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MEDIA & INVESTOR RELEASE

Novartis reports clinically relevant improvement in median overall survival data in final analysis of pivotal NETTER-1 study with targeted radioligand therapy Lutathera

- *At final analysis, study showed clinically relevant improvement in median overall survival with a difference of 11.7 months between arms (Hazard ratio (HR): 0.84 with 95% CI: (0.60, 1.17) (p=0.30, two-sided))[1]*
- *No new safety signals emerged in long-term follow-up with median of 6.3 years; safety profile consistent with previously reported results[1]*
- *Previously reported primary analysis demonstrated statistically significant improvement in progression free survival[2]*
- *Novartis is committed to reimagining cancer through radioligand therapy with more than 15 dedicated research and discovery programs; recent investments and partnerships further strengthen platform capabilities*

Basel, June 3, 2021 — Novartis today reported the final analysis from the NETTER-1 phase III study comparing treatment using Lutathera® (INN: lutetium (177Lu) oxodotreotide / USAN: lutetium Lu 177 dotatate) plus 30 mg octreotide LAR to 60 mg of octreotide LAR in patients with midgut neuroendocrine tumors. The previously reported primary analysis of the trial demonstrated a statistically significant improvement in progression free survival (PFS) (HR: 0.18*, $p < 0.0001$)[3]. In the final analysis of overall survival, a secondary objective of the trial, treatment with Lutathera resulted in a clinically relevant prolongation in median overall survival of 11.7 months [48.0 months (95%CI: 37.4-55.2) compared to the control arm (36.3 months (95%CI: 25.9-51.7)][1]. While this analysis did not reach statistical significance (Hazard ratio for OS (HR): 0.84 with 95% CI: (0.60, 1.17) (p=0.30, two-sided))[1], the analyses of overall survival may have been impacted by multiple factors, including the crossover of patients from the control arm receiving subsequent radioligand therapy (36% of patients) as well as heterogenous subsequent anti-cancer treatments in both study arms[1]. No new safety signals emerged in the final analysis[1]. These results will be presented during the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting on June 4.

Jonathan Strosberg, MD, Principal Investigator and Associate Professor, Section Head, Neuroendocrine Tumor Program at Moffitt Cancer Center, said, “Lutathera plus long-acting octreotide was associated with a nearly 12-month difference in median overall survival compared to high-dose long-acting octreotide in these difficult to treat patients with inoperable midgut NETs progressing under standard dose octreotide LAR treatment. While not statistically significant, I consider this difference to be clinically relevant for these patients. It is also important to emphasize that PFS was the primary endpoint of this study. Moreover, 36%

of patients in the control arm crossed over to receive subsequent radioligand treatment, which may have impacted the comparison of survival between both study arms."

"We are proud of our 30-year legacy as an innovator for patients in the neuroendocrine tumor community," said John Tsai, Head of Global Drug Development and Chief Medical Officer for Novartis. "Since its approval by the European Commission in 2017 and the FDA in 2018, Lutathera has been administered to more than 9,000 gastroenteropancreatic neuroendocrine tumor (GEP-NET) patients in Europe and the United States[1]. We believe in the potential of targeted radioligand therapy and are investing in new discovery and expansion of this important platform, including exploration of new radioisotopes and combinations with complementary mechanisms of action, such as immunotherapy and inhibitors of DNA damage response."

At this final analysis, no new safety signals emerged in the long-term safety follow-up with a median of 6.3 years. In terms of secondary hematological malignancies, no new cases of MDS or acute leukemia were reported in the long term follow up[4].

Radioligand therapy combines a targeting compound that binds to receptors expressed by tumors and a radioactive isotope, causing DNA damage that inhibits tumor growth and replication and may lead to cell death[5-7]. In the case of Lutathera, it binds to somatostatin receptor type 2, which is over-expressed on certain types of cells, such as gastroenteropancreatic neuroendocrine tumor cells[8,9].

Novartis has established global expertise and specialized supply chain and manufacturing capabilities across its network of four radioligand therapy production sites, and is further increasing capacity to ensure delivery of future targeted radioligand therapies to patients in need. Novartis is the only pharmaceutical company which is pursuing four different cancer treatment platforms. These include targeted radioligand therapy, cell and gene therapy, targeted therapy and immunotherapy, with an opportunity to combine these platforms for the best outcomes for each cancer patient.

Visit https://www.hcp.novartis.com/virtual-congress/a-2021/ for the latest information from Novartis, including our commitment to the Oncology community, and access to our ASCO21 Virtual Scientific Program data presentations (for registered participants).

* HR: 0.21 (0.13, 0.32) in the US Package Insert

About NETTER-1
NETTER-1 is a Phase III international, multicenter, controlled, randomized study that compared treatment using Lutathera® every eight weeks plus best standard of care (octreotide LAR 30 mg) to 60 mg of octreotide LAR (dosed every four weeks) in patients with inoperable midgut NETs progressing under standard dose octreotide LAR treatment and overexpressing somatostatin receptors[3].

The primary endpoint was to compare the progression-free survival (PFS) after treatment with Lutathera® plus octreotide LAR 30 mg versus octreotide LAR 60 mg using RECIST 1.1 criteria[3]. Secondary trial endpoints included comparing objective response rate, overall survival, time to tumor progression, duration of response and safety between the two study arms[3].

About GEP-NETs
Neuroendocrine tumors (NETs) are a type of cancer that originate in neuroendocrine cells throughout the body. NETs are commonly considered slow-growing malignancies. However, some NETs are associated with rapid progression and poor prognosis[10-11]. In many cases, NET diagnosis is delayed until patients have advanced disease[12]. Symptoms such as fatigue, diarrhea, and abdominal pain can occur on a daily basis[13]. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are subdivided into two categories: tumors of the gastrointestinal (GI) tract and pancreas[14]. There is a need for additional treatment options for

inoperable or advanced GEP-NET, including those who have progressed while taking first-line somatostatin analogs.

The estimated age-adjusted incidence, or rate of new cases of NETs in the United States is approximately 6.98/100,000 per year (as of 2012), while the estimated 20-year limited-duration prevalence for 2014, based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, was 171,321[11]. Even though NETs have historically been considered to be rare (orphan disease), their incidence has grown over 500% over the last 3 decades [10,11,12,15].

About Lutathera®

Lutathera® (lutetium Lu 177 dotatate) is an Advanced Accelerator Applications product approved in the United States for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut neuroendocrine tumors in adults[16].

Lutathera® (lutetium (^{177}Lu) oxodotreotide) is also approved in Europe for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults[3].

Important Safety Information

LUTATHERA® (lutetium Lu 177 dotatate) is a prescription medicine used to treat adults with a type of cancer known as gastroenteropancreatic neuroendocrine tumors (GEP-NETs) that are positive for the hormone receptor somatostatin, including GEP-NETs in the foregut, midgut, and hindgut.

LUTATHERA is associated with some serious safety considerations, and in some cases these may require a healthcare provider to adjust or stop treatment. Treatment with LUTATHERA will expose patients to radiation which can contribute to long-term radiation exposure. Overall radiation exposure is associated with an increased risk for cancer. The radiation will be detectable in urine for up to 30 days following administration of the drug. It is important to minimize radiation exposure to household contacts consistent with good radiation safety practices as advised by your healthcare provider. Treatment with LUTATHERA increases the risk of myelosuppression, a condition in which bone marrow activity is decreased, resulting in a drop in blood cell counts. You may experience blood-related side effects such as low red blood cells (anemia), low numbers of cells that are responsible for blood clotting (thrombocytopenia), and low numbers of white blood cells (neutropenia). Speak with your healthcare provider if you experience any signs or symptoms of infection, fever, chills, dizziness, shortness of breath or increased bleeding or bruising. Other serious conditions that you may develop as a direct result of treatment with LUTATHERA include blood and bone marrow disorders known as secondary myelodysplastic syndrome and cancer known as acute leukemia. Your healthcare provider will routinely check your blood cell counts and tell you if they are too low or too high. Treatment with LUTATHERA will expose kidneys to radiation and may impair their ability to work as normal. You may be at an increased risk for kidney problems after LUTATHERA treatment if you already have kidney impairment before treatment. In some cases, patients have experienced kidney failure after treatment with LUTATHERA. Your healthcare provider will provide you with an amino acid solution before, during, and after LUTATHERA to help protect your kidneys. You should stay well hydrated before, during, and after your treatment. You should urinate frequently during and after administration of LUTATHERA. Your doctor will monitor your kidney function and may withhold, reduce, or stop your LUTATHERA treatment accordingly. In clinical studies of LUTATHERA, less than 1% of patients were reported to have tumor bleeding (hemorrhage), swelling (edema) or tissue damage (necrosis) to the liver. If you have tumors in your liver, you may be more likely to experience these side effects. Signs that you may be experiencing liver damage include increases in blood markers called ALT, AST and GGT. Your healthcare provider will monitor your liver using blood tests and may need to withhold, reduce, or stop your LUTATHERA treatment accordingly. During your treatment you may experience certain symptoms that are related to hormones released from your cancer. These symptoms may

include flushing, diarrhea, difficulty breathing (bronchospasm), and low blood pressure (hypotension), and may occur during or within the 24 hours after your first LUTATHERA treatment. Your healthcare provider will monitor you closely. Speak with your healthcare provider if you experience any of these signs or symptoms. Tell your healthcare provider if you are pregnant. LUTATHERA can harm your unborn baby. Females should use an effective method of birth control during treatment and for 7 months after the final dose of LUTATHERA. Males with female partners should use an effective method of birth control during treatment and for 4 months after the final dose of LUTATHERA. You should not breastfeed during treatment with LUTATHERA and for 2.5 months after your final dose of LUTATHERA. Treatment with LUTATHERA may cause infertility. This is because radiation absorbed by your testes or ovaries over the treatment period falls in the range of exposure where temporary or permanent infertility may occur.

The most common and most serious side effects of LUTATHERA include: vomiting, nausea, decreased blood cell counts, increased liver enzymes, decreased blood potassium levels, and increased blood glucose. Talk to your doctor if you experience any of these, or any other side effects.

Tell your healthcare provider if you are taking any other medications. Somatostatin analogs and corticosteroids may affect how your LUTATHERA treatment works. You should stop taking your long-acting somatostatin analog at least 4 weeks before LUTATHERA treatment. You may continue taking short-acting somatostatin analogs up to 24 hours before your LUTATHERA treatment. Avoid repeated high doses of glucocorticosteroids during treatment with LUTATHERA.

Please see full **Prescribing Information** for LUTATHERA.

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,” “seek,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. 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 the investigational or approved products described in this press release 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 such products will be commercially successful in the future. In particular, our expectations regarding such products 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 Advanced Accelerator Applications S.A.
Advanced Accelerator Applications, S.A. (AAA), a Novartis company, is developing targeted radioligand therapies and precision imaging radioligands for oncology indications. We are committed to transforming patients' lives by leading innovation in nuclear medicine. AAA has a legacy as a leader in radiopharmaceutical drugs for Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) diagnostic imaging. For more information, please visit: https://www.adacap.com

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Novartis is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis products reach nearly 800 million people globally and we are finding innovative ways to expand access to our latest treatments. About 110,000 people of more than 140 nationalities work at Novartis around the world. Find out more at. https://www.novartis.com

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