Imaging Manual

Study ID:	**D5671C00002 (PROXYMO)**
Sponsor:	**AstraZeneca**

The original signature page is archived in the Imaging Master File at Antaros

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1 Introduction

1.1 About this Imaging Manual

This Imaging Manual describes the process to be followed at the imaging site when performing scans for the AstraZeneca D5671C00002 (PROXYMO) study "A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Pharmacodynamic Effects of MEDI0382 in Obese Subjects With Non-alcoholic Fatty Liver Disease (NAFLD)/ Non-alcoholic Steatohepatitis (NASH)".
Antaros control the versioning of this Imaging Manual. If a new version is released, please mark the previous version as obsolete and place the new version in the appropriate section of the Imaging Site Binder.

1.2 Imaging Site Training

Prior to the start of the study, the suitability of your imaging facility (scanner, software, experience of radiographers) has been evaluated by Antaros through the answers provided in the Site Survey. The imaging site staff will be trained in the procedures described in this manual, either remotely or via an on-site visit. As part of this training, the imaging protocol should be set up on the scanner selected for this study as described in this Imaging Manual. Test data from a healthy volunteer should be acquired for each of the sequences (if possible) for evaluation by Antaros.

This Imaging Manual is intended to be used by imaging staff who have been trained in the procedures by Antaros (see Training Log for trained members of staff at your site). Study trained staff members may train other staff using this Imaging Manual and the training materials in the Imaging Site Binder. In this case a signed copy of the Training Log should be sent to Antaros.

1.3 Imaging Workflow in this Study

The workflow for imaging is described in the figure below:

For details on your recruiting site, please see Recruiting Site Details in the imaging site binder (Appendix A).

2 Objectives

2.1 Objectives with the PROXYMO study

To investigate the effect of MEDI0382 on liver fibrosis compared with placebo in subjects with NASH and liver fibrosis stage F1, F2 or F3.

2.2 MRI Objectives

The primary endpoint of the study is:

- MEDI0382 will have an acceptable safety (including hepatic safety) and tolerability profile in subjects with NAFLD/NASH.

The secondary MRI endpoint is:

- Treatment with any one dose of MEDI0382 tested will lead to a reduction in hepatic fat in subjects with NAFLD/NASH

Imaging endpoints of the study are:

- Liver PDFF
- Liver fat volume
- Liver volume
- Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT)
- Liver diffusion
- Liver sagittal diameter and liver transversal diameter

3 Ethical/legal aspects

The study has undergone ethical review and been approved in each country where study sites are located. All subjects that will be referred to the Imaging site have signed an informed consent at the recruiting site.

If imaging is performed on test persons (healthy volunteers) as part of the study set-up and training process, staff at the imaging site should obtain informed consent from the test persons. The imaging sites are responsible for ensuring that applicable ethical/IRB approval is obtained separate to the CSP prior to scanning healthy volunteers.

4 Incidental findings

Incidental finding: An image feature of potential pathological nature that is discovered unintentionally in addition to the study protocol required imaging endpoints. The incidental finding can additionally not directly be discarded as caused by an imaging artefact.

A radiologist at the Imaging site, e.g. hospital, where the imaging is acquired must do a medical reading of the MRI, i.e. will be handled in accordance with local procedures. The assessment will be reported to the Investigator at the referring site, who will review and file the assessment in the subject´s source documents and take the needed actions.

5 Scanner Hardware or Software Changes/Upgrades

Your scanner has been deemed suitable for inclusion in this study at the site qualification stage. It is important to **use the same scanner and coil setup at each scan** to ensure consistency between visits and patients.

Please inform Antaros immediately should your MRI scanner have upcoming upgrades to scanner hardware or software, or if any other technical issues arise.

Antaros will evaluate the planned upgrade/change to your scanner to determine the potential impact of the upgrade on the study. You may be asked to acquire test scans using your scanner pre- and post-upgrade in order to determine the impact on the images and measured endpoints.

6 Procedure

6.1 Subject referral

The Recruiting Site:

- Will ask the subject if there is any contraindication for MRI, i.e. pacemaker, intra-cranial clip, etc.
- Ensure informed consent for the trial is obtained
- Will refer the subjects to the Imaging site and will state when the scan should be performed. It is important that the timing of the imaging procedure is in accordance with the protocol.

6.2 Initial procedures at imaging site

The Imaging site:

- Will schedule the imaging visit
- Identify the subject according to normal hospital procedure
- Perform routine check for all exclusion criterions for scanning, e.g. pacemakers, intra-cranial clips etc. prior to the scan
- Perform check of study restrictions, e.g. fasting, and record any deviations in the Scan Log
- Prepare the subject according to the local requirements for imaging investigations including removal of metal, such as eyeglasses and jewelry (including provision of ear protection)
- Instruct the subject on how to perform breath-holding for the scans prior to entering the scanner

6.3 MRI Visits

For the 300ug treatment arms the following visit codes apply for MRI scans:

- **Visit 2*** **Screening** (if MRI hasn't been completed within 60 days prior to Visit 2)
  *PDFF only
- **Visit 3** **Day 1**
- **Visit 10** **Week 12**
- **Visit 14** **Week 19**
- **Early Discontinuation Visit** (subjects who discontinue investigational product will be requested to attend an additional MRI unless the subject has already completed 3 MRI scans within the treatment period)

For the 600ug treatment arms the following visit codes apply for MRI scans:

- **Visit 2*** **Screening** (if MRI hasn't been completed within 60 days prior to Visit 2)
  *PDFF only
- **Visit 3** **Day 1**
- **Visit 14** **Week 12**
- **Visit 20** **Week 19**
- **Early Discontinuation Visit** (subjects who discontinue investigational product will be requested to attend an additional MRI unless the subject has already completed 3 MRI scans within the treatment period)

6.4 Imaging protocol

Prior to study start, the imaging sequences described below should be set up on your scanner and saved as an examcard or measurement program to ensure consistent imaging across the study.

For each subject scan follow the directives outlined below. The Scan Log should be completed at each scan. For follow-up scans of a subject (post-baseline) please refer to previously completed Scan Logs for the subject to ensure any special procedures or modifications to the protocol are consistent between visits for each individual subject.

6.4.1 Screening - PDFF only

Load the sequences	• Load the Examcard/Measurement program for this study	
Subject positioning	• The subject is positioned in supine position with the headfirst and a cushion under the knees. Preferably, make sure that the coil is positioned so that both the liver and the adipose tissue scan can be performed without repositioning. • Scanner isocenter should be landmarked on the xiphisternum of the patient.	
Coils	• Use the spine array and the large body flex coil.	
Respiration belt and breath-holding	• Use the respiration belt if available to guide and monitor the breath-holds. • **All imaging sequences are breath-hold and should be performed at end-expiration.**	
PLEASE NOTE:	• Do not change the FOV or angle of the scans except as specified.	
1. Survey of liver	Perform a survey scan in end-expiration breath-hold including a coronal view of the liver.	
2. Liver Fat (proton density fat fraction (PDFF)): (breath-hold at end-expiration)	 • The patient should hold their breath at end-expiration during all PDFF scans, as well as during scout scans and parallel imaging calibration scans. • Position the axial scan to **cover as much liver as possible**, as shown in the figure. o If the whole liver doesn't fit, cut equal amount of liver in both feet and head direction.	**3D PDFF scan:** o IDEAL-IQ (GE) o mDixonQuant (Philips) o LiverLab/qDixon (Siemens) • 12 point Dixon (6 point if monopolar selected) • Transverse, Read direction L-R • FOV = 384 x 288 x 150 mm • Matrix = 128 x 96 x 15 • FA = 3 deg (3 T) or 5 deg (1.5 T) • TR = shortest • deltaTE = shortest (ideally less than 0.8 ms at 1.5 T or 0.6 ms at 3 T) **PDFF maps should be reconstructed and transferred alongside image data.** **Check the image quality after the scan to make sure that the breath-hold was successful. If not, repeat the scan and make a note in the Scan Log.**

6.4.2 Day 1, Week 12 and Week 19 (and Early Discontinuation Visit if applicable)

Load the sequences	• Load the Examcard/Measurement program for this study	
Subject positioning	• The subject is positioned in supine position with the headfirst and a cushion under the knees. Preferably, make sure that the coil is positioned so that both the liver and the adipose tissue scan can be performed without repositioning. • Scanner isocenter should be landmarked on the xiphisternum of the patient.	
Coils	• Use the spine array and the large body flex coil.	
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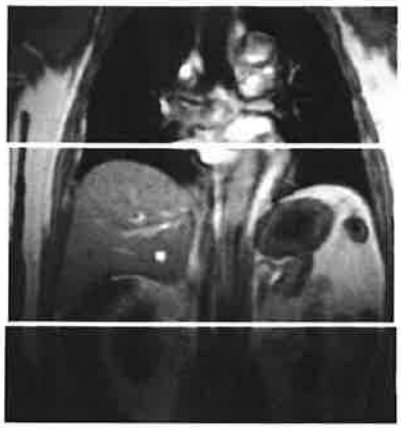
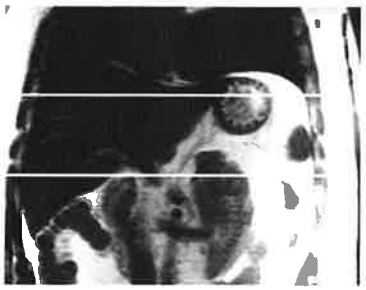
	• The patient should hold their breath at end-expiration during all PDFF scans, as well as during scout scans and parallel imaging calibration scans.
	• Position the axial scan to **cover as much liver as possible**, as shown in the figure.
	  ○ If the whole liver doesn't fit, cut equal amount of liver in both feet and head directions.
		3D PDFF scan:
		  ○ IDEAL-IQ (GE)
		  ○ mDixonQuant (Philips)
		  ○ LiverLab/qDixon (Siemens)
		• 12 point Dixon (6 point if monopolar selected)
		• Transverse, Read direction L-R
		• FOV = 384 x 288 x 150 mm
		• Matrix = 128 x 96 x 15
		• FA = 3 deg (3 T) or 5 deg (1.5 T)
		• TR = shortest
		• deltaTE = shortest (ideally less than 0.8 ms at 1.5 T or 0.6 ms at 3 T)
		PDFF maps should be reconstructed and transferred alongside image data.
		
		Check the image quality after the scan to make sure that the breath-hold was successful. If not, repeat the scan and make a note in the Scan Log.

3. Liver Volume: (breath-hold at end-expiration)	 • Run the scan in a single breath-hold. • Position the axial scan to cover the entire liver volume. o If the imaging slab is too small, increase the slice thickness so that the entire liver is covered.	**3D THRIVE (T1-TFE)/LAVA-FLEX/VIBE (fl3d)** • Transverse, Read direction L-R • FOV = 450 x 400 x 280 mm • In-plane resolution = 4.7 x 4.7 mm (Acq. Matrix 96 x 85) • Slice thickness = 10 mm (if possible, otherwise 5 mm) • FA = 12 deg • TR = shortest • Dixon water image, or fat suppressed **Make a note of any change to the slice thickness in the Scan Log and make sure the same slice-thickness is used for the follow-up scans.** **Check the image quality after the scan to make sure that the breath-hold was successful. If not, repeat the scan and make a note in the Scan Log.**
4. Liver Diffusion: (breath-hold at end-expiration)	 • Run the diffusion scan in a single breath-hold. • Position the imaging slab as shown in figure.	**SE-EPI** • For b0 NEX = 1, b200 NEX = 1, b600 NEX = 2 • TR = 3000 ms • TE min (< 60 ms) • 5 - 13 slices • Slice Thickness = 10 mm • For GEH: o Diffusion 3in1 o Dual Spin Echo Off **Check the image quality after the scan to make sure that the breath hold was successful. If not, repeat the scan and make a note in the Scan Log.**

5. Survey of lumbar spine	Perform a survey scan in end-expiration breath-hold including a sagittal view of the lumbar spine (if not already acquired).	
6. VAT/SAT: (breath-hold at end-expiration)	 • Position the adipose tissue scan as shown in figure **centred at the L4/L5 interface covering 20 cm** in the Head-Foot direction. • Make sure that the FOV covers the entire volume in L-R and A-P directions. If not, increase the FOV in the A-P direction. • Note any changes in the Scan Log and make sure to use the same FOV for the follow-up scan. • Run the scan in a single breath-hold.	**3D THRIVE (T1-TFE)/LAVA-FLEX/VIBE (fl3d)** • Transverse, Read direction L-R • FOV = 500 x 375 x 200 mm • Resolution: 2.8 x 2.8 x 10 mm • Matrix = 192 x 136 • 20 slices @ 10 mm, or 40 slices @ 5 mm • FA = 12 deg • TR = shortest • Dixon water and fat images **Check the image quality after the scan to make sure that the breath hold was successful. If not, repeat the scan and make a note in the Scan Log.** **Check that the FOV is large enough and there were no fold-over artefacts.**

7 Archiving

Image data should be archived at the Imaging site according to normal hospital procedure.

8 Data Submission

8.1 Data Transfer

Following each subject scan, the image data should be coded and transferred to Antaros as soon as possible **within 48 hours of the scan**.

Please see the Image Data Transfer Guidelines in the Imaging Site Binder (Appendix B) for instructions on how to code the data and send it to Antaros.

> *Note – all subject identifiable information (e.g. name, date of birth, etc.) MUST be removed from images and image headers prior to transfer to Antaros. Any data received by Antaros containing this information will be immediately destroyed, and a new coded transfer will be requested.*

The Scan Log for each scan must also be transferred to Antaros (see Image Data Transfer Guidelines in the Imaging Site Binder).

8.2 Antaros Corelab QC and Feedback

All incoming images will go through the Antaros Corelab QC process. The QC process performs three steps:

- Administrative QC (checking the Scan Log, files, who performed the scan, date/time)
- Data QC (verifying coding, checking scan parameters, checking reconstruction)
- Visual QC (visually inspecting images, image position and coverage, image quality, artefacts)

The Antaros Corelab will provide feedback after QC of the first study image. Thereafter, feedback will only be sent if a QC-issue is detected in the QC process.

Antaros Corelab will e-mail QC feedback to the imaging site within two working days. This is to prevent any issues being repeated in new scans and to inform site if a rescan will be needed.

Antaros will send the PDFF results from the screening visit to the recruiting site within 2-3 working days after image receipt at Antaros.

9 Contact Information

For general enquires and help for this study, please e-mail Antaros at corelab@antarosmedical.com.