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PRESS RELEASE

FDA approves Novartis radioligand therapy Pluvicto® for earlier use before chemotherapy in PSMA-positive metastatic castration-resistant prostate cancer

Ad hoc announcement pursuant to Art. 53 LR

- *New indication approximately triples eligible patient population, allowing Pluvicto® to be used after one androgen receptor pathway inhibitor (ARPI) and now before chemotherapy*
- *Pluvicto significantly reduced risk of progression or death by 59% and more than doubled median radiographic progression-free survival (rPFS) vs. change in ARPI in Phase III PSMAfore trial**
- *Approximately half of patients do not live long enough to receive a second treatment for mCRPC, highlighting need for earlier use of effective therapies with demonstrated tolerability*[1]
- *Multiple RLT manufacturing facilities in US fully meet supply needs for expanded indication, with industry-leading infrastructure to accelerate delivery of RLTs to patients*

Basel, March 28, 2025 – Novartis announced today that the US Food and Drug Administration (FDA) approved Pluvicto® (lutetium Lu 177 vipivotide tetraxetan) for patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with an androgen receptor pathway inhibitor (ARPI) therapy and are considered appropriate to delay chemotherapy.

The expanded indication, which approximately triples the number of patients eligible to receive Pluvicto, is based on results of the Phase III PSMAfore trial. In the study, Pluvicto reduced the risk of radiographic progression or death by 59% (HR=0.41; 95% CI: 0.29, 0.56; p<0.0001) compared to a change in ARPI in patients with PSMA-positive mCRPC after treatment with ARPI therapy. At an updated exploratory analysis, Pluvicto more than doubled median radiographic progression-free survival (11.6 months vs. 5.6 months)*.

“The earlier indication for Pluvicto could really change our treatment paradigms for patients with mCRPC. It offers a targeted therapy that better delays disease progression compared to a second ARPI,” said Michael Morris, MD, Prostate Cancer Section Head, GU Oncology, Memorial Sloan Kettering Cancer Center, and the Principal Investigator of the study in the US. “This approval is a significant step forward and should open the doorway to a therapy that has clear clinical advantages for the patient with mCRPC who has progressed on one ARPI and has not received chemotherapy.”

In PSMAfore, the final overall survival (OS) analysis numerically favored Pluvicto, with a hazard ratio of 0.91 (95% CI: 0.72, 1.14), but was not statistically significant. The OS analysis was confounded by the high rate of patients who crossed over from the control arm to Pluvicto (60.3%). When adjusted for crossover, the OS hazard ratio was 0.59 (95% CI: 0.38, 0.91) with the inverse probability of censoring weighting (IPCW) method**.

Additional findings from the PSMAfore study showed Pluvicto demonstrated a consistent and favorable safety profile. The most frequently reported all-grade adverse events for Pluvicto were primarily Grade 1-2 and included dry mouth (61%), fatigue (53%), nausea (32%), and constipation (22%). Pluvicto did not impair the ability of patients to be treated with subsequent chemotherapy.

“The clinical development of PSMA-targeting radioligand therapy has provided important insights into the treatment of metastatic castration-resistant prostate cancer,” said Oliver Sartor, MD, Chair of Genitourinary Cancer Disease Group and Director of Radiopharmaceutical Clinical Trials, Mayo Clinic. “The trial data demonstrated a clear clinical benefit in delaying disease progression in eligible patients, offering an additional therapeutic approach in this setting.”

More than 35,000 men die from prostate cancer each year, and the incidence of the disease is rising.[2] Half of patients with mCRPC will not live long enough to receive a second treatment.[1] While hormone therapy and chemotherapy are essential treatments for mCRPC, they may not be appropriate for all patients.[3] Many patients and their healthcare providers prefer to avoid or delay chemotherapy due to side effects, and treatment guidelines recommend avoiding the use of multiple ARPIs.[4-7]

“With worsening outcomes after each successive line of treatment, patients with this type of metastatic prostate cancer and their families have long faced limited options and uncertain outcomes,” said Gina Carithers, CEO and President of the Prostate Cancer Foundation.[8] “The now expanded approval of Pluvicto is an empowering development for the prostate cancer community. We now have more choices earlier in the treatment journey, enabling patients to advocate for their preferences and work with their oncologist or urologist to determine the treatment option that best suits their needs.”

“Today’s approval for an expanded indication for Pluvicto brings more choice to nearly three times as many patients, enabling us to further establish radioligand therapies as a pillar in cancer care,” said Victor Bultó, President US, Novartis. “As pioneers in the RLT space, Novartis is committed to providing education, resources, and practical solutions to healthcare providers to help ensure access for all patients navigating this challenging disease.”

Novartis RLT Patient and Office Support
As the only organization with a dedicated commercial RLT portfolio, we have established a strong infrastructure to ensure patient access and now offer Pluvicto in multiple administration methods, including prefilled syringes. With unparalleled customer experience in the RLT space, Novartis can deliver Pluvicto to the nearly 600 US RLT treatment sites, typically within 5 days to ensure prompt treatment initiation.

Novartis has introduced innovative solutions—including the newly launched RLT Institute—to educate and simplify the integration of RLT into routine clinical practice. The Novartis RLT Institute is an educational platform focused on radiation safety for the setup of treatment sites, equipping site staff with the necessary knowledge to safely administer RLT.

Novartis Patient Support is available to help eligible patients get started on treatment, including help understanding insurance coverage and identifying potential financial assistance options. Patients or providers can speak to a live agent at 1-844-638-7222 or visit https://us.pluvicto.com/support/novartis-patient-support.

About Pluvicto® (lutetium Lu 177 vipivotide tetraxetan)
Pluvicto is an intravenous radioligand therapy (RLT) combining a targeting compound (a ligand) with a therapeutic radionuclide (a radioactive particle, in this case lutetium-177). After administration into the bloodstream, Pluvicto binds to target cells, including prostate cancer cells that express PSMA, a transmembrane protein. Once bound, energy emissions from the radioisotope damage the target cells and nearby cells, disrupting their ability to replicate and/or triggering cell death.

Based on two Phase III studies, Pluvicto is the only PSMA-targeted agent proven to significantly improve rPFS and demonstrate a safety profile with proven tolerability in both pre- and post-taxane settings for patients with ARPI-treated, PSMA-positive mCRPC. Pluvicto is the first and only targeted radioligand therapy for patients with PSMA-positive mCRPC before the need for chemotherapy.

Novartis is investigating Pluvicto in earlier stages of disease, including metastatic hormone-sensitive prostate cancer (PSMAddition, NCT04720157) and oligometastatic prostate cancer (PSMA-DC, NCT05939414).

*Results observed at third interim analysis of PSMAfore (NCT04689828) with a data cutoff of February 2024. Pluvicto met its primary endpoint of rPFS at the primary analysis based on centrally confirmed rPFS events with an October 2022 data cut off.
**IPCW is an established statistical method that includes a number of assumptions

Novartis and Radioligand Therapy (RLT)
Novartis is reimagining cancer care with RLT for patients with advanced cancers. By harnessing the power of targeted radiation and applying it to advanced cancers, RLT is designed to deliver treatment directly to target cells anywhere in the body.

Novartis is investigating a broad portfolio of RLTs, exploring new isotopes, ligands and combination therapies to look beyond gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and prostate cancer and into breast, colon, lung and pancreatic cancer. Novartis has established global expertise, with specialized supply chain and manufacturing capabilities across its network of RLT production sites. To support growing demand for RLTs, we have expanded production capabilities in Millburn, N.J.; Zaragoza, Spain; Ivrea, Italy; and a state-of-the-art facility in Indianapolis, Ind. In Carlsbad, Calif., Novartis is establishing its third RLT US-based manufacturing site to support expanded use of RLTs, create resiliency in its manufacturing network and optimize the delivery of medicines to patients on the West Coast.

Disclaimer
This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “may,” “could,” “would,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “launch,” “goals,” “outcomes,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for Pluvicto, or regarding potential future revenues from Pluvicto. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Pluvicto will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that Pluvicto will be commercially successful in the future. In particular, our expectations regarding Pluvicto could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global

trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis
Novartis is an innovative medicines company. Every day, we work to reimagine medicine to improve and extend people's lives so that patients, healthcare professionals and societies are empowered in the face of serious disease. Our medicines reach nearly 300 million people worldwide.

Reimagine medicine with us: Visit us at **https://www.novartis.com** and connect with us on **LinkedIn**, **Facebook**, **X/Twitter** and **Instagram**.

Disclosure: Dr. Sartor was involved in the design of the clinical trial and was chairman of the steering committee for the trial. Dr. Sartor is a paid consultant for Novartis, with payments made directly to Mayo Clinic.

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