EXINI Diagnostics AB
% Donna-Bea Tillman, Ph.D.
Senior Consultant
Biologics Consulting Group, Inc.
1555 King Street, Suite 300
ALEXANDRIA VA 22314

August 5, 2019

Re: K191262
Trade/Device Name: aBSI
Regulation Number: 21 CFR 892.2050
Regulation Name: Picture archiving and communications system
Regulatory Class: Class II
Product Code: LLZ
Dated: May 9, 2019
Received: May 10, 2019

Dear Dr. Tillman:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for

devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

For

Thalia T. Mills, Ph.D.
Director
Division of Radiological Health
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
k191262

Device Name
aBSI

Indications for Use *(Describe)*
aBSI is intended to be used by trained healthcare professionals and researchers for acceptance, transfer, storage, image display, manipulation, quantification and reporting of digital medical images acquired using nuclear medicine (NM) imaging. The device provides general Picture Archiving and Communications System (PACS) tools as well as a clinical application for oncology including lesion marking and quantitative analysis.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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In accordance with 21 CFR 807.87(h) and (21 CFR 807.92) the 510(k) Summary for the *aBSI* is provided below.

1. SUBMITTER

K191262

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Date Prepared: May 9, 2019

2. DEVICE

Device Trade Name:	*aBSI*
Device Common Name:	Picture Archiving and Communications System (PACS)
Classification Name	21 CFR 892.2050 System, Image Processing, Radiological
Regulatory Class:	II
Product Code:	LLZ

3. PREDICATE DEVICE

Predicate Device: EXINI (K122205)

4. DEVICE DESCRIPTION

The *aBSI* is a software-only medical device that provides a fully quantitative assessment of a patient's skeletal disease on a bone scan, as the fraction of the total skeleton weight. The user of this product is typically a health-care professional using the software to view the patient images and analysis results.

5. INTENDED USE/INDICATIONS FOR USE

aBSI is intended to be used by trained healthcare professionals and researchers for acceptance, transfer, storage, image display, manipulation, quantification and reporting of digital medical images acquired using nuclear medicine (NM) imaging. The device provides general Picture Archiving and Communications System (PACS) tools as well as a clinical application for oncology including lesion marking and quantitative analysis.

6. SUBSTANTIVE EQUIVALENCE

Comparison of Indications

The image modality computed tomography (CT) has been removed from the intended use for *aBSI* compared to EXINI. The ability to also display CT images was a feature introduced in EXINI to allow for simultaneous viewing of both types of images. CT images are not required or used for BSI calculation and this feature was rarely used. Therefore, this feature has been removed and CT images are not accepted by the *aBSI* device. This change does not affect the fundamental intended use of the device, and EXINI can be used as a predicate for *aBSI*.

Technological Comparisons

The table below compares the key technological features of the subject devices to the predicate device

Table 1: Technological Comparison

	EXINI (predicate device)	***aBSI*** (subject device)	**Discussion of Differences**
Intended user	Health care professionals and researchers	Same	-
Intended use environment	Health care clinics	Same	-
Classification	System, Image Processing, Radiological (LLZ) 21 CFR 892.2050	Same	-
Installation	Product CDs or downloadable installation files	Cloud-based service and access with personal log-in.	Does not affect the clinical use of the device
Operating system	Microsoft Windows	Microsoft Windows or macOS with Chrome browser	Does not affect the clinical use of the device

	EXINI (predicate device)	***aBSI*** (subject device)	**Discussion of Differences**
DICOM compatibility	DICOM 3: • Whole body bone scans • Static (partial) bone scans • SPECT/CT	DICOM 3: • Whole body bone scans • SPECT	Static (partial) bone scans and CT images are not required or used for BSI calculation.
Image upload	Via DICOM SCP or folder on local computer or network	Via folder on local computer or network	Does not affect the clinical use of the device
Support for multiple Bone Scans	Yes, if multiple scans are provided, the images are automatically aligned vertically	Same	-
Colormaps	A selection of commonly used colormaps	Sub-Selection of previously provided colormaps.	Optimal colormaps continue to be provided
Zoom	Manually adjustable image size Zoom	Automatically adjusted image size Zoom	To improve the efficiency of *aBSI* automatic adjustment of images to screen size
Windowing	• Automatic adjustment of maximum and minimum thresholds for image windowing • Manual adjustment of maximum and minimum thresholds	• Automatic adjustment of maximum and minimum thresholds for image windowing (same) • Manual adjustment of maximum and minimum thresholds has a wider range	Both devices show normalized images at startup and have adjustable min and max thresholds for image windowing.
Intensity display	Local intensity displayed at mouse pointer when hovering over image	Local intensity displayed in left corner of the image when hovering over image	To improve visibility of the intensity
Image layouts	• Anterior and posterior images shown side by side • Mirror tool for switching between the anterior and posterior image in the same image frame	• Anterior and posterior images shown side by side	Removal of feature does not impact clinical utility of the device
Image Quality Control	• Total image intensity displayed • Skeletal image count displayed	• Total image intensity displayed	Both devices display total image intensities. Total image intensity is the common way of assessing image quality, therefore total skeletal intensity is not needed.
Hotspot display	• Hotspots displayed in image • Hotspot involvements are displayed in tables. One table per scan.	• Hotspots displayed in image	Both devices display hotspots in the images.

	EXINI (predicate device)	***aBSI*** (subject device)	**Discussion of Differences**
Segmentation of skeletal atlas	Segmentation of skeletal atlas covering the area from the skull down to ¾ of the femur and humerus.	Segmentation refined, and skeletal area covered by the atlas increased to cover the entire femur and humerus.	Allows for detection of hotspots further out in the limbs.
Normalization	Images are normalized so that healthy bone tissue intensities are automatically set to a predefined level.	Same	-
Hotspot detection	Algorithm to detect high intensity regions of interest within the skeletal atlas.	Improved algorithm to detect of high intensity regions of interest within the skeletal atlas.	Results of clinical performance testing demonstrate substantially equivalent performance.
Summary page export	Supported	Supported	-
CSV export	N/A	Supported	This feature was implemented to facilitate *aBSI* use in research studies.

The EXINI was cleared in 2012 with BSI quantification as an integral feature. Since its clearance, the device algorithm has evolved, and the device is now hosted in cloud infrastructure. However, the essential BSI quantification feature of the device remained substantially equivalent.

7. PERFORMANCE DATA

Biocompatibility Testing

There are no direct or indirect patient-contacting components of the subject device. Therefore, patient contact information is not needed for this device.

Electrical safety and electromagnetic compatibility (EMC)

Not applicable. The subject device is a software-only device. It contains no electric components, generates no electrical emissions, and uses no electrical energy of any type.

Software Verification and Validation Testing

Software verification and validation testing were conducted and documentation was provided as recommended by FDA's Guidance for Industry and FDA Staff, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices." The software for this device was considered as a **moderate** level of concern because, although unlikely, an incorrect BSI value could potentially contribute to the risk of an incorrect therapy decision or delay in the delivery of appropriate care.

Bench Testing

EXINI Diagnostics conducted verification to demonstrate the performance of the device, including:

- A set of analytical validation studies to evaluate the performance of the *aBSI* v3.4 in quantifying bone scans, including:
    - Linearity & Accuracy of BSI calculation
    - Precision of BSI calculation
    - Reproducibility with different cameras
    - Reproducibility with multiple images
- Patient study to demonstrate Reproducibility of BSI calculation with Repeated Bone Scans
- Comparison testing using a phantom simulation to compare the bone scan index determined with predicate EXINI 1.7 to that the subject device *aBSI*.

Animal Testing

Not applicable. Animal studies are not necessary to establish the substantial equivalence of this device.

Clinical Data

Results from the two clinical studies comparing *aBSI* assessment to standard interpretation of bone scan demonstrated the utility of *aBSI* device against the state of the art (PCWG criteria) and essential clinical outcomes.

Study Number	Title	Objective	Design	Patients
I	Phase 3 validation of the automated Bone Scan Index association with overall survival in men with metastatic castration-resistant prostate cancer	Association of *aBSI* with clinical outcome – overall survival, progression free survival, opioid induced survival	Prospective Planned Analysis – A multi-site study phase III: **NTC 01234311**	Prostate Cancer (N=721)
II	Optimizing Radiographic Progression Free Survival by Prostate Cancer Working Group (PCWG) Criteria using the Automated Bone Scan Index (*aBSI*)	Comparison of *aBSI* increase against counting number of new lesions (by PCWG criteria) in radiographic progression	Retrospective study at Memorial Sloan Kettering Cancer Center – single site	Prostate Cancer (N=169)

Study I involved a prospectively defined analysis of patients in a phase 3 international, multicenter study. This phase 3 study was a multicenter randomized, double-blind, placebo-controlled study of tasquinimod (10TASQ10) in metastatic castration-resistant prostate cancer mCRPC patients. Study subjects were recruited at 241 sites in 37 countries (including the US).

Of the total 1245 phase 3 patients enrolled in 37 countries, 721 patients were evaluable with aBSI. The aBSI population was representative of the total study population based on baseline characteristics. Automated BSI (median=1.07; range: 0–32.60) was significantly associated with OS (HR:1.20; 95%CI:1.14-1.26; P<0.001). Median OS by automated aBSI quartile (lowest to highest) was 34.7, 27.3, 21.7, and 13.3 months, respectively. In a multivariate survival model, the automated aBSI remained independently associated with OS (HR:1.06; 95%CI:1.01-1.11; P=0.03). The automated BSI was also independently associated with symptomatic progression (HR:1.18; 95%CI:1.13-1.23; P<0.001), and time to opiate use for pain (HR:1.21; 95%CI:1.15-1.29; P<0.001). The results of Study I provide compelling evidence that the clinical performance of quantitative *aBSI* assessment is additive to the existing clinical parameters.

In Study II, patients at Memorial Sloan Kettering Cancer Center (MSKCC) with metastatic prostate cancer (mCRPC) were enrolled in Phase II/III clinical trials of agents targeting the androgen receptor (AR) signaling axis and were assessed retrospectively for this analysis. A total of 257 patients were assessed, of whom 169 had bone scans available for the *aBSI* analysis. The median *aBSI* at baseline was 3.1 (IQR: 1.3 – 7.1). An increase in *aBSI* was associated with OS at a Kendall's Tau of 0.52 when the *aBSI* increased by 0.6. An *aBSI* increase beyond 0.6 from first follow-up did not result in further improvement in the association with OS. The same association of time to radiographic bone progression was observed (0.52) with PCWG criteria. Of the 169 patients, 90 (53%) had progression in bone cancer that met the PCWG criteria. The total *aBSI* increase in patients that met the PCWG criteria was 1.22 [IQR: 0.65-2.49] and a median relative increase of 109% [IQR: 40-377%]. These results demonstrate that the total quantitative assessment of increase in skeletal disease burden, with *aBSI* assessment, has the same association with overall survival as that defined by PCWG criteria.

8. CONCLUSION

Based on the detailed comparison between the predicate devices and the subject devices, the performance testing and clinical data, the *aBSI* can be found substantially equivalent to the predicate device.