MEDICAL IMAGING SERVICES

Astellas Pharma Global Development, Inc. 2693-CL-0304

A Randomized, Placebo-Controlled, Double-Blind Phase 3 Clinical Study to Investigate the Long-Term Safety of Fezolinetant in Women Suffering From Vasomotor Symptoms (Hot Flashes) Associated with Menopause

Image Acquisition Guidelines - Dual Energy X-ray Absorptiometry (DXA)

Project:	**Astellas Pharma Global Development, Inc. 2693-CL-0304 / PAREXEL 242902**
Document File Name:	**Image Acquisition Guidelines - DXA**
Document Revision:	**1.0**
Version Date:	**24-May-2019**
Author:	**Farhan Syed, PhD**

Copyright Page

Document Approvals

Document Title: **Image Acquisition Guidelines - DXA**
Document Version: **1.0**
Project: **Astellas Pharma Global Development, Inc. 2693-CL-0304 / PAREXEL 242902**

This document has completed a review and is understood and accepted by the following:

28 May 2019

Sharon Kennedy
Senior Clinical Study Manager
Astellas Pharma Global Development, Inc.

Date

28 MAY 2019

Christopher Lademacher, MD, PhD
Executive Medical Director, Medical & Development
Astellas Pharma Global Development, Inc.

Date

PAREXEL internal signatures will be captured electronically through the PMED system.

Farhan Syed, PhD
Senior Director Scientific and Medical Services
PAREXEL Informatics

Kate Francis
Senior Project Manager
PAREXEL Informatics

Document Revision History

Version	Date	Authors	Description
1.0	24-May-2019	Farhan Syed	Initial release of document

TABLE OF CONTENTS

For inquiries regarding these guidelines, please contact:

PAREXEL Informatics Medical Imaging Team 242902

Email: **242902-Imaging@parexel.com**

INTRODUCTION

PAREXEL Informatics has developed the following acquisition guidelines for standardization of the study imaging components across radiology centers participating in the 2693-CL-0304 trial. Scheduled imaging for this study should be acquired in strict adherence to these guidelines. It is required that all images acquired as detailed below be submitted to PAREXEL.

Imaging Modality	Imaged Anatomy	Imaging Schedule[a]
DXA (Dual Energy X-ray Absorptiometry)	Hip[b] and Lumbar spine	• Screening • Visit 15/Week 52 • Early Withdrawal

a. For practical reasons, the timing of DXA may vary from the actual time of the visit, depending on the DXA availability (DXA appointment). The screening visit (days -35 to -1 [visit 1]) DXA can be performed once the subject has been deemed eligible based on screening laboratory tests, or at visit 2 but must be performed before randomization. The week 52 (visit 15) DXA should be performed between week 51 and week 52, inclusive. For subjects who are withdrawn from the study prior to completion, a DXA will be completed as soon as possible after study drug discontinuation (preferably within 2 weeks).

b. Use left hip at Screening unless left is not evaluable. For subsequent scans perform scan on same hip as was scanned at screening.

Scheduled imaging for this study should be acquired in strict adherence to these guidelines

IMAGE TRANSFER METHOD:

Digital images will be submitted via electronic transfer. **Electronic transfer is the preferred method of transmission.** All images should be submitted to PAREXEL no later than 3 business days of acquisition, (ideally within 1 day).

For information regarding image submission please refer to the Site Operations Manual.

For inquiries regarding these guidelines, please contact:

PAREXEL Informatics Medical Imaging Team 242902

Email: **242902-Imaging@parexel.com**

Important Notes

IMPORTANT:	**Imaging modality, instrument, anatomical positioning and coverage and imaging parameters should remain consistent across all imaging visits for any given study subject.**

Confidentiality: Please ensure the **blinding of all confidential subject/site information** on all images.

Blinding: Images sent to PAREXEL should be clear of any analysis, marks or annotations determined at the investigator site. Please do not analyze the scans prior to sending to PAREXEL.

Archival: All imaging data must be archived at the site as required by regulatory agencies. PAREXEL may request re-transmittal of the archived images.

Deviations: The imaging for this study should be acquired in strict adherence to these guidelines. If there are any deviations from these parameters please provide an explanation in the comments section during electronic image transfer.

Consistency: PAREXEL recommends having only one primary experienced and trained technologist performing DXA scans for all trial subjects. Sites should have a trained back-up technologist for performing the DXA scans.

Sites with more than one DXA scanner should only use one instrument to collect data for the trial. If the site anticipates using more than one scanner, written approval and instrument qualification must first be obtained from PAREXEL. **All subject's subsequent DXAs must be acquired on the same scanner on which they had their baseline scan in Screening.**

Quality Control: Investigator sites will conduct Quality Control/Quality Assurance (hereafter QC) activities for DXA systems prior to subject enrollment, throughout the course of the study, and after the site's last subject's last DXA. If any quality control measurement falls outside the manufacturer specified limits, contact your service engineer and notify PAREXEL's staff.

All QC acquisitions and subject scans should always be performed in the same scan mode. Subject positioning should be reproduced in all subsequent visits.

DXA Evaluability: At least 3 of 4 vertebrae in the L1 to L4 region must be evaluable by DXA and significant scoliosis/sclerosis, bone trauma, degenerative joint disease, and hardware or sequelae of orthopedic procedures that result in anatomy that is unsuitable for accurate bone densitometry must be absent from the lumbar spine or hip.

Important Note: DXA values obtained at the Screening Visit determine the point from which change is measured for this study. Correct subject positioning, scan acquisition and consistency at subsequent visits are key to obtaining reliable bone density measures.

If you have any questions on these criteria, please contact PAREXEL staff at 242902-Imaging@parexel.com

DXA Technicians:

- This Image Acquisition Guidelines is a supplementary tool to the DXA Operator's Manual.
- The DXA operator's manual, and this Image Acquisition Guidelines should be read and understood prior to scanning trial subjects. It is expected that all technicians who acquire scans for this trial have expert knowledge in scan acquisition and maintenance of the densitometer.
- To ensure consistent trial imaging, a maximum of two original individual DXA technicians should be involved and dedicated to this trial at each site. PAREXEL recommends having only one primary experienced and trained DXA technician scanning all trial subjects. Sites should have a trained back-up DXA technician for performing DXA scans under unavoidable circumstances.

DXA Instrument QC (IQC) Spine Phantom Scanning

IQC Activities Preceding 1st Subject Scanning: Baseline IQC

1. Prior to first subject enrollment, sites should scan their local spine phantom (used for routine daily calibration and provided with your equipment) ten (10) consecutive times, without altering the scanner settings or re-positioning the phantom. Please do not use block phantoms that do not contain bone equivalency.
    - PAREXEL will be using the Baseline IQC to determine the Baseline Mean BMD and monitoring that the mean BMD is within ±1.5%.
    - We recommend that you calculate your site's Baseline mean BMD and allowable range of ±1.5% to monitor the thresholds for the duration of the study.

2. Submit the current IQC phantom database with the 10 phantom measurements on the provided media or by electronic transfer.

Lunar: If you currently don't have a QC Phantom database, don't currently acquire a Daily QC Spine Phantom, or are unsure on how to copy the QC phantom database please contact PAREXEL, refer to the DXA IQC User Guide.

On-going IQC Activities:

1. Site's local spine phantom (likely used for routine daily calibration and provided with your equipment) must be scanned at **least three times a week** and in optimal conditions every day during the course of the trial, even if no subjects will be scanned that week. Please do not use block phantoms or ESP phantoms.

2. The QC Spine phantom scan must be acquired and analysed in a consistent manner using the same scan mode and Region of Interest.

3. The QC Spine phantom results must be reviewed to ensure the total BMD is within the QC Limits (High and Low Range) calculated at Baseline.

4. Please continue to use the same IQC phantom for the duration of this study.

5. Please be sure to analyze these scans consistently and repeat any scan that exceeds the allowable range (set at Baseline) for your scanner. If two sequential BMD's exceed the allowable range please report to PAREXEL as soon as possible and do not scan study subjects until the issue is resolved. Contact the scanner manufacturer to discuss and resolve the problem. Please see Documenting DXA Software Upgrades or Mechanical Problems section for further details.

   Please keep an archive of your QC Spine Phantom scans for future reference.

Monthly IQC Submissions:

1. A copy of your QC database must be sent to PAREXEL once monthly. These submissions are critical for central monitoring of your scanner's calibration.. Cumulative digital QC database files that are required for central review are as follows:

   - The current QC Phantom database on disc/CD or via electronic transfer – please place the according IQC media label on disc/CD indicating the month for IQC data.
   - For Lunar sites: QA.mdb and Lunar.mdb file (must have QC database separate from subject scan database). For sites with Lunar Encore 15 or higher IQC spine phantom scan files must be submitted.
   - For Hologic sites: QDR/Apex – QDR or *.mdb file

2. If your DXA facility is working with PAREXEL on more than one trial, only one monthly submission is required.

Final IQC Activities:

1. Acquisition of the QC Spine phantom must continue until ten (10) scans have been acquired following site's last subject's last visit or after the cross calibration phantom is scanned, whichever is later, then a Final QC phantom database must be sent to PAREXEL.

Submission of IQC data (Baseline, Ongoing, and Final):

Submission of IQC data is to be managed in the same way as patient imaging and should be submitted via eTransfer. Please see the Site Operations Manual (SOM) for additional information regarding the eTransfer process.

DXA EQUIPMENT SERVICE AND MAINTENANCE

DXA equipment or software should not be replaced or updated during the course of the study. If replacing the equipment or upgrading the software is absolutely inevitable, PAREXEL Informatics should be notified immediately, and study subjects should not be scanned until the following actions are undertaken:

- It is the site's responsibility to make sure the DXA Equipment is appropriately serviced and maintained.
- Software upgrades to DXA equipment should be approved in advance by PAREXEL.
- As part of the monthly IQC submission to PAREXEL, please submit any Maintenance Reports for that particular month.

- All maintenance and service (including preventative maintenance, software upgrades, etc.) should be noted on the Service Record Form along with a copy of the service report (when applicable).
- **Please use the same machine during the study and try to avoid hardware or software changes unless necessary.** If hardware or software changes must occur, please inform PAREXEL prior to the upgrade at **242902-Imaging@parexel.com**

Software Updates
Software updates should be approved by PAREXEL in advance.

Equipment Service and Maintenance:

Equipment should be appropriately serviced and maintained. Maintenance records should be captured on the DXA IQC Spine Phantom Maintenance Form provided by PAREXEL Informatics for the study.

Repairing the equipment may affect its calibration. Please ensure to document all maintenance, service, and repairs on service record forms. A service record form should be completed and sent to PAREXEL Informatics **if service was performed.** If service has occurred, please ensure that the service engineer completes the DXA IQC Spine Phantom Maintenance Form after each service visit. Send a completed copy of the form to PAREXEL Informatics with your next shipment, even if no maintenance was performed.

Important:

- If any quality control measurement falls outside the manufacturer specified limits, please verify the same technique was used to acquire and analyze the IQC scan, if no changes were implemented then please contact your DXA machine service engineer and notify PAREXEL Informatics' staff immediately.
- IQC Phantom acquisitions should **always** be performed using the same scan mode.

The monthly DXA IQC must be submitted on a monthly basis, even if no maintenance was performed.

DXA SCANNING

DXA Subject Preparation

1. Ensure that the subject has not been given: **oral barium, radioisotope injection, oral contrast for CT in the past seven days**, otherwise DXA visit should be re-scheduled. If the scan absolutely cannot be re-scheduled, please inform PAREXEL by contacting **242902-Imaging@parexel.com**.

2. Please record occurrences of non-removable artifacts (pacemaker leads, bone fractures, previous surgeries, radioactive seeds, bone implants, surgical staples, foreign bodies, heavy metal poisoning, kidney stones, etc.) in the comments section of the media label or during electronic submission or inform PAREXEL by contacting **242902-Imaging@parexel.com**.
3. To avoid artifact, please ensure that removable metallic or dense plastic objects such as underwire bras, clothing fasteners, contents of pockets and jewelry are removed prior to scanning. If an artifact cannot be removed, indicate the source of the artifact in the Image Deviation Form and request that this be consistent on all subsequent DXA scans.
4. It is preferable to have the subject change into a hospital gown or scrubs to avoid clothing artifacts.
5. Inform the subject of the duration of the scans, to lay still and quiet, and breathe normally. Remind the subject that if they move (talk, cough, etc.) that you will need to restart the scan.

DXA Subject Biography Entry

GE LUNAR	HOLOGIC
First Name: Enter "X" **Middle initial**: Enter "X" **Last Name**: Enter "X" **Patient ID**: Enter 7 digit subject ID (concatenated 4 digit site number and 3 digit subject number) **Gender**: Female **Physician**: Enter "2693-CL-0304" **Birth Date**: January 1, Year of Birth **Height**: Enter Height **Weight**: Enter Weight **Ethnicity:** Enter Ethnicity (Caucasian or Black) **Secondary Tab**: Leave Blank	**Last Name**: Enter "X" **First Name**: Enter "X" **Middle initial**: Enter "2693-CL-0304" **Sex**: Female **Birth Date**: January 1, Year of Birth **Patient ID**: Enter the 7 digit subject ID (concatenated 4 digit site number and 3 digit subject number) **Weight**: Enter Weight **Height**: Enter Height **Ethnicity:** Enter Ethnicity (Caucasian or Black)

1. Enter demographic data as received from the study coordinator or designee.
2. To maintain confidentiality of the subject it is important that no personal information (i.e., names, birthdates, etc.) is entered, (Only what is stated above). Please note: First Name or Last Name should not be entered in the biography, please enter in an "X" into the required field. Only the subject's year of birth is entered – the default date that should be entered for all subjects is January 1.
3. Only one biography should be created for each subject; **do NOT create a new biography at subsequent visits**.
4. At **subsequent visits**, review the original biography information prior to scanning the subject and make any necessary updates in the event that information was entered incorrectly at prior visit. **Make sure you are in the correct biography**. If a subject is scanned under the wrong biography or a second biography they may have to be re-scanned under the correct biography.
5. **Please do not add any additional information other than the fields listed above**.

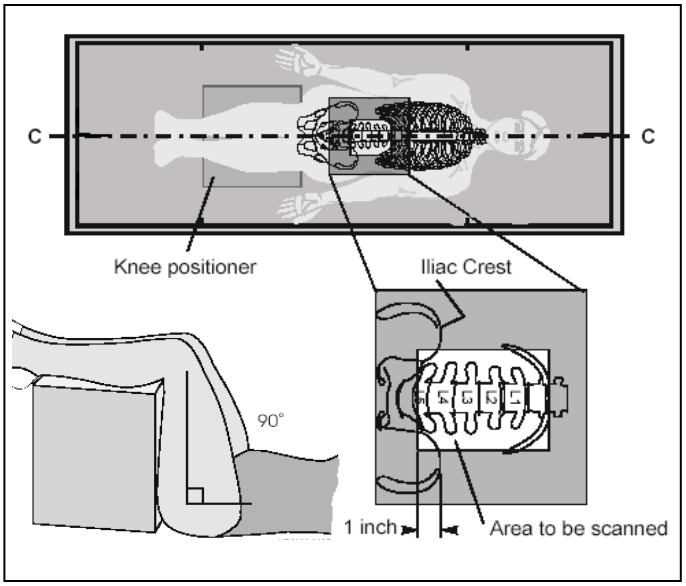
DXA Subject Scan Acquisition

AP LUMBAR SPINE SCAN

Scan type: AP Lumbar Spine. For GE Lunar, please do not use OneScan

Scan mode:

- Manufacturer recommended for optimal bone detail given subject size. Do not use 'fast' scan modes
- Use the same scan mode during subsequent scans.



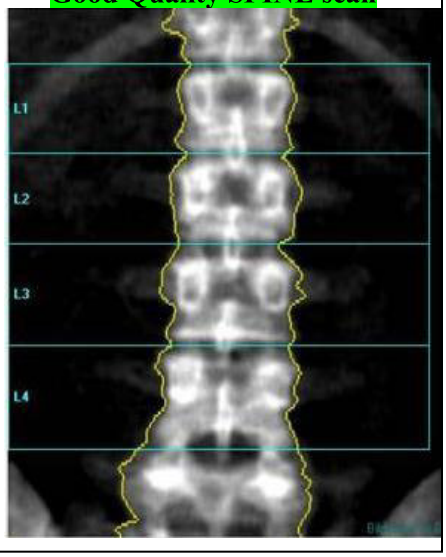
Subject positioning:

1. Help the subject to lie supine on the scan table in a supine position.
2. The subject's spine should be as straight as possible.
3. The subject's pelvis and shoulders should be aligned straight on the table pad.
4. Position the subject's lower legs on the support block until the subject's calves and thighs create a 60°-90° angle. This helps to reduce the lordotic curve of the subject's spine.
5. Arms should rest comfortably at the subject's sides.
6. **The area to be scanned must include the bottom half of T12 and the top half of L5**.

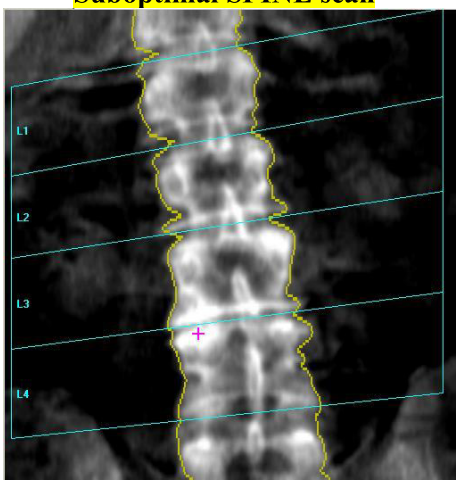
AP Lumbar Spine Scan Quality requirements:

- The AP Lumbar Spine is centered in the middle of the scan window.
- There are even amounts of soft tissue on each side of the spine.
- The top of the scan includes the middle of T12 (usually includes the lowest rib).
- The bottom of the scan includes at least half of L5 (usually includes some of the iliac crest).

Good Quality SPINE scan

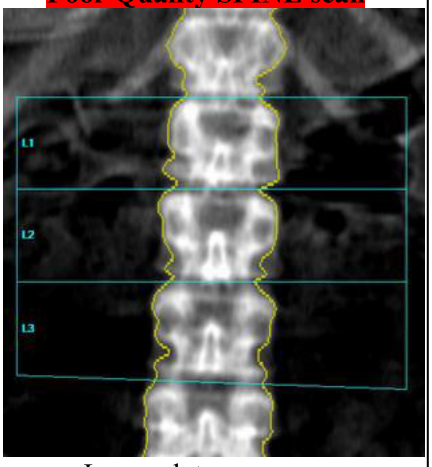


Suboptimal SPINE scan



Patient not positioned straight

Poor Quality SPINE scan

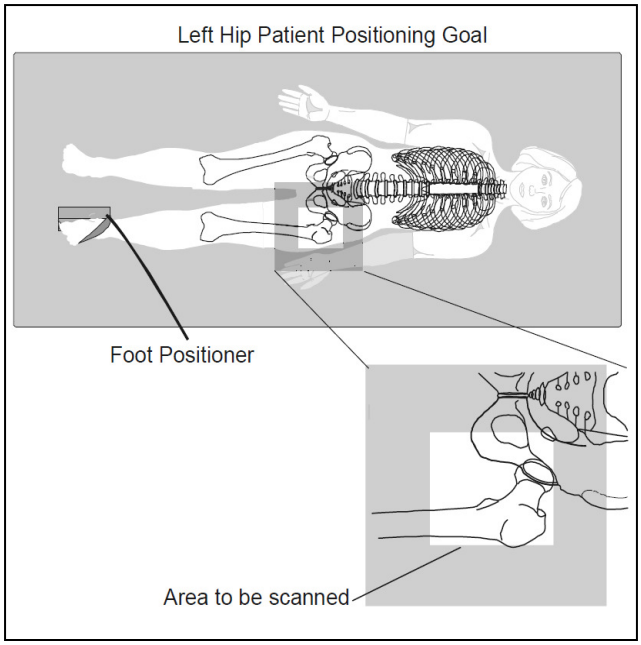


Incomplete coverage of L4 and L5

HIP (PROXIMAL FEMUR) SCAN

Scan type: Left Femur.

- The left hip is preferred, but right can be acquired only if left is not evaluable.
- **Sites should scan the same hip per subject throughout the duration of the study**.
- For GE Lunar please do not use 'Dual Femur' or 'OneScan'.



Scan mode:

- Manufacturer recommended for optimal detail given subject size
- Do not use 'fast' scan modes
- Use the same scan mode during subsequent scans.

Subject positioning:

1. The subject should be lying flat (supine) with pelvis centered on the table.
2. Place the foot positioner/foot brace under the subject's legs, and align the center of the positioner with the subject's midline. The foot positioner ensures the correct rotation of the leg for the scan.
3. Rotate the subject's entire leg (from hip socket to foot) 25° inward and place the medial edge of the foot against the foot positioning device. The foot should be flexed towards the ceiling.
4. Use straps to hold the foot in the correct position.
5. **Abduct the leg from the midline of the body in order to straighten femur and align the femur parallel to the table edge to provide adequate space for the neck box during analysis.**

Hip Scan Quality requirements:

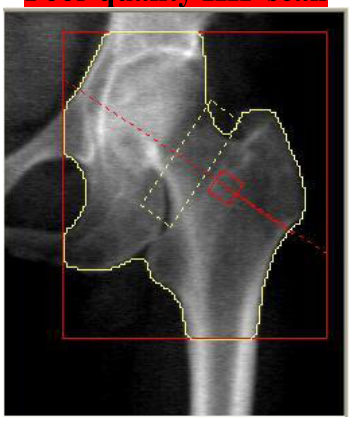
- The femoral shaft is straight and parallel to the edge of the scan.
- The greater trochanter is centered vertically in the scan window.
- The entire femoral head is visible.
- A 25° internal rotation of the hip showing minimal or no lesser trochanter on the scan.

Good Quality HIP scan

Suboptimal HIP scan

Leg not internally rotated and not centered in FOV

Poor quality HIP scan



Leg too close to body midline and not internally rotated

PAREXEL International Electronic Signature Page

This page is the manifestation of the electronic signature(s) used in compliance with PAREXEL International's electronic signature policies and procedures and in compliance with applicable regulations.

UserName: Syed, Farhan (syedf)
Title: Director, Scientific and Medical Services, MEDICAL IMAGING
Date: Wednesday, 29 May 2019, 07:27 PM GMT Standard Time
Meaning: Document contents approved.
==========

UserName: Francis, Kathryn (francik)
Title: Senior Project Manager, MEDICAL IMAGING
Date: Thursday, 30 May 2019, 04:04 PM GMT Standard Time
Meaning: Document contents approved.
==========