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MEDIA & INVESTOR RELEASE

Novartis Pluvicto™ shows statistically significant and clinically meaningful radiographic progression-free survival benefit in patients with PSMA–positive metastatic castration-resistant prostate cancer

Ad hoc announcement pursuant to Art. 53 LR

- *Phase III PSMAfore trial with Pluvicto™ met the primary endpoint of radiographic progression-free survival (rPFS) in PSMA–positive mCRPC who have been treated with androgen-receptor pathway inhibitor (ARPI) therapy*[1]
- *Pluvicto becomes the first PSMA-targeted radioligand therapy to demonstrate clinical benefit in mCRPC patients before receiving taxane-based chemotherapy*[1]*, addressing a significant unmet need*[2]
- *Findings to be presented at an upcoming medical meeting and submitted to regulatory authorities for approval in 2023*
- *Novartis is advancing a broad portfolio of radioligand therapies to treat cancer and is investing in manufacturing capacity to meet the growing global demand for treatment*

Basel, December 5, 2022 — Today, Novartis announced the pivotal Phase III PSMAfore study with Pluvicto™ (INN: lutetium (^{177}Lu) vipivotide tetraxetan), a prostate-specific membrane antigen (PSMA)-targeted radioligand therapy, met its primary endpoint. Pluvicto demonstrated a statistically significant and clinically meaningful improvement in radiographic progression-free survival (rPFS) in patients with PSMA–positive metastatic castration-resistant prostate cancer (mCRPC) after treatment with androgen-receptor pathway inhibitor (ARPI) therapy, compared to a change in ARPI[1]. No unexpected safety findings were observed in PSMAfore; data are consistent with the already-well established safety profile of Pluvicto[1,3].

This is the second positive read-out for Pluvicto in a Phase III trial following the VISION study, where patients with PSMA–positive mCRPC who received Pluvicto plus standard of care after being treated with ARPI and taxane-based chemotherapy had a statistically significant reduction in risk of death[1,3]. The PSMAfore results continue to support the important role of Pluvicto[1] in treating patients with prostate cancer. The Phase III data will be presented at an upcoming medical meeting and discussed with the US Food and Drug Administration (FDA) in 2023 for regulatory approval.

“With the announcement of these positive topline Phase III results, Pluvicto becomes the first PSMA-targeted radioligand therapy to demonstrate significant and clinically meaningful benefits for people living with this type of prostate cancer who have not received taxane-based chemotherapy,” said Shreeram Aradhye, M.D., President, Global Drug Development and Chief Medical Officer, Novartis. “We look forward to discussing the data with healthcare authorities in order to bring this innovative new early treatment option to many more prostate cancer patients sooner after their diagnosis.”

The vast majority of patients diagnosed with CRPC already present with metastases at time of diagnosis[4], patients with metastatic prostate cancer have an approximate 3 in 10 chance of surviving 5 years[5]. Despite recent advances, outcomes for those who progress after standard of care second-generation ARPI remain poor, and there is an urgent need for new targeted treatment options to help improve long-term outcomes[6,7,8,9].

Pluvicto is already approved for treatment in adult patients with PSMA–positive mCRPC who have been treated with ARPI and taxane-based chemotherapy in the United States and several other countries[10-12].

About the PSMAfore Study
PSMAfore is a Phase III, open-label, multi-center, 1:1 randomized study comparing the efficacy and safety of Pluvicto to a change in ARPI in patients with PSMA–positive mCRPC[13]. Patients enrolled must have progressed only once after receiving a second-generation ARPI[13]. There were 469 participants enrolled in the study[13]. The primary endpoint is rPFS, defined as the time from randomization to radiographic progression by PCWG3-modified RECIST v1.1 (as assessed by blinded independent central review) or death[13]. Evaluation of overall survival, the key secondary endpoint, is ongoing as data remain immature.

About Pluvicto™ (lutetium (^{177}Lu) vipivotide tetraxetan)
Pluvicto is an intravenous radioligand therapy combining a targeting compound (a ligand) with a therapeutic radionuclide (a radioactive particle, in this case lutetium-177)[3]. After administration into the bloodstream, Pluvicto binds to target cells, including prostate cancer cells that express PSMA, a transmembrane protein[3]. Once bound, energy emissions from the radioisotope damage the target cells and nearby cells, disrupting their ability to replicate and/or triggering cell death[10].

Pluvicto is approved in the US and other countries to treat adults with a type of advanced cancer called PSMA–positive mCRPC and who have already been treated with other anticancer treatments (ARPI and taxane-based chemotherapy)[10-12]. More specifically, in March 2022, the United States Food and Drug Administration (US FDA) approved Pluvicto[10]. In August and September 2022, the Medicines and Healthcare products Regulatory Agency (MHRA) and Health Canada approved Pluvicto in Great Britain and Canada, respectively[11,12]. In October 2022, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion recommending the granting of a marketing authorization for Pluvicto[14]. These regulatory decisions are supported by the results from the pivotal Phase III VISION study, where patients with pre-treated PSMA–positive mCRPC who received Pluvicto plus standard of care had a statistically significant reduction in the risk of death; both alternate primary endpoints of radiographic progression free survival and overall survival were met[3].

Novartis is also evaluating opportunities to investigate Pluvicto radioligand therapy in earlier stages of prostate cancer[15].

Novartis and Prostate Cancer
With more than 1.4 million new cases and 375,000 deaths in 2020 alone, prostate cancer is the most frequently diagnosed cancer in men in 112 countries—more than half the world[16].

At Novartis, we are harnessing the innovation of our world-class scientists, strategic partnerships, and one of the industry’s most competitive pipelines to explore the potential of

new, targeted therapies and precision medicine platforms to address the greatest unmet needs in prostate cancer.

Through the bold science of targeted therapies, our goal is to reduce the global disease burden, extend the lives of patients with prostate cancer, and elevate current standards of care.

Novartis and Radioligand Therapy (RLT)
Novartis is reimagining cancer care with radioligand therapy for patients with advanced cancers. By harnessing the power of radioactive atoms and applying it to advanced cancers, RLT is theoretically able to deliver radiation to target cells anywhere in the body[17,18]. Novartis has established global expertise, specialized supply chain and manufacturing capabilities across its network of radioligand therapy production sites. In order to support growing demand for our RLT platform, we are investing in the expansion of our RLT production capabilities in Millburn, New Jersey (US), Zaragosa (Spain) and Ivrea (Italy), as well as building a new radioligand manufacturing facility in Indianapolis, Indiana (US), that is planned to be operational in 2023. We are continually evaluating additional opportunities to expand capacity.

About Phenotypic Precision Medicine in Advanced Prostate Cancer
Despite advances in prostate cancer care, there is a high unmet need for new targeted treatment options to improve outcomes for patients with mCRPC[2]. More than 80% of patients with prostate cancer highly express a phenotypic biomarker called prostate specific membrane antigen (PSMA)[19-23], making it a promising diagnostic (through positron emission tomography (PET) scan imaging) and therapeutic target for radioligand therapy[24]. This differs from 'genotypic' precision medicine which targets specific genetic alterations in cancer cells[25].

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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," "will," "may," "could," "look forward," "pipeline," "to be presented," "upcoming" "ongoing," "evaluating," "to investigate," "to address," "continue," 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 such as COVID-19; 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 reimagining medicine to improve and extend people's lives. We deliver high-value medicines that alleviate society's greatest disease burdens through technology leadership in R&D and novel access approaches. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. About 108,000 people of more than 140 nationalities work together to bring Novartis products to nearly 800 million people around the world. Find out more at https://www.novartis.com

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