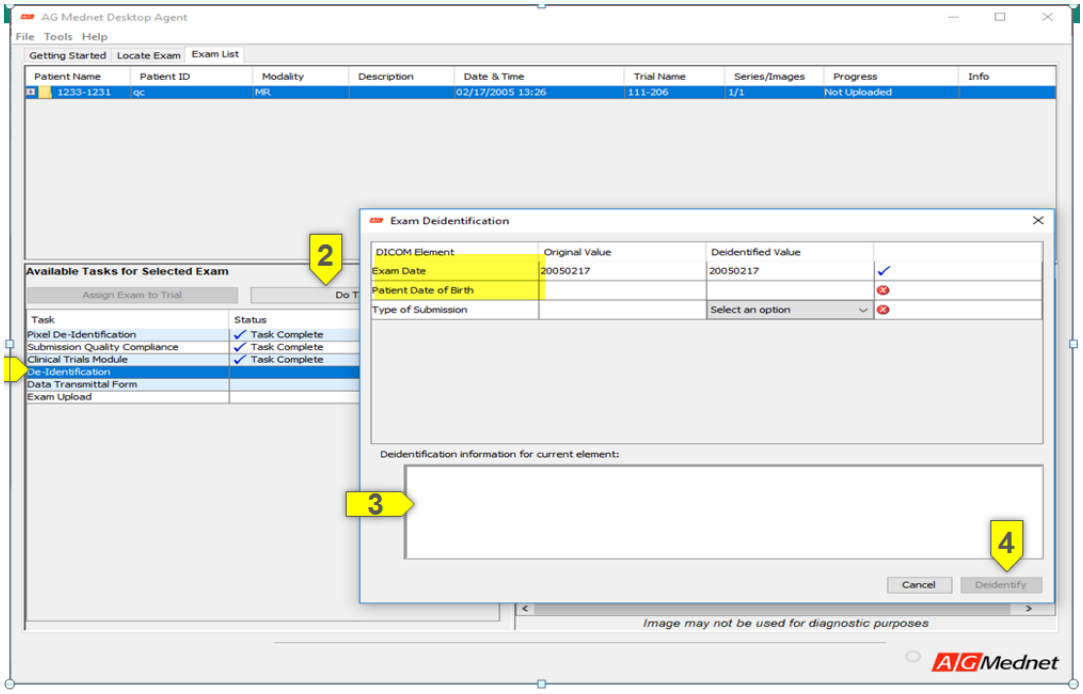
Figure 8: Imaging DTF Submission Instructions



9.3.1 Please ensure all phantom submissions via AG Mednet are submitted with a Subject ID of the 4-digit site number followed by a dash and then “Phantom” (ex: 1234-Phantom). Please select “Phantom Initial” for timepoint for MRI-PDFF and MRE phantoms and Patient Date of Birth as “19800101” as shown below.

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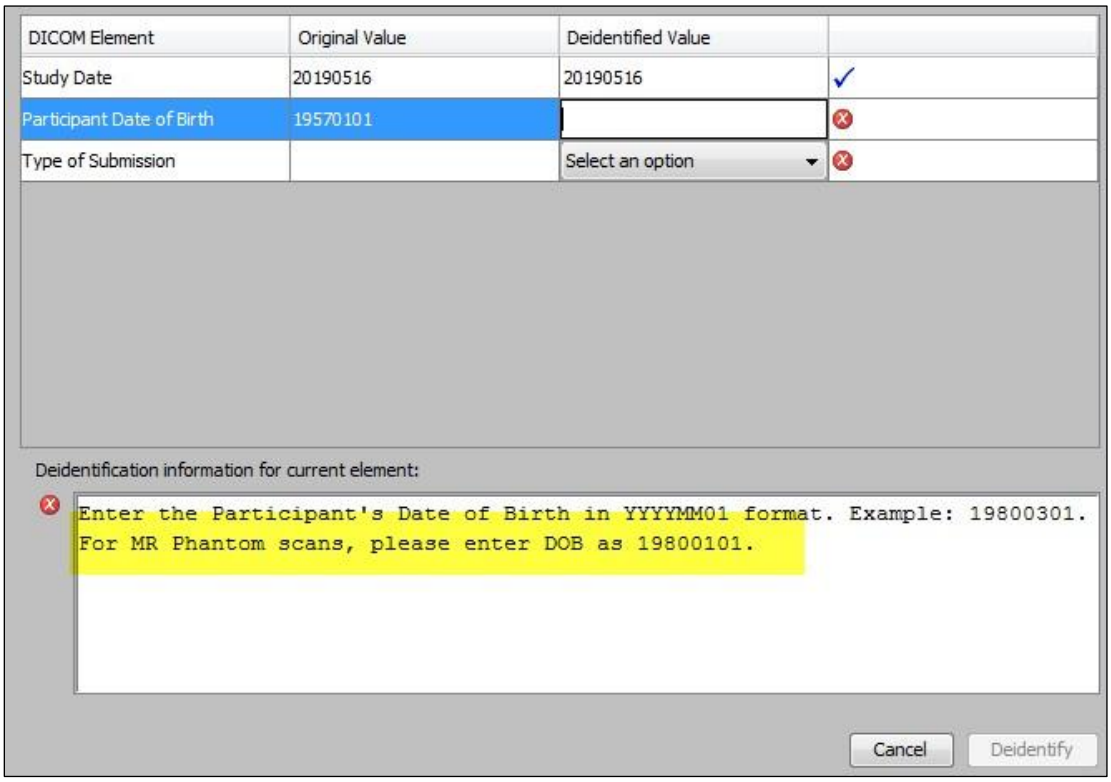
Figure 9: AG Mednet Submission Sample



9.4 Image Data Submission via Secure File Transfer Protocol

If the use of AG Mednet is not possible, Secure File Transfer Protocol (SFTP) is the preferred method for submitting image data to ICON.

9.4.1 SFTP Server Overview

ICON's SFTP Server is available 24 hours a day, 7 days a week. The server resides behind a firewall, but outside a secondary firewall protecting ICON's internal network. The SFTP server is configured with security in a manner that restricts access to only those users who have been granted permission. Additionally, each user is only able to transfer files to the designated site folder; users are **not** able to access folders associated with other sites, protocols, or projects. All transactions and user movements on the SFTP server may be tracked and monitored.

ICON's SFTP server is in compliance with the Health Insurance Portability and Accountability Act (HIPAA) regulations (Section 164.312) regarding access control and user identity, integrity and authentication in order to protect the security and privacy of personally identifiable health care information of study subjects.

9.4.2 SFTP Setup

ICON recommends that your site uses FileZilla to connect to the SFTP server. FileZilla is a cross-platform software application that can be downloaded for free from the internet (https://filezilla-project.org/). Once FileZilla is installed at your site, ICON will provide instruction on how to set up SFTP access with your login details.

- If your site has not already been provided with SFTP access, send an email request to either the ICON Project Manager or ICON Project Assistant listed on the ICON Project Team Contact List. Include in the email your site name/number, the study number, and the name and contact information (phone and email) for the person at the site who will be responsible for posting to ICON's SFTP server.
- An ICON IT Support representative will create an account for your site, grant access to the SFTP server, and email login credentials and access instructions to your site user (typically within 2 days of receipt of the initial request, unless contracted otherwise).

9.4.3 SFTP Use

***Note:* ICON will not process image data without a corresponding DTF.**

Send the completed DTF to ICON, along with the data submission, via the SFTP server.

If the completed DTF is not sent via SFTP, use one of the following alternative methods:

- **Email** as PDF attachment to the following email address:

  IMI-ClinOps-Warrington-Corelab-External@iconplc.com

- **Fax** to +1 267. 327.4370
- **Certified courier**

For PDF, SFTP, or fax, retain the original, completed DTF for your study regulatory files; the emailed PDF, scanned SFTP, or faxed version sent to ICON will serve as the ICON source document. For returns via courier, send a copy of the completed page to ICON and retain the original at your site.

9.4.4 SFTP Troubleshooting

For questions regarding setup of your SFTP software on your system, contact your internal IT department or system administrator.

For image data transfer issues, email ICON SFTP support at **IMISupport@iconplc.com**. ICON's IT Global Sponsor Support and IT Application Team will work to resolve the issue within 4 business days.

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9.5 Image Data Submission via Courier

If the use of electronic submission (AG Mednet or SFTP) is not possible, submissions via courier are acceptable. The use of Compact Disc (CD) and/or Digital Video Disc (DVD) is recommended for courier submissions. ICON keeps these media as source documentation per regulations.

Note: Labels (for digital media) and pre-printed air bills will be provided upon request.

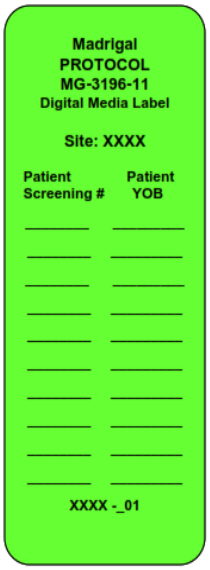
9.6 Digital Media Archive Label Instructions (For Courier Submission Only)

9.6.1 Affix 1 label on the outside of each case containing the archival media. To avoid damaging the media, DO NOT place the label directly on the media itself.

9.6.2 Record the following information on the label as you archive each subject's data to the media. Your 4-digit site number is pre-printed on the labels.

- 4-digit subject number as recorded on the DTF.
- Subject's year of birth as recorded on the DTF.

Note: the code at the bottom of the label is for internal ICON use only.



9.6.3 Refer to the sample Digital Media Label shown at right.

9.7 AG Mednet Submission Inventory

- Completed electronic DTF
- Image data uploaded to AG Mednet desktop agent

9.8 Confirmation email received with PDF of completed DTF

9.9 SFTP Submission Inventory

- De-identified image data
- Completed, signed, and dated DTF
- Image data submitted by SFTP
- Completed DTF submitted by SFTP, email (as PDF attachment), fax, or courier.

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9.10 Courier Shipping Inventory

- Completed, signed, and dated DTF (send copy of the completed page only; retain the original at your site)
- De-identified digital data on labeled (green label) media

For sites within the United States (US), send by FedEx using a padded shipping envelope. FedEx shipping supplies may be obtained by calling **1.800.GoFedEx** (**1.800.463.3339**) or by visiting the FedEx website at **www.fedex.com**.

OR

For sites outside of the US, send by DHL using a padded shipping envelope. DHL shipping supplies may be obtained by visiting the DHL website at **www.dhl.com** and then selecting the country of choice, or by calling the appropriate number below.

DHL telephone numbers:

Australia: +617 3837 7705
Austria: 0820 / 55 05 05
Belgium: +32-0800-265-03
Canada: 1.855.345.7447
France: +617 3837 7705
Germany: 0049 1806 345 300
Hungary: +36-170-08579
Israel: 1-700-707-345
Italy: 199.199.345
Spain: + 34 902 12 24 24
United Kingdom: +44(0) 844 248 084

- ICON Mailing Address:

ICON
Medical Imaging
2100 Pennbrook Parkway
North Wales, PA 19454
USA

Tel. +1 215.616.3000
Fax +1 267.327.4370

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10 Query Resolution Process

10.1 Overview

Imaging data received at ICON undergo a rigorous quality inspection to identify any deviations, missing documents, missing image data, or clerical discrepancies which would result in a query. Queries dealing with missing image data or incomplete images (eg, interrupted series) and submissions with mismatching or missing participant identifiers will be categorized as critical queries. All other queries will be categorized as non-critical.

Critical queries should be resolved within 1 business day of receipt and non-critical queries within 5 business days.

In order to resolve any issues that arise, ICON follows the query resolution process outlined below, using ICON's proprietary software application, the Site Query Assessment & Resolution Environment (SQUARE™). Access SQUARE via the following pathway:

https://services.iconmedicalimaging.com/SQUARE3

10.2 Start Up

At study start up, ICON will provide a username and password to designated site users identified on the Site Imaging Access Form. For changes or additions to site users after study start, contact the ICON Project Assistant listed on the ICON Project Team Contact List.

After initial login, the system will guide the user through an online training session for SQUARE.

10.3 SQUARE

10.3.1 Regularly monitor SQUARE for open queries linked to Madrigal Pharmaceuticals, Inc./MGL-3196-11 and complete the required fields to resolve the query.

10.3.2 You will receive critical queries immediately upon issue from ICON. Non-critical queries will be sent in a weekly report that details the open queries for your site. You will also receive a cumulative report of all closed queries (critical and non-critical) at the conclusion of the trial. Retain copies of these reports for your records.

10.3.3 ICON will notify you by email or phone if any outstanding query is not resolved within 14 days.

10.3.4 Once ICON has determined that the query is sufficiently resolved, the query will be closed.

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10.3.5 A Quick Guide for SQUARE is available within the SQUARE application and can be used as reference on system usage.

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11 Document Revision History

11.1 Draft_v4.0_31-JAN-2020

Section	Strike-through text indicates content deleted since previous version: Final_v3.0_14-OCT-2019	Bold text indicates content added to current version: Final_v4.0_31-JAN-2020
Section 2.1: Phantom Procedure	NA	**Please note that the use of a water bottle for phantom acquisition is acceptable. If the phantom scan is performed on an inert phantom, the MRE should be performed as though on a human, so please ensure the paddle is attached and turned on. The phantom will be assessed for wave transmission and will not be passes if evidence of wave transmission is not demonstrated**.
Table 4: Specific Pulse Sequence Parameters	NA	Multi-echo fat quant column-Flip Angle (º) was updated to-10**-15**
Section 4.1: General Sequence Guidelines	NA	**Multi-echo fat quant** • **At 3T:10 degrees** • **At 1.5T:15 degrees**
Section 7: DXA Phantom Requirements	~~DXA Equipment Phantom Plot Reports Requirements~~ ~~Use the Hologic Spine phantom for Hologic DXA scanners or the Black QA Phantom from GE Lunar.~~ ~~Perform a phantom measurement every day there is a study subject and at least 3 times a week even if the scanner is not being used for subject scans.~~ ~~It is required to submit a printed version of the Daily QA Phantom plot report.~~ ~~All phantom plot reports are required to be submitted via SQUARE queries issued to your site.~~	**Submission of DXA phantom data to ICON is not required for the study. However, ICON recommends the use of the Hologic Spine phantom for Hologic DXA scanners or the Black QA Phantom from GE Lunar for phantom acquisition at your site.** **Phantom measurements should be performed every day there is a study subject and atleast 3 times a week even if the scanner is not being used for subject scans.**

Section	Strike-through text indicates content deleted since previous version: Final_v3.0_14-OCT-2019	Bold text indicates content added to current version: Final_v4.0_31-JAN-2020
	• ~~Microsoft database access files are not accepted or the individual block/spine phantom scans.~~ ~~Print the Phantom plot report from the workstation or imaging software system.~~ ~~Initial Monthly Daily phantom plot report~~ ~~You are required to submit the Initial phantom plot report to include the previous 90 business days' worth of phantom plots. The initial report requires the first subject's scan date plus the prior 90 days within the plot. (Reference your manufacturer manuals for instructions to complete this report).~~ ~~SQUARE Outstanding data queries will be issued for all submissions of required Phantom QA plot reports.~~ ~~Quarterly submissions are required to include 90 days of phantom plots.~~ ~~**Initial Phantom QC plot report:**~~ ~~Your site will be instructed to upload the initial Phantom plot report to include the first DXA scan date for your site along with the prior 90 days within SQUARE for the required months per the ODQ request.~~ ~~**Subsequent Phantom QC plot report:**~~ ~~All subsequent ODQ DXA Phantom queries will require the last day of the last submitted report~~	

DocUUID : 9f8e72f2-1a29-47a2-a09f-de1f06371f3d

Section	Strike-through text indicates content deleted since previous version: Final_v3.0_14-OCT-2019	Bold text indicates content added to current version: Final_v4.0_31-JAN-2020
	~~and to include 90 days in SQUARE for the required months per the ODQ request.~~ ~~Contact your manufacturer directly for any issues creating the required QA Phantom plot report.~~	
9.11 Image Data Submission via SQUARE	The entire section 9.11 was deleted.	**NA**

11.2 Final_v3.0_14-OCT-2019

Section	Strike-through text indicates content deleted since previous version: Final_v2.0_24-MAY-2019	Bold text indicates content added to current version: Final_v3.0_14-OCT-2019
Table 1: MRE and MRI-PDFF Acquisition Schedule	Early Termination: Only performed if Early Termination is within the first year of the study; (i.e., patients who completed a Week 52 MRI-PDFF~~,~~ MRE ~~and/or cT1~~ do not need to be re-assessed at Early Termination); Imaging should be performed before the biopsy and may be up to 10 days before the biopsy.	Early Termination: Only performed if Early Termination is within the first year of the study; (i.e., patients who completed a Week 52 MRI-PDFF **and** MRE do not need to be re-assessed at Early Termination); Imaging should be performed before the biopsy and may be up to 10 days before the biopsy.
	Screening: Within 56 days prior to the first dose of study drug (ie, up to -8 wk.)	Screening: Within 56 days prior to the first dose of study drug (ie, up to -8 wk.) **and up to 7 days post randomization date**
2.1 Phantom Procedure	If that is not possible, please scan with the phantom utilized for routine site QA/QC.	If that is not possible, please scan with the phantom utilized for routine site QA/QC **and ensure to scan MRE sequence using driver set at 60 Hz**
7.3 DXA Phantom reports Upload Instructions using SQUARE 3.1	NA	New Section 7.3: DXA Phantom reports Upload Instructions using SQUARE 3.1 is added.

Section	Strike-through text indicates content deleted since previous version: Final_v2.0_24-MAY-2019	Bold text indicates content added to current version: Final_v3.0_14-OCT-2019
9.3 Image Data Submission via AG Mednet	NA	9.3.1 Please ensure all phantom submissions via AG Mednet are submitted with a Subject ID of the 4-digit site number followed by a dash and then “Phantom” (ex: 1234-Phantom). Please select “Phantom Initial” for timepoint for MRI-PDFF and MRE phantoms and Patient Date of Birth as “19800101” as shown below. <New Figure added>

11.3 Final_v2.0_24-MAY-2019

Section	Strike-through text indicates content deleted since previous version: Final_v1.0_30-APR-2019	Bold text indicates content added to current version: Final_v2.0_24-MAY-2019
1.3: Imaging Requirements	1.3.2: Acquire and submit ~~Total Body~~ dual-energy x-ray absorptiometry (DXA) according to the instructions outlined in this section.	1.3.2: Acquire and submit **Lumbar Spine and Hip** dual-energy x-ray absorptiometry (DXA) according to the instructions outlined in this section.
5.1: MRE Scanner Parameters	NA	Generate and submit the grayscale Stiffness Maps with 95% confidence intervals. Submit original wave images and confidence maps. Do not place ROIs on maps. PHI must be removed from all images. **DICOM tags (0028, 1052) Rescale Intercept and (0028, 1053) Rescale Slope must be present in DICOM header. Submit source phase and magnitude images.**
6.1: Lumbar Spine Region for BMD	Section on ~~Total Body Regions for BMD/BMC~~ deleted	Section on “Total Body Regions for BMD/BMC” replaced with section on “**Lumbar Spine Region for BMD**” along with Figure 1.

Section	Strike-through text indicates content deleted since previous version: Final_v1.0_30-APR-2019	Bold text indicates content added to current version: Final_v2.0_24-MAY-2019
6.2: Hip Region for BMD	NA	Section on "**Hip Region for BMD**" added along with **Figure 2, Figure 3 and Figure 4**.
Table 8: DXA Imaging Field Instructions	Anatomy: The required anatomy should be selected (cover of ~~whole body~~ for DXA).	Anatomy: The required anatomy should be selected (cover of **lumbar spine and hip** for DXA).
Figure 7: Sample DXA Imaging DTF	NA	Sample DTF updated to replace the anatomy of "whole body" with "**lumbar spine and hip"**
12: Appendix A: Imaging Data Transmittal Form	NA	DTF updated to replace the anatomy of "whole body" with "**lumbar spine and hip"**

11.4 Final_v1.0_30-APR-2019

This is the first approved version of the Imaging Manual. If the document is revised at a later date, this section will detail the changes made in each version.

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12 Appendix A: Imaging Data Transmittal Form

The following pages contain the PHANTOM DTF and the Imaging DTFs to be used when submitting images to ICON via SFTP or courier instead of AG Mednet. Refer to Section 8 of this Imaging Manual for detailed completion instructions.

DocUUID : 9f8e72f2-1a29-47a2-a09f-de1f06371f3d

Site #	Manufacturer/Model & TESLA	Scan Date (d d M M M y y y y)

☐ Check box if comments are not applicable.

Comments:

Note: Electronic Transfer is the preferred method of data submission.

Submission Method:	☐ Electronic Transfer (SFTP) ☐ CD/DVD ☐ Other - Specify:				
Printed Name:		**Signature:**		**Date:**	

Site #	Subject#	Participant Month and Year of Birth (M M M y y y y)	Scan Date (d d M M M y y y Y)

☐ Baseline ☐ Week 52 ☐ Month 54 ☐ Early Termination

Visit

Is the submission a re-scan? ☐ Yes ☐ No

Please submit one DTF per participant and modality scan date.

Modality *(check all that apply)*	☐ DXA

Anatomy (Scan Coverage) *(Check all that apply)*	**Required:**	☐ Whole Body

☐ Check box if comments are not applicable.

Comments:

Submission Method:	☐ Electronic Transfer (SFTP) ☐ CD/DVD ☐ Other - specify: _____				
Printed Name:		**Signature:**		**Date:**	

Site #	Subject#	Participant Year of Birth (y y y y)	Scan Date (d d M M M y y y Y)

☐ Baseline ☐ Week 16 ☐ Week 52 ☐ Month 54 ☐ Early Termination

Visit

Is the submission a re-scan?	☐ Yes ☐ No

Please submit one DTF per participant and modality scan date.

Modality *(check all that apply)*	☐ MRE ☐ MRI-PDFF

Anatomy (Scan Coverage) *(Check all that apply)*		
	Required:	☐ Liver
	Optional:	☐ Other - specify:

☐ Check box if comments are not applicable.
Comments:

Submission Method:	☐ Electronic Transfer (SFTP) ☐ CD/DVD ☐ Other - specify: _____				
Printed Name:		Signature:		Date:	