Quick Reference Guide for the Acquisition of Subject MRI Scans

STUDY OVERVIEW

- Protocol M14-397 is a **Randomized**, **Double-Blind**, **Parallel**-group, **Placebo**-Controlled Phase **2a** study of **elezanumab** in patients with **progressive forms of Multiple Sclerosis**.
- The study is designed to evaluate the **safety** and **efficacy** of elezanumab in subjects with progressive forms of MS. MRI endpoints include brain and cervical spinal cord T2 and T1-enhancing lesion number and volume, brain and cervical spinal cord atrophy measures, magnetization transfer ratio (MTR) and diffusion tensor imaging (DTI).
- Subject MRI scans are required at **Screening** (prior to first dose of study drug) and **Weeks 24, 52, or Early Discontinuation** (± 7 days).
- All MRI data must be sent to Bioclinica **within 1 business day** of acquisition for centralized Quality Control and analysis.

ENTERING STUDY SUBJECT DATA IN THE ELECTRONIC HEADER

- In order to ensure study subject confidentiality, please enter the following information into the specified fields in the digital (DICOM) MRI header when acquiring exams:

  In the **Subject Name** field, enter: **3-digit Site Number + 6-digit Subject Number** (1 + 3-digit site # + 2-digit screening #)

  In the **Date of Birth**, do not enter subject's actual DOB. Use 01-Jan-1950 for all subjects instead.

  In the **Sex** field enter: subject **Gender** (M: Male / F: Female).

  In the **Study Description** field, enter: **Visit name** (Screening, Week 24, Week 52, Early Discontinuation, Unscheduled).

  If identifying information *must* be entered, images should be **anonymized prior to transmission.**

IMPORTANT - Data in the digital header must match the accompanying transmittal form.

More details can be found in section 6.1 of the MRI Procedure Manual.

TEST SCAN

- A test scan is required as part of site qualification, in order to confirm proper implementation of the MRI protocol and ability to submit in a compatible DICOM format. **Please note**, the test scan should only be submitted into the **M18-918** trial, unless instructed otherwise by Bioclinica.
- A healthy volunteer, non-study subject or local phantom can be scanned as a test, provided that the MRI requirements are followed. If a phantom is not available, a plastic bottle filled with water can also be used.
- Test scans should be repeated during the course of the study after any major software/hardware upgrade. If so, please use the same phantom as during site qualification.
- Gadolinium injection is not needed on test scans.
- When submitting test data, use the dedicated Transmittal Form. DICOM header can be populated as follows:

  In the **Subject Name** and **Study Description** fields, enter: **TEST**

  In the **Date of Birth** field, enter current date, if allowed by the scanner.

More details can be found in section 3.3.1 of the MRI Procedure Manual.

For any question regarding MRI acquisition, please contact M14-397@bioclinica.com

For any question or issue regarding data transfer, please refer to the dedicated SMART Submit Quick Reference Guide and contact smart.submit@bioclinica.com if needed.

Quick Reference Guide for the Acquisition of Subject MRI Scans

MRI SEQUENCE ACQUISITION - PROTOCOL CONTENT

- Sequences to be scanned in exact order (detailed parameters available as an annex):

  Brain MRI protocol

  1. **3D** Sagittal **T1**
  2. 2D Axial **FLAIR**
  3. 3D Axial **MT** (without and with MTC pulse)

     Contrast agent injection
  4. 2D Axial **PD/T2**
  5. 2D Axial **T1 post Gadolinium**
  6. 2D Axial **DTI** – if available on the MRI scanner

  Cervical Spine MRI protocol

  7. 2D Sagittal **T1**
  8. 2D Sagittal **STIR**
  9. 2D Axial **T2***

- A **phased-array coil** (8 elements or more) **approved by Bioclinica must be used**. If you start the study with a particular multi-channel phased-array coil, **you may not switch coils during the study**, even if the imaging facility acquires an RF coil with more elements.
- Please use PURE (GE), CLEAR (Philips) or Prescan Normalize (Siemens) to reduce RF inhomogeneities. For older GE 3T scanners, do not use SCIC instead of PURE.
- Please refer to the system-specific table annexed to this document for details regarding MRI parameters. The first page contains parameters for subject scans. The second page is for phantom scans only.

More details can be found in section 6.3 of the MRI Procedure Manual.

MRI SEQUENCE ACQUISITION - GENERAL STUDY GUIDANCE

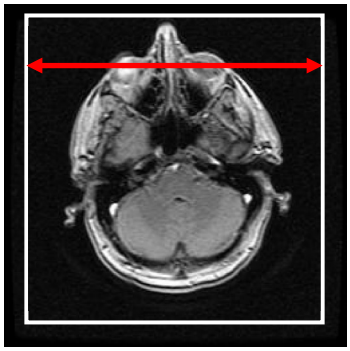
- Consistent image acquisition throughout this clinical trial is of utmost importance!
- For each follow-up visit, retrieve and use a subject's screening exam to ensure the settings and parameters are consistent between visits.
- The MRI protocol should be stored in your scanner and used for all visits
- The order of acquisitions should correspond to that indicated in the list above
- Any deviations from these instructions must be noted in the transmittal form comments and locally at the facility

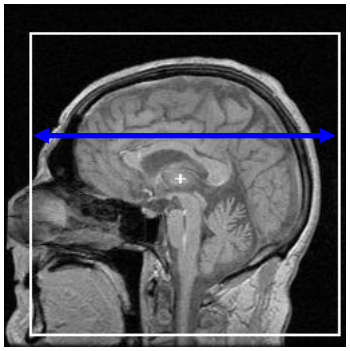
GADOLINIUM INJECTION

- Use your local injection procedures.
- **Macrocyclic agents are recommended (gadobutrol, gadoteric acid and gadoteridol).**
- Inject 0.1 mmol/kg over 30 seconds.
- There should be at least 5 minutes between injection and scanning the post-contrast Axial 2D T1-weighted MRI sequence. You can acquire the PD/T2 sequence right after injection, which should last long enough to avoid any waiting time before scanning the post-contrast T1.
- Should the bed have to be pulled out during the contrast injection, please perform another localizer to ensure consistent positioning prior to resuming scanning.

BRAIN MRI SEQUENCE ACQUISITION - PURPOSE AND ANGULATION

3D Sagittal T1



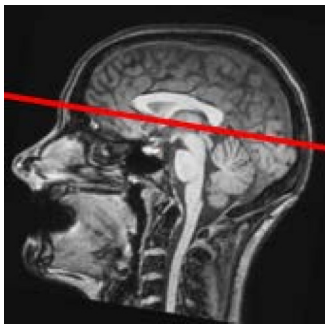


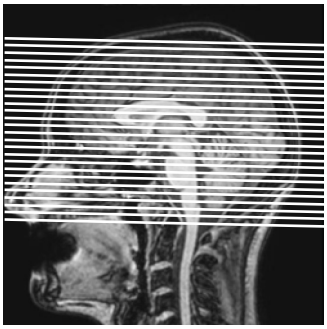
- Used to perform volumetric measurements (brain and upper cervical spine) and as a reference before injection in the detection of black holes.
- Orientation must be orthogonal Sagittal.
- Position the volume as shown. The **blue** and **red** lines show the phase and slice directions.
- Be sure to cover the brain both LR and AP.
- Since this brain sequence will also be used to measure the upper cervical spinal cord area, please ensure that the **FOV includes the C3/C4 intervertebral disc**, provided that there is **at least 5 mm left from top of the head to the top of the FOV**. The priority remains **full coverage of the brain** and skull.
- Parallel imaging is required (acceleration factor up to 2 depending on scanner).

3D Axial MT

- Used to assess structural integrity of tissues, and therefore global disease activity.
- 60 oblique axial slices (obtained with 60 partitions of 1 slab) must be acquired, parallel to the subcallosal line (see **red** line below).
- Stack must be positioned to acquire at least 2-3 blank slices (containing just air) above the top of the head.
- The MT scan MUST be performed prior to the administration of Gadolinium.
- **MT must be performed twice, first with no MTC pulse, then with the MTC pulse.**
- **For Philips scanners, a single interleaved sequence is expected. For other scanners, 2 sequences must be performed.**

2D Sequences – FLAIR, PD/T2, T1 Gd and DTI





- Used to detect T2-weighted lesions, Gd-enhancing lesions and black holes.
- Orientation: Angulate Axial 2D sequences parallel to the subcallosal line (see **red** line).
- Position on mid-sagittal slice. Be sure to obtain coverage of the entire brain. The acquisition stack should be placed at the most superior point of the brain, and fully cover the cerebellum as well as all the brain in the lateral and the anterior-posterior planes.
- Set angulation and positioning for the FLAIR sequence, by referring to the most relevant sagittal view from the localizer. Copy angulation settings for the DTI, PD/T2 and T1 Gd sequences.
- Inferior slab saturation should be applied for PD/T2 sequence only. Use approximately 50-mm flow saturation band inferior to the MRI slices and position just below the inferior slice and parallel to slice stack to reduce inflow effects (see **yellow** area).
- Parallel imaging is allowed, if available (acceleration factor up to 2).
- For the DTI sequence, please submit Trace and ADC maps along with all native images (b=0 and b=1000). NB: DTI is required only if available on the scanner.

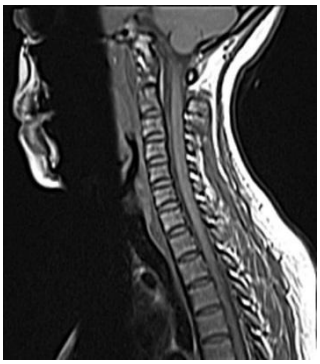
Gadolinium injection

- Use your local injection procedures. Cyclic contrast agents are preferred.
- Inject Gadolinium before acquiring the PD/T2 sequence. 5 minutes must pass before performing the post-contrast T1 sequence.

More details can be found in section 6.3 of the MRI Procedure Manual.

Cervical SPINE MRI SEQUENCE ACQUISITION - PURPOSE AND ANGULATION

Sagittal Sequences – T1 and STIR



- Used to detect cervical spine lesions and as a secondary measure of cervical spinal cord volume.
- Complete coverage of the cervical spine is required. Completely cover the cervical spine in R-L direction. The recommended number of slices will achieve required coverage in most cases. In exceptional cases, add as many slices as needed to ensure complete coverage.
- The FOV should be prescribed so that its **superior edge is 15-20 mm above C1 vertebral body** (approximately at the level of mid-pons).
- Set angulation and positioning for the T1 sequence and carry over those settings for the STIR.
- It is recommended to use a spatial saturation band placed on anterior neck to reduce swallowing artifacts over cervical spine, as shown (**yellow** area).

Axial Sequence – T2*

- Used to confirm the presence of focal cervical spinal cord lesions and diffuse signal abnormalities on another plane.
- Multi-echo gradient echo is required (GE: MERGE, Philips: mFFE, Siemens: MEDIC), in order to improve contrast. If these sequences are not available, a standard single-echo T2* sequence can be used.
- Complete coverage of the cervical spine is preferred.
- If full coverage is difficult to achieve and number of slices cannot be increased without greatly impacting scan time, position the top slice at the middle of C2/C3 disc and cover as much as possible caudally (e.g. downwards).

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