Imaging Manual

Study title:	**3V2640-CLIN-005**
Imaging site:	**Valley Radiology**

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

Approved by:

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This manual supersedes N/A First version of this document

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1 Objectives

This manual describes the process to be followed at the Imaging site when performing MRI in the 3VBio study 3V2640-CLIN-005 “A phase 2, Multicenter, Singe-Blind, Randomized, Placebo controlled study of TVB-2640 in subjects with Non-Alcoholic Steatohepatitis”
The workflow is described in the figure below:

2 Sites

Imaging site	Valley Radiology
Recruiting site	ProSciento

3 Objectives

3.1 Objectives with the 3V2640-CLIN-005 study

To determine the effect of once daily (QD) TVB-2640 for 12 weeks versus placebo on the change in hepatic fat fraction by proton density fat fraction magnetic resonance imaging (MRI-PDFF) from baseline in subjects with non-alcoholic steatohepatitis (NASH).

3.2 MRI Objectives

The primary endpoint is:

- The primary efficacy endpoint is percent change from baseline in liver fat at Week 12, as determined by MRI-PDFF.

A secondary endpoint is

- A Secondary MRI endpoints is percent change from baseline in visceral adipose tissue at Week 12, as determined by MR.

Note that MRE can be used for inclusion if Liver biopsy is not available. Therefore MRE may be performed on the screening visit.

4 Ethical/legal aspects

The study is approved by the Ethics Committee. All subjects that will be referred to the Imaging site have signed an informed consent at the recruiting site.

5 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.

6 Procedure

6.1 Subject referral

The Recruiting Site:

- Will ask the subject if there is any contraindication for MR, i.e. pace-maker, intra-cranial clip
- Ensure an informed consent for the MRI procedure is obtained
- Will refer the subjects to the Imaging site and will state when the MR should be performed. It is important that the timing of the MR procedure is in accordance with the protocol.
- Will remind the subjects of study restrictions i.e. not to eat four hours before the scan and that intake of water or liquid should be avoided or limited 2 hours before the scanning.

6.2 Initial procedures at imaging site

The Imaging site:

- Will schedule the MR process
- Inform the referring Investigator immediately about any change to the MRI appointment date
- Identify the subject according to normal hospital procedure
- Perform routine check for all exclusion criterions for MR, e.g. pace-makers, intra-cranial clips
- Preform check of study restrictions and record in Scan Log

6.3 MRI Visits and procedures

- **Screening** MRI-PDFF, Visceral Adipose Tissue, MRE (optional if the patients do not have a liver biopsy confirming NASH).
- **Week 12 (11-16)** MRI-PDFF and Adipose tissue imaging
- **Week 16 (15-20)** MRI-PDFF and Adipose tissue imaging

6.4 **Imaging protocol**

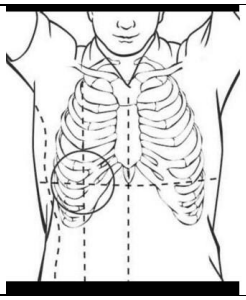
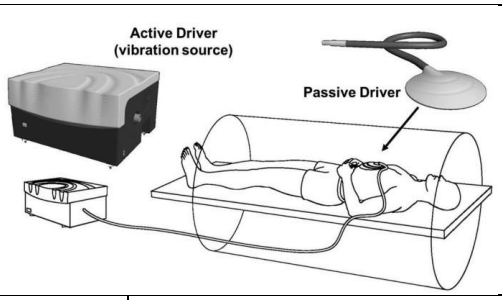
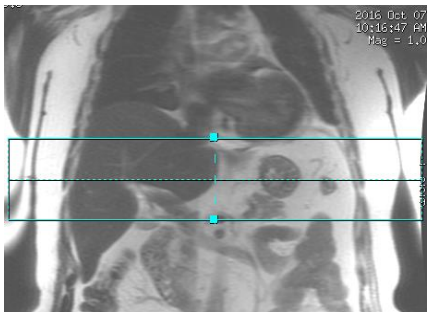
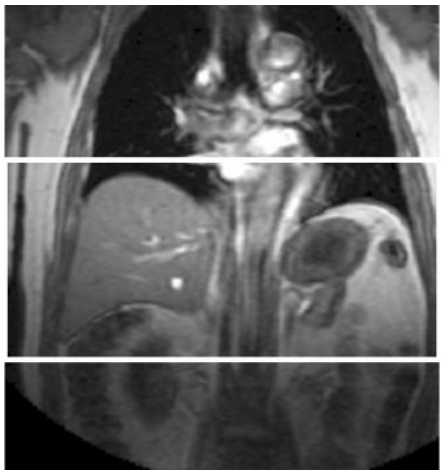
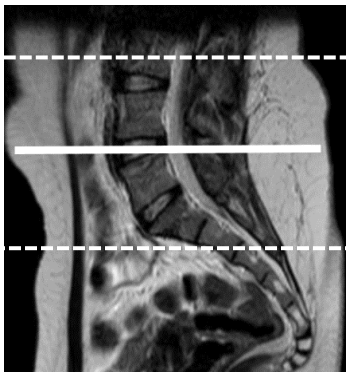
Scan preparation	• Load the Measurement program from: <<>>	
Subject positioning	• The subject is positioned in supine position with the head first and a cushion under the knees. Preferably, make sure that the coil is positioned so that both the liver and the adipose tissue scan can be performed without repositioning.	
Coils	•	
PLEASE NOTE:	• Do not change the FOV or angle of the scans except as specified below	
Survey of liver (breath hold, end exp).	• Perform a survey scan in breath hold including a coronal view of the liver.	
	 	
MR Elastography: (breath hold – end exp)	• The passive driver is placed over the right lower chest wall at the level of xiphisternum in midclavicular line (can be placed in the right mid-axillary line if colon is present between the anterior body wall and the liver). (see figure above) • The patient should hold the breath at end expiration during all MRE scans, as well as during scout scans and parallel imaging calibration scans • Acquired sections for MRE are positioned at the level of the widest transverse extent of the liver, avoiding the dome and inferior tip of the right lobe. Sections should be prescribed in a coronal	 **Scan parameters according to QIBA guidelines:** -2D MRE -4 axial slices (no angulation) -8-10 mm slice thickness (spacing 0-2 mm depending on scanner type) -FOV approx. 420-450 mm depending on scanner type

	image in relaxed end-expiration. • Do **NOT** angle the scan, use straight axial orientation **Check image quality to ensure the breath hold was successful. If not, repeat and make a note in the Scan Log**	
Liver Fat BH (PDFF): (breath hold – end exp)	• The patient should hold the 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 liver doesn't fit, cut equal amount of liver in both feet and head directions. • Do **NOT** angle the scan, use straight axial orientation **Check the image quality after the scan to make sure that the breath hold was successful. If not, repeat the investigation and make a note in the Scan Log.**	 **Typical Scan parameters:** 3D PDFF scan 30 slices 5 mm slice thickness FOV 380-400 mm IDEAL-IQ (GE) mDixonQuant (Philips) LiverLab: qDixon (Siemens) PDFF maps reconstructed
Adipose tissue imaging BH: (breath hold – end exp)	• Run a sagittal survey of the Lumbar spine • Center the scan on the L4-L5 interface as shown in the image. Do **NOT** angle the scan, use straight axial orientation **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.**	 **Typical Scan parameters:**

	Check the image quality after the scan to make sure that the breath hold was successful. If not, repeat the investigation and make a note in the Scan Log. **Make sure that no foldover appears that includes subcutaneous adipose tissue**	3D axial Water Fat Dixon scan 20 axial slices 10 mm slice thickness FOV 450 mm IDEAL (GE) mDixon (Philips) eDixon (Siemens) Water and Fat images reconstructed

7 Archiving

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

8 Coding the examination

- ☐ Select current subject under “Administration”

- ☐ Select **Tools** and **Anonymise Patient**
- ☐ In anonymised exam open **Edit Patient**
- ☐ Substitute the **subject’s name** with **subject ID**,
  - ☐ Substitute the subject’s **Patient ID** with the **Visit code** (Visit3 or Visit4)
  - ☐ Remove the **accession number**
  - ☐ Remove the **referring physician**
  - ☐ Replace the month and day in the subject’s date of birth with 01-Jan. Example, a subject with date of birth 29/10/1956 becomes 01/01/1956.

Save

9 Image File transfer to Antaros Core Lab

9.1 Timelines

Image file should be transferred to Antaros within 2 working days of acquisition.

9.2 Transfer the image file to a USB memory (GE)

- ☐ Insert USB-memory in the computer
- ☐ Click the Windows icon
- ☐ Select Settings

- ☐ Select Control Panel
- ☐ Select Folder (Up)
- ☐ In Administration, mark the subject to be exported
- ☐ Click “Disk Files”
- ☐ Navigate to the destination folder on the USB-drive.
- ☐ Export the images (DICOM Classic)
- ☐ After data transferral is complete eject the USB memory stick

9.3 Transfer file to fileserver

If you have questions on this section contact:

kristofer.osterlind@antarosmedical.com

- ☐ Insert the USB-drive on the computer used for file transfer or writing to CD
- ☐ Pack all images to a zip-file (Windows computers: right-click folder, select Send to, and then select Compressed (zipped) folder)
- ☐ Name the zip-file: **ID_VC_YYYYMMDD.zip** where
  - **ID** is **Subject Identifier** e.g. 101001,
  - **VC** is **Visit Code** (Visit2, Visit10, Visit12 or Visit12A), and
  - **YYYYMMDD** is **scan date**

Use a Web Browser to open the Antaros Medical SharePoint webpage

(Type in including underscore in your web browser)

https://antarosmedical.sharepoint.com/sites/external/ext_3vbio/103_b/

When asked for, use the following username (including underscore) below and password:

- ☐ Username: **EXT.3VBIO_103B@antarosmedical.com**
- ☐ Password: **XXXXX**

- ☐ Open the **File Manager**:
  - ☐ Select the folder: <<>>
  - ☐ Click: **Upload**
  - ☐ Select the zipped file and select **Open**

MRI Site’s staff shall use Antaros’ cloud server Microsoft SharePoint (“Server”) for uploading files in accordance with the directions and trainings provided by Antaros.

The access to the Server shall be permitted only to the MRI Site’s staff that have been previously trained and approved by Antaros. MRI Site shall not allow access to the Server to other external parties.

MRI Site's staff is not permitted to undertaking actions or upload files on the Server that are contrary to the directions and trainings provided by Antaros.

In case the electronic upload of images is not possible, then transfer file to CD and Courier to Antaros

- ☐ To transfer to a CD:
  - ☐ First insert a blank CD into the CD writer
  - ☐ Transfer the zipped file to the CD using the computer's CD writing application
  - ☐ The CD should be couriered to Antaros Medical:
    - Phone Fedex Express (+49 (0)1806 111 800)
    - Book pick-up on behalf of Antaros Medical (Account nr 696333106)
    - Address:
      Kristofer Osterlind
      Antaros Medical
      Dag Hammarskjölds väg 14B
      751 83 Uppsala
      Sweden
      Phone: +46 72 5177909

9.4 Inform Antaros Medical

Send an e-mail to corelab@antarosmedical.com and inform that the zipped scan file is uploaded.
The mail should include:

- Study Name
- Subject ID (a 6-digit number)
- Visit code
- Scan date
- Also include a copy of the completed Scan Log

9.5 Transfer Scan Log to the referring investigator

Send an email with the Scan Log to the referring investigator.

9.6 Antaros Corelab QC and feedback

All incoming images will go through Antaros Corelab QC process. Process is described in detail in the Corelab manual.

Corelab will perform three major QC steps:

- Administrative QC (Scan log, documentation, files, signing, dates)
- Data QC (Verifying coding, check parameters, reconstruction)
- Visual QC (Check export, image position, image quality)

If a QC-issue is detected in the QC process Corelab will mail QC feedback to site preferably within two working days. This is to prevent that issue will not be repeated in new scans and to inform site if a rescan will be needed.