PRESS RELEASE

This press release is for U.S. audiences only

Blue Earth Diagnostics Announces Publication of Post-hoc Analysis Evaluating Impact of Urinary Activity on Image Interpretation of POSLUMA® (Flotufolastat F 18) PET in Prostate Cancer

– Qualitative analysis showed 96% of POSLUMA PET/CT scan interpretations not impacted by urinary activity –

– Results published in Molecular Imaging and Biology based on data from prospective Phase 3 LIGHTHOUSE and SPOTLIGHT studies in newly diagnosed and recurrent prostate cancer –

MONROE TOWNSHIP, NJ, and OXFORD, UK, November 28, 2023 – Blue Earth Diagnostics, a Bracco company and recognized leader in the development and commercialization of innovative PET radiopharmaceuticals, today announced the publication of results of a post-hoc analysis assessing the impact of urinary activity on the interpretation of POSLUMA® (flotufolastat F 18) injection (formerly known as ^{18}F-rhPSMA-7.3) PET/CT in prostate cancer. The analysis was based on data from Blue Earth Diagnostics' prospective Phase 3 LIGHTHOUSE[1] and SPOTLIGHT[2] studies that evaluated the diagnostic performance and safety of POSLUMA in newly diagnosed and recurrent prostate cancer. Majority read results from 3 blinded readers assessing 712 evaluable POSLUMA scans showed that urinary activity in the bladder and ureters did not influence disease assessment for the vast majority (96%, 682/712) of patients. Halo artifacts, which can inhibit image assessment, were very rare, and were absent in 99.7% (710/712) of patients by majority read. Ureteric activity, which can also limit assessment of lymph nodes distant to the bladder, was also absent in a majority of patients (56%, 401/712). FDA-approved POSLUMA is indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy or with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.

The results, "Quantitative and qualitative assessment of urinary activity of ^{18}F-flotufolastat-PET/CT in patients with prostate cancer: A post-hoc analysis of the LIGHTHOUSE and SPOTLIGHT studies," were published online in *Molecular Imaging and Biology* (2023), https://doi.org/10.1007/s11307-023-01867-w and will also appear in an upcoming print issue. Authors are Phillip H. Kuo, Departments of Medical Imaging, Medicine, and Biomedical Engineering, University of Arizona, Tucson, AZ, USA, and Southern Arizona Veterans Administration Healthcare System; Rick Hermsen, Department of Nuclear Medicine, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands; Ross Penny and Ernst J. Postema, Blue Earth Diagnostics Ltd, Oxford, UK.

"The ability to gather actionable information from PSMA PET scans is important for physicians to make informed decisions about patient management for men with prostate cancer," said Phillip Kuo, MD, Ph.D., Departments of Medical Imaging, Medicine, and Biomedical Engineering. "Activity in the urinary

bladder and ureters is a common feature of PSMA-PET radiopharmaceuticals. It can potentially obscure tumors and lymph nodes in the prostate region – the most common site of recurrence – as well as pelvic and retroperitoneal lymph nodes distant to the prostate region, interfering with accurate image interpretation. In early clinical experience, POSLUMA demonstrated a high binding affinity for PSMA, with low urinary activity, providing enhanced image evaluation in the prostate and regions near the ureters for patients with prostate cancer. Results from this large dataset, based on images from two Phase 3 prospective trials, build on that experience and demonstrate that POSLUMA urinary activity is low and rarely impacts disease assessment."

"This analysis of FDA-approved POSLUMA marks the first and only published assessment of urinary activity for a PSMA-targeted PET/CT prostate cancer agent, and we are pleased that the results have been published in *Molecular Imaging and Biology* where they can be widely shared with the imaging community," said David E. Gauden, D.Phil., Chief Executive Officer of Blue Earth Diagnostics. "POSLUMA represents a new class of PSMA-targeted PET radiopharmaceuticals based on novel radiohybrid technology. It is engineered to advance clinical decision-making by providing clinically precise information for treatment planning in men with prostate cancer, which can lead to changes in patient management. We believe that POSLUMA's diagnostic performance, high-affinity PSMA binding and low urinary activity characteristics make it a valuable diagnostic tool that is radiolabeled with ^{18}F for high image quality and readily available patient access."

Published results were based on 712 evaluable POSLUMA scans (348 newly diagnosed patients and 364 patients with recurrent prostate cancer from LIGHTHOUSE and SPOTLIGHT, respectively). Of the 718 eligible scans, 6 were excluded on the basis of cystectomy, renal failure or presence of a urinary catheter. Findings included quantitative analyses of activity in the urinary bladder, based on maximum and mean standardized uptake values (SUV_{max} and SUV_{mean}, respectively). Qualitative analyses conducted by 3 blinded, independent PET readers examined the impact of any urinary activity on the ability to assess the prostate/prostate bed and pelvic lymph nodes using a 3-point scale.

The median bladder SUV_{max} and SUV_{mean} for POSLUMA were 17.1 and 12.5, respectively. For the qualitative metrics, by majority read, it was possible to distinguish urinary activity from disease uptake in 96% (682/712) of patients. Halo artifacts impacting assessment around the ureters and bladder were only observed in 0.3% (2/712) of patients.

There were several limitations to the study. It was not designed as a head-to-head comparison with other PSMA-PET radiopharmaceuticals and any comparisons with other radiopharmaceuticals reported in the literature should be made with caution. Another limitation was that reader agreement was not formally tested, however the authors noted that patient-level inter-reader agreement has been previously reported as ≥ 95%[3] and ≥ 75%[4] for LIGHTHOUSE and SPOTLIGHT respectively. Image interpretation errors can occur with POSLUMA PET. A negative image does not rule out the presence of prostate cancer and a positive image does not confirm the presence of prostate cancer.

Blue Earth Diagnostics' LIGHTHOUSE Phase 3 clinical trial (NC04186819) was a prospective, Phase 3, multi-center, single-arm, imaging study conducted in the United States and Europe to evaluate the safety and diagnostic performance of POSLUMA PET in men with newly diagnosed prostate cancer. Results from the SPOTLIGHT study were published in *European Urology* DOI.org/10.1016/j.eururo.2023.06.018[1]. The SPOTLIGHT trial (NCT04186845) was a Phase 3, multi-center, single-arm imaging study conducted in the United States and Europe to evaluate the safety and diagnostic performance of POSLUMA PET imaging in men with suspected prostate cancer recurrence

based on elevated PSA following prior therapy. Results from the SPOTLIGHT study were published in the *Journal of Urology*: DOI: 10.1097/JU.0000000000003493.[2]

About POSLUMA® (flotufolastat F 18)

POSLUMA® (flotufolastat F 18) injection (formerly referred to as ^{18}F-rhPSMA-7.3) is an optimized, targeted radiohybrid diagnostic imaging agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy or with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level. Precision PET imaging with POSLUMA can help identify the location and extent of prostate cancer, providing clinically valuable information to guide patient management. POSLUMA represents a new class of high-affinity PSMA-targeted PET radiopharmaceuticals based on novel radiohybrid technology and is labeled with the radioisotope ^{18}F to provide readily available patient access and leverage the high image quality of ^{18}F-labeled PSMA PET imaging to facilitate effective detection of disease. POSLUMA was approved by the U.S. Food and Drug Administration in May 2023.

About Radiohybrid Prostate-Specific Membrane Antigen (rhPSMA)

Radiohybrid Prostate-Specific Membrane Antigen (rhPSMA) compounds consist of a radiohybrid ("rh") Prostate-Specific Membrane Antigen-targeted receptor ligand which attaches to and is internalized by prostate cancer cells, and they may be radiolabeled with imaging isotopes for PET imaging, or with therapeutic isotopes for therapeutic use – providing the potential for creating a true theranostic technology. Radiohybrid technology and rhPSMA originated from the Technical University of Munich, Germany. Blue Earth Diagnostics acquired exclusive, worldwide rights to rhPSMA diagnostic imaging technology from Scintomics GmbH in 2018, and therapeutic rights in 2020, and sublicensed the therapeutic application to its sister company Blue Earth Therapeutics. Blue Earth Diagnostics received U.S. Food and Drug Administration approval for its radiohybrid PET diagnostic imaging product for use in prostate cancer in 2023. rhPSMA compounds for potential therapeutic use are investigational and have not received regulatory approval.

Indication and Important Safety Information About POSLUMA

INDICATION

POSLUMA® (flotufolastat F 18) injection is indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer

- with suspected metastasis who are candidates for initial definitive therapy
- with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level

IMPORTANT SAFETY INFORMATION

- Image interpretation errors can occur with POSLUMA PET. A negative image does not rule out the presence of prostate cancer and a positive image does not confirm the presence of prostate cancer. The performance of POSLUMA for imaging metastatic pelvic lymph nodes in patients prior to initial definitive therapy seems to be affected by serum PSA levels and risk grouping. The performance of POSLUMA for imaging patients with biochemical evidence of recurrence of prostate cancer seems to be affected by serum PSA levels. Flotufolastat F 18 uptake is not specific for prostate cancer and may occur in other types of cancer, in non-malignant processes, and in normal tissues. Clinical correlation, which may include histopathological evaluation, is recommended.

- Risk of Image Misinterpretation in Patients with Suspected Prostate Cancer Recurrence: The interpretation of POSLUMA PET may differ depending on imaging readers, particularly in the prostate/prostate bed region. Because of the associated risk of false positive interpretation, consider multidisciplinary consultation and histopathological confirmation when clinical decision-making hinges on flotufolastat F 18 uptake only in the prostate/prostate bed region or only on uptake interpreted as borderline.
- POSLUMA use contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Advise patients to hydrate before and after administration and to void frequently after administration. Ensure safe handling to minimize radiation exposure to the patient and health care providers.
- The adverse reactions reported in ≥0.4% of patients in clinical studies were diarrhea, blood pressure increase and injection site pain.
- Drug Interactions: androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, may result in changes in uptake of flotufolastat F 18 in prostate cancer. The effect of these therapies on performance of POSLUMA PET has not been established.

To report suspected adverse reactions to POSLUMA, call 1-844-POSLUMA (1-844-767-5862) or contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Full POSLUMA prescribing information is available at www.posluma.com/prescribing-information.pdf.

About Blue Earth Diagnostics
Blue Earth Diagnostics, an indirect subsidiary of Bracco Imaging S.p.A., is a growing international molecular imaging company focused on delivering innovative, well-differentiated diagnostic solutions that inform patient care. Formed in 2014, the Company's success is driven by its management expertise and supported by a demonstrated track record of rapid development and commercialization of positron emission tomography (PET) radiopharmaceuticals. Blue Earth Diagnostics' expanding oncology portfolio encompasses a variety of disease states, including prostate cancer and neuro-oncology. Blue Earth Diagnostics is committed to the timely development and commercialization of precision radiopharmaceuticals for potential use in imaging and therapy. For more information, please visit: www.blueearthdiagnostics.com.

About Bracco Imaging
Bracco Imaging S.p.A., part of the Bracco Group, is a world-leading diagnostic imaging provider. Headquartered in Milan, Italy, Bracco Imaging develops, manufactures and markets diagnostic imaging agents and solutions. It offers a product and solution portfolio for all key diagnostic imaging modalities: X-ray imaging (including Computed Tomography-CT, Interventional Radiology, and Cardiac Catheterization), Magnetic Resonance Imaging (MRI), Contrast Enhanced Ultrasound (CEUS), and Nuclear Medicine through radioactive tracers and novel PET imaging agents to inform clinical management and guide care for cancer patients in areas of unmet medical need. Our continually evolving portfolio is completed by a range of medical devices, advanced administration systems and dose-management software. In 2019 Bracco Imaging enriched its product portfolio by expanding the range of oncology nuclear imaging solutions in the urology segment and other specialties with the acquisition of Blue Earth Diagnostics. In 2021, Bracco Imaging established Blue Earth Therapeutics as a separate, cutting-edge biotechnology vehicle to develop radiopharmaceutical therapies. Visit: www.braccoimaging.com.

References

[1]Surasi DS, Eiber M, Maurer T, et al. (2023) Diagnostic performance and safety of positron emission tomography with ^{18}F-rhPSMA-7.3 in patients with newly diagnosed unfavourable intermediate to very high-risk prostate cancer: results from a phase 3, prospective, multicentre study (LIGHTHOUSE). *Eur Urol* 84(4):361-370.
[2]Jani AB, Ravizzini G, Gartrell BA, et al. (2023) Diagnostic performance and safety of ^{18}F-rhPSMA-7.3 PET in men with suspected prostate cancer recurrence: Results from a phase 3, prospective, multicenter study (SPOTLIGHT). *J Urol* 210:299-311.
[3]Kuo P, Ravizzini G, Ulaner GA, Yoo D, Zukotynski K, LIGHTHOUSE Study Group. (2023) Inter- and intra-reader reproducibility of ^{18}F-rhPSMA-7.3 PET interpretation in patients with newly diagnosed prostate cancer: Results from a phase 3, prospective, multicenter study (LIGHTHOUSE) [abstract]. In: Proceedings of SNMMI Annual Meeting 2023: *J Nucl Med*;64(1):P58.
[4]Kuo P, Esposito G, Yoo D, Zukotynski K, SPOTLIGHT Study Group. (2022) Inter- and intra-reader reproducibility of ^{18}F-rhPSMA-7.3 PET image interpretation in patients with suspected prostate cancer recurrence: Results from a phase 3, prospective, multicenter study (SPOTLIGHT) [abstract]. In: Proceedings of SNMMI Annual Meeting 2022. *J Nucl Med*; 63(2):2539.

Contact:

For Blue Earth Diagnostics (U.S.)
Priscilla Harlan
Vice President, Corporate Communications
(M) (781) 799-7917
priscilla.harlan@blueearthdx.com

For Blue Earth Diagnostics (UK)
Clare Gidley
Associate Director Marketing and Communications
Tel: +44 (0) 7917 536939
clare.gidley@blueearthdx.com

Media
Sam Brown Inc.
Mike Beyer
(M) (312) 961-2502
mikebeyer@sambrown.com

# # #