NOVARTIS

CAAA601A11401 Study Results Synopsis for Public Disclosure

Title	LUTATHERA Injection General use result study (somatostatin receptor-positive neuroendocrine tumor, CAAA601A11401)
Date	September 17, 2025
NIS Type	NIS with Primary Data Collection; Novartis Drug NIS
Keywords	Japan, LUTATHERA, lutetium oxodotreotide (^{177}Lu), somatostatin receptor-positive neuroendocrine neoplasm, non-interventional study, post-marketing study
Rationale and background	In the Risk Management Plan for LUTATHERA Injection, “Renal dysfunction”, “Myelosuppression”, and “Myelodysplastic syndrome/acute myeloid leukaemia” are specified as important identified risks, and “Hormone release induced crises” as important potential risk. Since the experience of the use of LUTATHERA Injection in Japanese patients is limited in clinical trials, a clinical use result study (all-case surveillance) was planned to collect information on these safety specifications.
Research objectives	This study was conducted as all-case surveillance to collect information on safety specifications including “Renal dysfunction”, “Myelosuppression”, “Myelodysplastic syndrome/acute myeloid leukaemia”, and “Hormone release induced crises” in a real world setting.
Study design	This study was a multicenter observational study of LUTATHERA Injection in a real world setting with a central registration system and all-case surveillance system without a control group.
Population	Inclusion criteria All patients treated with LUTATHERA Injection for the following indications during a certain post-marketing period • Indication: Somatostatin receptor-positive neuroendocrine tumor Patients who started to receive LUTATHERA Injection before the contract for this study were also included in the study population and it was allowed to register them after contract so that all patients who received LUTATHERA Injection in the post-marketing setting were included in this study. Patients treated with LUTATHERA Injection for off-label indication were included in this study to register all patients who received LUTATHERA Injection. Exclusion criteria Not applicable
Variables	Registration items (date of test, patient identification code, sex, year and month of birth or age at 1st dose of LUTATHERA Injection, history of hypersensitivity to any ingredient of LUTATHERA Injection, and reason for use), patient characteristics, results of confirmation of somatostatin receptor, results of other diagnostic imaging, history of treatment for neuroendocrine neoplasm (NEN), status of administration of LUTATHERA Injection, status of use of drugs for treating NEN other than LUTATHERA Injection, vital signs/laboratory tests, etc., adverse events related to safety specifications, pregnancy status, death, schedule of next administration of LUTATHERA Injection, and results of treatment with LUTATHERA Injection

Results	[Study overview] This study was started on September 29, 2021, with 347 patients registered as patients subject to CRF recording by the end date of the study (database lock of June 10, 2025). All 347 patients were included in the safety analysis set. In the safety analysis set, 57.9% (201 patients) were male. The median age (range) at the start of treatment with LUTATHERA Injection was 63.0 years (23 to 87 years), with 53.9% (187 patients) aged < 65 years and 46.1% (160 patients) ≥ 65 years. The classification of NEN by the primary site(s) (all that applied) was as follows: “pancreatic NET” in 48.1% (167 patients), “gastrointestinal NET” in 35.4% (123 patients), “pulmonary NET” in 4.9% (17 patients), “thymic NET” in 3.5% (12 patients), and “NET of unknown primary origin” in 3.2% (11 patients). ECOG PS was 0 in 66.9% (232 patients), 1 in 26.8% (93 patients), 2 in 4.3% (15 patients), 3 in 1.4% (5 patients), and 4 in 0% (0 patients). For the functional/non-functional classification, 8.9% (31 patients) had “functional tumor”, and 90.5% (314 patients) had “non-functional tumor”. The details of functional tumor (all that applied) were as follows: “gastrinoma” in 3.5% (12 patients), “insulinoma” in 2.6% (9 patients), “glucagonoma” and “ACTHoma” in 1.2% (4 patients) each, and “VIPoma” in 0.6% (2 patients). The most common sites for specimen collection (primary sites, all that applied) were the pancreas in 32.9% (114 patients), rectum in 17.0% (59 patients), and duodenum, lung, and thymus in 3.2% (11 patients) each. For history of treatment for NEN (somatostatin analogues [from 6 weeks before the first dose of LUTATHERA Injection to the day before the first dose of LUTATHERA Injection]), 81.0% (281 patients) reported as “absent” and 18.2% (63 patients) as “present”, and the somatostatin analogues included lanreotide acetate in 15.0% (52 patients) and octreotide acetate in 3.5% (12 patients). The total number of doses of LUTATHERA Injection was 1 in 8.4% (29 patients), 2 in 10.7% (37 patients), 3 in 6.1% (21 patients), 4 in 73.5% (255 patients), and 5 in 1.4% (5 patients). The mean (standard deviation) dose of LUTATHERA Injection administered was 7.22 (0.612) GBq for the 1st dose, 7.11 (0.865) GBq for the 2nd dose, 7.08 (0.862) GBq for the 3rd dose, 7.04 (0.887) GBq for the 4th dose, and 6.56 (0.981) GBq for the 5th dose. Many patients received antiemetic premedication for any dosing. [Safety] As described below, the incidences of adverse events and adverse reactions related to safety specifications observed in this study were comparable to the results of Studies NETTER-1 (overseas phase III clinical study), Erasmus MC (overseas phase I/II clinical study), P-1515-11 (Japanese phase I clinical study), or P-1515-12 (Japanese phase I/II clinical study). • The incidences of adverse events, Grade ≥ 3 adverse events, adverse reactions, and Grade ≥ 3 adverse reactions related to “Renal dysfunction” as a safety specification were 11.0% (38 patients), 1.7% (6 patients), 9.2% (32 patients), and 1.4% (5 patients), respectively. • The incidences of adverse events, Grade ≥ 3 adverse events, adverse reactions, and Grade ≥ 3 adverse reactions related to “Myelosuppression” as a safety specification were 48.1% (167 patients), 20.2% (70 patients), 47.6% (165 patients), and 20.2% (70 patients), respectively.

	• The incidences of adverse events and Grade ≥ 3 adverse events related to “Myelodysplastic syndrome/acute myeloid leukaemia” as a safety specification were 10.7% (37 patients) and 4.6% (16 patients), respectively; all were adverse reactions. Grade ≥ 3 adverse reactions included myelosuppression in 4.6% (16 patients) and plasma cell myeloma in 0.3% (1 patient). • The incidences of adverse events and Grade ≥ 3 adverse events related to “Hormone release induced crises” as a safety specification were 1.4% (5 patients) and 0.9% (3 patients), respectively; all were adverse reactions. • For adverse reactions related to “Renal dysfunction” as a safety specification, factors for which the 95% CI of the odds ratio did not include 1 were “presence or absence of concurrent condition: renal disease” and “presence or absence of medical history: hematological disease”. The incidence of adverse reactions related to “Renal dysfunction” was 18.8% (9/48 patients) and 7.7% (23/299 patients) in patients with and without concurrent renal disease, respectively, (odds ratio: 2.77; 95% CI: 1.20, 6.42). The incidence was 66.7% (2/3 patients) and 8.7% (30/343 patients) in patients with and without medical history of hematological disease, respectively, (odds ratio: 20.87; 95% CI: 1.84, 236.90). These suggested that concurrent renal disease and medical history of hematological disease could affect the occurrence of adverse reactions related to “Renal dysfunction”. • For adverse reactions related to “Myelosuppression” as a safety specification, factors for which the 95% CI of the odds ratio did not include 1 were “presence or absence of concurrent condition: hematological disease” and “age (elderly)”. The incidence of adverse reactions related to “Myelosuppression” was 72.9% (35/48 patients) and 43.5% (130/299 patients) in patients with and without concurrent hematological disease, respectively, (odds ratio: 3.50; 95% CI: 1.78, 6.88). The incidence was 55.0% (88/160 patients) in patients aged ≥ 65 years and 41.2% (77/187 patients) in patients aged < 65 years (odds ratio: 1.75; 95% CI: 1.14, 2.67). These suggested that concurrent hematological disease and age (elderly) could affect the occurrence of adverse reactions related to “Myelosuppression”. • For adverse reactions related to “Myelodysplastic syndrome/acute myeloid leukaemia” as a safety specification, factors for which the 95% CI of the odds ratio did not include 1 were “presence or absence of concurrent condition: hematological disease” and “ECOG PS”. The incidence of adverse reactions related to “Myelodysplastic syndrome/acute myeloid leukaemia” was 20.8% (10/48 patients) and 9.0% (27/299 patients) in patients with and without concurrent hematological disease, respectively, (odds ratio: 2.65; 95% CI: 1.19, 5.91). The incidence was 25.0% (5/20 patients) in patients with ECOG PS of ≥ 2 and 9.5% (31/325 patients) in patients with ECOG PS of 0 to 1 (odds ratio: 3.16; 95% CI: 1.08, 9.29). These suggested that concurrent hematological disease and ECOG PS could affect the occurrence of adverse reactions related to “Myelodysplastic syndrome/acute myeloid leukaemia”. • For adverse reactions related to “Hormone release induced crises” as a safety specification, the factor for which the 95% CI of the odds ratio did not include 1 was “ECOG PS”. The incidence of adverse reactions related to “Hormone release induced crises” was 10.0% (2/20

	patients) in patients with ECOG PS of ≥ 2 and 0.9% (3/325 patients) in patients with ECOG PS of 0 to 1 (odds ratio: 11.93; 95% CI: 1.87, 75.93). These suggested that ECOG PS could affect the occurrence of adverse reactions related to “Hormone release induced crises”. • Among the 347 patients included in the safety analysis set, 44 deaths were reported during the observation period. The causes of death were exacerbation of primary disease in 37 patients, adverse events in 6 patients, and others in 1 patient. The adverse events leading to death in the 6 patients were renal cancer, disseminated intravascular coagulation, pancytopenia, cardiac failure, pulmonary embolism, and blood pressure decreased in 1 patient each. • Among the 347 patients in the safety analysis set, those with available laboratory values had decreases in the levels of red blood cells, hemoglobin, white blood cells, neutrophils, monocytes, lymphocytes, and platelets over time, starting before the second dose of LUTATHERA Injection, compared to those levels before the start of treatment, but showed a trend toward slight recovery at the time of final evaluation (at the time of the last observation immediately before the end of the observation period).
Conclusion	In this study, there was no new safety concern identified for adverse reactions related to safety specifications of “Renal dysfunction”, “Myelosuppression”, “Myelodysplastic syndrome/acute myeloid leukaemia”, and “Hormone release induced crises”. Therefore, based on the results of this study, it was concluded that no additional safety measures would be required.

List of abbreviations

Abbreviations	Full forms (English)
ACTH	adrenocorticotropic hormone
CI	confidence interval
ECOG	Eastern Cooperative Oncology Group
NEN	neuroendocrine neoplasm
NIS	Non-interventional Study
PS	performance status
VIP	vasoactive intestinal polypeptide