EMA/CHMP/165811/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lutathera

International non-proprietary name: Lutetium (^{177}Lu) oxodotreotide

Procedure No. EMEA/H/C/004123/II/0052

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	22 Jun 2024		☐
☐	CHMP Rapporteur Assessment Report	16 Aug 2024	26 Aug 2024	☐
☐	PRAC Rapporteur Assessment Report	23 Aug 2024	27 Aug 2024	☐
☐	PRAC members comments	28 Aug 2024	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	29 Aug 2024	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	05 Sep 2024	05 Sep 2024	☐
☐	CHMP members comments	09 Sep 2024	09 Sep 2024	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 Sep 2024	13 Sep 2024	☐
☐	RSI	19 Sep 2024	19 Sep 2024	☐
☐	Re-start of procedure	30 Dec 2024		☐
☐	CHMP Rapporteur Assessment Report	03 Feb 2025	14 Feb 2025	☒
☐	CHMP members comments	17 Feb 2025	17 Feb 2025	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 Feb 2025	26 Feb 2025	☐
☒	RSI	27 Feb 2025	27 Feb 2025 Withdrawn by the Applicant on 09 May 2025	☐

Procedure resources	
Rapporteur:	Janet Koenig
PRAC Rapporteur:	Adam Przybylkowski

List of abbreviations

^{177}Lu	Lutetium-177
AE	Adverse event
BOR	Best overall response
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CT	Computerized Tomography
DCR	Disease Control Rate
DOR	Duration of Response
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
eCRF	Electronic Case Report Form
EBRT	External beam radiation therapy
EORTC	European Organization for Research and Treatment of Cancer
FAS	Full Analysis Set
FUP	Follow-up period
G1	Grade 1
G2	Grade 2
G3	Grade 3
GBq	Giga Becquerel
GCP	Good Clinical Practice
GEP-NET	Gastroenteropancreatic neuroendocrine tumour
Gy	Gray (unit of radiation exposure; equal to 100 rad)
HR	Hazard ratio
INN	International Nonproprietary name
IRC	Independent Review Committee
IRT	Interactive Response Technology
ITT	Intent to treat
KPS	Karnofsky Performance Score
LAR	Long-acting release
mCi	millicurie
NE	Not estimable
NET	Neuroendocrine tumour
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive disease
PFS	Progression Free Survival
PH	Proportional hazard
pNET	pancreatic NET
PR	Partial response
PRRT	Peptide receptor radionuclide therapy
PSUR	Periodic Safety Update Report
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QLQ	Quality of Life Questionnaires
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumours

RLT	Radioligand therapy
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Stable Disease
SmPC	Summary of product characteristics
SPECT	Single photon-emission computed tomography
SSA	Somatostatin analogue
SSTR	Somatostatin receptor
SSTR2	Somatostatin receptor subtype 2
TKI	Tyrosine kinase inhibitor
TTD	Time to Deterioration
ULN	Upper limit of normal
USAN	United States Adopted Names
USPI	United States Prescribing Information
WHO	World Health Organization

Table of contents

List of abbreviations

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Advanced Accelerator Applications submitted to the European Medicines Agency on 29 May 2024 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of newly diagnosed, unresectable or metastatic, well-differentiated (G2 and G3), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) adult patients for LUTATHERA, based on primary analysis results from study CAAA601A22301 (NETTER-2); NETTER-2 is a Phase III, multicenter, stratified, open-label, randomized, comparator-controlled study comparing treatment with Lutathera plus octreotide LAR 30 mg (Lutathera arm) to treatment with high-dose octreotide LAR 60 mg (control arm). The main purpose of the NETTER-2 study was to determine if treatment in the Lutathera arm prolongs PFS in subjects with newly diagnosed SSTR-positive, G2 and G3 advanced GEP-NET when compared with treatment in the control arm.
As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes in the SmPC. Version 3.0 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

COMP granted an Orphan Designation (EMEA/OD/093/07) on 2008-01-31 based on the criterion "significant benefit" (Community Register of Orphan Medicinal Products: EU/3/07/523). The applicant has applied for an orphan designation maintenance for this new indication.

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised

orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Derogation(s) of market exclusivity

Not applied.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Protocol assistance

The MAH did not seek Protocol assistance from CHMP.

2. Scientific discussion

2.1. Introduction

Lutathera®, also referred to as [177Lu]Lu-DOTA-TATE (INN: lutetium (177Lu) oxodotreotide, USAN: lutetium Lu 177 dotatate, chemical name: DOTA-Tyr3-Octreotate), is a radiopharmaceutical consisting of a ligand (an oligopeptide, coupled to the metal chelating moiety 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)), and radiolabelled with lutetium-177 [177Lu].

The ligand binds to somatostatin receptors (SSTRs) with the highest affinity for somatostatin subtype 2 receptors (SSTR2s), thus making it a treatment option for patients with tumours that express SSTRs. These receptors are an attractive target for radioligand therapy, as the SSTR density is much higher on tumours than on non-tumour tissue.

The biological basis for radioligand therapy with Lutathera is the receptor-mediated internalization and intracellular retention of this radiolabeled SSA. The specific binding of [177Lu]Lu-DOTA-TATE to malignant cells enables the direct delivery of tumouricidal radiation doses to target tissue expressing SSTRs. Lutetium-177 is a β-emitting radionuclide that causes the death of targeted tumour cells, with a limited effect on neighboring normal cells.

Lutathera is supplied as a sterile, ready-to-use radiopharmaceutical solution for infusion with a fixed volumetric activity of 370 MBq/mL at the date and time of calibration. The volume of the solution in the vial ranges between 20.5 and 25.0 mL in order to provide the required amount of radioactivity at the date and time of infusion.

In the European Union, Lutathera was approved via centralized procedure in 2017

for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), SSTR-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults.

The purpose of this submission is to obtain an extension of the indication for Lutathera

for the treatment of newly diagnosed, unresectable or metastatic, well-differentiated (G2 and G3), SSTR-positive GEP-NETs in adults.

This submission is based on the primary analysis results from study CAAA601A22301 (also referred to as NETTER-2), a Phase III, multicenter, stratified, open-label, randomized, comparator-controlled study comparing treatment with Lutathera plus octreotide LAR 30 mg (Lutathera arm) to treatment with high-dose octreotide LAR 60 mg (control arm) in adult patients with newly diagnosed, advanced, SSTR-positive G2 or G3 GEP-NETs.

Safety data from NETTER-2 are pooled with data from NETTER-1 to facilitate a review of the safety profile across GEP-NET populations. These collective safety results, from a total of 465 patients (280 patients treated with Lutathera and 185 patients treated with the control (high-dose octreotide LAR 60 mg)), contribute to the overall assessment of the benefit-risk of Lutathera.

2.1.1. Problem statement

Disease or condition

GEP-NETs are a rare, heterogeneous group of neoplasms that arise from the diffuse endocrine system, accounting for approximately 0.5% of all human tumours, and recognized as an orphan disease in the EU and USA. The prevalence and incidence of GEP-NETs appears to be rising steadily (Das, Dasari 2021 and Meeker, Heaphy 2014).

The historical classification of GEP-NETs is based on the embryonic origin of the tumour site, i.e., foregut, midgut, and hindgut tumours (Cives, Strosberg 2018). However, in a more recent and clinically relevant WHO classification system, distinction is made between well-differentiated NETs (previously designated as carcinoid tumours) and poorly differentiated neuroendocrine carcinomas (Klöppel 2017, WHO 2019). Well-differentiated GEP-NETs express SSTR, specifically subtype 2 (SSTR2), in high abundance (Krenning et al 1993, Reubi et al 2000) and are further differentiated by grades (Grade (G)1, G2, and G3) with differing Ki-67 index (i.e., <3%, 3–20%, and >20%, respectively) (Rindi et al 2022). These well-differentiated GEP-NETs can be further characterized as functional or non-functional, with treatment of functional GEP-NETs requiring management of clinical symptoms in addition to anti-cancer therapy (Pavel et al 2020). About 70% of well-differentiated NETs are diagnosed as non-functioning, and 45 to 60% of pancreatic NETs (pNETs) are non-functioning (Öberg et al 2010).

GEP-NET patients with early-stage disease are often asymptomatic or present with poorly defined symptoms and consequently, at the time of confirmed diagnosis, a significant percentage have advanced disease and hepatic metastases.

State the claimed the therapeutic indication

With this application the MAH ask for approval of the following wording for the indication:

"Lutathera is indicated for the treatment of newly diagnosed, unresectable or metastatic, well-differentiated (G2 and G3), somatostatin receptor-positive GEP-NETs in adults."

Epidemiology and risk factors, screening tools/prevention

Based on national and regional registries in Europe, the incidence of GEP-NETs has increased over the last two decades from 2.5/100,000 population (van der Zwan et al 2013) to 3.35 - 6.22/100,000 population (Grundmann et al 2023, Thiis-Evensen, Cetinkaya 2023, Alwan et al 2020, Genus et al 2019, Gudmundsdottir et al 2019).

The estimated incidence rate of GEP-NETs in the US increased from 1.05 (95% CI: 0.9, 1.21) per 100,000 persons in 1975 to 5.45 (95% CI: 5.31, 5.61) per 100,000 persons in 2015 (Xu et al 2021).

Overall, the estimated prevalence of GEP-NETs in the recent studies in the EU, Norway, and USA ranged from 31 per 100,000 individuals to 63 per 100,000 individuals, depending on region and duration of prevalence period (Thiis-Evensen, Cetinkaya 2023, Dasari et al 2017).

Clinical presentation, diagnosis and stage/prognosis

Historically, high grade neuroendocrine neoplasms were universally described as poorly differentiated and often thought to be similar to small cell malignancies.

It was not until 2017 that well-differentiated G3 NETs were formally recognized by the World Health Organization (WHO) as a distinct entity from the poorly differentiated G3 neuroendocrine carcinomas. Therefore, there is limited robust data with respect to the efficacy of high grade GEP-NET treatments, especially in the first-line (1L).

Data from randomized studies do not specifically include 1L treatments for high grade tumours, and no prospective Phase III study has evaluated 1L options for G3 GEP-NETs to date. Clinical data is mainly limited to G1/G2 tumours or comes from small non-randomized studies.

Available literature data in newly diagnosed (1L treatment) G2 and G3 GEP-NET patients shows mPFS up to 17 months across studies of SSAs (octreotide and lanreotide), targeted treatments (everolimus and sunitinib), and chemotherapy (capecitabine/temozolomide (CAPTEM), streptozocin/5-fluoruracil (STZ/5FU), and platinum-based regimens).

ORR in high grade GEP-NET patients has not been reported for SSAs, according to our knowledge to date. For targeted therapies, ORR has not been reported for 1L treatment of patients with G3 tumours, while for G1/G2 patients, it ranged from 11 to 28%. For 1L chemotherapy with CAPTEM or STZ/5-FU, an ORR of up to 45% was reported in G2/G3 GEP-NET patients. For platinum-based chemotherapy, while high ORR rates have been shown in some small studies, PFS in G3 GEP-NET patients appears to be lower than that of other treatments, and platinum-based therapy is not considered an optimal treatment for NET G3 (Elvebakken et al 2021, Sonbol, Halfdanarson 2019).

Management

Clinical management in patients with advanced GEP-NETs typically involves a multi-modal approach that includes surgery, liver-targeted therapy, radiotherapy and medical treatment with chemotherapy, targeted therapies, peptide receptor radionuclide therapy (PRRT, a commonly used term for RLTs, specifically targeting peptide receptors), and somatostatin analogs (SSAs) (ESMO guidelines: Pavel et al 2020, NCCN guidelines: Shah et al 2021).

Only a few approved treatment options exist for newly diagnosed patients with advanced GEP-NETs, and there is no universally accepted standard of care therapy.

Approved therapies in the first-line setting have limited application because they can only be used in specific subsets of GEP-NET patients (i.e., octreotide LAR for midgut tumours or tumours of unknown origin and for symptomatic control of functional GEP-NETs (Sandostatin LAR SmPC 2022); lanreotide for G1 and G2 GEP-NETs with Ki-67 <10% (Somatuline Autogel SmPC 2023); and streptozocin in combination with 5- fluorouracil for symptomatic G1 and G2 pNETs (Zanosar SmPC 2022)).

Other approved therapeutic options are limited to the progressive population and use in newly diagnosed patients occurs off-label, following treatment guideline recommendations.

Thus, there is a high unmet medical need in newly diagnosed, advanced G2 and G3 GEP-NET patients.

The applicant emphasises that NETTER-2 study presents the first randomized, controlled Phase III study for first-line treatment of high grade GEP-NETs with superior efficacy results compared to reported literature results, thus providing another therapeutic option for this population with high unmet need.

2.1.2. About the product

Lutathera® is a tumour-targeted radioligand therapy (RLT) that has been approved in more than 40 countries worldwide for the treatment of somatostatin receptor (SSTR)-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults.

Lutathera, also referred to as [177Lu]Lu-DOTA-TATE (INN: lutetium (177Lu) oxodotreotide, USAN: lutetium Lu 177 dotatate, chemical name: DOTA-Tyr3-Octreotate), is a radiopharmaceutical consisting of a ligand (an oligopeptide, coupled to the metal chelating moiety 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)), and radiolabeled with lutetium-177 [177Lu]. The ligand binds to SSTRs with the highest affinity for somatostatin subtype 2 receptors (SSTR2s), thus making it a treatment option for patients with tumours that express SSTRs. These receptors are an attractive target for radioligand therapy, as the SSTR density is much higher on tumours than on non-tumour tissue.

The biological basis for radioligand therapy with Lutathera is the receptor-mediated internalization and intracellular retention of this radiolabeled SSA. The specific binding of [177Lu]Lu-DOTA-TATE to malignant cells enables the direct delivery of tumouricidal radiation doses to target tissue expressing SSTRs. Lutetium-177 is a β-emitting radionuclide that causes the death of targeted tumour cells, with a limited effect on neighbouring normal cells. Tumour regression has been demonstrated both in animal models and in humans after administration of [177Lu]Lu-DOTA-TATE.

Lutathera is supplied as a sterile, ready-to-use radiopharmaceutical solution for infusion. The currently approved dosage administration consists of four infusions of 7.4 GBq (200 mCi) each, administered at 8±1 week intervals, which can be extended up to 16 weeks in cases where dose interruptions due to toxicity are necessary.

The approved indication is based on studies in progressive, well-differentiated (G1/G2) disease.

The purpose of this variation is to update the label to include the indication in newly diagnosed, unresectable or metastatic, well-differentiated (G2 and G3), somatostatin receptor positive GEP-NETs in adults.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The initial approval of Lutathera for the treatment of SSTR-positive GEP-NETs in adults was based on results from the randomized, controlled Phase III NETTER-1 study that compared treatment with Lutathera (4 cycles of 7.4 GBq, every 8 weeks) plus octreotide LAR 30 mg to high-dose octreotide LAR (60 mg) in patients with inoperable, progressive, SSTR-positive, G1 and G2 midgut tumours.

The NETTER-1 study met its primary PFS endpoint, showing at the time of the primary analysis (data cut-off (DCO): 24-July-2015), a significant difference between treatment arms, with an 82% reduction of the risk of disease progression or death in favour of the Lutathera arm (hazard ratio (HR) 0.18, 95% CI: 0.11-0.29; p <0.0001).

Although final OS analysis results (five years after randomization of the last patient (data cut-off: 18-Jan-2021)), did not reach statistical significance, median OS was prolonged by a clinically relevant 11.7 months in patients randomized to the Lutathera arm (48.0 months; 95% CI: 37.4, 55.2) compared to patients randomized to the control arm (36.3 months (95% CI: 25.9, 51.7).

Safety results showed that Lutathera was well-tolerated, with a manageable safety profile.

The initial submission was also supported by efficacy and safety findings from the single-arm, investigator-sponsored, Phase I/II Study MEC 127.545/1993/84 (hereinafter referred to as the ERASMUS study), conducted by the Erasmus Medical Center on patients with SSTR-positive tumours, regardless of tumour subtype and tumour status. This study provided data to support the approval for other subsets beyond midgut, i.e., foregut and hindgut, including pancreatic NETs. The efficacy and safety results of this study were consistent with the data from NETTER- 1, and reflected results of treatment with Lutathera, with or without concomitant octreotide LAR 30 mg.

Based on the data from NETTER-1 and the unmet medical need in newly diagnosed, high grade GEP-NET patients, the randomized, controlled, Phase III NETTER-2 trial was conducted in adult patients with newly diagnosed, advanced, SSTR-positive G2 or G3 GEP-NETs to complement the NETTER-1 study with clinical evidence in an earlier line of treatment and in higher grade tumours.

In addition, the NETTER-2 study confirms with additional data from a randomized, controlled trial, efficacy and safety in GEP-NET patient subgroups, which have so far only been covered with data from the single arm ERASMUS study.

Based on the efficacy and safety outcomes of Lutathera in NETTER-2 the MAH aims to make Lutathera available for this patient population studied.

Similar to the NETTER-1 study, the selection criteria for the NETTER-2 study were based on SSTR-imaging; however, unlike NETTER-1, which used scintigraphy with Octreoscan, more recently developed SSTR-targeted PET imaging agents (e.g., NetSpot®, SomaKit TOC®) were largely used in NETTER-2 instead. Additionally, NETTER-2 administered a 2.5% Lys-Arg amino acid solution (i.e., LysaKare®, where nationally approved) in place of the commercially available, complex amino acid solutions used in NETTER-1.

These differences show advances in the use of this practice-changing treatment for GEP-NET patients since Lutathera's approval, with improvements in tumour detection and use of tailored, more tolerable concomitant amino acid solutions for kidney protection in NETTER-2.

Lutathera was designated as an orphan drug for the treatment of GEP-NETs in the EU, US, and other regions.

2.1.4. General comments on compliance with GMP, GLP and GCP

The applicant provided a statement that the NETTER-2 trial was performed according all relevant GCP standards ICH E6 Guideline for Good Clinical Practice that have their origin in the Declaration of Helsinki. The study protocol and its two amendments were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each center.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

The applicant provided an environmental risk assessment of the procedure Luthathera (lutetium (177Lu) EMEA/H/C/4123.The changes in indication and patient population in this Type II variation do not lead to an increase in the calculated environmental exposure of Luthathera. Therefore, an updated ERA is not required.

Lutetium(177Lu)-DOTA0-Tyr3-Octreotate PECsurfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

Lutathera is not expected to pose a risk to the environment when used according to the SmPC.

Summary of main study results

Substance (INN/Invented Name): Lutetium(177Lu)-DOTA0-Tyr3-Octreotate			
CAS-number (if available): 437608-50-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log Kow	Schottelius et al. (2015)	-3.16	Potential PBT N
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PECsurfacewater, default	0.00131	µg/L	> 0.01 threshold N
Other concerns	radiopharmaceutical		

2.2.2. Discussion and Conclusion on non-clinical aspects

Considering the above data, Lutetium (^{177}Lu) oxodotreotide is not expected to pose a risk to the environment. No other new non-clinical data have been submitted in this application, which is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

Based on the data from NETTER-1 trial and supportive information from the ERASMUS trial, Lutathera is currently approved for the indication:

Lutathera is indicated for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEPNETs) in adults.

With this variation based on the outcome of the NETTER-2 trial, the applicant intends to extend the indication to adult patients with newly diagnosed, advanced, SSTR-positive G2 or G3 GEP-NETs to complement the NETTER-1 study with clinical evidence in an earlier line of treatment and in higher grade tumours.

The following wording is proposed:

Lutathera is indicated for the treatment of newly diagnosed, unresectable or metastatic, well-differentiated (G2 and G3), somatostatin receptor-positive GEP-NETs in adults

The application is based on the primary analysis data from the ongoing NETTER-2 study with a cut- off date 20-Jul-2023 which is considered pivotal for the applied extension of indication "for the treatment of newly diagnosed, unresectable or metastatic, well-differentiated (G2 and G3), SSTR-positive, GEP-NETs in adults.

2.3.2. Pharmacokinetics

No new information on pharmacokinetics were provided.

This is justified in the Clinical Overview that states that "no new information on clinical pharmacology was generated as part of this submission, since the proposed dose regimen is identical to the established regimen used in the pivotal, Phase III NETTER-1 study and no differences in organ biodistribution and exposure-safety relationships are expected between the two GEP-NET populations."

2.3.3. Pharmacodynamics

No new information on pharmacodynamics were provided.

2.3.4. PK/PD modelling

N/A

2.3.5. Discussion on clinical pharmacology

N/A

2.3.6. Conclusions on clinical pharmacology

No new information on pharmacokinetics or pharmacodynamics have been provided which is regarded acceptable since the proposed dose regimen is identical to the established regimen used in the pivotal, Phase III NETTER-1 study and posology (e.g. 4.2) and clinical pharmacology (e.g. 4.5, 5.2) related sections of the SmPC (and PIL) have remained unchanged in content (only formal amendment).

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No formal dose response study was performed.

Rationale for dose selected studied

The Lutathera dose and regimen in the NETTER-2 study is identical to the approved Lutathera regimen (Lutathera SmPC 2024, Lutathera USPI 2024), which is based on the pivotal Phase III NETTER-1 study (Strosberg et al 2017) conducted in midgut NETs and the Phase I/II ERASMUS study conducted in a broad population with SSTR-positive tumours, with a cumulative dose of 29.6 GBq (4 administrations of 7.4 GBq each, every 8 weeks).

This dose and regimen was considered adequate to be implemented for the NETTER-2 study based on the following rationale:

- Organ dosimetry is expected to be independent of the line of therapy or grade of the disease. Thus, the safety profile, in particular relating to SSA, should not be different between different populations of the same disease.
- Since organ dosimetry was not expected to be different, dosimetry assessments have not been mandated in NETTER-2. However, SPECT/CT imaging and whole-body planar imaging for quantitative dosimetry were performed locally in Germany after each Lutathera administration [NETTER-2-Section 11.4.1]:
  - Dosimetry estimates for kidney and red marrow were derived by the individual sites based on institutional guidelines and standard procedures. The dosimetry results from 5 subjects, who were enrolled in Germany and received at least one dose of Lutathera, showed an absorbed dose coefficient ranging between 0.331 and 0.802 Gy/GBq across subjects and cycles for the kidneys and 0.015 and 0.065 Gy/GBq in the red marrow [NETTER-2-Listing 16.2.5-1.8]. These values are well in line with the NETTER-1 mean ± standard deviation estimates for kidneys 0.654 ± 0.295 Gy/GBq and red marrow 0.035 ± 0.029 Gy/GBq (Lutathera SmPC 2024, Lutathera USPI 2024), confirming that the biodistribution was indeed unchanged.
- The frequency of Lutathera administration (every 8 weeks) provides sufficient time to recover from acute hematotoxicities, as was established in the NETTER-1 study.
- There are no expected differences in the safety profile between the NETTER-1 and NETTER-2 patient populations (see [SCS-Section 2.2.6] for more details). Additionally, considering that newly diagnosed patients in NETTER-2 were not exposed to any prior therapy, no cumulative toxicities from previous treatments were to be expected. Thus, there was no strong rationale to consider a lower dose in a population in first line with a more aggressive disease setting.
- Considering the magnitude of anti-tumour effect observed in NETTER-1 and ERASMUS studies and that Lutathera regimen is given as the first antineoplastic line of treatment in NETTER-2, which should not negatively impact subsequent lines of therapies, there was no strong rationale to increase the dose for the first-line patient population in NETTER-2.

2.4.2. Main study

NETTER 2

The ongoing NETTER-2 study is a Phase III, multicenter, stratified, open-label, randomized, comparator-controlled study comparing treatment with Lutathera plus octreotide LAR 30 mg (Lutathera arm) to treatment with high-dose octreotide LAR 60 mg (control arm) (Figure 1).

NETTER-2 is a multicenter, stratified, randomized, open-label comparator-controlled, Phase III study in subjects with somatostatin receptor positive, well-differentiated grade 2 and grade 3, advanced newly diagnosed GEP-NETs. The aim of the NETTER-2 study was to determine if Lutathera administered with 30 mg octreotide LAR (Lutathera arm) prolongs PFS in this patient population in comparison to treatment with high dose (60 mg) octreotide LAR (control arm). Eligible subjects included SSA-naive, or previously treated with SSAs in the absence of progression (i.e., study treatment was administered as 1L). Patients

treated with targeted or chemotherapy for less than 1 month and beyond 12 weeks prior to randomization in the study were also allowed.

The study consisted of a screening phase, a treatment phase, an optional cross-over phase for subjects assigned to the control arm, optional re-treatment phase for subjects assigned to the Lutathera arm, and a follow-up phase. This study compared treatment with Lutathera (7.4 GBq/200 mCi 4 × administrations every 8 weeks ± 1 week; cumulative dose: 29.6 GBq/800mCi) plus octreotide LAR (30 mg every 8 weeks during Lutathera treatment and every 4 weeks after last Lutathera treatment and high dose octreotide LAR (60 mg every 4 weeks).

Overall, 222 subjects were planned to be randomized (2:1) to Lutathera arm or control arm. Randomization was stratified by grade (grade 2 vs grade 3) and tumour origin (pancreatic neuroendocrine tumour (pNET) vs other origins).

Protocol number: CAAA601A22301 (NETTER-2)

Regulatory agency identifier number(s): EUDRACT number: 2019-001562-15

Test drug/investigational product: 177Lu-DOTA0-TATE or Lutetium (177Lu) oxodotreotide (INN) or (USAN)/AA601

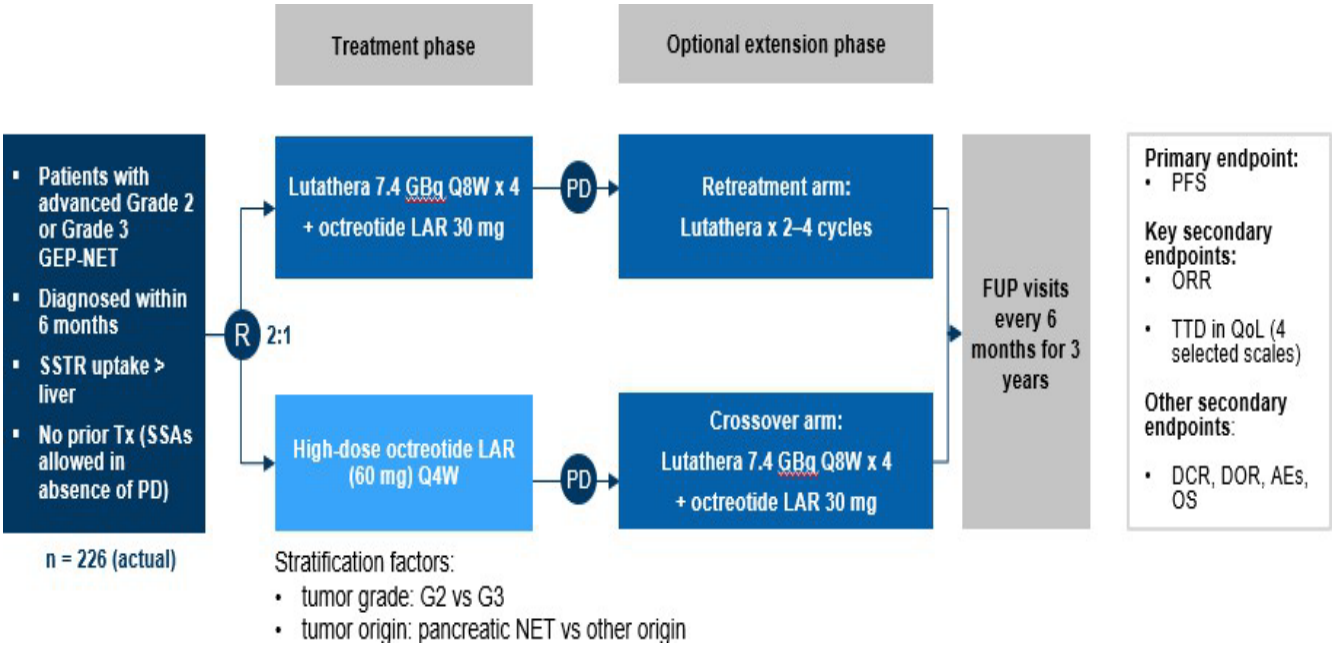
Study Sponsor: Advanced Accelerator Applications, a Novartis company

Development phase of study: III

Study initiation date: 08-Jan-2020 (first subject first visit)

Data cut-off date: 20-Jul-2023

Figure 1. Study design of NETTER-2



GEP-NET: gastroenteropancreatic neuroendocrine tumour; SSTR: somatostatin receptor; SSA: somatostatin analogue; PD: progressive disease; LAR: long-acting release; Q8W: every 8 weeks; Q4W: every 4 weeks; G: grade; GBq: Giga Becquerel; FUP: follow-up period; PFS: progression-free survival; ORR: objective response rate; TTD: time to deterioration; QoL: quality of life; DCR: disease control rate; DOR: duration of response; AE: adverse event; OS: overall survival. Source: [NETTER-2-CSR Figure 9-1]

2.4.2.1. Study participants

Diagnosis and main criteria for inclusion:

The study population included subjects with somatostatin receptor-positive, well-differentiated grade 2 (Ki67 index ≥10% to ≤ 20%), and grade 3 (Ki67 index > 20% to ≤ 55%) newly diagnosed advanced GEP-NETs.

2.4.2.2. Main inclusion criteria

Subjects who met the following criteria were included in the study:

1. Presence of metastasized or locally advanced, inoperable (curative intent), histologically proven, well-differentiated grade 2 or grade 3 (GEP-NET) tumour diagnosed within 6 months prior to screening.
2. Ki67 index ≥10 and ≤ 55%.
3. Subjects ≥15 years of age and a body weight of >40 kg at screening.
4. Expression of somatostatin receptors on all target lesions documented by CT/MRI scans, assessed by a somatostatin receptor imaging modality within 3 months prior to randomization.
5. The tumour uptake observed in the target lesions must be > normal liver uptake.
6. Karnofsky Performance Score ≥ 60.
7. Presence of at least 1 measurable site of disease.
8. Subjects who have provided a signed informed consent form to participate in the study obtained prior to the start of any protocol-related activities.

2.4.2.3. Main exclusion criteria

Subjects who met any of the following criteria were excluded from the study:

1. Creatinine clearance <40 mL/min calculated by the Cockcroft-Gault method.
2. Hemoglobin concentration <5.0 mmol/L (<8.0 g/dL); WBC <2x10^9/L (2000/mm^3); platelets <75x10^9/L (75x10^3/mm^3).
3. Total bilirubin >3 x ULN.
4. Serum albumin <3.0 g/dL unless prothrombin time was within the normal range.
5. Pregnancy or lactation.
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, were not allowed to participate in this study UNLESS they were using highly effective methods of contraception throughout the study treatment period (including cross-over and re-treatment, if applicable) and for 7 months after study drug discontinuation. Highly effective contraception methods include:
    - True abstinence when this was in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of contraception.

- Male or female sterilization
- Combination of any two of the following (a+b or a+c or b+c):
    a. Use of oral, injected, or implanted hormonal methods of contraception. In case of use of oral contraception, women should be stable on the same pill for a minimum of 3 months before taking study treatment.
    b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository. Post- menopausal women are allowed to participate in this study. Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age-appropriate, history of vasomotor symptoms) confirmed by a high follicle stimulating hormone (FSH) level or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment was she considered not of childbearing potential.
    d. Sexually active male subjects, unless they agree to remain abstinent (refrain from heterosexual intercourse) or be willing to use condoms and highly effective methods of contraception with female partners of childbearing potential or pregnant female partners during the treatment period (including cross-over and re- treatment, if applicable) and for 4 months after study drug discontinuation. In addition, male subjects must refrain from donating sperm during this same period.

7. Peptide receptor radionuclide therapy (PRRT) at any time prior to randomization in the study.
8. **Documented RECIST progression to previous treatments for the current GEP-NET at any time prior to randomization.**
9. Subjects for whom, in the opinion of the investigator, other therapeutic options (e.g., chemo-, targeted therapy) are considered more appropriate than the therapy offered in the study, based on subject and disease characteristics.
10. Any previous therapy with Interferons, Everolimus (mTOR-inhibitors), chemotherapy, or other systemic therapies of GEP-NET administered for more than 1 month or within 12 weeks prior to randomization in the study.
11. Any previous radioembolization, chemoembolization, and radiofrequency ablation for GEP-NET.
12. Any surgery within 12 weeks prior to randomization in the study.
13. Known brain metastases unless these metastases have been treated and stabilized for at least 24 weeks prior to screening in the study. Subjects with a history of brain metastases must have a head CT or MRI with contrast to document stable disease prior to randomization in the study.
14. Uncontrolled congestive heart failure (NYHA II, III, IV). Subjects with a history of congestive heart failure who do not violate this exclusion criterion underwent an evaluation of their cardiac ejection fraction prior to randomization via echocardiography. The results from an earlier assessment (not exceeding 30 days prior to randomization) may substitute the evaluation at the discretion of the Investigator if no clinical worsening was noted. The subject's measured cardiac ejection fraction in these subjects must be ≥40% before randomization.

15. QTcF > 470 msec for females and QTcF > 450 msec for males or congenital long QT syndrome.
16. Uncontrolled diabetes mellitus as defined by hemoglobin A1c value > 7.5%.
17. Hyperkalemia >6.0 mmol/L (Common Terminology Criteria for Adverse Events (CTCAE grade 3), which was not corrected prior to study enrolment.
18. Any subject receiving treatment with short-acting octreotide, which cannot be interrupted for 24 h before and 24 h after the administration of Lutathera, or any subject receiving treatment with SSAs (e.g., octreotide LAR), which cannot be interrupted for at least 6 weeks before the administration of Lutathera.
19. Subjects with any other significant medical, psychiatric, or surgical condition currently uncontrolled by treatment, which may interfere with the completion of the study.
20. Prior external beam radiation therapy to more than 25% of the bone marrow.
21. Current spontaneous urinary incontinence
22. Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and proven no evidence of recurrence for 5 years.
23. Subject with known incompatibility to CT scans with I.V. contrast due to allergic reaction or renal insufficiency. If such a subject could be imaged with MRI, then the subject would not be excluded.
24. Hypersensitivity to any somatostatin analogs, the IMPs active substance or any of the excipients.
25. Subjects who participated in any therapeutic clinical study/received any investigational agent within the last 30 days.

2.4.2.4. Treatments

Lutathera was the investigational drug used during this study. Octreotide LAR was also given to all randomized subjects, at 30 mg in Lutathera arm. Octreotide LAR alone was administered at 60 mg in the control arm. Lutathera treatment consisted of a cumulative administered radioactivity of 29.6 GBq (800mCi) (4 administrations). Concomitantly with Lutathera, a 2.5% Lys-Arg sterile amino acid solution was administered to minimize renal radiation exposure during Lutathera treatment.

Dose modifying toxicities (DMTs) for Lutathera and the Control arm are sufficiently defined and dose adjustments were permitted to allow subjects who did not tolerate the protocol-specified dosing schedule to continue the trial.

2.4.2.5. Objectives

2.4.2.5.1. Primary Objective and Primary Endpoint (PEP)

Primary Objective	Endpoint	Primary estimand

To demonstrate that Lutathera is superior to active comparator in delaying the time-to-first occurrence of progression or death (PFS) as first line treatment.	**PFS:** Time from randomization to the first line progression (centrally assessed according to RECIST 1.1) or death due to any cause.	The scientific objective guiding the primary analysis was to demonstrate the superiority of Lutathera plus octreotide LAR compared to the active comparator, high dose octreotide LAR, in delaying the time to first occurrence of progression or death, for the target population, based on central assessment, had no participant initiated new antineoplastic therapy, crossed over to Lutathera or being re-treated with Lutathera.

2.4.2.5.2. Secondary objectives

Key secondary objectives endpoints and estimands

Key secondary Objective	Endpoint	Estimand
To demonstrate the superiority of Lutathera, compared to active comparator, in terms of objective response	**ORR**: Rate of subjects with best overall response of partial response (PR) or complete response (CR) (centrally assessed according to RECIST 1.1)	The scientific question of interest for the first key secondary estimand was: what the treatment effect is based on objective response rate per central assessment for Lutathera plus octreotide LAR for the target population, had no participant initiated new anti-neoplastic therapy, crossed over to or being re-treated with Lutathera
To demonstrate the superiority of Lutathera, compared to active comparator, in terms of time to deterioration in selected QoL items/ scales	**Time to deterioration (TTD) by 10 points from baseline in the following scores** measured by EORTC QLQ-C30 questionnaire: global health status, diarrhea, fatigue, and pain.	The scientific question of interest for the second key secondary estimand was: what the treatment effect is based on time to deterioration in selected QoL items/scales for Lutathera plus octreotide LAR for the target population while on treatment, had no participant initiated new antineoplastic therapy crossed over to or being re-treated with Lutathera.

Other Secondary Objectives

Other secondary Objective	Endpoints for other secondary objectives
To evaluate the efficacy of Lutathera, compared to active comparator, in keeping the disease under control	**DCR**: Rate of subjects with best overall response of partial response (PR), complete response (CR) or stable disease (SD) (centrally assessed according to RECIST 1.1)
To evaluate the efficacy of Lutathera, compared to active comparator, in terms of duration of response	**DOR**: The Duration of Response (DOR) is defined as the time from initially meeting the criteria for response (CR or PR) until the time of progression according to RECIST 1.1 or death due to underlying disease only.
To evaluate the safety and tolerability of Lutathera	**Safety**: Rate of adverse events and laboratory toxicities (scored according to CTCAE v5.0 grading).
To evaluate the effect of Lutathera on overall survival	**OS**: Time from the randomization date until the day of death due to any cause.

Criteria of evaluation

All radiological assessments were performed both by central, blinded, real-time IRC (Independent Review Committee) and locally at the Investigator's site or designated facility, and tumour responses were determined utilizing computed tomography (CT)/magnetic resonance imaging (MRI) according to RECIST version 1.1.

The primary efficacy endpoint was PFS as measured by objective tumour response, which was determined by RECIST criteria, Version 1.1.

The impact of treatment on health-related QoL was assessed using the EORTC QLQ-G.I.NET21, EORTC QLQ-C30 and EQ-5D-L5 questionnaires, which were filled in by the patient prior to knowing the CT scan/MRI result. Changes from baseline were assessed every 12±1 week from the first treatment date until the end of treatment.

2.4.3. Biostatistical aspects

Target of estimation (estimand)

The scientific objective guiding the primary analysis is to demonstrate the superiority of Lutathera plus octreotide long-acting compared to high dose octreotide long-acting in delaying the time to first occurrence of radiological progression or death, for the target population, based on central assessment, had no participant initiated new antineoplastic therapy, crossed over to Lutathera or being re-treated with Lutathera.

The primary estimand was comprehensively described by the following attributes:

1. The target population comprised all subjects randomized with somatostatin receptorpositive, well-differentiated grade 2 (Ki67 index ≥10% to ≤ 20%) or grade 3 (Ki67 > 20% and ≤ 55%) advanced GEP-NETs, previously untreated with any systemic therapies other than somatostatin analogs (SSAs) for inoperable metastatic disease. Subjects with documented RECIST progression to SSAs for the current GEP-NET at any time prior to randomization were not eligible to participate in this study.

2. The primary variable was PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause, based on central assessment and using RECIST v1.1 criteria.

3. The analysis accounted for different intercurrent events as explained in the following:

   a. Discontinuation of study treatment for any reason before central PFS event: this intercurrent event was ignored (treatment policy strategy).

   b. New anti-neoplastic therapy, including cross-over to Lutathera, before central PFS event: PFS was censored at the date of the last adequate tumour assessment prior to initiation of the new anti-neoplastic therapy (hypothetical strategy).

   c. Re-treatment before central PFS event: PFS was censored at the date of the last adequate tumour assessment prior to re-treatment (hypothetical strategy).

4. The summary measure was the hazard ratio for PFS between the 2 treatments. It was estimated using the Cox proportional hazards (Cox PH) model stratified by randomization stratification factors. The primary comparison was performed using a log-rank test stratified by randomization stratification factors.

2.4.3.1. Sample size

The sample size calculation was based on the primary variable PFS. Assuming a median PFS in the control arm (high dose octreotide LAR (60 mg)) of approximately 15 months, it was hypothesized that treatment with Lutathera added to standard dose octreotide LAR results in a 50% reduction in the hazard rate (corresponding to an increase in median PFS from 15 months to 30 months).

To ensure 90% power to test the null hypothesis: PFS hazard ratio = 1, versus the specific alternative hypothesis: PFS hazard ratio = 0.50, it was calculated that a total of 99 PFS events need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, subjects randomized to the two treatment arms in a 2:1 ratio.

Assuming that enrolment continued for approximately 22.2 months at a rate of 10 subjects per month and a 15% dropout rate by the time of the final PFS analysis, a total of 222 subjects (148 for the Lutathera arm and 74 for the control arm) were to be randomized to observe the targeted 99 PFS events at about 12.8 months after the randomization date of the last subject, i.e., 35 months after the randomization date of the first subject.

2.4.3.2. Randomisation

After the screening period, eligible subjects were randomly assigned (ratio 2:1) to one of the two study arms for treatment with Lutathera plus octreotide LAR (30 mg) or high-dose octreotide LAR (60 mg). The randomization system assigned a unique randomization number to the subject, which was used to link the subject to a treatment arm. Randomization was stratified by tumour grade (grade 2 vs grade 3) and tumour origin (pNET vs other origins).

2.4.3.3. Blinding (masking)

This study was open-label due to the radioactive nature of Lutathera and its method of infusion. It was not possible to implement a blinded design for the study.

2.4.3.4. Statistical methods

Analysis populations:

The Full Analysis Set (FAS) comprised all subjects to whom study treatment was assigned by randomization. According to the intent to treat principle, subjects were analysed according to the treatment and strata they had been assigned to during the randomization procedure. The FAS was the primary population for all efficacy analyses.

The Safety Set included all subjects who received at least one dose of study treatment. Subjects were analysed according to the study treatment received, where treatment received was defined as the randomized treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

The cross-over set comprised all subjects randomized to the control arm who received at least one dose of Lutathera following confirmed disease progression per central, blinded, real-time image reading in the randomized period.

The re-treatment set comprised all subjects randomized to the Lutathera arm who received at least one dose of Lutathera during the re-treatment period after confirmed disease progression per central, blinded, real-time images reading in the randomized period.

The primary efficacy and safety analyses were planned after observing approximately 99 evaluable PFS events per central assessment. The actual number of PFS events documented by the cutoff date (20-Jul-2023) of the primary PFS analysis was 101 events.

Suppose that $S_L(t)$ was the survival function of PFS in the Lutathera plus 30 mg octreotide LAR (investigational arm), and $S_C(t)$ was the survival function of PFS in the 60 mg octreotide LAR (control arm). The null hypothesis H_{01} stating that $S_L(t)$ is not superior to $S_C(t)$ was tested against the alternative hypothesis H_{a1} stating that $S_L(t)$ is superior to $S_C(t)$.

H_{01} (null hypothesis): $S_L(t) \leq S_C(t)$ was tested against the following.

H_{a1} (alternative hypothesis): $S_L(t) > S_C(t)$,

The primary efficacy analysis to test this hypothesis and compare the two treatment arms consisted of a stratified log-rank test at an overall one-sided 2.5% level of significance in favour of the Lutathera plus standard dose octreotide LAR (30 mg) arm. The stratification was based on the following randomization stratification factors (tumour grade: grade 2 vs. grade 3; and tumour origin: pNET vs other origins).

The PFS distribution was estimated using the Kaplan-Meier method, and Kaplan-Meier curves, median, and associated 95% confidence intervals were presented for each treatment arm. The hazard ratio for PFS was calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test. The proportional hazards assumption was checked visually and, if the visual check was not conclusive, the assumption of proportional hazards was tested.

PFS was censored at the date of the last adequate tumour assessment if no PFS event was observed prior to the analysis cut-off date.
Disease progressions (i.e., central review RECIST 1.1 documented disease progression) or deaths documented after the initiation of new anti-cancer therapy were not counted as PFS events for the primary analysis.
The date of the last adequate tumour assessment was the date of the last tumour assessment with an overall response of CR, PR, or stable disease before an event or a censoring reason occurred.

Sensitivity analyses:

The hazard ratio and 95% confidence interval for PFS per blinded independent central review were obtained from an unstratified and covariate unadjusted Cox model.

To evaluate the effect of other baseline demographic or disease characteristics on the estimated hazard ratio, a stratified and covariate-adjusted Cox model included covariates at baseline: age, gender, and race, tumour burden at baseline, CgA, and SSTR tumour uptake score per central review.

PFS as per local review was analysed using a stratified Cox model, with the same analysis conventions as the primary efficacy analysis.

Supplementary analysis:

The primary efficacy endpoint was also summarized using different censoring mechanisms, including an analysis including events that occur after the start of new antineoplastic therapy if no PFS event is observed prior to the start of new antineoplastic therapy.

Subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics was performed. The subgroups included the stratification factors (tumour grade: grade 2 vs. grade 3, and tumour origin: pNET vs. other origin), age (< 65 vs. ≥ 65 years), gender, race, tumour burden at baseline (limited, moderate, extensive), and SSTR uptake with central assessment (grade 3 vs. grade 4). Efficacy analyses in subgroups were intended to explore the consistency (homogeneity) of treatment effect. Forest plot (including sample size/number of events and HR with 95% CI) was produced to graphically depict the treatment effect estimates in different subgroups.

ORR and its 95% confidence interval were presented by treatment arm. The null hypothesis of the ORR in the investigational arm was less than or equal to the ORR in the control arm were tested against the one-sided alternative. The statistical hypotheses were:

H_{02}: $ORR_R \leq ORR_C$ versus H_{A2}: $ORR_R > ORR_C$,

for a one-sided test where ORR_R was the probability of response in investigational arm and ORR_C was the probability of response in control arm. The Cochran-Mantel-Haenszel chi-square test, stratified by the randomization stratification factors, was used to compare ORR between the two treatment arms, at the 1-sided 2.5% level of significance.

The analysis of QoL Time to Deterioration (TTD) was the same as for PFS, employing log rank test and Cox regression.

Overall Survival: The time from the randomization date until the day of death due to any cause will be analysed with three different approaches, that all employ Cox regression to obtain the hazard ratio and its 95% confidence interval. ITT approach is primary. Approaches 2 (Rank Preserving Structural Failure Time model (RPSFT)) and 3 (Inverse Probability of Censoring Weighting to adjust for crossover) are outside the scope of the primary analysis, and will be conducted in the final analysis. The analysis proceeds by Cox regression as in the primary analysis of PFS.

Primary PFS endpoint and key secondary endpoints were tested in a hierarchical fashion to protect the type I error rate. The order of the hypothesis testing was PFS, then ORR followed by QoL Global Health Scale (TTD), QoL Diarrhea (TTD), QoL Fatigue (TTD), and QoL Pain (TTD).

2.4.4. Outcomes and estimation

2.4.4.1. Recruitment

This study randomized subjects in 38 centers in 9 participating countries: Canada (4 centers), France (5 centers), Germany (2 centers), Italy (8 centers), Netherlands (2 centers), Republic of Korea (4 centers), Spain (4 centers), United Kingdom (4 centers) and United States of America (5 centers).

Study period:

Study initiation date: 08-Jan-2020 (first subject first visit)

Data cut-off date: 20-Jul-2023 (study is ongoing).

2.4.4.2. Conduct of the study

Protocol amendments

The study protocol was amended twice before the primary analysis, after which there were no amendments until the data cut off for this study. The original and amended protocol versions are provided in Appendix 16.1.1. Previous sections of this report describe the study conduct as amended. The key features of each amendment are given in the table below:

Table 1. Protocol amendments

Version and Date	Summary of key changes
1.0	**Amendment 1** was issued when 123 subjects have been randomized in the study. The main purpose of protocol amendment version 1.0 was to introduce optional re-

01st-Oct-2021	treatment with additional doses of Lutathera for subjects treated in the Lutathera arm upon disease progression. Subjects for re-treatment with Lutathera are subjects with centrally documented tumor progression in Lutathera arm (if RECIST progression occurs after Week 72 post the primary end point analysis, the decision to enroll the subject in re-treatment will be based on local assessment), who have completed the 4 doses/cycles of Lutathera during the treatment phase, had CR/PR/ stable disease as best response for at least 6 months after the 4th Lutathera dose, and had tolerated the treatment (according to criteria defined in [Section 16.1.1-Section 5.2.2]). An SSTR uptake must be documented in target lesions by SRI before starting re-treatment. Subjects were offered to receive initially two Lutathera doses in re-treatment period. Based on the physician judgment of clinical benefit derived from the first 2 doses, subjects received up to 2 additional doses of Lutathera (criteria for additional doses are listed in [Section 16.1.1-Section 3.4]. A maximum of 4 doses of Lutathera is allowed during the re-treatment period. The assessment of Lutathera re-treatment has been added as an exploratory objective in the study: To explore the safety and efficacy (ORR, PFS, PFS2, DoR, OS) of re-treatment with Lutathera in progressive subjects. in Lutathera arm
2.0 05th-Oct-2022	At the time of this amendment (No.2) release, subject screening in the study was completed. The primary purpose of amendment version 2.0 was to implement modifications in contraception requirements in line with Lutathera Investigator's Brochure version 17, dated 09 March 2022. The changes were based on Sponsor Guideline on Prevention of Pregnancies in Subjects in Clinical Trials as well as the Clinical Trials Facilitation and Coordination Group (CTFG) guideline on recommendations related to contraception and pregnancy testing in clinical trials. According to these guidelines, for radioligand therapies, highly effective contraception should be used during treatment and for (5 x T ½ + 6 months) after treatment in women of childbearing potential, and condom should be used during treatment and contraception period in male subjects. For Lutathera, the effective half-life is 49 hours, and therefore, as per the calculation, the period of contraception for female subjects should continue for 6 months and 10 days after the last dose. However, as a precautionary measure, the Sponsor decided to extend the highly effective contraception period from 6 months to 7 months for female subjects. In addition, the contraception requirements for male subjects have been modified by specifying the use of condom and highly effective methods of contraception with female partners of childbearing potential or pregnant female partners during the treatment period (including cross-over and retreatment, if applicable) and for 4 months after study drug discontinuation. This duration is based on an exposure of 5 terminal half-lives (49 hours for Lutathera) plus 90 days (life span of spermatozoa of 60–75 days for sperm production + 10–14 days for transport to epididymis) (EMA Safety Working Party recommendations on the duration of contraception following the end of treatment with a genotoxic drug" dated on 27-Feb-2020.

Other important changes in study conduct

The following changes occurred during the study:

- Lutathera supply interruption in May 2022: On 02 May 2022, due to a series of quality issues, Novartis decided to issue a temporary, and voluntary, suspension of the manufacturing of Lutathera at two production sites (Ivrea, Italy and Millburn, New Jersey, USA). NETTER-2 study recruitment was ongoing at the time of the incident and 17 subjects in US/CAN were affected (in Europe and South Korea, Lutathera could be supplied by Zaragoza, Spain) with cancellation of the US/CAN Lutathera doses planned in May 2022. NETTER-2 screening, and randomization were halted in US/CAN on 04 May 2022 (IRT decommissioned for Screening, Crossover and Randomization). Screening and Randomization halt was lifted on 25 May 2022 based on production re- activation on 31 May 2022. All subjects in need for a dose restarted doses from 01 Jun 2022. 100% of

the cancelled doses were injected during the month of June (81% by 15 Jun 2022, 100% by 21 Jun 2022). No subjects discontinued the study due to the production incident.

Protocol deviations:

Overall, 38.1% of subjects (86/226) reported at least one major protocol deviation. The most frequently reported protocol deviations were due to missing procedures or assessments (mostly deviations related to the timing of lesion assessments) (36.4% subjects in the Lutathera arm and 21.3% of subjects in control arm).

2.4.4.3. Baseline data

In total, 226 subjects were randomized between 22-Jan-2020 and 13-Oct-2022 in a 2:1 ratio into Lutathera arm (n=151) or control arm (n=75).

The demographic and baseline characteristics were generally well balanced between treatment arms in the study.

Demographic:

The median age of the subjects was 61 years (range: 23-88) and 40.7% subjects were ≥ 65 years old. No upper age limit was imposed. Overall, 53.5% of subjects were males. Most of the subjects were Caucasian (White; 73%) or Asian (15%) and a broad representation of ethnicities reflects the geographical location of the enrolling sites who participated in this study. As per the study inclusion criteria, all subjects had Karnofsky performance status ≥60, a majority (82.7%) of whom had a baseline Karnofsky performance status ≥90.

Table 2. Demographic and baseline characteristics (Safety set)

Demographic variable	Lutathera N=151	Octreotide LAR N=75	All subjects N=226
Age (vears)			
N	151	75	226
Mean (SD)	60.2 (13.21)	59.6 (11.52)	60.0 (12.65)
Median	61.0	60.0	61.0
Q1-Q3	51.0-72.0	51.0-69.0	51.0-70.0
Min-Max	23-88	34-82	23-88
Age (catefgorised) n (%)			
18-64 years	86 (57.0)	48 (64.0)	134 (59.3)
≥65-74 years	45 (29.8)	19 (25.3)	64 (28.3)
75-84 years	19 (12.6)	8 (10.7)	27 (11.9)
≥85 years	1 (0.7)	0	1 (0.4)
Sex-n (%)			
Male	81 (53.6)	40 (53.3)	121 (53.5)
Female	70 (46.4)	35 (46.7)	105 (46.5)
Race-n (%)			
White	115 (76.2)	50 (66.7)	165 (73.0)
Black or African American	3 (2.0)	2 (2.7)	5 (2.2)
Asian	23 (15.2)	11 (14.7)	34 (15.0)
Indian	2 (1.3)	1 (1.3)	3 (1.3)

Korean	21 (13.9)	10 (13.3)	31 (13.7)
American Indian or Alaska Native	1 (0.7)	0	1 (0.4)
Multiple	1 (0.7)	0	1 (0.4)
Missing	8 (5.3)	12 (16.0)	20 (8.8)
Karnofsky performance score at baseline -n (%)			
60	0	1 (1.3)	1 (0.4)
70-80	28 (18.5)	10 (13.3)	38 (16.8)
90-100	123 (81.5)	64 (85.3)	187 (82.7)

Baseline disease characteristics

Baseline disease characteristics were similar and balanced between the two treatment arms. Prognostic factors and risk groups (grade 2 or 3 disease, tumour site, Ki-67 index, presence of metastasis, location of metastatic sites, overall tumour burden) were evenly distributed. 54.4% of subjects had pancreatic NET, and 65% of subjects had grade 2 NET.

Table 3. Baseline disease characteristics

Disease history	Lutathera	Octreotide LAR	All subjects
Primary tumour site (GEP-NET) - n (%)			
Pancreas	82 (54.3)	41 (54.7)	123 (54.4)
Small Intestine	45 (29.8)	21 (28.0)	66 (29.2)
Other	24 (15.9)	13 (17.3)	37 (16.4)
Presence of metastases – n (%)			
Yes	150 (99.3)	74 (98.7)	224 (99.1)
No	1 (0.7)	1 (1.3)	2 (0.9)
Site of Metastases - n (%)			
Bone	37 (24.5)	18 (24.0)	55 (24.3)
Colon	3 (2.0)	0	3 (1.3)
Ileum	5 (3.3)	4 (5.3)	9 (4.0)
Jejunum	2 (1.3)	1 (1.3)	3 (1.3)
Kidney	1 (0.7)	0	1 (0.4)
Liver	134 (88.7)	69 (92.0)	203 (89.8)
Lung	15 (9.9)	2 (2.7)	17 (7.5)
Skin	1 (0.7)	0	1 (0.4)
Lymph node distant	37 (24.5)	14 (18.7)	51 (22.6)
Lymph nodes regional	88 (58.3)	32 (42.7)	120 (53.1)
Mediastinum	1 (0.7)	2 (2.7)	3 (1.3)
Pelvis (non-bone)	4 (2.6)	3 (4.0)	7 (3.1)
Peritoneum	26 (17.2)	9 (12.0)	35 (15.5)
Pleura	0	1 (1.3)	1 (0.4)
Spleen	4 (2.6)	0	4 (1.8)
Other	25 (16.6)	6 (8.0)	31 (13.7)
Histopathology grade at diagnosis per eCRF - n (%)			
Grade 2	99 (65.6)	48 (64.0)	147 (65.0)
Grade 3	52 (34.4)	27 (36.0)	79 (35.0)
Tumour Origin by Grade per eCRF – n (%)			
pNET grade 2	50 (33.1)	26 (34.7)	76 (33.6)
Small intestine grade 2	36 (23.8)	12 (16.0)	48 (21.2)

Disease history	Lutathera	Octreotide LAR	All subjects
Other grade 2	13 (8.6)	10 (13.3)	23 (10.2)
pNET grade 3	32 (21.2)	15 (20.0)	47 (20.8)
Small intestine grade 3	9 (6.0)	9 (12.0)	18 (8.0)
Other grade 3	11 (7.3)	3 (4.0)	14 (6.2)
Time since initial diagnosis of GEP-NET			
N	151	74	225
Mean (SD)	5.1 (12.11)	6.5 (16.91)	5.6 (13.85)
Median	1.8	2.1	1.9
Q1 - Q3	1.2-3.7	1.4-3.9	1.3-3.7
Min-Max	0-102	0-94	0-102
Disease stage - n (%)			
IIA	0	1 (1.3)	1 (0.4)
IIB	0	0	0
IIIA	1 (0.7)	0	1 (0.4)
IIIB	2 (1.3)	0	2 (0.9)
IV	148 (98.0)	74 (98.7)	222 (98.2)
Highest SSTR Tumour uptake score* –			
Grade 3	56 (37.1)	25 (33.3)	81 (35.8)
Grade 4	95 (62.9)	50 (66.7)	145 (64.2)
Extent of overall tumour burden – n			
Limited	17 (11.3)	9 (12.0)	26 (11.5)
Moderate	69 (45.7)	36 (48.0)	105 (46.5)
Extensive	65 (43.0)	29 (38.7)	94 (41.6)
Missing	0	1 (1.3)	1 (0.4)
Results of Ki67			
Mean (SD)	19.7 (10.08)	20.0 (10.42)	19.8 (10.17)
Median	17.0	16.0	16.0
Q1-Q3	12.0-25.0	12.0-25.0	12.0-25.0
Min-Max	10-50	10-50	10-50
SD: Standard deviation *Highest SSTR tumour update score is based on the cancer diagnosis page. Source: Table 14.1-2.1			

Duration of treatment / Exposure:

In the randomized treatment period, the median duration of exposure to the study treatment was 71.1 weeks in the Lutathera arm (range: 8.1 to 182.9 weeks) and 40.3 weeks (range: 4 to 124.4 weeks) in the control arm. The median duration of exposure to Lutathera was 32 weeks with 87.8% subjects receiving all 4 cycles of treatment.

In the crossover period, the median duration of exposure to study treatment was 32 weeks (range: 8.0 to 37.1 weeks). In the re-treatment period, the median duration of exposure to the study treatment was 12 weeks (range: 8.0 to 27.3 weeks).

In the randomized treatment period, among the 147 treated subjects, all subjects either completed or discontinued Lutathera treatment and the median duration of exposure to Lutathera was 32 weeks (range: 8.0-40.0) with 87.8% subjects receiving all 4 cycles of treatment. The median cumulative dose

was 29.2 GBq (range: 7.0, 31.2) (Table 4) with the median dose per administration at 7.3 GBq/cycle. The median relative dose intensity was 98.2% for Lutathera during the randomized treatment period.

By the time of data cutoff, all subjects in the Lutathera arm had completed or discontinued Lutathera treatment in the randomized treatment period.

Table 4. Lutathera exposure, dose of Lutathera including number of cycles, in the randomized treatment period (Safety Set)

Randomized treatment period	
Duration of exposure (weeks)	
N	147
Mean (SD)	31.11 (4.971)
Median	32.00
Min-Max	8.0-40.0
Number of cycles started by subject, n (%)	
1 cycle	1 (0.7)
2 cycles	(6.8)
3 cycles	(4.8)
4 cycles	129 (87.8)
Cumulative Dose (GBq)	
Mean (SD)	27.57 (4.594)
Median	29.21
Min-Max	7.0-31.2
Dose per administration (GBq/cycle)	
Mean	7.25 (0.387)
Median	7.34
Min-Max	4.1-7.8

Lutathera cycles are once every 8 weeks for a maximum of 4 cycles.
Randomized treatment period starts from first dose of study treatment to last dose of study treatment in the randomized treatment phase + 30 days before the 1st injection of Lutathera in extension (cross-over/re-treatment) phase
Source: Table 14.3-1.2, Table 14.3-1.4

2.4.4.4. Numbers analysed

Of the 226 randomized subjects, all subjects randomized to the Lutathera arm (n=151), or the control arm (n=75) were included in the FAS. Among these subjects, 6 subjects (2.7%) were excluded from the Safety set because they did not receive study treatment (4 in the Lutathera arm and 2 in the control arm).

Twenty-nine subjects who received treatment with octreotide LAR in the control arm subsequently crossed over to receive Lutathera in the crossover period following disease progression and were included in the crossover set (Table 5).

Eight subjects received at least one dose of Lutathera in the re-treatment period and were included in the retreatment set.

Table 5. Analysis sets (Full analysis set)

	Lutathera	**Octreotide LAR**	**All subjects**
	n (%)	**n (%)**	**n (%)**
Analysis Set	**N=151**	**N=75**	**N=226**
Full Analysis Set	151 (100)	75 (100)	226 (100)
Safety Set	147 (97.4)	73 (97.3)	220 (97.3)
Cross-over Set	0	29 (38.7)	29 (12.8)
Re-treatment Set	8 (5.3)	0	8 (3.5)

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned by randomization.

The Safety Set includes all subjects who received any study treatment
The Cross-over Set includes all subjects who received at least one dose of Lutathera after centrally evaluated progression per RECIST after receiving treatment in the control arm
The Re-treatment Set includes all subjects who received at least one dose of Lutathera after centrally evaluated progression per RECIST after receiving treatment in the Lutathera arm.
Source: Table 14.1-1.4

Stratification according to GEP-NET tumour grade (grade 2 or grade 3) and tumour origin (pNET vs other origin) was incorporated into the randomization design.

Overall, 100% of the enrolled subjects had either grade 2 (64.2%) or grade 3 (35.8%) GEP-NETs across both treatment arms. Overall, 124 (54.9%) of the enrolled subjects had GEP-NETs of pancreatic origin. Analysis sets by stratification factor at randomization are summarized in Table 6. Stratification factors as per IRT vs. eCRF by treatment are highly consistent (>95% match with each other) and summarized in Table 6.

Table 6. Randomization by stratification factor (Full analysis set)

Strata	**Tumour Grade**	**Tumour Origin**	**Lutathera N=151**	**N Octreotide LAR N=75 n (%)**	**All subjects N=226 N (%**
			n (%)	n (%)	n (%)
1	Grade 2	pNET	50 (33.1)	26 (34.7)	76 (33.6)
2	Grade 2	Other	47 (31.1)	22 (29.3)	69 (30.5)
3	Grade 3	pNET	32 (21.2)	16 (21.3)	48 (21.2)
4	Grade 3	Other	22 (14.6)	11 (14.7)	33 (14.6)
Summary	Grade 2	---	97 (64.2)	48 (64.0)	145 (64.2)
	Grade 3	---	54 (35.8)	27 (36.0)	81 (35.8)
	---	pNET	82 (54.3)	42 (56.0)	124 (54.9)
	---	Other	69 (45.7)	33 (44.0)	102 (45.1)

Strata as entered in the IRT during randomization Source: Table 14.1-1.5

Table 7. Subject disposition (Full Analysis Set) - Treatment Phase

	Lutathera N=151 n (%)	**Octreotide LAR N=75** n (%)	**All subjects N=226** n (%)
Subjects Treated in Treatment Phase	147 (97.4)	73 (97.3)	220 (97.3)
Subjects Currently in Initial Treatment Phase*	78 (51.7)	15 (20.0)	93 (41.2)
Subjects Discontinued Randomized Treatment Phase	73 (48.3)	60 (80.0)	133 (58.8)
Reason for End of Randomized Treatment Phase			
Progressive Disease	42 (27.8)	44 (58.7)	86 (38.1)
Physician Decision	13 (8.6)	7 (9.3)	20 (8.8)
Adverse Event	8 (5.3)	1 (1.3)	9 (4.0)
Death	4 (2.6)	4 (5.3)	8 (3.5)
Withdrawal By Subject	3 (2.0)	4 (5.3)	7 (3.1)
Other	3 (2.0)	0	3 (1.3)

*At the time of the data cut-off date 20-Jul-2023 Percentages is based on N. Percentaes is based on N.
Source: [NETTER-2-Table 14.1-1.2]

2.4.5. Results

2.4.5.1. Primary endpoint results

The study met the primary objective of demonstrating that treatment in the Lutathera arm is superior to treatment in the control arm in prolonging PFS as first-line treatment. Results from multiple supportive and sensitivity analyses confirmed the robustness of the observed PFS benefit in favor of Lutathera arm.

Primary analysis of PFS (per central review)

As of the data cut-off date, there were 55 events in the Lutathera arm (47 progressions and 8 deaths) and 46 events in the control arm (41 progressions and 5 deaths) based on central review. A statistically and clinically significant reduction of the risk of disease progression or death by 72% was demonstrated in the Lutathera arm as compared to the control arm (stratified HR=0.276; 95% CI: 0.182, 0.418; stratified p<0.0001). The median PFS was 22.8 months (95% CI: 19.4, NE) in the Lutathera arm vs. 8.5 months (95% CI: 7.7, 13.8) in the control arm (Table 8).

The Kaplan-Meier PFS curves for the 2 treatment arms diverged after 2 months, with the progression-free probability remaining higher for the Lutathera arm at all subsequent time points, indicating an early and sustained advantage of treatment with Lutathera (Figure 2).

The estimated event-free probability at 24 months was 49.8% (95% CI: 38.5%, 60.1%) in the Lutathera arm and 19.5% (95% CI: 9.1%, 32.7%) in the control arm (Table 8).

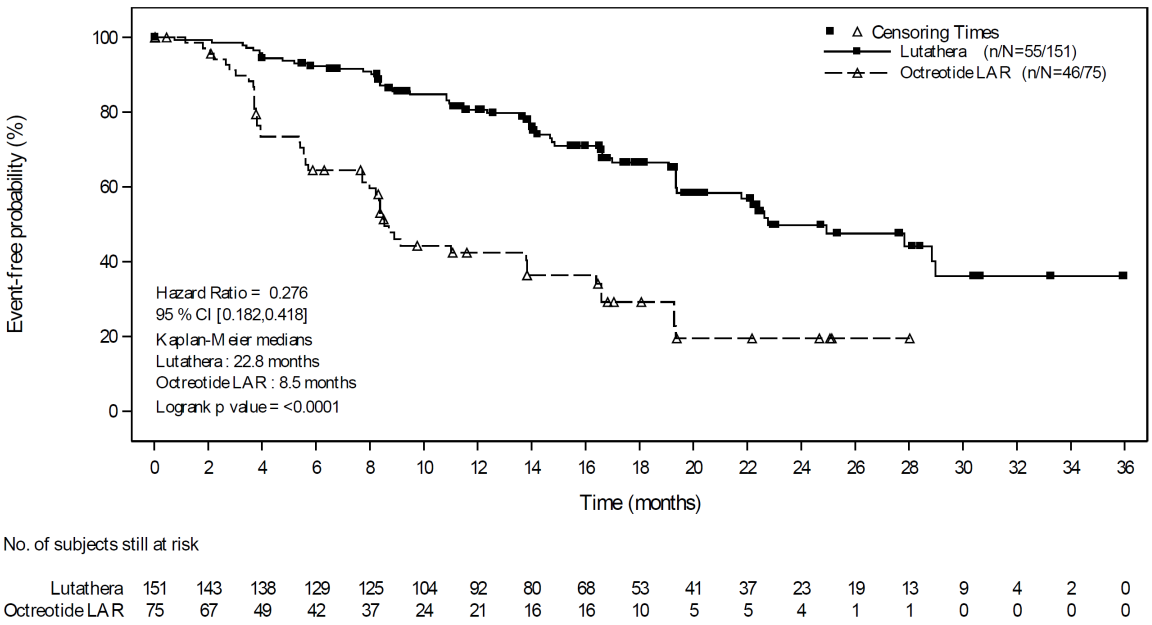
Table 8. Kaplan-Meier estimates of PFS (months) based on central review using RECIST 1.1 criteria (Full Analysis Set)

Progression-free survival (PFS), n (%)	Lutathera N=151	Octreotide LAR N=75
Events	**55 (36.4)**	**46 (61.3)**
Progression	47 (31.1)	41 (54.7)
Deaths	8 (5.3)	5 (6.7)
Censored	96 (63.6)	29 (38.7)
Ongoing without event	70 (46.4)	14 (18.7)
Lost to follow-up	0	0
Adequate assessment no longer available	2 (1.3)	1 (1.3)
Withdrew consent	3 (2.0)	2 (2.7)
New anti-cancer therapy	21 (13.9)	12 (16.0)
Event after two or more missed visits (1)	0	0
Percentiles for PFS (95% CI) (2)		
25th percentile	14.1 (10.9, 17.0)	3.9 (3.7, 5.7)
Median PFS	22.8 (19.4, NE)	8.5 (7.7, 13.8)
75th percentile	NE (29.0, NE)	19.3 (13.8, NE)
Kaplan-Meier event-free estimates (95% CI) (3)		
4 months	95.8 (91.0, 98.1)	73.5 (61.2, 82.4)
6 months	92.3 (86.6, 95.7)	64.5 (51.8, 74.6)

9 months	85.6 (78.6, 90.5)	46.0 (33.4, 57.7)
12 months	80.7 (72.9, 86.4)	42.4 (30.0, 54.3)
15 months	71.0 (61.9, 78.3)	36.4 (24.3, 48.5)
18 months	66.5 (56.9, 74.4)	29.2 (17.7, 41.7)
24 months	49.8 (38.5, 60.1)	19.5 (9.1, 32.7)
30 months	36.1 (22.3, 50.1)	NE (NE, NE)
36 months	NE (NE, NE)	NE (NE, NE)
Hazard ratio (Stratified Cox PH model) (4,5)	**0.276**	
95% CI	(0.182, 0.418)	
Hazard ratio (Unstratified Cox PH model) (4)	**0.309**	
95% CI	(0.207, 0.462)	
Log-rank test (one-sided) Mean (Standard Deviation)		
Stratified p-value (5)	**<0.0001**	
Unstratified p-value	**<0.0001**	
Follow-up time (months) (6)		
Mean (Standard Deviation)	15.2	9.0 (6.94)
Median	14.1	8.0
Min-Max	0.0 - 36.0	0.0 – 28.0

(1) Refer to [NETTER-2-Appendix 16.1.9-Section 5] for details of calculation.
(2) Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
(3) % Kaplan-Meier Event-free estimate is the estimated probability that a subject will remain event-free up to the specified time point; Greenwood formula is used for CIs of KM event-free estimates.
(4) Hazard Ratio of Lutathera arm versus Octreotide LAR arm.
(5) Both Log-rank test and Cox PH model are stratified by tumour grade (G2 vs G3) and tumour origin (pNET vs Other origin) per IRT.
(6) Follow-up time = (Date of event or censoring – randomization date + 1)/30.4375 (months). Source: [NETTER-2-Table 14.2-1.1]

Figure 2. Kaplan-Meier plot of PFS (months) based on central review and using RECIST 1.1 criteria (Full Analysis Set)



No. of subjects still at risk

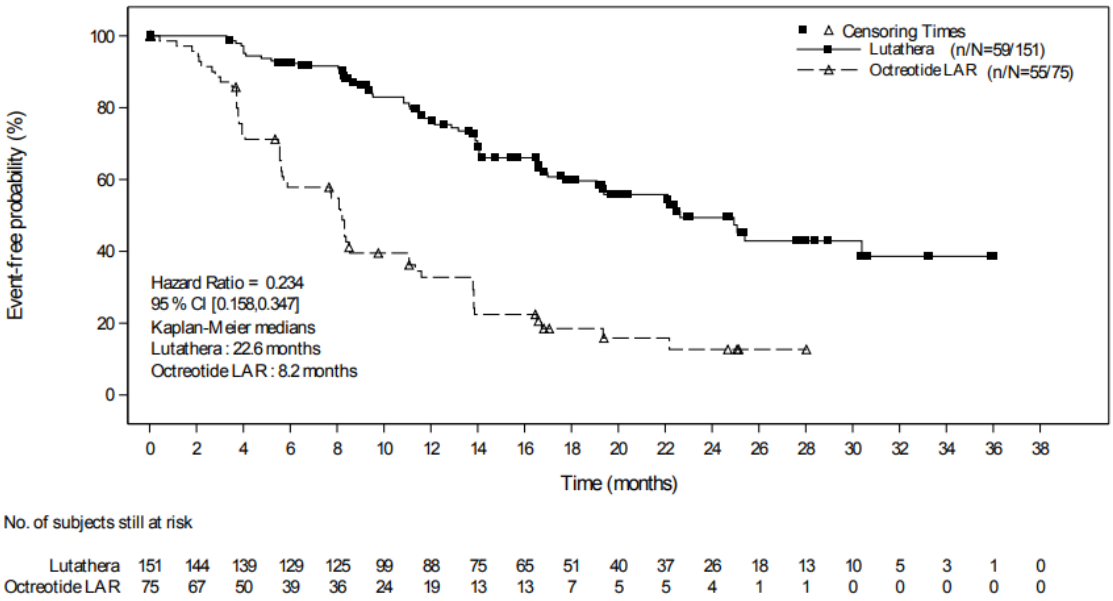
Lutathera	151	143	138	129	125	104	92	80	68	53	41	37	23	19	13	9	4	2	0
Octreotide LAR	75	67	49	42	37	24	21	16	16	10	5	5	4	1	1	0	0	0	0

Both Log-rank test and Cox PH model are stratified by tumor grade (G2 vs G3) and tumor origin (pNET vs Other origin) per IRT.
Source: [NETTER-2-Figure 14.2-1.1]

PFS per local investigator review

The supplementary analysis results of PFS based on local investigator review were consistent with those observed for the primary analysis and in favor of the Lutathera arm, with a 77% reduction of the risk of disease progression or death as compared to the control arm (stratified HR: 0.234; 95% CI: 0.158, 0.347) (Figure 3). The median PFS was 22.6 months (95% CI: 17.7, NE) in the Lutathera arm vs. 8.2 months (95% CI: 5.6, 11.1) in the control arm. The estimated event-free probability at 24 months was 49.4% (95% CI: 38.8%, 59.2%) in the Lutathera arm vs. 12.7% (95% CI: 5.1%, 23.9%) in the control arm [NETTER-2 Table 14.2-1.4].

Figure 3. Kaplan-Meier plot of PFS (months) based on local investigator review and using RECIST 1.1 criteria (Full Analysis Set)



Both Log-rank test and Cox PH model are stratified by tumor grade (G2 vs G3) and tumor origin (pNET vs Other origin) per IRT.
Source: [NETTER-2-Figure 14.2-1.2]

2.4.5.2. Key secondary endpoints results

2.4.5.2.1. Overall Response Rate (ORR) Primary analysis of ORR:

The key secondary objective of ORR based on central review was also met. The ORR was statistically significantly higher in the Lutathera arm (43.0%; 95% CI: 35.0%, 51.3%) compared with the control arm (9.3%; 95% CI: 3.8%, 18.3%), with a stratified odds ratio of 7.81 ($p<0.0001$) (Table 9). Of note, the BOR of CR was observed in 8 subjects (5.3%) in the Lutathera arm vs. none in the control arm as per central review. The BOR of PR was observed in 57 subjects (37.7%) in the Lutathera arm vs. 7 subjects (9.3%) in the control arm as per central review.

Table 9. Best overall response based on central review using RECIST 1.1 criteria (Full Analysis Set)

	Lutathera N=151	**Octreotide LAR N=75**
Best Overall Response (BOR), n (%)		
Complete Response (CR)	8 (5.3)	0
Partial Response (PR)	57 (37.7)	7 (9.3)
Stable Disease (SD)	72 (47.7)	42 (56.0)
Non-CR/Non-PD	0	1 (1.3)
Progressive Disease (PD)	8 (5.3)	14 (18.7)
Unknown (UNK)	6 (4.0)	11 (14.7)
Objective Response Rate (ORR: CR+PR), n (%) (95% CI)	65 (43.0) (35.0, 51.3)	7 (9.3) (3.8, 18.3)
Stratified Odds Ratio (95% CI) (1)	7.81 (3.32, 18.40)	
Stratified One-sided p-value(1)	<0.0001	
Unstratified Odds Ratio (95% CI)	7.34 (3.16, 17.04)	
Unstratified One-sided p-value	<0.0001	
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD), n (%) (95% CI)	137 (90.7) (84.9, 94.8)	50 (66.7) (54.8, 77.1)

[1] (1) Odds Ratio of Lutathera arm vs. Octreotide LAR arm based on stratified CMH method using IRT stratification factors: tumour grade (G2 vs G3) and tumour origin (pNET vs Other origin). P-value based on CMH Chi-Square test.
[2] Source: [NETTER-2-Table 14.2-2.1]

Supplementary analyses of ORR:

Similarly, the ORR based on local investigator review was in favor of the Lutathera arm (46.4%; 95% CI: 38.2%, 54.6%) compared with the control arm (10.7%; 95% CI: 4.7%, 19.9%), with a stratified odds ratio of 7.22 (95% CI: 3.25, 16.05). Of note, the BOR of CR was observed in 2 subjects (1.3%) in the Lutathera arm vs. 1 subject (1.3%) in the control arm as per local investigator review. The BOR of PR was observed in 68 subjects (45.0%) in the Lutathera arm vs. 7 subjects (9.3%) in the control arm as per local investigator review [NETTER-2-Table 14.2-2.2].

Subgroup analyses results of the ORR based on central review were also consistently in favor of the Lutathera arm across the baseline pre-defined subgroups [NETTER-2-Table 14.2-2.5] and the strata (Table 10).

Table 10. Best overall response based on central review and using RECIST 1.1 criteria by strata (Full Analysis Set)

	CR (%)	PR (%)	Total responders/N	ORR (95% CI) [1]	Odds Ratio (95% CI) [2]
Tumour grade: G2					
Lutathera	6 (6.1)	34 (34.3)	40/99	40.4 (30.7, 50.7)	5.83 (2.12, 16.00)
Octreotide LAR	0	5 (10.4)	5/48	10.4 (3.5, 22.7)	
Tumour grade: G3					
Lutathera	2 (3.8)	23 (44.2)	25/52	48.1 (34.0, 62.4)	11.57 (2.48, 53.97)
Octreotide LAR	0	2 (7.4)	2/27	7.4 (0.9, 24.3)	
Tumour origin: pNET					
Lutathera	5 (6.1)	37 (45.1)	42/82	51.2 (39.9, 62.4)	7.56 (2.70, 21.19)
Octreotide LAR	0	5 (12.2)	5/41	12.2 (4.1, 26.2)	
Tumour origin: Other					
Lutathera	3 (4.3)	20 (29.0)	23/69	33.3 (22.4, 45.7)	8.00 (1.76, 36.35)
Octreotide LAR	0	2 (5.9)	2/34	5.9 (0.7, 19.7)	

[3] Two-sided exact binominal 95% CIs.
[4] Odds Ratio of Lutathera arm vs. Octreotide LAR arm based on unstratified CMH method. Source: [NETTER-2-Table 14.2-2.5]

2.4.5.2.2. Time to Deterioration (TTD) Primary analysis of TTD:

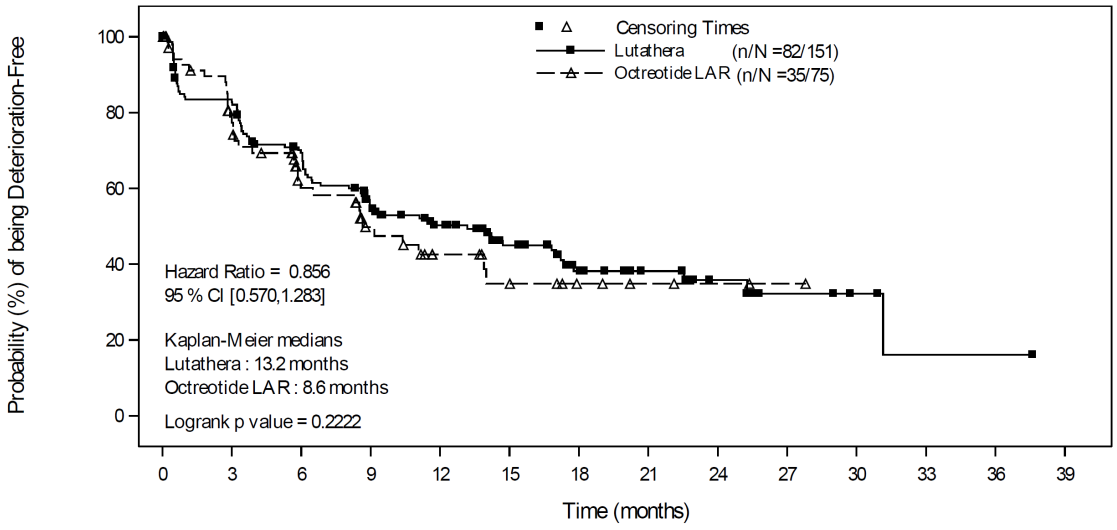
For the key secondary objective of TTD, no statistically significant difference was noted between the Lutathera and control arms for the Global Health Status based on EORTC QLQ- C30. As per the hierarchical testing strategy, the subsequent endpoints of TTD of Diarrhea, Fatigue and Pain, were not tested. The HRs for these 4 subscales based on EORTC QLQ-C30 ranged from 0.856 to 0.998, with all 95% CIs of HRs including 1:

- The stratified HR of TTD by at least 10 points for Global Health Status was 0.856 (95% CI: 0.570, 1.283) for the Lutathera arm vs. control arm. The median TTD for Global Health Status was 13.2 months (95% CI: 8.8, 17.2) in the Lutathera arm vs. 8.6 months (95% CI: 5.8, 14.0) in the control arm [NETTER-2-Table 14.2-3.1.1].
- The stratified HR of TTD by at least 10 points for Diarrhea was 0.877 (95% CI: 0.555, 1.386) for the Lutathera arm vs. control arm. The median TTD for Diarrhea was 17.4 months (95% CI: 14.4, 28.2) in the Lutathera arm vs. 17.3 months (95% CI: 8.1, NE) in the control arm [NETTER-2-Table 14.2-3.1.2].
- The stratified HR of TTD by at least 10 points for Fatigue was 0.998 (95% CI: 0.695, 1.432) for the Lutathera arm vs. control arm. The median TTD for Fatigue was 6.0 months (95% CI: 3.4, 6.8) in the Lutathera arm vs. 6.0 months (95% CI: 3.9, 11.0) in the control arm [NETTER-2-Table 14.2-3.1.3].

- The stratified HR of TTD by at least 10 points for Pain was 0.918 (95% CI: 0.623, 1.351) for the Lutathera arm vs. control arm. The median TTD for Pain was 10.3 months (95% CI: 6.0, 13.6) in the Lutathera arm vs. 8.6 months (95% CI: 3.9, 13.7) in the control arm [NETTER-2-Table 14.2-3.1.4].

Figure 4. Kaplan-Meier plot of TTD by at least 10-points for Global Health Scale, Diarrhea, Fatigue, and Pain based on EORTC QLQ-C30 (Full Analysis Set)

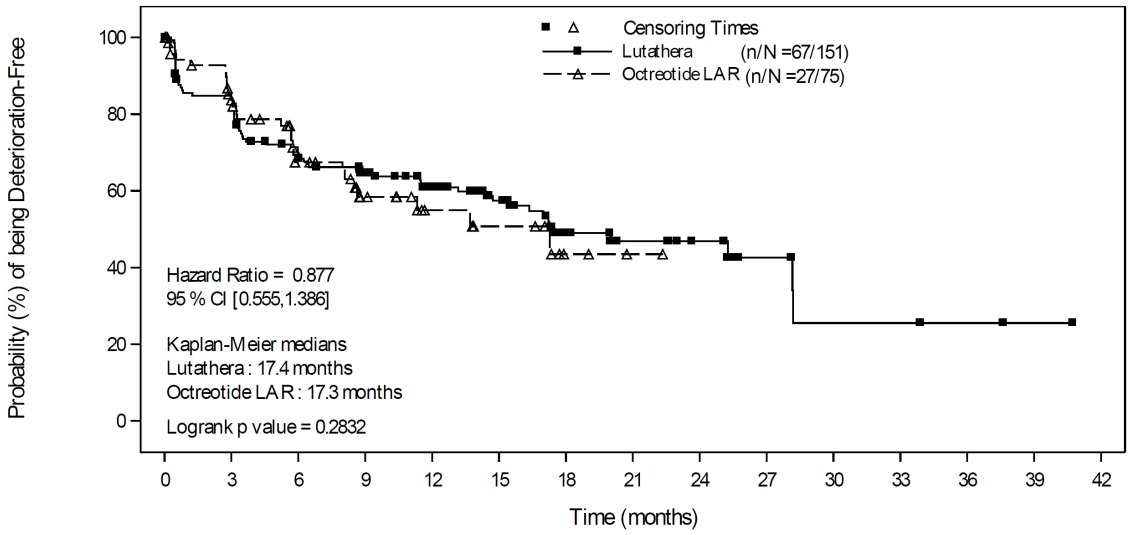
Scale: Global Health Status/QoL



No. of subjects still at risk

Lutathera	151	119	96	69	54	39	25	17	10	5	3	1	1	0
Octreotide LAR	75	49	31	21	13	9	5	3	2	1	0	0	0	0

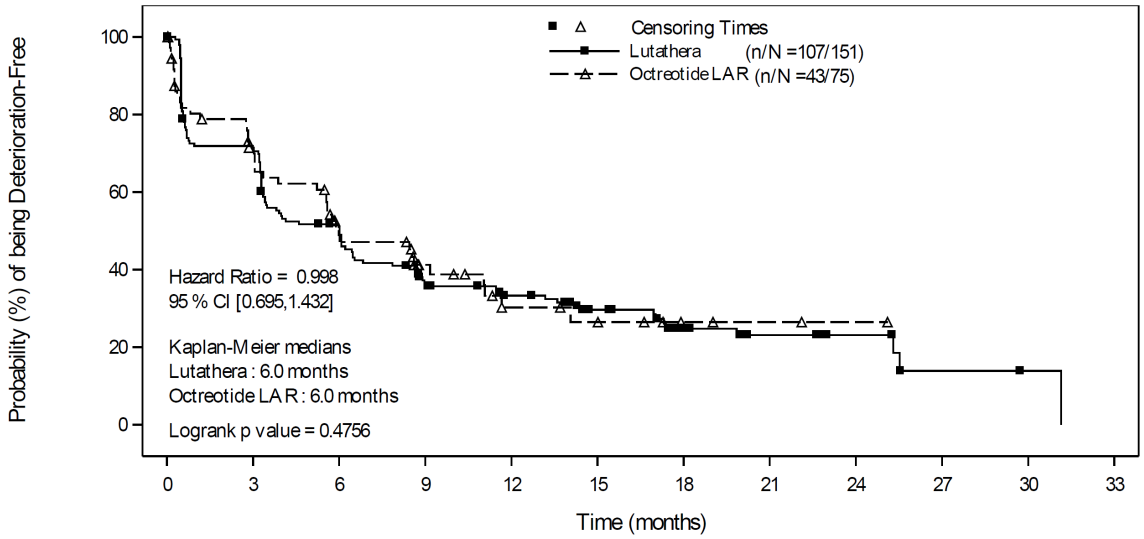
Scale: Diarrhea



No. of subjects still at risk

Lutathera	151	120	95	80	61	46	27	18	12	6	3	3	2	1	0
Octreotide LAR	75	52	33	21	13	9	3	1	0	0	0	0	0	0	0

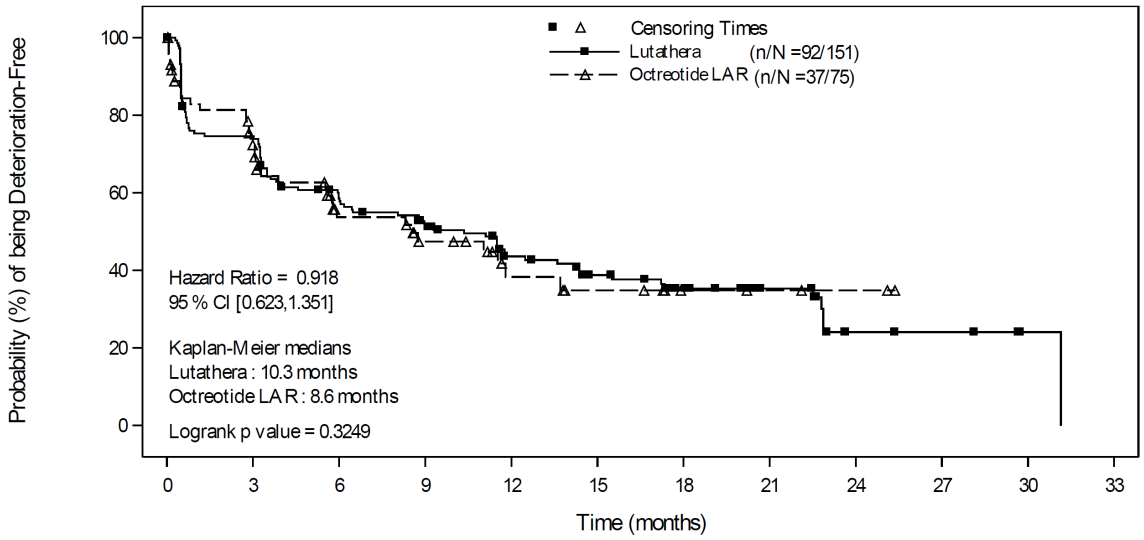
Scale: Fatigue



No. of subjects still at risk

Lutathera	151	103	71	48	39	28	17	12	6	2	1	0
Octreotide LAR	75	46	27	17	9	7	3	2	1	0	0	0

Scale: Pain



No. of subjects still at risk

Lutathera	151	108	81	67	47	35	26	17	5	4	1	0
Octreotide LAR	75	46	27	20	11	8	4	3	2	0	0	0

Both Log-rank test and Cox PH model are stratified by tumor grade (G2 vs G3) and tumor origin (pNET vs Other origin) per IRT.
Source: [NETTER-2-Figure 14.2-3.1.1]

Sensitivity analysis of TTD:

Consistent with those observed for the primary analysis, the HRs of TTD using an unstratified Cox model ranged from 0.855 to 1.018 between the Lutathera and control arms for the QoL scales of Global Health Status, Diarrhea, Fatigue, and Pain, with all 95% CIs of HRs including 1 [NETTER-2-Table 14.2-3.1.1 to Table 14.2-3.1.4].

Supplementary analysis of TTD:

The supplementary analysis results of TTD with a different censoring mechanism (including TTD events whenever they occur, even after 2 or more missing QoL assessments) were also consistent with those observed for the primary analysis.

2.4.5.3. Other secondary endpoints results

2.4.5.3.1. Disease Control Rate (DCR)

The DCR based on central review was higher in the Lutathera arm (90.7%; 95% CI: 84.9%, 94.8%) compared with the control arm (66.7%; 95% CI: 54.8%, 77.1%), with no overlap of CIs.

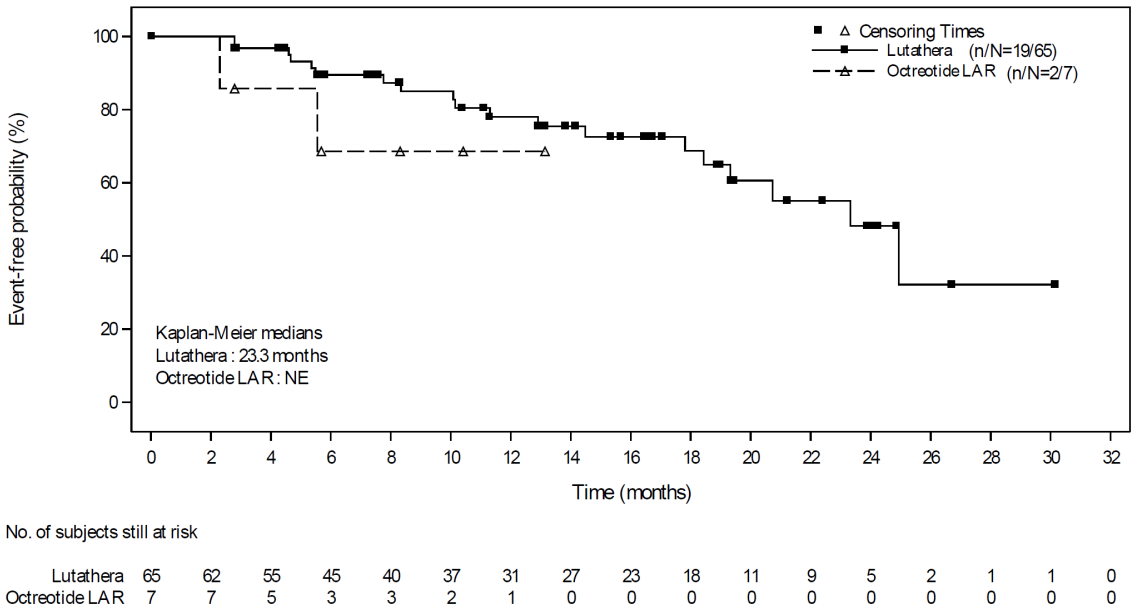
Similarly, the DCR based on local investigator review was also higher in the Lutathera arm (89.4%; 95% CI: 83.4%, 93.8%) compared with the control arm (66.7%; 95% CI: 54.8%, 77.1%), with no overlap of CIs [NETTER-2-Table 14.2-2.2].

2.4.5.3.2. Duration of Response (DOR)

The median DOR based on central review was 23.3 months (95% CI: 18.4, NE) for the 65 responders in the Lutathera arm and not estimable (95% CI: 2.3, NE) for the 7 responders in the control arm. The number of responders (7 per central review) in the control arm was too small to allow a meaningful comparison of DOR between the 2 treatment arms. The event-free probability at 24 months for the Lutathera arm was 48.2% (95% CI: 27.2%, 66.4%).

The median DOR based on local investigator review was 19.9 months (95% CI: 13.4, NE) for the 70 responders in the Lutathera arm vs. 16.6 months (95% CI: 2.3, NE) for the 8 responders in the control arm. The number of responders (8 per local investigator review) in the control arm was too small to allow a meaningful comparison of DOR between the 2 treatment arms. The estimated event-free probability at 24 months was 48.3% (95% CI: 31.6%, 63.1%) in the Lutathera arm [NETTER-2-Table 14.2-2.4].

Figure 5. Kaplan-Meier plot of DOR (months) based on central review and using RECIST 1.1 criteria (Full Analysis Set)



Source: [NETTER-2-Figure 14.2-2.3]

Table 11. DOR based on central review using RECIST 1.1 criteria (Full Analysis Set)

	Lutathera N=151	**Octreotide LAR N=75**
Number of responders (CR or PR)*	**65**	**7**
Event (Progression or Death)	**19 (29.2)**	**2 (28.6)**
Death	**1 (1.5)**	**0**
PD	**18 (27.7)**	**2 (28.6)**
Censored	**46 (70.8)**	**5 (71.4)**
Event after two or more missed visits (1)	0	0
Adequate assessment no longer available	1 (1.5)	0
New cancer therapy added	7 (10.8)	0
Ongoing without event	38 (58.5)	5 (71.4)
DOR percentiles (95% CI) (2)		
25th percentile	**14.5 (8.3, 19.3)**	**5.6 (2.3, NE)**
Median DOR	**23.3 (18.4, NE)**	**NE (2.3, NE)**
75th percentile	**NE (24.9, NE)**	**NE (5.6, NE)**
Kaplan-Meier event-free estimates (95% CI) (3)		
4 months	96.8 (87.7, 99.2)	85.7 (33.4, 97.9)
6 months	89.5 (78.0, 95.1)	68.6 (21.3, 91.2)
9 months	85.0 (72.0, 92.3)	68.6 (21.3, 91.2)
12 months	78.0 (63.4, 87.3)	68.6 (21.3, 91.2)
15 months	72.5 (56.9, 83.3)	NE (NE, NE)
18 months	68.7 (51.9, 80.7)	NE (NE, NE)
24 months	48.2 (27.2, 66.4)	NE (NE, NE)
30 months	32.1 (8.1, 59.9)	NE (NE, NE)

NE= not estimable

*Confirmation of response was not required.
(1) Refer to [NETTER-2-Appendix 16.1.9-Section 5] for details of calculation.
(2) Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
(3) Kaplan-Meier Event-free estimate is the estimated probability that a subject will remain event-free up to the specified time point. Greenwood formula is used
for CIs of KM event-free estimates. Source: [NETTER-2-Table 14.2-2.3]

2.4.5.3.3. Overall survival (OS)

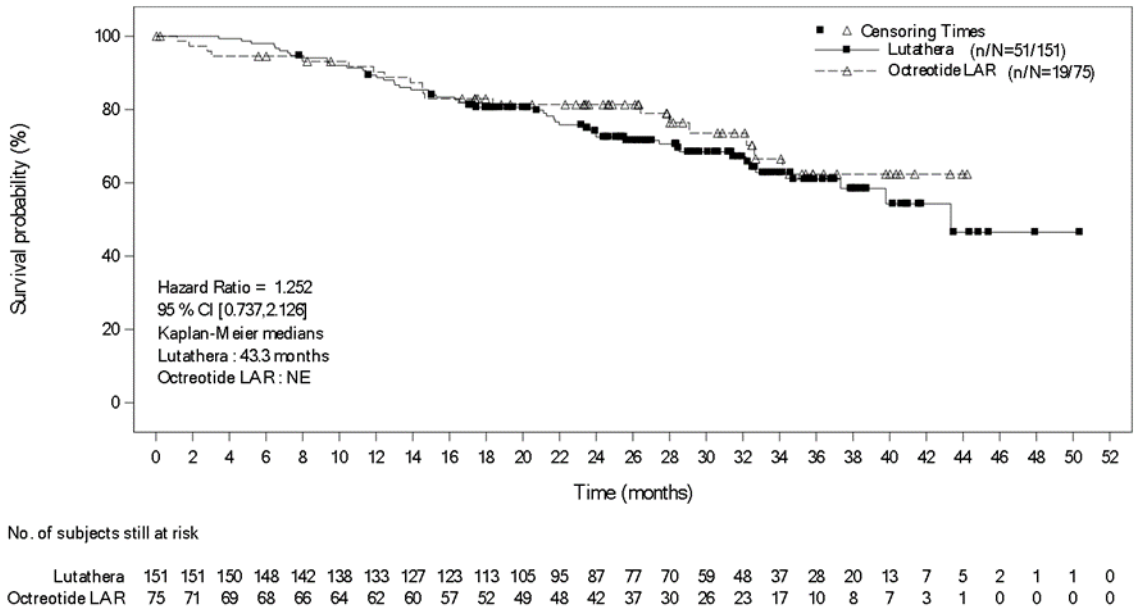
After treatment discontinuation (including cross-over or re-treatment), subjects continued to be followed up at least every 6 months (± 1 month) and up to 3 years for secondary endpoints including overall survival.

Survival data were analysed at the time of the primary PFS analysis (20-July-2023 cut-off date), at the second OS interim analysis (24-May-2024 cut-off date) and will continue to be assessed up to 4 years from the randomization of the last subject or 6 months after the last cross-over/re-treatment dose in the study, whichever occurs last.

The most recent available OS data were immature with ~31% deaths among all randomized subjects at the time of the second OS interim analysis (Figure 6).

A total of 70 deaths were reported (51 in the Lutathera arm and 19 in the control arm). The median follow-up time from the randomization date to date of OS event or censoring was 26.3 months for the Lutathera arm versus 25.6 months for the control arm. The median OS was 43.3 months (95% CI: 37.3, NE) in the Lutathera arm and was not estimable in the control arm. The observed hazard ratio (HR) was 1.25 (95% CI: 0.74, 2.13).

Figure 6. Kaplan-Meier plot of OS (months) (Full Analysis Set)



Source: [NETTER-2-Figure 14.2-5.1]

These interim results should be interpreted with caution, considering several aspects:

- This analysis was performed with only 31% of randomized subjects with OS events, and most subjects (>60% in each arm) are still in follow-up.
- Results are heavily confounded by the high rate of crossover to Lutathera in the control arm. As of the 24-May-2024 cut-off date, a total of 42 subjects (56%) in the control arm crossed over to Lutathera or received other PRRT targeting SSTRs (32 directly crossing over to Lutathera after disease progression, as allowed by the protocol and received a median of 4 (range: 1-4) additional cycles of Lutathera, and 10 subjects receiving Lutathera or other PRRT targeting SSTRs during the follow-up phase, as a subsequent therapy). The crossover to Lutathera occurred early in the study for most subjects, right after the progression on octreotide LAR (the median time to crossover among the 42 subjects was approximately 11 months from randomization).
- There was a notable imbalance in the lost to follow-up between the two arms (i.e., 9.3% (n= 7/ 75) of subjects in the control arm vs. 1.3% (n= 2/151) in the Lutathera arm), which could be attributable to the open label nature of the study. Such an imbalance in dropouts may have biased the estimation of the OS HR.
- NETTER-2 subjects were randomized in a 2:1 ratio to the Lutathera arm (n=151) or control arm (n=75). Considering the small size of the control arm, the weight of each patient on the OS results is relatively high.

Due to these factors, the OS results of the octreotide LAR arm in the study may not be reflective of the true OS in the general population treated with octreotide LAR. Therefore, any OS comparisons should be interpreted with caution.

Considering the high censoring rate, the hazard ratio may not be the best measurement of OS results at this stage. Therefore, the treatment effect on OS was further estimated using the Restricted Mean Survival Time (RMST) method, at timepoints less affected by censoring, i.e., up to 24 months. Overall, there was no notable difference between the study arms in mean survival time restricted to 24 months: 21.3 months (95% CI: 20.5, 22.2) in the Lutathera arm vs. 21.4 months (95% CI: 20.0, 22.8) in the control arm with a p-value of 0.9578 (Table 12).

Table 12. Restricted mean survival time for overall survival (Full Analysis Set)

Time point	Lutathera N=151	Octreotide LAR N=75	Mean survival time difference	p-value
At 12 months	11.6	11.4	0.2	
(95% CI)	(11.3, 11.8)	(10.9, 11.9)	(-0.4, 0.8)	0.5023
At 18 months	16.6	16.5	0.1	
(95% CI)	(16.1, 17.2)	(15.6, 17.4)	(-0.9, 1.2)	0.7960
At 24 months	21.3	21.4	-0.0	
(95% CI)	(20.5, 22.2)	(20.0, 22.8)	(-1.7, 1.6)	0.9578
Cut-off date: 24-May-2024. Source: [NETTER-2 2nd OS IA-Table E4.1-1.3.2]				

2.4.6. Summary of Efficacy for NETTER-2 trial- Table

Title: NETTER 2 A Phase III multi-center, randomized, open-label study to evaluate the efficacy and safety of Lutathera in subjects with Grade 2 and Grade 3 advanced GEP-NET			
Study identifier	CAAA601A22301 (NETTER-2)		
Design	This is a multicenter, stratified, randomized, open-label comparator-controlled, Phase III study in subjects ⩾15 years with somatostatin receptor positive, well-differentiated grade 2 and grade 3, advanced newly diagnosed GEP-NETs. The aim of the NETTER-2 study was to determine if Lutathera administered with 30 mg octreotide LAR prolongs PFS in newly diagnosed advanced GEP-NET subjects with high proliferation rate tumours (grade 2 and grade 3) in comparison to treatment with high dose (60 mg) octreotide LAR. The study consisted of a screening phase, a treatment phase, an optional cross-over phase for subjects assigned to the control arm and optional re-treatment phase for subjects assigned to the Lutathera arm, and a follow-up phase. This study was aimed at comparing treatment with Lutathera (7.4 GBq/200 mCi 4 × administrations every 8 weeks ± 1 week; cumulative dose: 29.6 GBq/800mCi) plus octreotide LAR (30 mg every 8 weeks during Lutathera treatment and every 4 weeks after last Lutathera treatment) (Lutathera arm) and high dose octreotide LAR (60 mg every 4 weeks) (control arm).		
	Duration of main phase: **Duration of Extension phase:**		Study initiation date**:** 08-Jan-2020 (first subject first visit) Data cut-off date**:** 20-Jul-2023 Subjects will be assessed for up to 4 years from the randomization of the last subject or 6 months after the last cross-over/re-treatment dose in the study, whichever occurs last.
Hypothesis	Superiority		
Treatments groups	Lutathera arm		Lutathera (7.4 GBq/200 mCi 4 × administrations every 8 weeks ± 1 week; cumulative dose: 29.6 GBq/800mCi) plus octreotide LAR (30 mg every 8 weeks during Lutathera treatment and every 4 weeks after last Lutathera treatment) N= 151
	Control arm		High dose octreotide LAR (60 mg every 4 weeks) until progression, than crossover possible to Lutathera N=75
Endpoints and definitions	Primary endpoint	PFS per central review	Time from the date of randomization to the date of the first documented progression or death due to any cause, based on central assessment and using RECIST v1.1 criteria.
	Key Secondary endpoint	ORR per central review	Rate of subjects with best overall response of partial response (PR) or complete response (CR) (centrally assessed according to RECIST 1.1)
	Secondary endpoint	TTD for Global Health Status	Time to decline (TTD) by 10 points from baseline in the following scores measured by EORTC QLQ-C30 questionnaire: global health status.
	Secondary endpoint	TTD for Diarrhea	Time to decline (TTD) by 10 points from baseline in diarrhea.

	Secondary endpoint	TTD for Fatigue	Time to decline (TTD) by 10 points from baseline in fatigue.
	Secondary endpoint	TTD for Pain	Time to decline (TTD) by 10 points from baseline in pain.
	Secondary Endpoint	DCR per central review	Rate of subjects with best overall response of partial response (PR), complete response (CR) or stable disease (SD) (centrally assessed according to RECIST 1.1)
	Secondary Endpoint	DOR per central review	The Duration of Response (DOR) is defined as the time from initially meeting the criteria for response (CR or PR) until the time of progression according to RECIST 1.1 or death due to underlying disease only.
	Secondary endpoint	OS	Time from the randomization date until the day of death due to any cause. Median OS (months) (95% CI)
Database lock	20-Jul-2023 (For OS, 24-May-2024)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	**Treatment group**	**Lutathera**	**Octreotide LAR**
	Number of subject	**N=151**	**N=75**
	Primary endpoint: PFS per central review	22.8 (19.4, NE)	8.5 (7.7, 13.8)
	Hazard ratio (stratified Cox PH model) (95% CI)	0.276 (0.182, 0.418) One-sided stratified p-value <0.0001<variability>	
	Key secondary endpoints: ORR per central review (95% CI)	43.0% (35.0%, 51.3%)	9.3% (3.8%,18.3%)
	Stratified odds ratio (95% CI)	7.81 (3.32, 18.40) One-sided stratified p-value <0.0001	
	TTD for Global Health Status Median TTD (months) (95% CI)	13.2 (8.8, 17.2)	8.6 (5.8, 14.0)
	Hazard ratio (stratified Cox PH model) (95% CI)	0.856 (0.570, 1.283) One-sided stratified p-value=0.2222	
	TTD for Diarrhea Median TTD (months) (95% CI)	17.4 (14.4, 28.2)	17.3 (8.1, NE)
	Hazard ratio (stratified Cox PH model) (95% CI)	0.998 (0.695, 1.432)	
	TTD for Fatigue Median TTD (months) (95% CI)	6.0 (3.4, 6.8)	6.0 (3.9, 11.0)

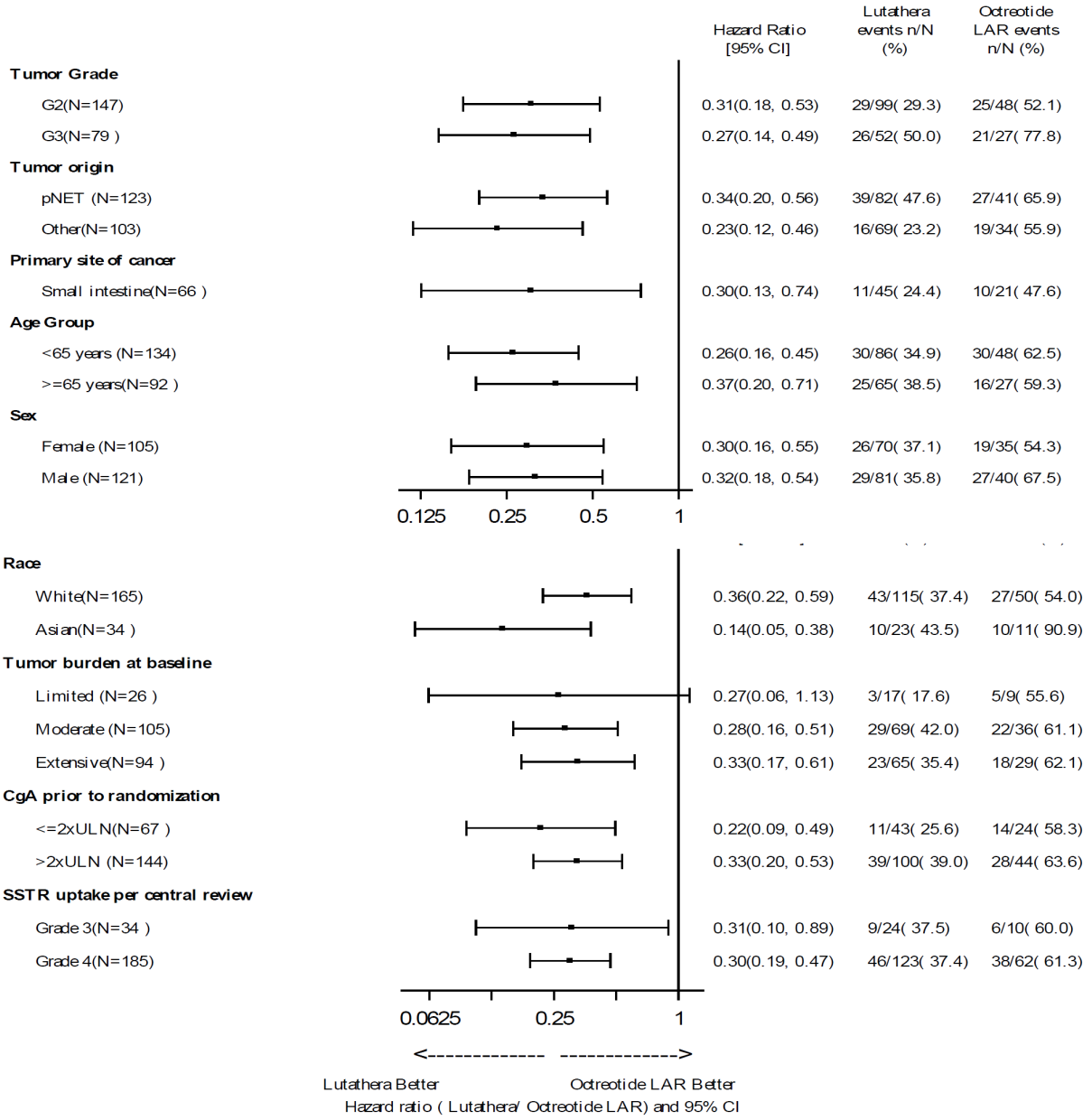
	Hazard ratio (stratified Cox PH model) (95% CI)	0.998 (0.695, 1.432)	
	TTD for Pain Median TTD (months) (95% CI)	10.3 (6.0, 13.6)	8.6 (3.9, 13.7)
	Hazard ratio (stratified Cox PH model) (95% CI)	0.918 (0.623, 1.351)	
	Other secondary endpoints: DCR per central review	90.7% (84.9%, 94.8%)	66.7% (54.8%, 77.1%)
	DOR per central review Median DOR (months) (95% CI)	23.3 (18.4, NE)	NE (2.3, NE)
	OS Median OS (months) (95% CI)	43.3 months (95% CI: 37.3, NE)	NE (NE, NE)
	Observed hazard ratio (HR): 1.25 (95% CI: 0.74, 2.13)		
Notes	Source: [NETTER-2-Table 14.2-1.1, Table 14.2-2.1, Table 14.2-3.1.1, Table 14.2-3.1.2, Table 14.2-3.1.3, Table 14.2-3.1.4, Table 14.2-2.3, and Table 14.2-4.1]		
Analysis description	**Primary analysis (OS results are based on 2nd OS interim analysis)**		

Subgroup analysis

Subgroup analysis of PFS

The consistency of the treatment effect on PFS was confirmed across the subgroups assessed, which were all in favor of the Lutathera arm, with HRs ranging between 0.14 and 0.37 (Figure E9). The Kaplan-Meier estimates for each subgroup were consistent with those for the overall population [NETTER-2-Table 14.2-1.3].

Figure 7. Forest plot of PFS (months) based on central review and using RECIST 1.1 criteria - Key subgroups of interest (Full Analysis Set)



Unstratified Cox model was used for subgroup analysis.
n/N= number of events / number of subjects in the subgroup.
Source: [NETTER-2-Figure 14.2-1.4]

Analysis performed across trials (pooled analyses and meta-analysis)

Not provided.

Clinical studies in special populations

Not available.

2.4.7. Supportive study(ies)

2.4.7.1. NETTER-1

Summary of main efficacy results

The following table summarises the efficacy results from the NETTER-1 trial at the time of approval for the product for the indication:

Lutathera is indicated for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEPNETs) in adults.

Table 13. Summary of efficacy for NETTER-1 trial at the time of approval

Title: A multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours.		
Study identifier	NETTER-1; EudraCT/IND: AAA-III-01 (2011-005049-11/77219)	
Design	A multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study. Stratification based on: *1. OctreoScan® tumour uptake score (Grade 2, 3 and 4);* *2. The length of time that patients have been on the most recent constant dose of Octreotide prior to randomization (≤6 and >6 months).*	
	Duration of main phase:	Started with date of first enrolment on 10 Jul 2012 Randomization not complete at time of primary- end-point analysis.
Hypothesis	Superiority	
Treatments groups	**Test Product**	**177Lu-DOTA0-Tyr3-Octreotate (Lutathera**) In total 29.6 GBq (800 mCi) of Lutathera administered in four equally divided doses. Four administrations of 7.4 GBq (200 mCi) of Lutathera, each dose to be infused over 30 minutes 116 patients randomised
	Reference Therapy/ Comparator	Octreotide acetate powder for suspension for intramuscular (i.m.) injection. 60 mg Octreotide acetate (Sandostatin® LAR) treatment every 4 weeks (i.m. injections) ± 3 days until the final overall analysis of PFS, unless the patient progressed or died. After the final PFS analysis, the treatment/assessment period for each patient became fixed and all patients received 60 mg for a maximum of 72 weeks and then proceeded to the long-term follow-up assessment phase for evaluation of survival. 113 patients randomised

	Concomitant and Rescue Treatment		**In the Lutathera arm only: 30 mg Octreotide LAR treatment for symptoms control** administered until the final overall analysis of, unless the patient progressed or died. After the final PFS analysis, the treatment/assessment period became fixed and all patients received 30 mg for a maximum of 72 weeks and then proceeded to the long-term follow-up assessment phase for evaluation of survival and long term toxicities. **In the Lutathera arm only: amino acid infusion (Vamin 18 in Europe and Aminosyn II 10% in USA)** was given concomitantly with each administration of Lutathera for kidney protection. **In both arms:** in case patients experienced clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, **Octreotide s.c. rescue injections** were allowed.
Endpoints and definitions	Primary endpoint	**Progression free survival (PFS)**	Time from randomization to documented, centrally assessed disease progression, as evaluated by the Independent Reading Centre (IRC), and death due to any cause.
	Secondary endpoint	**Objective Response Rate (ORR)**	Objective Response Rate (ORR) was calculated as the proportion of patients with tumour size reduction (sum of partial responses (PR) and complete responses (CR)). Response duration was calculated from the time of initial response until documented tumour progression.
	Secondary endpoint	**Overall Survival (OS)**	Overall Survival (OS) was calculated from the randomization date until the day of death due to any cause; OS was not censored if a patient received other anti-tumour treatments after study medication.
	Secondary endpoint	**Time to Tumour Progression (TTP)**	TTP is defined as the time from randomization to progression centrally assessed. It includes patients who dropped out due to toxicity, but omits patients who died without measured progression (censored to last follow-up date or death date).
	Secondary endpoint	**Duration of Response (DoR)**	The Duration of Response (DoR) is defined as the time from initially meeting the criteria for response (CR or PR) until the time of progression by RECIST.
Data Cut-off point	24th July 2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set		
Descriptive statistics and estimate variability	**Treatment group**	***Lutathera***	***Octreotide LAR 60 mg***
	Number of subjects	116	113
	Primary endpoint (Median PFS-months)	Not reached	8.4

	95% CI	Not reached	(5.8; 9.1)
	Secondary Endpoint: ORR (%)	17.8	3.0
	95% CI	10.4; 25.3	0.0; 6.3
	Secondary endpoint: median OS (months)	Not reached	Not reached
	95% CI	Not reached	Not reached
	Secondary endpoint: TTP (months)	Not reached	8.7
	95% CI	Not reached	6.4; 11.1
	Secondary endpoint: DoR (months)	Not reached	Not reached
	<variability statistic>	Not reached	Not reached

Effect estimate per comparison	Primary endpoint: **PFS**	Lutathera vs. Octreotide LAR 60 mg	
		Hazard Ratio	0.205
		95% CI	0.127; 0.332
		P-value	<0.0001
	Secondary endpoint: **ORR**	Lutathera vs. Octreotide LAR 60 mg	
		Difference in ORR	14.8
		95% CI	6.6; 23.0
		P-value	0.000825
	Secondary endpoint: **TTP**	Lutathera vs. Octreotide LAR 60 mg	
		Hazard Ratio	0.171
		95% CI	0.099; 0.296
		P-value	<0.0001
Notes	Study has not completed randomisation at the data cut-off point. Large numbers of patients counted as missing data as treatment ongoing in the randomised arms.		

NETTER-1 was a multicentre, stratified, open-label, randomized, comparator-controlled, parallel-group Phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate plus 30 mg Octreotide LAR (best supportive care) to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable, progressive (as determined by RECIST 1.1), somatostatin receptor-positive midgut carcinoid tumours.

The plan was to randomize a total of 230 patients (115 patients per group).

Key criteria for enrolment were: i) metastatic or locally advanced, histologically proven midgut carcinoid tumours with centrally confirmed Ki67 index ≤20%; ii) somatostatin receptor positive target lesions based on OctreoScan® scintigraphy within 24 weeks prior to randomization while the patient was on a fixed dose of Octreotide LAR; iii) patient receiving a fixed dose of 20 mg or 30 mg Octreotide at 3-4

weeks intervals for at least 12 weeks prior to randomization; and iv) progressive disease centrally confirmed according to RECIST Criteria.

After the screening period, patients randomised were randomly assigned to treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera) arm or the Octreotide LAR arm.

Results

Primary endpoint: Progression free survival

At the time of the cut-off date for the primary end-point analysis (July 24, 2015), the number of centrally confirmed disease progressions or deaths was 21 events in the Lutathera and 70 events in the Octreotide LAR group.

The median PFS was not reached for Lutathera and was 8.5 months for 60 mg Octreotide LAR [95% CI: 5.8-9.1 months]; differences in PFS between treatment groups was statistically significant p<0.0001, with a hazard ratio of 0.18 [95% CI: 0.11-0.29], indicating a significantly lower risk for a PFS event with Lutathera treatment compared to Octreotide LAR.

In the Lutathera arm 82% of the observations were censored (2.6% because of start of new anti-cancer therapy, 2.6% due to death or progression after two or more missed visits, 5.2% because of treatment discontinuations for toxicity or other reason with no additional scans, 7.8% because of no post-baseline tumour assessments and 63.8% due to no documented progression); versus, 38.1% in the Octreotide LAR arm (1.8% due to death or progression after two or more missed visits, 2.7% because of treatment discontinuations for toxicity or other reason with no additional scans, 5.3% because of start of new anti-cancer therapy, 6.2% because of no post-baseline tumour assessments and 22.1% due to no documented progression).

Key secondary endpoint: Overall Response Rate (ORR)

The ORR for the FAS at the primary end-point cut-off date was statistically significantly different between the treatment groups in favour of Lutathera (p=0.0141), 14.7% of patients under Lutathera treatment had PR or CR compared to 4.0% in the Octreotide LAR arm.

Overall survival

OS was defined as the time (number of months) from the randomisation date until the day of death due to any cause or the date of last contact (censored observation) at the date of data cut-off, and during the entire study period (i.e. the treatment phase + follow-up). OS was not censored if a patient received other anti-tumour treatments after study medication.

Survival data were collected at the time of the analysis of the primary end-point (PFS), thus the following results as displayed in table and figure below were derived from an interim analysis for OS at the cut-off date (24 July 2015). The same analyses were performed for all randomized patients through the data cut-off date 30 June 2016.

Final analysis of OS:

At the time of this final overall survival (OS) analysis, the median follow-up duration was 76 months in each study arm. There were 73 deaths in the Lutathera® arm (62.4%) and 69 deaths in the high-dose octreotide Long-acting Release (LAR) arm (60.5%), yielding a Hazard Ratio (HR) of 0.84 (95% Confidence Interval [CI]: 0.60, 1.17; unstratified Log-rank test p=0.3039, two-sided) in favour of the Lutathera® arm.

The median OS was prolonged by a clinically relevant extent of 11.7 months in patients randomized to the Lutathera® arm compared to patients randomized to high-dose octreotide

LAR, with a median OS of 48.0 months (95% CI: 37.4, 55.2) and 36.3 months (95% CI: 25.9, 51.7), respectively. However, the final OS results did not reach statistical significance.

2.4.8. Discussion on clinical efficacy

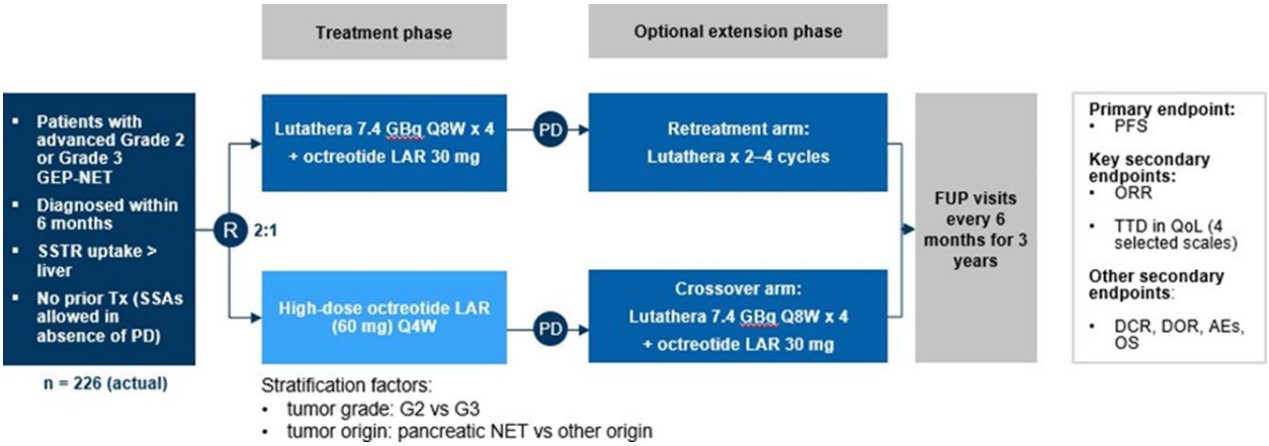
Based on the data from NETTER-1 trial and supportive information from the ERASMUS trial, Lutathera is currently approved for the indication: *Lutathera is indicated for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEPNETs) in adults.*

With this variation based on the outcome of the NETTER-2 trial, the applicant intends to extend the indication to adult patients with newly diagnosed, advanced, SSTR-positive G2 or G3 GEP-NETs to complement the NETTER-1 study with clinical evidence in an earlier line of treatment and in higher grade tumours. The following wording is proposed: *Lutathera is indicated for the treatment of newly diagnosed, unresectable or metastatic, well-differentiated (G2 and G3), somatostatin receptor-positive GEP-NETs in adults*

The application is based on the primary analysis data from the ongoing NETTER-2 study (cutoff-date 20-Jul-2023) which is considered pivotal for the applied extension of indication.

Design and conduct of the NETTER-2 study

The ongoing NETTER-2 study is a Phase III, multicenter, stratified, open-label, randomized, comparator-controlled study comparing treatment with Lutathera plus octreotide LAR 30 mg (Lutathera arm) to treatment with high-dose octreotide LAR 60 mg (control arm). The figure below provides an overview:



The aim of the NETTER-2 study was to show superiority of Lutathera administered with 30 mg octreotide LAR (Lutathera arm) in prolonging PFS in the target population in comparison to treatment with a high dose (60 mg) octreotide LAR (control arm).

The primary endpoint was PFS centrally assessed by blinded Independent Review Committee (IRC) according to the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. The key secondary endpoints included ORR as per central review by blinded IRC according to RECIST v1.1, and the time to deterioration (TTD) in the selected scales of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ-C30): Global Health Status, Diarrhea, Fatigue, and Pain. Other secondary efficacy endpoints included disease control rate (DCR), duration of response (DOR), and overall survival (OS). The primary endpoint (PFS) and key secondary endpoints (ORR and

TTD) were tested in a hierarchical fashion to protect the type I error rate. The order of the hypothesis testing was PFS, then ORR, followed by TTD for Global Health Status, Diarrhea, Fatigue, and Pain. OS is not included in this testing.

Although the selected endpoints, which are rather similar to those investigated in NETTER-1, are clinically relevant and generally acceptable, it is necessary to point out, that the hierarchical testing strategy, which is being used in NETTER 2 to control the type 1 error does not reflect the clinical relevance of the endpoints in their entirety.

Notably, no confirmatory conclusions concerning overall survival will be possible (whereby it is acknowledged that the possibility to cross over and the 2:1 randomisation will hamper the interpretation of overall survival anyway).

Therefore, it will probably remain uncertain, whether the first line treatment (in the way in which it has been applied here) will also lead to any reliable overall survival benefit as shown for the already approved indication in the advance grade 1 GEP-NET population. Considering that it is not known, whether subjects in the target population will have any benefit from re-treatment, it is currently questionable, whether besides the PFS and ORR surrogate efficacy outcome any hard endpoint outcome will become available. Thus, it remains uncertain whether efficacy shown can be translated into a reliable clinical relevant benefit for the patients. Moreover, even a detrimental effect on overall survival in the target population cannot be excluded at the end.

The study population included subjects with metastasised or locally advanced, inoperable (curative intent), histologically proven, somatostatin receptor-positive, well-differentiated GEP-NETs of grade 2 (Ki67 index ≥10% to ≤ 20%), and grade 3 (Ki67 index > 20% to ≤ 55%).

Only subjects newly diagnosed within 6 months prior to screening were included, who were SSA-naive, or previously treated with SSAs in the absence of progression (i.e., study treatment was administered as first line).

In principle, the chosen inclusion and exclusion criteria are adequate to characterise the intended target population and to exclude subjects with specific risks or other reasons that might increase heterogeneity in the study population. The exact wording of a potential indication will be decided in the next round.

The study consisted of a screening phase, a treatment phase, an optional cross-over phase for subjects assigned to the control arm, optional re-treatment phase for subjects assigned to the Lutathera arm, and a follow-up phase.

Overall, 222 subjects were planned to be randomised (2:1) to Lutathera arm or control arm. Randomization was stratified by grade (grade 2 vs grade 3) and tumour origin (pancreatic neuroendocrine tumour (pNET) vs other origins).

While stratification is acknowledged and may prevent imbalance between treatment arms for known factors that influence prognosis, the 2:1 randomisation and the crossover option for control arm subjects appears critical.

The applicant reasoned this approach by the intention to allow subjects to have a higher chance of getting the treatment, which is hypothesized to be more effective.

Crossover to the Lutathera arm was allowed after centrally confirmed RECIST progression (or locally confirmed if it occurs after Week 72 post the primary end point analysis). The applicant justifies this as an effort to minimise the possible higher drop-out rate in the control arm. Although the applicant's view is respected, it appears that this issue should have been discussed at least with CHMPA's SAWP before the start of the trial. In particular, since from the results in NETTER-1 it was foreseeable that this approach will significantly increase the probability that overall survival data will remain non-informative at the end.

NETTER-2 study compared treatment with Lutathera (7.4 GBq/200 mCi 4 × administrations every 8 weeks ± 1 week; cumulative dose: 29.6 GBq/800mCi) plus octreotide LAR (30 mg every 8 weeks during Lutathera treatment and every 4 weeks after last Lutathera treatment and high dose octreotide LAR (60 mg every 4 weeks).

The posology for Lutathera was based from experience the NETTER-1 trial in advance midgut NETs and the dose finding in Phase I/II ERASMUS study. No formal dose study was performed for the different target population in NETTER-2. This posology was mainly based on safety (recovery from the haematotoxicities) in order to reach a good treatment tolerability, which is fully acknowledged. Nevertheless, it remains challenging to presume that that the more aggressive tumours now applied treated with the same posology as in NETTER-1 without any attempt of specific dose finding. The applicant clarified that the standard treatment schedule has been widely adopted in clinical practice, and validated in the randomized, controlled NETTER-1 trial. Absorbed doses to OARs were confirmed to be independent of the disease, with limited inter-patient variability and thereby may allow the conclusion that no need for additional dose finding for the NETTER-2 population is evident. This conclusion is also in line with the finding that safety risks between NETTER-1 and the newly applied NETTER 2 population are not different, no new safety signals were detected and that a longer safety follow-up of 7.5 - 10 years is available from a large post approval safety study (SALUS, EUPAS25735). In summary, although the hypothesis that individualized dosing based on absorbed dose may provide incremental benefit for some patients remains valid, it needs also to be considered that an increase in benefit-risk would need to be high enough (and not just marginal) to justify the burden for the patients from additional imaging procedures and more intensive monitoring.

Whether high dose octreotide LAR (60 mg every 4 weeks) used as comparator is an appropriate treatment for grade 2 and 3 PGEP-NETs is difficult to assess. As there is no universally accepted standard of care therapy for a substantial number of newly diagnosed subjects with grade 2/3 GEP-NET, and only a few approved treatment options exist, including SSAs and chemotherapy, the decision about the appropriateness of the comparator is difficult. The applicant clarified that at the time of designing the NETTER-2 study there was limited evidence to support first-line treatment decisions in high grade GEP-NET patients. According to the clinical guidelines available at that time chemotherapy was recommended for well-differentiated high grade GEP-NETs, but in the absence of prospective chemotherapy data for the first line (including the newly established G3 classification entity), the recommendations for commonly used regimens were different across different regions and guidelines. Thus, there was no panel consensus on which chemotherapy regimen was the best nor informing best treatment sequence considering different MoAs. In addition, there were no prospective randomized data with chemotherapy or targeted therapies in 1L pNETs; while the available data in pNETs was limited to progressive setting or in lower/intermediate grades.

Due to the radioactive nature of Lutathera and its method of infusion, and the different modalities of treatment in the study arms (similarly to the NETTER-1 study design), it was probably not possible to implement a fully double-blinded design for this study. This was already acknowledged during the assessment of the NETTER-1 and remains hence acceptable. In order to increase reliability in the reported results, a central, blinded, real-time Independent Review Committee (IRC) assessment was implemented to ensure an independent evaluation of the tumour response according to RECIST 1.1 criteria in addition to local investigator's assessment. However, the assessment of the IRC appears to be more favourable for Lutathera than that reported by the local investigators (e.g. significantly higher CR events were assessed by IRC), which appears unusual. Further clarification is needed to exclude concerns regarding the reliability of the IRC-reported outcome.

The study protocol was amended twice before the primary analysis, after which there were no amendments until the data cut off for this study. In the first Amendment after randomisation of 123 subjects the option for re-treatment with Lutathera after disease progression was introduced, and

administered performed in 8 subjects until cutoff date. Applicant clarified that introduction of re-treatment with protocol amendment 1 did not affect the evaluation of endpoints related to the centrally assessed tumor response, i.e., PFS, ORR, DOR and DCR. Also the TTD endpoint was not affected by a re-treatment that started after the treatment discontinuation upon progression. Therefore, it is agreed that the trial outcome in terms of primary and key secondary endpoints was not affected by the retreatment option. Moreover, there was a supply interruption due to quality issues which affected 17 subjects mainly by treatment delay by more than 4 weeks, but from assessment of the details is appears not likely that trial outcome was relevantly affected.

Efficacy data and additional analyses

In total, 226 subjects were randomized between 22-Jan-2020 and 13-Oct-2022 in a 2:1 ratio into Lutathera arm (n=151) or control arm (n=75). The demographic and baseline characteristics were generally well balanced between treatment arms in the study. The median age of the subjects was 61 years (range: 23-88) and 40.7% subjects were ≥ 65 years old. No upper age limit was imposed. Overall, 53.5% of subjects were males, mostly Caucasian (White; 73%). (82.7%) of whom had a baseline Karnofsky performance status ≥90.

At baseline, more than 50% of the subjects had pancreatic tumours, followed by about 30 % with small intestinal GEP-NETs and 20 % with other primary sites. With 2 exceptions all subjects had metastatic disease (disease stage IV), mainly in located in the liver (~90%), regional and distant lymph nodes (53.1%/ 22.6%) and bone (~24%). Histopathological Grade at diagnosis was balance between the arms (Grade 2: L: 65.5 vs C:64.0% / Grade 3: L:34.4 vs C:36.0 %). Tumour burden was in nearly 90 % of the subjects moderate (46.5%) or extensive (41.6%) and balanced between the arms.

It is noted that the median of Ki67 % the trial subjects, reported with 19.8 (SD:10.1) was relatively low and also Q1-Q3 range ends with an upper boundary of 25%. Thus, information in more aggressive tumours with Ki67% ≥ 25% is limited from this trial. Nevertheless, in general it is agreed that overall the included population appears to representative for the applied broad population with advanced GEP-NET.

In the randomized treatment period, among the 147 treated subjects the median duration of exposure to Lutathera was 32 weeks (range: 8.0-40.0) and 87.8% subjects receiving all 4 cycles of treatment. The median cumulative dose was 29.2 GBq (range: 7.0, 31.2) with the median dose per administration at 7.3 GBq/cycle. The median relative dose intensity was 98.2% for Lutathera during the randomized treatment period. Exposure shows that overall Lutathera treatment was tolerable.

In NETTER-2 133/226 (58.8%) subjects discontinued the randomized treatment phase. Discontinuation was significantly in the Control Arm (L: 48.3% vs. C:80.0%); only 15/75 (20%) subjects are still in the control arm at cutoff date (vs L: 73/151(58.8%). As could be expected, discontinuation due to progressive disease was significantly higher in the Control arm (L:27.8 % vs C:58.7%) whereas discontinuation due to adverse events was slightly more frequent in the Lutathera arm (L:5.3% vs C:1.3%). Discontinuation due to death occurred more frequent in the Control arm (L: 4/141, 2.6% vs C: 4/75, 5.3%).

The study met the primary objective of demonstrating that treatment in the Lutathera arm is superior to treatment in the control arm **in prolonging PFS as first-line treatment**.

A statistically and clinically significant reduction of the risk of disease progression or death by 72% was demonstrated in the Lutathera arm as compared to the control arm (stratified HR=0.276; 95% CI: 0.182, 0.418; stratified p<0.0001). The median PFS was 22.8 months (95% CI: 19.4, NE) in the Lutathera arm vs. 8.5 months (95% CI: 7.7, 13.8) in the control arm.

The Kaplan-Meier PFS curves for the 2 treatment arms diverged after 2 months, with the progression-free probability remaining higher for the Lutathera arm at all subsequent time points, indicating an early and sustained advantage of treatment with Lutathera (Figure 2).

Results from multiple supportive and sensitivity analyses confirmed the robustness of the observed PFS benefit in favor of Lutathera arm.

Thus, Lutathera treatment was clearly superior regarding PFS compared to the control arm treatment, while death events occurred in rather similar degree (L: 5.3 % vs C: 6.7%). Median PFS was significantly longer with 22.8 months (95% CI: 19.4, NE) in the Lutathera arm vs. 8.5 months (95% CI: 7.7, 13.8) in the control arm.

With respect to the **key secondary objective of ORR** based on central review, which is related to PFS also a statistically significantly higher response was observed in the Lutathera arm (43.0%; 95% CI: 35.0%, 51.3%) compared with the control arm (9.3%; 95% CI: 3.8%, 18.3%), with a stratified odds ratio of 7.81 ($p<0.0001$). This outcome is confirmed by best overall response (BOR) with a complete remission in 8 subjects (5.3%) in the Lutathera arm vs. none in the control arm, while BOR of PR was observed in 57 subjects (37.7%) in the Lutathera arm vs. 7 subjects (9.3%) in the control arm (both central review). Interestingly, the BOR of CR was only observed in 2 subjects (1.3%) in the Lutathera arm vs. 1 subject (1.3%) in the control arm as per local investigator review. A discrepancy was noted regarding the reported numbers of CR: In NETTER-2 complete remission (CR) is reported in 8 subjects (5.3%) in the Lutathera arm vs. none in the control arm by central review but was only observed in 2 subjects (1.3%) in the Lutathera arm vs. 1 subject (1.3%) in the control arm as per local investigator review. Assessment of the provided details for the central and the local review showed that overall the assessments of target lesions were similar for most of the patients, and differences in best response with centrally assigned CR vs. locally assigned PR were related to minor divergences in target and non-target lesions selection and measurements. The overall concordance rate for best overall response was ~77.4% (175/226) between local and central review. Non-concordant assessments between central and local reviews both in terms of selection of measurable lesions and their evolvement over time. Moreover, it appears that in general -with one significant exception- assessments over time were quite close, but the difference in outcome (CR vs PR) was mostly due to additional lesion and/or differences in determination of target lesions between CR versus locally review.

For the **key secondary objective of TTD**, no statistically significant difference was noted between the Lutathera and control arms for the Global Health Status based on EORTC QLQ- C30. As predefind in the SAP for the hierarchical testing strategy, the subsequent endpoints of TTD of Diarrhea, Fatigue and Pain, were not tested. The HRs for these 4 subscales based on EORTC QLQ-C30 ranged from 0.856 to 0.998, with all 95% CIs of HRs including 1.

The applicant interprets the absence of notable differences between the 2 arms for the QoL TTD results, as prove that treatment with Lutathera did not deteriorate the subject's QoL as compared to the control treatment (octreotide LAR), which is known to be safe and well-tolerated. Although this view may be formally correct and may be understood as an additional evidence that safety risk do not differ, it also means from an efficacy perspective that Lutathera treatment is not associated with a benefit in terms of symptomatic relief. Obviously, Lutathera treatment cannot claim convincingly a benefit regarding a better quality of life from the PFS or PFS prolongation observed according the data. However, it should be also noted that QoL results are only reasonable interpretable from double blinded clinical trials.

With respect to the other secondary endpoints **Disease control rate (DCR)** was higher in the Lutathera arm (90.7%; 95% CI: 84.9%, 94.8%) compared with the control arm (66.7%; 95% CI: 54.8%, 77.1%) based on central review and also on the local investigator level. The CIs do not overlap. Insofar, it appears that disease control rate indicates again Lutathera's superior efficacy compared to control arm.

The median **DOR** based on central review was 23.3 months (95% CI: 18.4, NE) for the 65 responders in the Lutathera arm and not estimable (95% CI: 2.3, NE) for the 7 responders in the control arm. Thus, a meaningful comparison of DOR between the 2 treatment arms will remain impossible.

Survival data were analysed at the time of the analysis of the primary endpoint (PFS) and will continue to be assessed up to 4 years from the randomization of the last subject or 6 months after the last cross-over/re-treatment dose in the study, whichever occurs last. **However, the available OS data are immature:** In a second OS interim analysis (24-May-2024) the update was based on 31% OS events among all randomized subjects (versus 21% in the primary analysis), with an additional ~9 months of OS follow-up (median). In this OS Analysis, 51 subjects (33.8%) in the Lutathera arm died compared with 19 subjects (25.3%) in the control arm after a median follow-up time from the randomisation date to date of OS event or censoring of 26.3 months for the Lutathera arm versus 25.6 months for the control arm. While median OS was 43.3 months (95% CI: 37.3, NE) in the Lutathera arm, it was still not estimable in the control arm. Thus, the observed hazard ratio (HR) was 1.25 (95% CI: 0.74, 2.13). Using the Restricted Mean Survival Time (RMST) method, there was no notable difference between the study arms in mean survival time restricted to 24 months: 21.3 months (95% CI: 20.5, 22.2) in the Lutathera arm vs. 21.4 months (95% CI: 20.0, 22.8) in the control arm with a p-value of 0.9578.

The limitations of any (definitive) decision need to be acknowledged. This means that the clinical relevance of the observed impressive PFS and ORR outcome will probably never reliably correlated with the only hard endpoint OS, which makes the decision whether the applied first line treatment can be approved very difficult.

Additional expert consultation

CHMP agreed to consult the SAG Oncology and ask the following question:

1. Given the lack of an established overall survival (OS) benefit for Lutetium (^{177}Lu) oxodotreotide in the NETTER-2 study, is early initiation of treatment justified in selected patients with a high tumor burden based on its impact on progression-free survival (PFS) and response rates?

Assessment of paediatric data on clinical efficacy

N/A

2.4.9. Conclusions on the clinical efficacy

A clear statistically significant and robust PFS was demonstrated with Lutathera treatment and numerically more patient probably reached complete remission in the NETTER-2 population. Thus, efficacy in the target population was proven. However, there is currently no established overall survival (OS) benefit for Lutetium (^{177}Lu) oxodotreotide in the NETTER-2 study. Due to crossover from the control arm and the 2:1 randomisation for Lutathera, more mature OS results will likely remain inconclusive.

This issue raises a significant major concern against the applied first line treatment in the applied target population. In particular, since it remains not clear, whether re-treatment in a more advanced stage or after early progression (as investigated in the NETTER-2) will be beneficial. Insofar, it appears uncertain whether first line treatment is a clinical relevant benefit for the applied target population or whether later treatment would be more preferable at the end.

2.5. Clinical safety

2.5.1. Introduction

The safety profile of Lutathera has been mainly characterized from results of NETTER-1 and ERASMUS studies for the initial approval.

Safety assessment for the applied new indication is based on the key safety results from the NETTER-2 study, pooled safety results reported from NETTER-2 and NETTER-1 and supportive safety data from the ERASMUS study.

Table 14. Details about the total safety population in pivotal clinical trials with Lutathera

	CAAA601A22301 (NETTER-2) **[Registration Study]**	**CAAA601A12301 (NETTER-1)** **[Registration study]**	**ERASMUS** **[Supportive study]**
No. of subjects treated	N= 220	N= 223	[^{177}Lu]Lu-DOTA-TATE group: 1214
	Lutathera group (Lutathera + octreotide LAR 30 mg): 147	Lutathera group (Lutathera + octreotide LAR 30 mg): 111	
	Control group (high-dose 60 mg octreotide LAR): 73	Control group (high-dose 60 mg octreotide LAR): 112 Additional 22 non- randomized subjects in PK sub-study	
Safety endpoints	Incidence and severity of AEs and laboratory toxicities according to NCI- CTCAE v5.0.	Incidence and severity of AEs and laboratory toxicities according to NCI- CTCAE v4.03	Safety evaluated by incidence of SAEs (retrospectively collected) and monitoring of selected laboratory evaluations.
Milestone and Data cut-off date	PFS Primary Analysis (20-July-2023)	PFS Primary Analysis (24-Jul-2015) Interim OS analysis (30-June-2016) Final OS Analysis (18-Jan-2021)	Data cut-off date of last available analysis*: December 2012

A brief description of NETTER-1 and ERASMUS study, which supported the initial approval of Lutathera, is provided here:

NETTER-1 Study

[NETTER-1] was a multicenter, stratified, open, randomized, comparator-controlled, parallel-group Phase III study comparing treatment with Lutathera + octreotide LAR 30 mg (Lutathera group) to treatment with high-dose (60 mg) octreotide LAR (Control group) in patients with metastasized or locally advanced, inoperable, G1 or G2, SSTR-positive, histologically proven midgut carcinoid tumours with progression despite octreotide LAR treatment.

Eligible patients were ≥18 years of age with a tumour Ki67 index ≤20% and progressive disease based on RECIST Version 1.1 while receiving an uninterrupted fixed dose of octreotide LAR (20-30 mg every 3-4 weeks) for at least 12 weeks prior to randomization in the study.

Subjects were randomized in a 1:1 to either Lutathera group (n=117, of them 111 treated) or Control group (n=114, of them 111 treated + 1 subject randomized to Lutathera group who received only octreotide and thus included in the Control group for safety). Randomization was stratified by OctreoScan® tumour uptake score and by the length of time that a subject was on a constant dose of octreotide LAR (≤ 6 vs. > 6 months). The study consisted of screening, treatment, and follow-up stages. Before the PFS primary analysis, subjects continued the planned treatment until centrally confirmed progression; after the PFS primary analysis, the treatment phase duration was limited to 72 weeks. However, subjects may have continued treatment with octreotide LAR outside of the NETTER-1 planned study treatment. The end of study occurred 5 years after the date of randomization of the last randomized subject.

Safety was assessed on the basis of AEs, AESIs, laboratory results for haematology, blood chemistry and urinalysis, physical examinations, vital signs and ECG.

In parallel, a sub-study was conducted at selected sites to evaluate dosimetry, pharmacokinetics, and ECG in a subset of 30 subjects treated with Lutathera. Of these 30 subjects, 8 were part of the randomized study and 22 were non-randomized subjects, who were also included in the safety analysis [NETTER-1-Table 14.1.1.1].

ERASMUS Study

[ERASMUS] was an open-label, non-randomized, single institution, single arm study to assess the efficacy and safety of [^{177}Lu]Lu-DOTA-TATE administered to patients with SSTR-positive tumours.

The standard treatment regimen consisted of 4 intravenous administrations of 7.4 GBq at 6- to 13-week intervals. Concomitant amino acids were given with each administration for kidney protection. Follow-up monitoring for all enrolled Dutch subjects continued beyond treatment until the subject was lost to follow-up, subject death, or for a maximum of 10 years, whichever occurred first.

Safety information was not routinely recorded. Non-serious adverse events (AEs) were not recorded in the study. Serious AEs (SAEs) were initially not typically reported in the case report form (except for a few pre-coded symptoms). A post-hoc review of the patient's medical charts was conducted by an independent clinical research organization to retrospectively collect all SAEs. In addition, a list of hematology and biochemistry data with all NCI CTCAE grade-3 and -4 toxicities, was extracted from the study database and submitted to the Investigators for review and were further integrated into the list of SAEs previously identified during the retrospective data verification. The Investigators scored the causality of all these retrospectively collected SAEs. SAEs were not graded for their severity.

A total of 1,214 subjects received [^{177}Lu]Lu-DOTA-TATE in ERASMUS, of which 811 were Dutch. Because of the percentage of subjects lost to follow up in the non-Dutch population compared to the Dutch population, the safety analyses were conducted on the Dutch population only.

Known safety risk for the previous approval procedure:

The safety profile of Lutathera is well characterized and described in the current prescribing/product information. Safety considerations that arose from prior experience with Lutathera are addressed in the Risk Management Plan (RMP). Data from NETTER-1 and ERASMUS studies have shown that Lutathera has generally been well-tolerated in patients with advanced NETs with limited, transient toxic events. The following are the important identified and important potential risks for Lutathera included in the RMP. The important identified risks are of particular focus of the safety evaluation of Lutathera for this submission. Some of these identified safety topics of interest are also described further in Section 2.6. Of note, an international post-authorization safety registry to assess the long-term safety of Lutathera (Study A-LUT-T-E02-402 [SALUS]) is ongoing, as an additional PV activity, to assess all

the important risks and missing information. For further information on the important identified and potential risks, please refer to Lutathera EU RMP v 3.0.

Important identified risks

- Renal dysfunction
- Myelosuppression/cytopenias (immediate hematologic toxicity)
- Myelodysplastic syndrome (MDS)/acute leukemia (AL) (late hematologic toxicity)
- Hepatotoxicity
- Tumour lysis syndrome
- Hormonal release-induced crisis (HRIC)
- Hypogonadism, sexual dysfunction
- Drug interaction with somatostatin/somatostatin analogues

Important potential risks

- Radiotoxicity, including occupational exposure and inadvertent exposure
- Secondary malignancies (solid tumours)
- Embryo-fetal toxicity

Safety assessment approach:

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), hematology, blood chemistry, urinalysis, and regular assessments of vital signs, physical condition, body weight, ECG, Karnofsky performance score, pregnancies (if applicable). Tolerability was assessed by the incidence of AEs leading to study treatment delay or discontinuation according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

In addition, four AEs of special interest (AESIs) were defined for this study: nephrotoxicities, immediate hematotoxicities, secondary hematological malignancies, and cardiovascular and electrolyte disorders.

In principle, the mode of safety assessment in NETTER-1 and NETTER-2 allows pooling of the data.

2.5.2. Patient exposure

In NETTER-2, a total of 226 subjects were randomized to the study, in a 2:1 ratio, with 151 subjects in the Lutathera group (of which 147 received treatment) and 75 subjects in the Control group (of which 73 received treatment).

The median duration of study follow-up from randomization to primary analysis DCO date of 20-Jul-2023 for all randomized subjects in NETTER-2 was 23.2 months (range: 9.2 – 41.9) [NETTER-2-Table 14.2-8.1].

Apart from the analysis sets described for the treatment period on the efficacy section above the NETTER-2 trial also defines the crossover and re-treatment set as follows [NETTER-2-Section 10.3]:

- Twenty-nine subjects who received treatment with octreotide LAR in the Control group subsequently crossed over to receive Lutathera in the crossover period following disease progression and were included in the crossover set
- Eight subjects received at least one dose of Lutathera in the re-treatment period and were included in the retreatment set

Table 15. Lutathera exposure, including number of cycles, in the treatment phase (Safety Set + PK Sub-Study)

	NETTER-2 Lutathera + Octreotide LAR N=147	NETTER-1 Lutathera + Octreotide LAR N=111	Pooled data 1 Lutathera + Octreotide LAR N=280
Duration of Lutathera Exposure (weeks)			
Mean	31.11	29.25	29.99
SD	4.971	7.371	6.542
Median	32.00	32.00	32.00
Min-Max	8.0 - 40.0	8.0 - 45.0	8.0 - 45.0
Number of Lutathera cycles [1], n (%)			
n	147	111	280
1 cycle	1 (0.7)	6 (5.4)	10 (3.6)
2 cycles	10 (6.8)	12 (10.8)	25 (8.9)
3 cycles	7 (4.8)	9 (8.1)	19 (6.8)
4 cycles	129 (87.8)	84 (75.7)	226 (80.7)
Average duration of Lutathera treatment cycles (weeks)			
n	147	111	280
Mean	8.20	8.29	8.24
SD	0.505	0.780	0.658
Median	8.00	8.04	8.00
Min-Max	7.5 - 11.6	7.5 - 15.0	7.5 - 15.0
Subjects with at least one	10 (6.8)	10 (9.0)	22 (7.9)
Reason for Lutathera dose reduction, n (%)			
Lutathera-related toxicity	3 (2.0)	7 (6.3)	10 (3.6)
Other [2]	7 (4.8)	3 (2.7)	12 (4.3)
Subjects with at least one infusion interruption, n (%)	5 (3.4)	12 (10.8)	17 (6.1)

Lutathera cycles administered once every 8 weeks for a maximum of 4 cycles. A subject may be counted in more than one row in case of dose reduction.

[1] Any cycle started is considered as received.

[2] "Other" includes "Baseline condition or AE not related to Lutathera" for NETTER-2.

Pooled data 1 includes NETTER-1 Lutathera Safety Set (111) and PK Sub-study Set (22), and NETTER-2 Lutathera Safety Set (147).
Source: [SCS Appendix 1-Table 2.2-2]

Table 16. Dose of Lutathera in the treatment phase (Safety Set + PK Sub-Study)

	Statistics	NETTER-2 Lutathera + Octreotide LAR N=147	NETTER-1 Lutathera + Octreotide LAR N=111	Poold data 1 Lutathera + Octreotide LAR N=280
Cumulative dose (GBq)	n	147	111	280
	Mean	27.57	25.61	26.45
	SD	4.594	6.745	6.011
	Median	29.21	28.54	29.02
	Min-Max	7.0 - 31.2	6.5 - 31.8	6.5 - 31.8
Dose per administration (GBq/cycle)	n	147	111	280
	Mean	7.25	7.22	7.24
	SD	0.387	0.427	0.405
	Median	7.34	7.25	7.33
	Min-Max	4.1 – 7.8	5.5 – 7.9	4.1 – 7.9
Dose intensity (GBq/week)	n	147	111	280

	Statistics	NETTER-2 Lutathera + Octreotide LAR N=147	NETTER-1 Lutathera + Octreotide LAR N=111	Poold data 1 Lutathera + Octreotide LAR N=280
	Mean	0.89	0.88	0.88
	SD	0.072	0.085	0.080
	Median	0.91	0.89	0.90
	Min-Max	0.5 - 1.0	0.4 - 1.0	0.4 - 1.0
Relative dose intensity (%)	n	147	111	280
	Mean	95.89	94.88	95.52
	SD	7.752	9.157	8.624
	Median	98.24	96.34	97.04
	Min-Max	52.2 - 105.5	43.3 - 106.8	43.3 - 109.1

Lutathera cycle administered once every 8 weeks for a maximum of 4 cycles.
Pooled data 1 includes NETTER-1 Lutathera Safety Set (111) and PK Sub-study Set (22), and NETTER-2 Lutathera Safety Set (147).
Source: [SCS Appendix 1-Table 2.2-4]

2.5.3. Adverse events

In NETTER-2, the most common TEAEs by SOC regardless of causality reported for the Lutathera group were (Table 17):

<u>All grades (>50%):</u>

- gastrointestinal disorders (66.7%)
- investigations (55.8%)
- general disorders and administration site conditions (51.7%)

<u>Grade ≥3 (>9%):</u>

- investigations (17.0%)
- gastrointestinal disorders (9.5%)

The most common all grades TEAEs by SOC regardless of causality occurring with a greater frequency (≥10% difference) in the Lutathera group vs. the Control group, include (Table 17):

- investigations (all grades: 55.8% vs. 41.1%)
- nervous system disorders (all grades: 31.3% vs. 16.4%)
- blood and lymphatic system disorders (all grades: 29.3% vs. 9.6%)

Table 17. Overview of the observed Adverse Events regardless of causality from NETTER 2 and the initial NETTER-1 trial

Trial	**NETTER-2**				**NETTER-1**				**Pooled data 1**	
Treatment group	**Lutathera + Octreotide LAR N=147**		**Octreotide LAR N=73**		**Lutathera + Octreotide LAR N=111**		**Octreotide LAR N=112**		**Lutathera + Octreotide LAR N=280**	
Primary system organ class	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Number of subjects with at least one event	136 (92.5)	52 (35.4)	69 (94.5)	20 (27.4)	109 (98.2)	60 (54.1)	105 (93.8)	39 (34.8)	267 (95.4)	127 (45.4)

Trial	NETTER-2				NETTER-1				Pooled data 1	
Treatment group	Lutathera + Octreotide LAR N=147		Octreotide LAR N=73		Lutathera + Octreotide LAR N=111		Octreotide LAR N=112		Lutathera + Octreotide LAR N=280	
Primary system organ class	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Blood and lymphatic system disorders	43 (29.3)	6 (4.1)	7 (9.6)	1 (1.4)	42 (37.8)	17 (15.3)	9 (8.0)	0	96 (34.3)	31 (11.1)
Cardiac disorders	15 (10.2)	2 (1.4)	6 (8.2)	1 (1.4)	15 (13.5)	4 (3.6)	12 (10.7)	2 (1.8)	31 (11.1)	6 (2.1)
Ear and labyrinth disorders	6 (4.1)	0	2 (2.7)	0	8 (7.2)	0	2 (1.8)	0	14 (5.0)	0
Endocrine disorders	10 (6.8)	0	3 (4.1)	1 (1.4)	6 (5.4)	0	4 (3.6)	1 (0.9)	17 (6.1)	0
Eye disorders	7 (4.8)	0	3 (4.1)	0	8 (7.2)	1 (0.9)	5 (4.5)	0	16 (5.7)	1 (0.4)
Gastrointestinal disorders	98 (66.7)	14 (9.5)	52 (71.2)	8 (11.0)	97 (87.4)	19 (17.1)	71 (63.4)	14 (12.5)	215 (76.8)	41 (14.6)
General disorders and administration site conditions	76 (51.7)	2 (1.4)	35 (47.9)	3 (4.1)	65 (58.6)	3 (2.7)	53 (47.3)	5 (4.5)	154 (55.0)	8 (2.9)
Hepatobiliary disorders	12 (8.2)	4 (2.7)	2 (2.7)	1 (1.4)	7 (6.3)	3 (2.7)	7 (6.3)	2 (1.8)	21 (7.5)	8 (2.9)
Immune system disorders	2 (1.4)	0	1 (1.4)	0	3 (2.7)	0	2 (1.8)	0	5 (1.8)	0
Infections and infestations	**46 (31.3)**	4 (2.7)	20 (27.4)	2 (2.7)	33 (29.7)	4 (3.6)	34 (30.4)	2 (1.8)	88 (31.4)	10 (3.6)
Injury, poisoning and procedural complications	22 (15.0)	3 (2.0)	6 (8.2)	1 (1.4)	17 (15.3)	4 (3.6)	9 (8.0)	1 (0.9)	41 (14.6)	7 (2.5)
Investigations	82 (55.8)	25 (17.0)	30 (41.1)	4 (5.5)	55 (49.5)	12 (10.8)	38 (33.9)	5 (4.5)	149 (53.2)	41 (14.6)
Metabolism and nutrition disorders	54 (36.7)	3 (2.0)	26 (35.6)	5 (6.8)	47 (42.3)	5 (4.5)	34 (30.4)	5 (4.5)	109 (38.9)	11 (3.9)
Musculoskeletal and connective tissue disorders	35 (23.8)	0	20 (27.4)	1 (1.4)	45 (40.5)	3 (2.7)	34 (30.4)	1 (0.9)	86 (30.7)	3 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (2.0)	2 (1.4)	0	0	9 (8.1)	2 (1.8)	8 (7.1)	5 (4.5)	14 (5.0)	6 (2.1)
Nervous system disorders	46 (31.3)	2 (1.4)	12 (16.4)	2 (2.7)	46 (41.4)	5 (4.5)	26 (23.2)	4 (3.6)	101 (36.1)	7 (2.5)

Trial	NETTER-2				NETTER-1				Pooled data 1	
Treatment group	Lutathera + Octreotide LAR N=147		Octreotide LAR N=73		Lutathera + Octreotide LAR N=111		Octreotide LAR N=112		Lutathera + Octreotide LAR N=280	
Primary system organ class	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Product issues	0	0	0	0	1 (0.9)	1 (0.9)	0	0	1 (0.4)	1 (0.4)
Psychiatric disorders	16 (10.9)	1 (0.7)	6 (8.2)	0	29 (26.1)	3 (2.7)	15 (13.4)	0	51 (18.2)	4 (1.4)
Renal and urinary disorders	12 (8.2)	1 (0.7)	5 (6.8)	1 (1.4)	28 (25.2)	3 (2.7)	12 (10.7)	2 (1.8)	46 (16.4)	6 (2.1)
Reproductive system and breast disorders	9 (6.1)	1 (0.7)	1 (1.4)	0	4 (3.6)	1 (0.9)	2 (1.8)	0	14 (5.0)	2 (0.7)
Respiratory, thoracic and mediastinal disorders	26 (17.7)	4 (2.7)	7 (9.6)	1 (1.4)	33 (29.7)	1 (0.9)	20 (17.9)	0	61 (21.8)	5 (1.8)
Skin and subcutaneous tissue disorders	43 (29.3)	0	17 (23.3)	0	23 (20.7)	0	18 (16.1)	0	74 (26.4)	1 (0.4)
Surgical and medical procedures	0	0	0	0	1 (0.9)	0	1 (0.9)	0	2 (0.7)	0
Vascular disorders	25 (17.0)	4 (2.7)	14 (19.2)	2 (2.7)	35 (31.5)	4 (3.6)	25 (22.3)	3 (2.7)	64 (22.9)	8 (2.9)

Table 18. Treatment-Emergent Adverse Events by preferred term, all grades and grade ≥3, in the treatment phase (Safety Set + PK Sub-Study) (cut-off: ≥15% in all grades Lutathera+Octreotide LAR arm in either NETTER-2 or NETTER-1)

Trial	NETTER-2				NETTER-1				Pooled data 1	
Treatment group	Lutathera + Octreotide LAR N=147		Octreotide LAR N=73		Lutathera + Octreotide LAR N=111		Octreotide LAR N=112		Lutathera + Octreotide LAR N=280	
Primary system organ class	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of subjects with at least one event	136 (92.5)	52 (35.4)	69 (94.5)	20 (27.4)	109 (98.2)	60 (54.1)	105 (93.8)	39 (34.8)	267 (95.4)	127 (45.4)
Nausea	40 (27.2)	1 (0.7)	13 (17.8)	0	74 (66.7)	5 (4.5)	13 (11.6)	2 (1.8)	124 (44.3)	8 (2.9)
Diarrhoea	38 (25.9)	2 (1.4)	25 (34.2)	1 (1.4)	29 (26.1)	2 (1.8)	21 (18.8)	1 (0.9)	76 (27.1)	7 (2.5)
Anaemia	29 (19.7)	1 (0.7)	5 (6.8)	1 (1.4)	18 (16.2)	0	8 (7.1)	0	52 (18.6)	2 (0.7)
Fatigue	29 (19.7)	0	13 (17.8)	0	43 (38.7)	1 (0.9)	30 (26.8)	2 (1.8)	79 (28.2)	2 (0.7)
Asthenia	28 (19.0)	1 (0.7)	9 (12.3)	0	9 (8.1)	2 (1.8)	8 (7.1)	0	39 (13.9)	3 (1.1)
COVID-19	28 (19.0)	0	10 (13.7)	0	0	0	0	0	28 (10.0)	0
Abdominal pain	26 (17.7)	4 (2.7)	20 (27.4)	3 (4.1)	29 (26.1)	3 (2.7)	22 (19.6)	3 (2.7)	60 (21.4)	9 (3.2)
Platelet count decreased	25 (17.0)	2 (1.4)	4 (5.5)	0	13 (11.7)	0	2 (1.8)	0	39 (13.9)	2 (0.7)
Alopecia	22 (15.0)	0	1 (1.4)	0	13 (11.7)	0	2 (1.8)	0	37 (13.2)	0
Vomiting	21 (14.3)	1 (0.7)	6 (8.2)	1 (1.4)	60 (54.1)	8 (7.2)	11 (9.8)	1 (0.9)	88 (31.4)	9 (3.2)
Decreased appetite	19 (12.9)	0	7 (9.6)	0	24 (21.6)	0	12 (10.7)	3 (2.7)	45 (16.1)	0
Oedema peripheral	17 (11.6)	0	6 (8.2)	1 (1.4)	18 (16.2)	0	10 (8.9)	1 (0.9)	37 (13.2)	1 (0.4)
Headache	16 (10.9)	0	5 (6.8)	0	21 (18.9)	0	6 (5.4)	0	44 (15.7)	0
Abdominal distension	12 (8.2)	0	6 (8.2)	0	18 (16.2)	0	13 (11.6)	0	30 (10.7)	0
Dizziness	12 (8.2)	0	3 (4.1)	0	17 (15.3)	0	10 (8.9)	0	30 (10.7)	0
Lymphopenia	9 (6.1)	4 (2.7)	0	0	20 (18.0)	13 (11.7)	0	0	36 (12.9)	23 (8.2)

Numbers (n) represent counts of subjects.
Pooled data 1 includes NETTER-1 Lutathera Safety Set (111) and PK Sub-study Set (22), and NETTER-2 Lutathera Safety Set (147).
MedDRA version 26.0, CTCAE version 4.03 for NETTER-1 and 5.0 for NETTER-2.
Source: [SCS Appendix 1-Table 2.3-2.2]

Potential relationship of adverse events to study treatment

In NETTER-2, the most common TEAEs by PT assessed as related to Lutathera by the Investigator reported in the Lutathera group were (Table 18):

All grades (>20%):

- nausea (20.4%)

Grade ≥3 (≥2%):

- lymphocyte count decreased (4.8%)
- lymphopenia (2.7%)
- white blood cell count decreased (2.0%)

Table 19. Treatment-Emergent Adverse Events related to Lutathera by preferred term, all grades and grade ≥3, in the treatment phase (Safety Set + PK Sub-Study) (cut-off: ≥10.0% in all grades Lutathera+Octreotide LAR arm in either NETTER-2 or NETTER-1)

Trial	**NETTER-2**		**NETTER-1**		**Pooled data 1**	
Treatment group	**Lutathera + Octreotide LAR N=147**		**Lutathera + Octreotide LAR N=111**		**Lutathera + Octreotide LAR N=280**	
Primary system organ class	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Number of subjects with at least one event	**96 (65.3)**	**22 (15.0)**	**82 (73.9)**	**22 (19.8)**	**196 (70.0)**	**54 (19.3)**
Nausea	30 (20.4)	1 (0.7)	29 (26.1)	1 (0.9)	61 (21.8)	3 (1.1)
Alopecia	20 (13.6)	0	9 (8.1)	0	30 (10.7)	0
Fatigue	19 (12.9)	0	25 (22.5)	0	48 (17.1)	1 (0.4)
Platelet count decreased	19 (12.9)	0	13 (11.7)	0	33 (11.8)	0
Anaemia	18 (12.2)	0	14 (12.6)	0	37 (13.2)	1 (0.4)
Asthenia	18 (12.2)	1 (0.7)	4 (3.6)	0	23 (8.2)	1 (0.4)
White blood cell count decreased	17 (11.6)	3 (2.0)	7 (6.3)	0	27 (9.6)	4 (1.4)
Lymphocyte count decreased	15 (10.2)	7 (4.8)	10 (9.0)	4 (3.6)	26 (9.3)	11 (3.9)
Thrombocytopenia	10 (6.8)	1 (0.7)	15 (13.5)	3 (2.7)	28 (10.0)	6 (2.1)
Lymphopenia	9 (6.1)	4 (2.7)	15 (13.5)	9 (8.1)	31 (11.1)	19 (6.8)
Vomiting	8 (5.4)	1 (0.7)	15 (13.5)	0	23 (8.2)	1 (0.4)
Decreased appetite	7 (4.8)	0	13 (11.7)	0	21 (7.5)	0

Numbers (n) represent counts of subjects.
Pooled data 1 includes NETTER-1 Lutathera Safety Set (111) and PK Sub-study Set (22), and NETTER-2 Lutathera Safety Set (147).
MedDRA version 26.0, CTCAE version 4.03 for NETTER-1 and 5.0 for NETTER-2.
Source: [SCS Appendix 1-Table 2.3-2.6]

The 4 **key safety topics of interest (AESI)** for Lutathera are

- Nephrotoxicity,
- immediate Haematotoxicity,
- secondary haematological Malignancies,
- Cardiovascular and Electrolyte disorders.

In NETTER-2, the following AESI were observed (Lutathera group vs. Control group) [SCS Appendix 1-Table 2.3-8.1]:

Nephrotoxicities were reported slightly higher in the Lutathera group.

- all grades: 8.8% vs. 5.5%
- grade ≥3: 2.0% vs. 1.4%

Immediate haematotoxicities were reported more frequently in the Lutathera group.

- all grades: 20.4% vs. 1.4%
- grade ≥3: 13.6% vs. 1.4%

Secondary haematological Malignancies (DCO date of 20-Jul-2023),

- One subject (0.7%) of a secondary hematological malignancy that was a grade 3 myelodysplastic syndrome (MDS) reported in the Lutathera group that occurred 14.1 months after receiving the first Lutathera dose. The case evolved to AML after the DCO of 20-July-2023.
- Two cases were reported after the primary analysis DCO date (and therefore are not included in the present analysis/pool) that were grade 4 MDS also reported in the Lutathera group that occurred about 34 months and 2 years, respectively after receiving the first Lutathera dose.

Cardiovascular and electrolyte disorders were reported more frequently (≥5%) in the Control group.

- all grades: 7.5% vs. 13.7%
- grade ≥3: 7.5% vs. 13.7%

The **most common AESI PTs (all grades: >2%)** reported in the Lutathera group include (Table S6):

Nephrotoxicities

- blood creatinine increased (all grades: 6.8% and grade ≥3: 0.7%)

Immediate hematotoxicities

- platelet count decreased (all grades: 8.2% and grade ≥3: 1.4%)
- lymphocyte count decreased (all grades: 5.4% and grade ≥3: 5.4%)
- thrombocytopenia (all grades: 3.4% and grade ≥3: 0.7%)
- lymphopenia (all grades: 2.7% and grade ≥3: 2.7%)

Cardiovascular and electrolyte disorders

- hypertension (all grades: 2.7% and grade ≥3: 2.7%)

Table 20. Overview about the results for most common AESI PTs (all grades: >2%)

Trial	**NETTER-2**				**NETTER-1**				**Pooled data 1**	
Treatment group	**Lutathera + Octreotide LAR N=147**		**Octreotide LAR N=73**		**Lutathera + Octreotide LAR N=111**		**Octreotide LAR N=112**		**Lutathera + Octreotide LAR N=280**	
Adverse Events of Special Interest Preferred term	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Nephrotoxicities	13 (8.8)	3 (2.0)	4 (5.5)	1 (1.4)	19 (17.1)	3 (2.7)	11 (9.8)	2 (1.8)	34 (12.1)	7 (2.5)
Blood creatinine increased	10 (6.8)	1 (0.7)	2 (2.7)	0	7 (6.3)	0	6 (5.4)	0	18 (6.4)	1 (0.4)
Chronic kidney disease	2 (1.4)	1 (0.7)	1 (1.4)	0	0	0	0	0	2 (0.7)	1 (0.4)
Acute kidney injury	1 (0.7)	1 (0.7)	1 (1.4)	1 (1.4)	5 (4.5)	2 (1.8)	1 (0.9)	1 (0.9)	7 (2.5)	4 (1.4)
Creatinine renal clearance decreased	1 (0.7)	1 (0.7)	0	0	0	0	0	0	1 (0.4)	1 (0.4)
Nephropathy toxic	1 (0.7)	0	0	0	0	0	0	0	1 (0.4)	0
Proteinuria	1 (0.7)	0	0	0	3 (2.7)	0	4 (3.6)	1 (0.9)	4 (1.4)	0
Renal failure	1 (0.7)	0	0	0	3 (2.7)	1	0	0	4 (1.4)	1

Trial	NETTER-2				NETTER-1				Pooled data 1	
Treatment group	**Lutathera + Octreotide LAR N=147**		**Octreotide LAR N=73**		**Lutathera + Octreotide LAR N=111**		**Octreotide LAR N=112**		**Lutathera + Octreotide LAR N=280**	
Adverse Events of Special Interest Preferred term	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
						(0.9)				(0.4)
Blood urea increased	0	0	0	0	4 (3.6)	0	2 (1.8)	0	4 (1.4)	0
Glomerular filtration rate decreased	0	0	0	0	2 (1.8)	0	1 (0.9)	0	2 (0.7)	0
Protein urine present	0	0	0	0	2 (1.8)	0	0	0	2 (0.7)	0
Renal impairment	0	0	0	0	1 (0.9)	0	2 (1.8)	1 (0.9)	1 (0.4)	0
Immediate Hematotoxicities	30 (20.4)	20 (13.6)	1 (1.4)	1 (1.4)	27 (24.3)	23 (20.7)	1 (0.9)	1 (0.9)	66 (23.6)	52 (18.6)
Platelet count decreased	12 (8.2)	2 (1.4)	0	0	0	0	0	0	12 (4.3)	2 (0.7)
Lymphocyte count decreased	8 (5.4)	8 (5.4)	0	0	6 (5.4)	6 (5.4)	1 (0.9)	1 (0.9)	14 (5.0)	14 (5.0)
Thrombocytopenia	5 (3.4)	1 (0.7)	0	0	9 (8.1)	3 (2.7)	0	0	16 (5.7)	6 (2.1)
Lymphopenia	4 (2.7)	4 (2.7)	0	0	13 (11.7)	13 (11.7)	0	0	23 (8.2)	23 (8.2)
Neutrophil count decreased	3 (2.0)	3 (2.0)	0	0	0	0	0	0	3 (1.1)	3 (1.1)
White blood cell count decreased	3 (2.0)	3 (2.0)	0	0	0	0	0	0	4 (1.4)	4 (1.4)
Anaemia	1 (0.7)	1 (0.7)	1 (1.4)	1 (1.4)	0	0	0	0	2 (0.7)	2 (0.7)
Myelodysplastic syndrome	1 (0.7)	1 (0.7)	0	0	0	0	0	0	2 (0.7)	2 (0.7)
Leukopenia	0	0	0	0	1 (0.9)	1 (0.9)	0	0	3 (1.1)	3 (1.1)
Neutropenia	0	0	0	0	1 (0.9)	1 (0.9)	0	0	1 (0.4)	1 (0.4)
Secondary Hematological Malignancies	1 (0.7)	1 (0.7)	0	0	3 (2.7)	1 (0.9)	0	0	5 (1.8)	3 (1.1)
Myelodysplastic syndrome	1 (0.7)	1 (0.7)	0	0	0	0	0	0	2 (0.7)	2 (0.7)
Diffuse large B-cell lymphoma	0	0	0	0	1 (0.9)	1 (0.9)	0	0	1 (0.4)	1 (0.4)
Pancytopenia	0	0	0	0	2 (1.8)	0	0	0	2 (0.7)	0
Cardiovascular and Electrolyte Disorders	**11 (7.5)**	**11 (7.5)**	**10 (13.7)**	**10 (13.7)**	**16 (14.4)**	**16 (14.4)**	**13 (11.6)**	**13 (11.6)**	**30 (10.7)**	**30 (10.7)**
Hypertension	4 (2.7)	4 (2.7)	1 (1.4)	1 (1.4)	2 (1.8)	2 (1.8)	2 (1.8)	2 (1.8)	6 (2.1)	6 (2.1)
Pulmonary embolism	2 (1.4)	2 (1.4)	0	0	0	0	0	0	2 (0.7)	2 (0.7)
Angina unstable	1 (0.7)	1 (0.7)	0	0	0	0	0	0	1 (0.4)	1 (0.4)
Ascites	1 (0.7)	1 (0.7)	1 (1.4)	1 (1.4)	2 (1.8)	2 (1.8)	1 (0.9)	1 (0.9)	3 (1.1)	3 (1.1)
Atrial flutter	1 (0.7)	1 (0.7)	0	0	0	0	0	0	1 (0.4)	1 (0.4)
Bradycardia	1 (0.7)	1 (0.7)	0	0	0	0	0	0	1 (0.4)	1 (0.4)
Dyspnoea	1 (0.7)	1 (0.7)	0	0	0	0	0	0	1 (0.4)	1 (0.4)
Epistaxis	1 (0.7)	1 (0.7)	0	0	0	0	0	0	1 (0.4)	1 (0.4)

Trial	NETTER-2				NETTER-1				Pooled data 1	
Treatment group	Lutathera + Octreotide LAR N=147		Octreotide LAR N=73		Lutathera + Octreotide LAR N=111		Octreotide LAR N=112		Lutathera + Octreotide LAR N=280	
Adverse Events of Special Interest Preferred term	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Hyperkalaemia	1 (0.7)	1 (0.7)	1 (1.4)	1 (1.4)	0	0	0	0	1 (0.4)	1 (0.4)
Pulmonary valve disease	1 (0.7)	1 (0.7)	0	0	0	0	0	0	1 (0.4)	1 (0.4)
Syncope	1 (0.7)	1 (0.7)	1 (1.4)	1 (1.4)	3 (2.7)	3 (2.7)	2 (1.8)	2 (1.8)	4 (1.4)	4 (1.4)
Tricuspid valve disease	1 (0.7)	1 (0.7)	0	0	0	0	0	0	1 (0.4)	1 (0.4)
Acute myocardial infarction	0	0	0	0	1 (0.9)	1 (0.9)	0	0	1 (0.4)	1 (0.4)
Arteriospasm coronary	0	0	0	0	0	0	1 (0.9)	1 (0.9)	0	0
Atrial fibrillation	0	0	0	0	1 (0.9)	1 (0.9)	0	0	1 (0.4)	1 (0.4)
Atrioventricular block second degree	0	0	0	0	1 (0.9)	1 (0.9)	0	0	1 (0.4)	1 (0.4)
Carcinoid heart disease	0	0	1 (1.4)	1 (1.4)	0	0	0	0	0	0
Cardiac failure congestive	0	0	0	0	0	0	1 (0.9)	1 (0.9)	0	0
Cutaneous vasculitis	0	0	0	0	0	0	0	0	1 (0.4)	1 (0.4)
Deep vein thrombosis	0	0	1 (1.4)	1 (1.4)	0	0	0	0	0	0
Dehydration	0	0	0	0	1 (0.9)	1 (0.9)	2 (1.8)	2 (1.8)	1 (0.4)	1 (0.4)
Endocarditis	0	0	0	0	0	0	0	0	1 (0.4)	1 (0.4)
Flushing	0	0	0	0	1 (0.9)	1 (0.9)	0	0	1 (0.4)	1 (0.4)
Gastric ulcer haemorrhage	0	0	1 (1.4)	1 (1.4)	0	0	0	0	0	0
Generalised oedema	0	0	1 (1.4)	1 (1.4)	0	0	1 (0.9)	1 (0.9)	0	0
Haematemesis	0	0	0	0	0	0	0	0	1 (0.4)	1 (0.4)
Haemorrhage intracranial	0	0	0	0	0	0	1 (0.9)	1 (0.9)	0	0
Hypertensive crisis	0	0	0	0	0	0	1 (0.9)	1 (0.9)	0	0
Hypokalaemia	0	0	0	0	2 (1.8)	2 (1.8)	1 (0.9)	1 (0.9)	2 (0.7)	2 (0.7)
Hyponatraemia	0	0	0	0	1 (0.9)	1 (0.9)	0	0	1 (0.4)	1 (0.4)
Inferior vena cava syndrome	0	0	0	0	1 (0.9)	1 (0.9)	0	0	1 (0.4)	1 (0.4)
Lower gastrointestinal haemorrhage	0	0	1 (1.4)	1 (1.4)	0	0	0	0	0	0
Oedema peripheral	0	0	1 (1.4)	1 (1.4)	0	0	1 (0.9)	1 (0.9)	1 (0.4)	1 (0.4)
Silent myocardial infarction	0	0	0	0	1 (0.9)	1 (0.9)	0	0	1 (0.4)	1 (0.4)
Thrombotic cerebral infarction	0	0	0	0	0	0	1 (0.9)	1 (0.9)	0	0
Tumour lysis syndrome	0	0	1 (1.4)	1 (1.4)	0	0	0	0	0	0

Numbers (n) represent counts of subjects.

MedDRA version 26.0, CTCAE version 4.03 for NETTER-1 and 5.0 for NETTER-2, Case Retrieval Strategy version released 09-August-2023. Pooled data 1 includes NETTER-1 Lutathera Safety Set (111) and PK Sub-study Set (22), and NETTER-2 Lutathera Safety Set (147).
Source: [SCS Appendix 1-Table 2.3-8.2]

Comparison of TEAEs observed in NETTER-2 and NETTER-1

Comparing the TEAEs observed in NETTER-2 and NETTER-1

Comparison of the TEAEs according SOCs observed in NETTER-2 and NETTER-1

Differences in TEAEs between NETTER-2 and NETTER-1 for Lutathera group TEAEs regardless of causality

A few all grades TEAEs by SOC regardless of causality were reported at a much lower incidence (≥10% difference) in the Lutathera group of NETTER-2 vs. NETTER-1 [SCS Appendix 1-Table 2.3-2.3]:

- gastrointestinal disorders (66.7% vs. 87.4%) with the main difference coming from PTs of nausea (27.2% vs. 66.7%) and vomiting (14.3% vs. 54.1%) likely because of the difference in the concomitant amino acid solution used in the 2 studies: complex amino acid solutions used in NETTER-1 [NETTER-1-Section 9.4.7] vs. a standardized amino acid solution containing 2.5% arginine and 2.5% lysine that was used consistently in NETTER-2 [NETTER-2-Section 9.4.2]
- musculoskeletal and connective tissue disorders (23.8% vs. 40.5%) due to generalized lower frequency in several PTs like arthralgia (9.5% vs. 12.6%), back pain (8.2% vs. 13.5%), pain in extremity (4.1% vs. 10.8%) and muscle spasms (2.0% vs. 6.3%) in NETTER-2
- nervous system disorders (31.3% vs. 41.4%) with the main difference coming from PTs of headache (10.9% vs. 18.9%) and dizziness (8.2% vs. 15.3%)
- respiratory, thoracic and mediastinal disorders (17.7% vs. 29.7%) with the main difference coming from PTs of dyspnea (4.8% vs. 10.8%) and cough (4.1% vs. 11.7%)
- vascular disorders (17.0% vs. 31.5%) with the main difference coming from PT of flushing (4.8% vs. 14.4%)
- psychiatric disorders (10.9% vs. 26.1%) with the main difference coming from PT of anxiety (1.4% vs. 12.6%)
- renal and urinary disorders (8.2% vs. 25.2%) due to lower frequency in several PTs like hematuria (2.0% vs. 6.3%), acute kidney injury (0.7% vs. 4.5%), proteinuria (0.7% vs. 2.7%), renal failure (0.7% vs. 2.7%) and urinary incontinence (0.7% vs. 2.7%) in NETTER-2.

None of the all grades TEAEs by SOC regardless of causality were reported at a higher incidence (≥10% difference) in the Lutathera group of NETTER-2 vs. NETTER-1 [SCS Appendix 1-Table 2.3-2.3].

A few grade **≥3 TEAEs by SOC** regardless of causality were reported at a much lower incidence (≥5% difference) in the Lutathera group of NETTER-2 vs. NETTER-1 [SCS Appendix 1-Table 2.3-2.3]:

- blood and lymphatic system disorders (4.1% vs. 15.3%) with the main difference coming from PT of lymphopenia (2.7% vs. 11.7%)
- gastrointestinal disorders (9.5% vs. 17.1%) with the main difference coming from PTs of nausea (0.7% vs. 4.5%) and vomiting (0.7% vs. 7.2%)

The only grade ≥3 TEAE by SOC regardless of causality reported at a higher incidence (≥5% difference) in the Lutathera group of NETTER-2 vs. NETTER-1 was [SCS Appendix 1-Table 2.3-2.3]:

- investigations (17.0% vs. 10.8%) with the main difference coming from PT of gamma-glutamyl transferase increased (4.8% vs. 1.8%)

TEAEs assessed by Investigator as related to Lutathera

None of the all grades TEAEs by PT assessed as related to Lutathera by the Investigator were reported at either a lower or a higher incidence (≥10% difference) in the Lutathera group of NETTER-2 vs. NETTER-1.

The only grade ≥3 TEAE by PT assessed as related to Lutathera by the Investigator reported at a lower incidence (≥5% difference) in the Lutathera group of NETTER-2 vs. NETTER-1 was lymphopenia (2.7% vs. 8.1%). None of the grade ≥3 TEAEs by PT assessed as related to Lutathera by the Investigator were reported at a higher incidence (≥5% difference) in the Lutathera group of NETTER-2 vs. NETTER-1.

Safety profile of the Control group in NETTER-2 and NETTER-1

The frequency and severity of TEAE were overall similar (difference <10% for all grades SOCs and PTs and <5% for grade ≥3 SOCs and PTs) in the Control groups of NETTER-2 vs. NETTER-1 except for all causality and all grades PTs of diarrhea (34.2% vs. 18.8%) and Covid-19 (13.7% vs. 0) which were reported at a higher incidence in NETTER-2.

The above overall findings from the Control group in NETTER-2 and NETTER-1 reflect the comorbidities and underlying risk factors of a subject population treated with somatostatin analogues in this setting. Findings from this Control group provide an important context for assessing the safety of Lutathera in combination with octreotide LAR 30 mg.

Safety profile of the Lutathera group in NETTER-2 and NETTER-1

The differences in frequencies in the SOCs which were reported in the Lutathera group of NETTER-2 vs. NETTER-1 (as described above) were not reflected in the Control group, indicating these are unrelated to the comorbidities and underlying risk factors of a subject population treated with somatostatin analogues in this setting.

In general, all subjects in NETTER-1 have completed their initial treatment period vs. >50% of subjects in NETTER-2 who are still in their initial treatment period (Table 1-8). This could have possibly contributed to the differences seen between the Lutathera group in NETTER-2 vs. NETTER-1.

Some of these differences in frequency particularly for the gastrointestinal disorders observed in the Lutathera group are possibly driven by the difference in amino acid solutions used in the 2 studies. A complex amino acid solutions not tailored to the actual use was administered in NETTER-1, while standardized amino acid solution containing 2.5% arginine and 2.5% lysine solution specifically designed for renal protection that was used consistently in NETTER-2.

Regarding differences in the renal toxicity observed in the Lutathera group in NETTER-2 vs. NETTER-1 (Table 2-2), the renal function (CrCl) at baseline was better in NETTER-2 subjects than in NETTER-1 (i.e. NETTER-2 had fewer subjects below 60 ml/min and more subjects above 90 ml/min than NETTER-1) [SCS Appendix 1-Table 2.6-1.4]. This might have contributed to the better outcome in terms of renal event seen in NETTER-2.

Adverse events in the crossover and retreatment period of NETTER-2 Crossover period

No new AEs or major differences in SOCs/frequencies were seen in the cross-over subjects. [NETTER-2-Section 12] [NETTER-2-Table 10-1].

Retreatment period

No new AEs or major differences in SOCs/frequencies were seen in the re-treated subjects. There is a very small pool of re-treated subjects at the time of this submission and further evaluation will be carried out at the time of the final analysis of NETTER-2 [NETTER-2-Section 12] [NETTER-2-Table 10-1].

2.5.4. Serious adverse event/deaths/other significant events

Deaths

In NETTER-2, the incidence of all-causality SAEs with a fatal outcome during the treatment period was similar between the 2 treatment groups (3 subjects, 2.0% vs. 2 subjects 2.7%, Lutathera group vs. Control group) and all of them were due to the disease under study and not drug related (Table S7).

The SAE by PT for these fatal events include blood bilirubin increased, dyspnoea and intestinal perforation (1 subject 0.7%, each) in the Lutathera group, and diarrhoea and tumour lysis syndrome (1 subject 1.4%, each) in the Control group. No fatal events were reported as related to Lutathera treatment in the treatment period (Table 22).

There were fewer deaths during the treatment period in the Lutathera group vs. the Control group (2 subjects, 1.4% vs. 4 subjects, 5.5%) and all of them were due to the disease under study. The number of deaths during the study was similar between the 2 treatment groups (21.8% vs. 19.2%) with majority of the deaths due to disease under study (20.4% vs. 17.8%) (Table 21).

Table 21. Death by primary reason (Safety Set + PK Sub-Study)

Trial	NETTER-2		NETTER-1		Pooled data 1
Treatment group	**Lutathera + Octreotide LAR N=147**	**Octreotide LAR N=73**	**Lutathera + Octreotide LAR N=111**	**Octreotide LAR N=112**	**Lutathera + Octreotide LAR N=280**
Number of Subjects who died in the treatment phase	2 (1.4)	4 (5.5)	0	3 (2.7)	3 (1.1)
Primary reason:					
Disease under study	2 (1.4)	4 (5.5)	0	3 (2.7)	3 (1.1)
Other [1]	0	0	0	0	0
Unknown	0	0	0	0	0
Number of Subjects who died during the study	32 (21.8)	14 (19.2)	70 (63.1)	68 (60.7)	114 (40.7)
Primary reason:					
Disease under study	30 (20.4)	13 (17.8)	55 (49.5)	54 (48.2)	95 (33.9)
Other [1]	2 (1.4)	1 (1.4)	15 (13.5)	14 (12.5)	19 (6.8)
Unknown	0	0	0	0	0

Numbers (n) represent counts of subjects.
[1] "Other" includes "Adverse Event" for NETTER-2.
Pooled data 1 includes NETTER-1 Lutathera Safety Set (111) and PK Sub-study Set (22), and NETTER-2 Lutathera Safety Set (147).
Source: [SCS Appendix 1-Table 2.3-4.1] [NETTER-2-Listing 14.3.2-1.1]

Table 22. SAEs with fatal outcome

Trial	NETTER-2		NETTER-1		Pooled data 1
Treatment group	**Lutathera + Octreotide LAR N=147**	**Octreotide LAR N=73**	**Lutathera + Octreotide LAR N=111**	**Octreotide LAR N=112**	**Lutathera + Octreotide LAR N=280**
SAEs with fatal outcome	3 (2.0)	2 (2.7)	1 (0.9)	7 (6.3)	6 (2.1)
Reported in subjects with primary reason for death=Disease under study	3 (2.0)	2 (2.7)	1 (0.9)	7 (6.3)	5 (1.8)

Blood bilirubin increased	1 (0.7)	0	0	0	1 (0.4)
Dyspnoea	1 (0.7)	0	0	0	1 (0.4)
Intestinal perforation	1 (0.7)	0	0	0	1 (0.4)
Acute kidney injury	0	0	0	1 (0.9)	0
Diarrhoea	0	1 (1.4)	0	0	0
Generalised oedema	0	0	0	1 (0.9)	0
Malignant neoplasm progression	0	0	1 (0.9)	4 (3.6)	2 (0.7)
Neoplasm progression	0	0	0	1 (0.9)	0
Tumour lysis syndrome	0	1 (1.4)	0	0	0
Vomiting	0	0	0	1 (0.9)	0
Reported in subjects with primary reason for death=Other [1]	0	0	0	0	1 (0.4)
Acute kidney injury	0	0	0	0	1 (0.4)
Treatment-related SAEs with fatal outcome 0	0	0	0	1 (0.4)	
Reported in subjects with primary reason for death=Other [1]	0	0	0	0	1 (0.4)
Acute kidney injury	0	0	0	0	1 (0.4)

Numbers (n) represent counts of subjects. A subject may have more than one SAE with fatal outcome. MedDRA version 26.0.
[1] "Other" includes "Adverse Event" for NETTER-2.
Pooled data 1 includes NETTER-1 Lutathera Safety Set (111) and PK Sub-study Set (22), and NETTER-2 Lutathera Safety Set (147).
Source: [SCS Appendix 1-Table 2.3-3.4]

Serious adverse events

In NETTER-2, the most common SAE in the Lutathera group was small intestinal obstruction, which were reported:

- regardless of causality in 5 subjects (3.4%)
- treatment-related in 2 subjects (1.4%)

The incidence of all SAEs regardless of causality was similar between the 2 treatment groups (20.4% vs. 20.5%, Lutathera group vs. Control group); higher incidence of treatment related SAEs was reported in the Lutathera vs. Control group (5.4% vs. 1.4%).

Table 23. Serious Treatment-Emergent Adverse Events by preferred term, regardless of causality, in the treatment phase (Safety Set + PK Sub-Study) (cut-off: ≥1.0% in Lutathera + octreotide LAR in either NETTER-2 or NETTER-1)

	NETTER-2		NETTER-1		Pooled data 1
Preferred term	**Lutathera + Octreotide LAR N=147**	**Octreotide LAR N=73**	**Lutathera + Octreotide LAR N=111**	**Octreotide LAR N=112**	**Lutathera + Octreotide LAR N=280**
Number of subjects with at least one event	30 (20.4)	15 (20.5)	31 (27.9)	28 (25.0)	71 (25.4)
Small intestinal obstruction	5 (3.4)	0	1 (0.9)	2 (1.8)	7 (2.5)
Abdominal pain	2 (1.4)	0	3 (2.7)	1 (0.9)	6 (2.1)
Anaemia	2 (1.4)	1 (1.4)	0	1 (0.9)	3 (1.1)
Blood bilirubin increased	2 (1.4)	1 (1.4)	0	0	2 (0.7)
Gastrointestinal stoma complication	2 (1.4)	0	0	0	2 (0.7)
Pyrexia	2 (1.4)	0	1 (0.9)	0	3 (1.1)
Lymphopenia	1 (0.7)	0	2 (1.8)	0	5 (1.8)
Vomiting	1 (0.7)	0	2 (1.8)	2 (1.8)	3 (1.1)
Acute kidney injury	0	1 (1.4)	4 (3.6)	1 (0.9)	5 (1.8)
Femur fracture	0	1 (1.4)	2 (1.8)	0	2 (0.7)

Numbers (n) represent counts of subjects. MedDRA version 26.0.
Pooled data 1 includes NETTER-1 Lutathera Safety Set (111) and PK Sub-study Set (22), and NETTER-2 Lutathera Safety Set (147).
Source: [SCS Appendix 1-Table 2.3-3.2]

Table 24. Serious Treatment-Emergent Adverse Events related to any study treatment by preferred term, in the treatment phase (Safety Set + PK Sub-Study) (cut-off: at least one subject in Lutathera + octreotide LAR in either NETTER-2 or NETTER-1)

	NETTER-2		NETTER-1		Pooled data 1
Preferred term	**Lutathera + Octreotide LAR N=147**	**Octreotide LAR N=73**	**Lutathera + Octreotide LAR N=111**	**Octreotide LAR N=112**	**Lutathera + Octreotide LAR N=280**
Number of subjects with at least one event	8 (5.4)	1 (1.4)	11 (9.9)	3 (2.7)	23 (8.2)
Small intestinal obstruction	2 (1.4)	0	0	0	2 (0.7)
Abdominal pain	1 (0.7)	0	0	0	1 (0.4)
Anaemia	1 (0.7)	0	0	0	2 (0.7)
Blood creatinine increased	1 (0.7)	0	0	0	1 (0.4)
Cholestasis	1 (0.7)	0	0	0	1 (0.4)
Lymphopenia	1 (0.7)	0	1 (0.9)	0	4 (1.4)
Myelodysplastic syndrome	1 (0.7)	0	0	0	2 (0.7)
Nausea	1 (0.7)	0	0	0	1 (0.4)
Platelet count decreased	1 (0.7)	0	0	0	1 (0.4)
Vomiting	1 (0.7)	0	1 (0.9)	0	2 (0.7)
Acute kidney injury	0	0	3 (2.7)	0	4 (1.4)
Ascites	0	0	1 (0.9)	0	1 (0.4)
Dehydration	0	0	1 (0.9)	0	1 (0.4)
Endocarditis	0	0	0	0	1 (0.4)
Hepatic encephalopathy	0	0	1 (0.9)	0	1 (0.4)
Injection site hypersensitivity	0	0	1 (0.9)	0	1 (0.4)
Intestinal obstruction	0	0	1 (0.9)	0	1 (0.4)
Leukopenia	0	0	0	0	2 (0.7)
Neutropenia	0	0	1 (0.9)	0	1 (0.4)
Syncope	0	0	1 (0.9)	0	1 (0.4)
Thrombocytopenia	0	0	0	0	1 (0.4)

Numbers (n) represent counts of subjects.
Pooled data 1 includes NETTER-1 Lutathera Safety Set (111) and PK Sub-study Set (22), and NETTER-2 Lutathera Safety Set (147)
MedDRA version 26.0.
Source: [SCS Appendix 1-Table 2.3-3.3]

2.5.5. Laboratory findings

Haematology

In NETTER-2, the most common (≥50% of subjects in any group) worsening haematological abnormalities from baseline were reported more frequently (≥20% difference) in the Lutathera group vs. the Control group. This was expected considering the mechanism of action of Lutathera:

- decreased lymphocytes (96.6% vs. 61.6%)
- decreased hemoglobin (78.9% vs. 57.5%)
- decreased leukocytes (62.6% vs. 20.5%)
- decreased platelets (55.1% vs. 20.5%)

Regarding grade ≥3 abnormalities, a notable difference was observed between the 2 groups for decreased lymphocytes (38.1% vs. 2.7%). In general, lymphopenia is not considered clinically significant and is not considered a dose modifying toxicity, in spite of the one case of Lutathera dose interruption due to grade≤3 lymphopenia [SCS Appendix 1-Table 2.3-6.1]. This decrease was not associated with an increased rate of infections in the Lutathera group vs. the Control group (Table 2-2).

During the treatment period of NETTER-1 and NETTER-2, based on laboratory evaluations, Grade ≥3 neutropenia and Grade ≥3 thrombocytopenia were reported in 7 subjects (2.7%) and 4 subjects (1.6%), respectively. The time to first occurrence during the treatment period, after the first Lutathera dose, ranged from 22 to 60 weeks for Grade ≥3 neutropenia and from 4 to 48 weeks for Grade ≥3 thrombocytopenia [NETTER-2-Appendix 16.2.8-Listing 16.2.8-1.1.1] [NETTER-2-Appendix 16.2.8-Listing 16.2.8-1.1.2] [NETTER-1-Appendix 16.2.8-Listing 16.2.8-1.1.2].

Clinical chemistry

In NETTER-2, the most common (≥50% of subjects in any group) worsening biochemistry abnormalities from baseline were (Lutathera group vs. Control group):

- decreased CrCl (70.1% vs. 60.3%)
- increased gamma glutamyl transferase (GGT) (69.4% vs. 76.7%)
- increased alkaline phosphatase (ALP) (53.7% vs. 54.8%)
- increased aspartate aminotransferase (AST) (51.0% vs. 54.8%)
- increased alanine aminotransferase (ALT) (42.9% vs. 52.1%)

Most of these abnormalities were comparable between the 2 groups, except for (≥5% difference) decreased CrCl which was reported more frequently in the Lutathera group, and increased ALT and GGT which were reported more frequently in the Control group.

Regarding grade ≥3 abnormalities in chemistry parameters, no major differences were observed between the 2 groups, including renal parameters (creatinine, creatinine clearance)

Liver enzymes

Elevations in liver parameters are summarized in Table 25.

In NETTER-2, the most frequent elevation in hepatic laboratory parameters (≥15% of subjects in any group) were (Lutathera group vs. Control group):

- ALP ≥ 2x ULN (21.8% vs. 26.0%)
- ALP ≥ 3x ULN (15.0% vs. 15.1%)
- ALT or AST ≥ 3x ULN (12.2% vs. 20.5%)
- ALT ≥ 3x ULN (9.5% vs. 15.1%)

Most of these post-baseline elevations in liver enzymes were comparable between the 2 groups, except for (≥5% difference) ALT > 3x ULN (9.5% vs. 15.1%), AST > 3x ULN (8.2% vs. 13.7%) and ALT or AST > 3x ULN (12.2% vs. 20.5%) which were reported more frequently in the Control group. The biochemical definition of Hy's law (ALT or AST > 3x ULN and total bilirubin >2x ULN with ALP <2x ULN) was not met by any subject in NETTER-2, NETTER-1 and the Pooled data 1 (Table S11).

Combined elevations based on the peak post-baseline values for each parameter for each subject.

Table 25. Overview about Post-baseline elevations in liver enzymes in NETTER-2 and NETTER-1

	NETTER-2		NETTER-1		Pooled data 1
	Lutathera + Octreotide LAR N=147 n(%)	**Octreotide LAR N=73 n(%)**	**Lutathera + Octreotide LAR N=111 n(%)**	**Octreotide LAR N=112 n(%)**	**Lutathera + Octreotide LAR N=147 n(%)**
Post baseline values					
ALT >3x ULN	14 (9.5)	11 (15.1)	9 (8.1)	1 (0.9)	24 (8.6)
ALT >5x ULN	6 (4.1)	3 (4.1)	4 (3.6)	0	11 (3.9)
ALT >20x ULN	0	1 (1.4)	1 (0.9)	0	1 (0.4)
AST >3x ULN	12 (8.2)	10 (13.7)	8 (7.2)	2 (1.8)	21 (7.5)
AST >5x ULN	4 (2.7)	5 (6.8)	4 (3.6)	0	9 (3.2)
AST >20x ULN	0	1 (1.4)	0	0	0
ALT or AST >3x ULN	18 (12.2)	15 (20.5)	11 (9.9)	2 (1.8)	30 (10.7)
ALT or AST >5x ULN	8 (5.4)	5 (6.8)	5 (4.5)	0	14 (5.0)
ALT or AST >20x ULN	0	1 (1.4)	1 (0.9)	0	1 (0.4)
ALP ≥2x ULN	32 (21.8)	19 (26.0)	20 (18.0)	22 (19.6)	58 (20.7)
ALP ≥3x ULN	22 (15.0)	11 (15.1)	11 (9.9)	14 (12.5)	37 (13.2)
ALP ≥5x ULN	7 (4.8)	3 (4.1)	4 (3.6)	6 (5.4)	14 (5.0)
ALP ≥8x ULN	2 (1.4)	1 (1.4)	2 (1.8)	3 (2.7)	4 (1.4)
ALP ≥10x ULN	0	1 (1.4)	2 (1.8)	2 (1.8)	2 (0.7)
Total bilirubin (BILI) >2x ULN	8 (5.4)	4 (5.5)	7 (6.3)	5 (4.5)	15 (5.4)
Total bilirubin (BILI) >3x ULN	4 (2.7)	4 (5.5)	0	0	4 (1.4)
Total bilirubin (BILI) >5x ULN	0	2 (2.7)	0	0	0
Total bilirubin (BILI) >10x ULN	0	1 (1.4)	0	0	0
Combined elevations post-baseline					
AST and ALT ≤ULN at baseline					
ALT or AST >3x ULN & BILI >2x ULN	0	0	1 (0.9)	0	1 (0.4)
ALT or AST >3x ULN & BILI >2x ULN & ALP ≥2x ULN	0	0	1 (0.9)	0	1 (0.4)
ALT or AST >3x ULN & BILI >2x ULN & ALP <2x ULN	0	0	0	0	0
ALT or AST > ULN at baseline					
Elevated ALT or AST (*) + BILI (>2x Bsl and 2x ULN)	2 (1.4)	1 (1.4)	0	0	2 (0.7)
Elevated ALT or AST (*) + BILI (>2x Bsl and 2x ULN) & ALP ≥2x ULN	2 (1.4)	1 (1.4)	0	0	2 (0.7)
Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN) & ALP <2x ULN	0	0	0	0	0

* Elevated AST or ALT defined as: >3x ULN if ≤ULN at baseline, or (>3x Bsl or 8x ULN) if > ULN at baseline.
Pooled data 1 includes NETTER-1 Lutathera Safety Set (111) and PK Sub-study Set (22), and NETTER-2 Lutathera Safety Set (147).
Source: [SCS Appendix 1-Table 2.4-2]

In general, the laboratory chemistry data post base with respect to hepatotoxicity appear more favourable for the Lutathera arm, subjects than for treated in the control arm. In particular, taken the high degree of cross-over and the 2:1 randomisation into acount. Nevertheless, it is noted that only in NETTER-2 cases with elevated ALT or AST (*) + BILI (>2x Bsl and 2x ULN) occurred. Thus, the applicant is requested to provide the narratives of these subjects and to discuss the reasons for these events to further assess these events in the context of the disease and the treatment.

Vital signs

In NETTER-2, the number and percentage of subjects with notable vital signs abnormalities (systolic or diastolic blood pressure, pulse rate, or body weight) were comparable between the 2 groups. An increase in body weight by more than 10% was reported more frequently in the Lutathera group. The increase in body weight in oncology patients may represent a sign of disease stabilization, and does not generally constitute a clinical concern. Overall, none of the changes in vital signs were considered to be clinically meaningful.

Electrocardiograms

In NETTER-2, the number and percentage of subjects with notable ECG values (QTcF, QT, PR, QRS and HR) were comparable between the 2 groups with no clinically meaningful differences observed

2.5.6. Safety in special populations

2.5.6.1. Intrinsic factors

Analyses of AEs and worst post-baseline hematology and biochemistry abnormalities were conducted to evaluate the impact of age, gender, race and baseline renal function [SCS Appendix 1-Table 2.6-1.1 to Table 2.6-4.4].

- Age (<65 years vs. ≥ 65 years)
- Sex (male vs. female)
- Race (White vs. Asian)
- Baseline CrCl (<60 mL/min vs. ≥ 60 mL/min)

Age

In NETTER-2, majority of the subjects in the Lutathera group were <65 years of age (57.1%). Most of the TEAEs in the Lutathera group were proportionally similar for subjects aged <65 years and ≥65 years old. Also a treatment group comparisons (Lutathera group vs. Control group) showed in general similarity regarding all TEAEs in both age subgroups. However, grade ≥3 AEs in <65 years old subgroup that were reported more frequently (≥10% difference) in the Lutathera group (36.9% vs. 23.4%) which was expected due to the additional toxicity of Lutathera.

Subjects <65 years and ≥65 years old within the Lutathera group had a similar profile of TEAEs as observed for the overall population, with no important differences between subgroups, except for some PTs (all grades) that were more frequently reported (≥ 10% difference) in one age subgroup than the other (<65 years vs. ≥65 years):

- investigations (65.5% vs. 42.9%)
    - platelet count decreased (22.6% vs. 9.5%)
    - WBC decreased (17.9% vs. 6.3%)
- blood and lymphatic system disorders (27.4% vs. 31.7%)
    - thrombocytopenia (1.2% vs. 17.5%)

Overall, with regards to TEAE profile of Lutathera, there was no meaningful trend in either the direction of the younger subjects <65 years of age nor in the direction of the older subjects ≥65 years in age.

Treatment group comparisons were proportionally similar for both age subgroups for PTs across all grades and grade ≥3 [SCS Appendix 1-Table 2.6-2.1]. However, a few TEAEs (all grades) were reported more frequently (≥ 10% difference) in one treatment group than the other (Lutathera group vs. Control group) when stratified by age subgroups:

<u>In subjects aged ≥ 65 years the following PT differences are reported:</u>

- nausea (30.2% vs. 7.7%)
- asthenia (22.2% vs. 3.8%)
- diarrhea (22.2% vs. 34.6%)
- alopecia (20.6% vs. 0)
- abdominal pain (20.6% vs. 30.8%)
- anemia (19.0% vs. 7.7%)
- thrombocytopenia (17.5% vs. 0)
- lymphopenia (11.1% vs. 0)
- blood bilirubin increased (0 vs. 15.4%)

Worst post-baseline hematology abnormalities based on CTC grades

Most of the worst post-baseline hematology abnormalities in the Lutathera group were proportionally similar for both age subgroups, except for all grades decreased leukocytes that were reported more frequently (≥10% difference) in the <65 years vs. ≥65 years old subgroup (70.2% vs. 52.4%) [SCS Appendix 1-Table 2.6-3.1].

The higher frequency of bone metastasis in the <65 years old subgroup as compared to the ≥65 years old subgroup (30.9% vs. 15.9%) in the Lutathera group may have contributed to the higher incidence of leukocyte decrease observed in the younger subjects [NETTER-2-Appendix 16.2.4-Listing 16.2.4-2.1].

Treatment group comparisons were proportionally similar for both age subgroups for majority of abnormalities across all grades and grade ≥3 [SCS Appendix 1-Table 2.6-3.1].

Treatment group comparisons were proportionally similar for both age subgroups for majority of abnormalities across all grades and grade ≥3 [SCS Appendix 1-Table 2.6-4.1]. However, a few abnormalities (all grades) were reported more frequently (≥10% difference) in one treatment group than the other (Lutathera group vs. Control group) when stratified by age subgroups:

<u>by subjects aged <65 years:</u>

- decreased CrCl (57.1% vs. 46.8%)

- decreased calcium corrected (42.9% vs. 14.9%)

by subjects aged ≥ 65 years:

- increased ALT (28.6% vs. 42.3%)
- decreased magnesium (22.2% vs. 11.5%)
- decreased albumin (17.5% vs. 34.6%)
- increased bilirubin (11.1% vs. 34.6%)
- increased sodium (3.2% vs. 15.4%)

Gender

In NETTER-2, there was a slightly higher number of male subjects (53.7%) compared to the female subjects (46.3%) in the Lutathera group.

Most of the AE categories in the Lutathera group were proportionally similar for both sex subgroups, except for all grades SAEs that were reported more frequently (≥10% difference) in the male vs. the female subgroup (26.6% vs. 13.2%).

Treatment group comparisons (Lutathera group vs. Control group) were in general proportionally similar for both sex subgroups.

Both male and female subjects had a similar profile of TEAEs as observed for the overall population, with no important differences between subgroups, except for all grades alopecia that was reported more frequently (≥10% difference) in the female subgroup (male vs. female: 2.5% vs. 29.4%) [SCS Appendix 1-Table 2.6-2.2].

Treatment group comparisons were proportionally similar for both sex subgroups for PTs across all grades and grade ≥3 [SCS Appendix 1-Table 2.6-2.2]. However, a few TEAEs (all grades) were reported more frequently (≥10% difference) in one treatment group than the other (Lutathera group vs. Control group) when stratified by sex subgroups.

Analysis of this differences show that in male subjects AEs with respect to PTs regarding haematological disorders (mainly anaemia, thrombocytopenia and lymphocytopenia) as well as asthenia, increased TSH levels abdominal pain and peripheral edema occurred more often in NETTER-2.

Female subjects had more frequent AEs with respect to PTs in the gastrointestinal disorders section, as nausea (30.9% vs. 14.7%), alopecia (29.4% vs. 2.9%) and diarrhea (23.5% vs. 35.3%) as well as platelet count decreased (22.1% vs. 8.8%), white blood cell (WBC) count decreased (17.6% vs. 2.9%) and anemia (16.2% vs. 5.9%).

Most of the worst post-baseline hematology abnormalities in the Lutathera group were proportionally similar for both sex subgroups, except for a few abnormalities (all grades) that were reported more frequently (≥10% difference) in the female subjects (male vs. female) [SCS Appendix 1-Table 2.6-3.2], and the difference was mainly for grade 1 or 2 abnormalities.

- decreased leukocytes (46.8% vs. 80.9%)
- decreased neutrophils (20.3% vs. 57.4%)

The trend of higher incidence of decreased leukocytes and neutrophils in female subjects vs. the male subjects was also observed in NETTER-1. However, this is not supported by published literature where women treated with Lutathera reported higher incidences of anemia and thrombocytopenia but not of leukopenia and neutropenia compared to men (Minczeles et al 2022).

Race

In NETTER-2, majority of the subjects within the Lutathera group were White (75.5% vs. 15.6% Asian vs. 5.4% missing vs. 2.0% Black or African American and 1.4% other race types. Although again most of the AE categories in the Lutathera group were proportionally similar for race subgroups, interpretation of observed exceptions for a few AE categories that were reported more frequently (≥10% difference) in one subgroup than the other in the Lutathera group (White vs. Asian) remains not meaningful. The dominance by White subjects preclude any reliable interpretation and identification of potential signals (as usual in small studies).

Baseline creatinine clearance

In NETTER-2, there were fewer subjects with a moderate renal impairment (baseline CrCl <60 - ≥30 mL/min) (11.6%) compared to subjects with mild or no renal impairment (baseline CrCl ≥60 mL/min (88.4%) in the Lutathera group [SCS Appendix 1-Table 2.6-1.4]. Thus, analyses with respect to baseline creatinine clearance need to be interpreted cautiously because of the limited subjects with baseline CrCl < 60 mL/min (N=17).

Most of the AE categories in the Lutathera group were proportionally similar for both baseline CrCl subgroups, except for a few AE categories listed below that were reported more frequently (≥10% difference) in the baseline CrCl <60 mL/min subgroup vs. ≥60 mL/min [SCS Appendix 1-Table 2.6-1.4]:

- all grades AEs requiring additional therapy (88.2% vs. 68.8%)
- grade ≥3 AEs (58.8% vs. 32.3%)
- all grades AEs related to octreotide (52.9% vs. 35.4%)
- grade ≥3 AEs requiring additional therapy (41.2% vs. 16.2%)
- grade ≥3 AEs related to any treatment (29.4% vs. 13.8%)
- grade ≥3 AEs related to Lutathera (29.4% vs. 13.1%)
- grade ≥3 AEs leading to any treatment discontinuation (11.8% vs. 1.5%)

There were limited subjects with baseline CrCl < 60 mL/min (N=17) compared to subjects with baseline CrCl ≥ 60 mL/min (N=130) in the Lutathera group in NETTER-2, therefore the results should be interpreted cautiously. Overall, the greater incidence of TEAEs observed in subjects with lower baseline CrCl compared to those with a higher CrCl correlates with the expected AE profile for this subpopulation.

Treatment group comparisons (Lutathera group vs. Control group) were proportionally similar for both CrCl subgroups, except for a few AE categories that were reported more frequently (≥10% difference) in the Lutathera group by subjects with a baseline CrCl <60 mL/min [SCS Appendix 1-Table 2.6-1.4].

As indicated by the difference regarding, more all grades AEs related to any treatment (70.6% vs. 43.8%), grade ≥3 AEs (58.8% vs. 31.3%) and grade ≥3 AEs leading to discontinuation of any treatment (11.8% vs. 0), subjects with baseline CrCl < 60 mL/min, Lutathera's toxicity may be less tolerated in renally impaired subjects. However, this could be expected from the mode of action in principle and not a general issue for concern. Most important, subjects with baseline CrCl of < 60 mL/min and ≥ 60 mL/min within the Lutathera group had a similar profile of TEAEs as observed for the overall population. Difference reported do not indicate any valid new safety signal in comparison to NETTER-1 data.

No relevant new information was revealed by analysis of treatment group comparisons.

In summary, although no specific safety signal appears to be clearly associated with Lutathera in subjects with baseline CrCl < 60 mL/min, a higher degree of general toxicity PTs in this subgroup documented.

2.5.6.2. Extrinsic factors

No extrinsic factors were evaluated.

2.5.7. Safety related to drug-drug interactions and other interactions

No new information about drug interactions has been generated in support of this application; recommendations are described in the approved prescribing information. The product information summarises DDI in SmPC Section 4.5 as follows:

Somatostatin analogues

Somatostatin and its analogues competitively bind to somatostatin receptors and may interfere with the efficacy of Lutathera. Therefore, administration of long-acting somatostatin analogues should be avoided within 30 days prior to the administration of this medicinal product. If necessary, patients may be treated with short-acting somatostatin analogues up to 24 hours preceding Lutathera administration.

Glucocorticoids

There is some evidence that glucocorticoids can induce down-regulation of subtype 2 somatostatin receptors (SSTR2). Therefore, as a matter of caution, repeated administration of high doses of glucocorticoids should be avoided during Lutathera treatment. Patients with a history of chronic use of glucocorticoids should be carefully evaluated for sufficient somatostatin receptor expression. It is not known whether the intermittent use of glucocorticoids for the prevention of nausea and vomiting during Lutathera administration could induce SSTR2 down-regulation. As a matter of caution, glucocorticoids should also be avoided as preventive antiemetic treatment. In the event that the treatment administered for the prevention of nausea and vomiting before the amino acid solution infusion proves insufficient, a single glucocorticoid dose can be used, provided it is not given before initiating or within one hour after the end of Lutathera infusion.

2.5.8. Discontinuation due to adverse events

In NETTER-2, TEAEs leading to Lutathera discontinuation were reported in 3 subjects (2.0%) in the Lutathera group, with 1 subject (0.7%) being grade ≥3 (Table 26). The TEAEs were reported in the following PTs in the Lutathera group:

- cardiac failure (all grades: 1 subject and grade ≥3: 0)
- small intestinal obstruction (all grades and grade ≥3: 1 subject, each)
- platelet count decreased (all grades: 1 subject and grade ≥3: 0)

Table 26. Treatment-Emergent Adverse Events leading to Lutathera discontinuation by preferred term, all grades and grade ≥3, in the treatment phase (Safety Set + PK Sub-Study) (NETTER-2: cut-off: ≥0.7% all grades in Lutathera + octreotide LAR)

	NETTER-2		NETTER-1		Pooled data 1	
	Lutathera + Octreotide LAR N=147		Lutathera + Octreotide LAR N=111		Lutathera + Octreotide LAR N=280	
Preferred Term	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Number of subjects with at least one event	**3 (2.0)**	**1 (0.7)**	**10 (9.0)**	**3 (2.7)**	**17 (6.1)**	**7 (2.5)**
Cardiac failure	**1 (0.7)**	**0**	**0**	**0**	**1 (0.4)**	**0**

Platelet count decreased	**1 (0.7)**	**0**	**0**	**0**	**1 (0.4)**	**0**
Small intestinal obstruction	**1 (0.7)**	**1 (0.7)**	**0**	**0**	**1 (0.4)**	**1 (0.4)**

Numbers (n) represent counts of subjects.
Pooled data 1 includes NETTER-1 Lutathera Safety Set (111) and PK Sub-study Set (22), and NETTER-2 Lutathera Safety Set (147) MedDRA version 26.0, CTCAE version 4.03 for NETTER-1 and 5.0 for NETTER-2.
Source: [SCS Appendix 1-Table 5.1]

Adverse events leading to dose interruption or change

Information on TEAEs leading to dose interruption of any study drug is provided in [SCS Appendix 1-Table 2.3-6.1], and for dose reduction is provided in [SCS Appendix 1-Table 2.3-7.1].

TEAEs leading to dose interruption

In NETTER-2, TEAEs leading to Lutathera dose interruption (delay in the administration beyond the 8 weeks) were reported in 9.5% of subjects in the Lutathera group, with 2.0% being grade ≥3 (Table S11). The most commonly reported TEAEs by PT (≥1%) in the Lutathera group was blood creatinine increased (all grades: 1.4% and grade ≥3: 0).

Information on TEAEs leading to dose interruption of any study drug is provided in [SCS Appendix 1-Table 2.3-6.1].

TEAEs leading to dose reduction

In NETTER-2, TEAEs leading to Lutathera dose reduction were reported in 1.4% of subjects in the Lutathera group, with 1 subject (0.7%) being grade ≥3 (Table S11). The most commonly reported TEAEs by PT (≥ 0.7%) in the Lutathera group were:

- platelet count decreased (all grades: 1.4% and grade ≥3: 0.7%)
- cholangitis (all grades and grade ≥3: 0.7%, each)

2.5.9. Post marketing experience

Lutathera is currently approved in 40 countries (i.e., Canada, EEA countries, Hong Kong, Israel, Japan, Taiwan, United Kingdom, USA, Singapore, South Korea and Switzerland) and has been marketed since the International Birth Date (IBD) of 26-Sep-2017.

Post-marketing data for Lutathera has been reviewed on a regular basis as part of Periodic Safety Update Report (PSUR). The cumulative post-authorization subject exposure since the IBD (26-Sep-2017) and up to November 2022 includes 19,265 patients treated and 63,253 doses injected**.**

In the most recent PSUR for Lutathera with a reporting period from 20-Dec-2021 to 19-Dec-2022, the benefits and risks of treatment with Lutathera were assessed based on both clinical studies and post-marketing experience and, overall, indicate a positive benefit-risk profile for Lutathera. Since last PSUR (19-Dec-2022), no new safety signals were found to date.

Based on the overall assessment of post-marketing safety information available from 26-Sep-2017 to 19-Dec-2022, as well as cumulative data, no new or changing safety signal has emerged that would substantially alter the known safety profile in the GEP-NET setting.

2.5.10. Discussion on clinical safety

The safety profile of Lutathera has been sufficiently characterized in the NETTER-1 and ERASMUS studies for the initial approval procedure for the indication "for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEPNETs)" in adults". The meanwhile available post-marketing data confirmed that Lutathera is generally well-tolerated in this target population with limited, transient toxic events mainly resulting from the known radiation exposure.

For the now applied first line indication "for the treatment of newly diagnosed, unresectable or metastatic, well differentiated (G2 and G3), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults", safety assessment is based on the results from the new NETTER-2 study. In this trial, subjects were randomized in a 2:1 ratio to either Lutathera group (n=151, of them 147 treated) or Control group (n=75, of them 73 treated). In NETTER-2, 29/111 (26%) of subjects who received treatment with octreotide LAR in the Control group subsequently crossed over to receive Lutathera in the crossover period following disease progression and were included in the crossover set. Moreover, 8 subjects received at least one dose of Lutathera in the re-treatment period and were included in the re-treatment set.

The provided safety data was assessed on the basis of AEs, adverse events of special interest (AESIs), clinical laboratory results for haematology, blood chemistry, physical examinations, vital signs and electrocardiogram (ECG) during the NETTER-2 randomized treatment period (i.e., up to the last randomized treatment + 30 days before entering into cross-over/re-treatment).

The median duration of **exposure** to study treatment in the randomized treatment period was longer in the Lutathera arm with 71.1 weeks compared to 40.3 weeks (range: 4 to 124.4 weeks) in the octreotide arm. This finding appears to reflect the earlier termination of treatment in the control arm because of crossover due to disease progression. It may have contributed at least partially to lower event rates for some AEs in the control arm.

The median duration of exposure to Lutathera was 32 weeks (range: 8.0-40.0) with 87.8% subjects receiving all 4 cycles of treatment and a median relative dose intensity of 98.2%.

The median duration of exposure to octreotide was 71.0 weeks in the Lutathera arm and 40.3 weeks in the control arm. However, the median relative dose intensity for octreotide were similar in the Lutathera and control arms (104.4% vs 95.3%).

In conclusion, exposure was sufficient to allow an adequate assessment of safety risks in the context of the applied posology in the first line indication.

99% of the patients in the Lutathera arm and 95% in the Octreotide LAR arm experienced at least one AE during the study. The frequency and severity of TEAE categories were similar (difference <10% for all grades and <5% for grade ⩾3) in both treatment groups. Majority of subjects in both treatment groups experienced AEs (all grades: 92.5% in Lutathera group vs. 94.5% in Control group).

None of the AE categories for all grades were reported more frequently (⩾10% difference) in the Lutathera group vs. the Control group. Grade ⩾3 AE [all causalities (35.4% vs 27.4%) and drug related (15.6% vs 4.1%)]) were reported more frequently (⩾5% difference) in the Lutathera group vs. the Control group:

In general, the incidence of AEs (irrespective of causal relationship) was rather similar between the two arms (Lutathera vs. control arms). The most common TEAEs by SOC (regardless of causality) reported for the Lutathera group were due

- gastrointestinal disorders (66.7%, grade ≥3: 9.5%), PTs mainly nausea (27.2%) and diarrhoea 25.9%
- investigations (55.8% grade ≥3: 17.0%),
- general disorders and administration site conditions (51.7%),

Similarly, the most common all grades TEAEs by SOC regardless of causality occurring with a greater frequency (⩾10% difference) in the Lutathera group vs. the Control group, include were investigations (all grades: 55.8% vs. 41.1%)m nervous system disorders (all grades: 31.3% vs. 16.4%) and blood and lymphatic system disorders (all grades: 29.3% vs. 9.6%).

In NETTER-2, the most common TEAEs by PT regardless of causality reported for the Lutathera group were nausea (27.2%) and diarrhea (25.9%) for all grade TEAES. Grade ≥3 (>2%) TEAEs were observed for lymphocyte count decreased/lymphocytopenia (8.1%), GGT increased (4.8%), small intestinal obstruction (3.4%), abdominal pain (2.7%) and hypertension (2.7%).

Most common probably drug related all grade and grade ≥3 AEs by PT irrespective of causality, occurring with a greater frequency (≥10% difference for all grades) among subjects in the Lutathera arm vs. control arm include were:

- anaemia (all grades: 19.7% vs. 6.8% and grade ≥3: 0.7% vs. 1.4%),
- platelet count decreased/thrombocytopenia (all grades: 17.0% vs. 5.5% and grade ≥3: 1.4% vs. 0),
- alopecia (all grades: 15.0% vs. 1.4% and grade ≥3: 0 vs. 0) and
- lymphocyte count decreased (all grades: 10.9% vs. 0 and grade ≥3: 5.4% vs. 0).

The only grade ≥3 TEAE by PTs regardless of causality that was reported at a higher incidence (≥5% difference) in the Lutathera group vs. the Control group was lymphocyte count decreased (5.4% vs. 0).

The AESI categories of nephrotoxicities, immediate hematotoxicities and secondary hematological malignancies are related to known Lutathera risks, while cardiovascular and electrolyte disorder risk is probably more related to the co-administered amino acid and its potential to cause hyperkalemia

The most identified drug related adverse events are discussed more in detail below:

Renal dysfunction

Renal dysfunction can develop during and after treatment with Lutathera. Cases of chronic renal impairment have been reported in patients several years following treatment with Lutathera, which were mild in nature and were confirmed by serum/urine analyses [PSUR 20-Dec-2021 to 19-Dec-2022].

For renal protection, all patients receive an intravenous amino acid solution containing L-lysine and L-arginine concomitantly with Lutathera. The amino acid solution helps to decrease the reabsorption of Lutathera through the proximal tubules resulting in the decrease of the radiation dose to the kidneys. However, the supportive administration of the amino-acid solution is likely to cause cardiovascular and electrolyte disorder due to the additional volume and the content of the solution.

In NETTER-2 AEs caused by nephrotoxicity were observed in 13/147 (8.8%) of the Lutathera arm compared with 4/111 (5.5%) in the control arm. This frequency is significantly lower than in NETTER-1 (Lu:17.1%) and may at least partially confirm the efficacy of the pretreatment with the optimized standardised amino acid solution and the increased experience with the product in the already approved indication. Nevertheless, impairment of renal function due to Lutathera remains beside secondary haematological malignancies the main chronic risks in Lutathera treatment.

Immediate and late hematologic toxicity

Repeated administration of Lutathera increases the cumulative radiation dose to normal tissues and thereby increases the risk of accumulation of unrepaired DNA damage. In the short term, this leads to

apoptosis of cells in the peripheral blood and bone marrow, resulting in cytopenias in peripheral blood and myelosuppression. In the long term, it can lead to genetic instability and, potentially, to MDS and AML.

In the applied NETTER-2 population, immediate hematologic toxicity was comparable to that observed in NETTER-1 (20.4% vs 24.3%). Mainly thrombocytopenia (12.6%) and Lymphocytopenia (8.1% all ≥Grade3), while clinical relevant drug related anemia (0.7%) and neutropenia (2%) occurred relatively rare in this trial.

Drug relationship is best illustrated by the difference in grade ⩾3 AE for immediate haematotoxicities, which were more frequently reported in the Lutathera group grade ≥3 (13.6%) than in the control arm (1.4%).

At cutoff-date (20-Jul-2023), there was a single occurrence (0.7%) of a secondary hematological malignancy that was a grade 3 myelodysplastic syndrome (MDS) reported in the Lutathera group that occurred 14.1 months after receiving the first Lutathera dose; the case evolved to AML after the data cut-off Two cases were reported after the primary analysis DCO date (and therefore are not included in the present analysis/pool) that were grade 4 MDS also reported in the Lutathera group that occurred about 34 months and 2 years, respectively after receiving the first Lutathera dose.

Hepatotoxicity

The deleterious effects of ionizing radiation to hepatocytes and other liver structures most likely mediate hepatotoxicity induced by Lutathera. Approximately 80% of all patients with GEP-NET treated with Lutathera have liver metastases at their baseline staging, thus an altered liver function and liver enzyme elevations are common in the target population. While Lutathera does not show high radiation uptake in the normal liver, the presence of liver metastasis can lead to an increased radiation absorbed dose to the surrounding healthy liver tissue. In NETTER-2, the laboratory chemistry data post base with respect to hepatotoxicity appear more favourable for the Lutathera arm, subjects than for treated in the control arm. The biochemical definition of Hy's law (ALT or AST > 3x ULN and total bilirubin >2x ULN with ALP <2x ULN) was not met by any subject in NETTER-2, NETTER-1 and the Pooled data 1

In NETTER-2, the laboratory chemistry data post base with respect to hepatotoxicity appear more favourable for the Lutathera arm, subjects than for treated in the control arm. The biochemical definition of Hy's law (ALT or AST > 3x ULN and total bilirubin >2x ULN with ALP <2x ULN) was not met by any subject in NETTER-2, NETTER-1 and the Pooled data 1.

Tumour lysis syndrome

Tumour lysis syndrome occurs due to rapid tumour cell destruction caused by cell death. It can lead to a massive release of intracellular contents such as potassium, phosphorus, and uric acid. This release overloads excretory mechanisms, leading to a clinic-laboratory derangement of cellular metabolism that might finally result in acute renal failure, cardiac arrhythmia, central nervous system toxicity, and ultimately death. Serious outcomes can be prevented with risk monitoring and so the impact of this risk is low in advanced NET patients. In NETTER-2 the only case of tumour lysis syndrome occurred in the control arm and thus raise no specific concern regarding Lutathera.

Hormonal release-induced crisis (HRIS) and hypogonadism

The exact mechanism of increased hormonal release in the patients developing a hormonal crises after treatment with Lutathera as described in the literature has not been fully elucidated. Direct receptor-mediated hormonal release by Lutathera seems unlikely as the SSTR binding leads to decrease in hormonal secretion in majority of the patients. However, other factors that may contribute to the published cases of HRIC include tumour lysis because of β-irradiation from the radiolabeled SSA,

discontinuation of short-acting SSA before Lutathera administration, administration of amino acid solution (2.5% arginine and 2.5% lysine) and emotional stress response to hospitalization and/or therapy. No HRIS case was reported form both NETTER trials, but published in the literature. The applicant was requested to illustrate the relevance of this risk according the current state of knowledge from the observed cases and the experience with treatment strategies options used for the management of this adverse event. The review of the cases did not present any significant new or changing safety information on the topic of interest compared with the knowledge at the time of the initial approval.

Similarly, hypogonadism and sexual dysfunction are known risks for Lutathera from case reports in the literature, but were not observed in the pivotal trials. The anterior pituitary gland and the testes express SSTR, especially SSTR2; hence, these organs are potentially targeted by Lutathera. The radiotoxic effect on the testes and ovaries is likely secondary to the high activity received by the urinary bladder, with consequent irradiation of the gonads from γ rays, especially in men. The applicant clarified that hypogonadism and sexual dysfunction were not considered AE of special interest (AESI) in NETTER-2 due to the lack of cases in NETTER-1 and the low number of cases from post-marketing sources. For the same reasons, no specific laboratory measurements of gonadotropins (LH, FSH) and gonadal hormones (testosterone, estradiol) were planned in NETTER-2. This appears acceptable. The risk of hypogonadism and sexual dysfunction was only monitored through the reporting of AEs as per criteria described in the protocol. According the evidence available it appears that the effect of hypogonadism/sexual dysfunction on male and female gonads can be considered mostly transient/temporary. In women, a mild and no clinically significant effect was observed mostly in the post-menopausal population. Importantly, testosterone deficiency is treatable with exogenous testosterone replacement. In any case, in patients who wish to have children, cryopreservation of sperm or eggs can be discussed as an option before Lutathera treatment, which is clearly described as a recommendation in the EU SmPC.

Comparing the adverse events between NETTER-2 and NETTER-1, it is obvious, that significant lower event rates in the SOC gastrointestinal disorders (66.7% vs. 87.4%) with the main difference coming from PTs of nausea (27.2% vs. 66.7%) and vomiting (14.3% vs. 54.1%). This may be explained by the issue that a complex full amino acid solutions was used in NETTER-1 and a standardized amino acid solution containing only 2.5% arginine and 2.5% lysine that was used consistently in NETTER-2. The same is probably correct for lower event rates in NETTER-2 in the SOCs musculoskeletal and connective disorders (arthralgia, pain in back and extremity) as well as headache and dizziness, which may be at least partially explained also by the optimized AS infusion solution used in NETTER-2.

The need for renal protection with and relative large volume of an amino acid solution might have also contributed to the cardiovascular events and some electrolyte disorders (hyperkaliaemia) TEAEs. However, . cardiovascular and electrolyte disorders were reported more frequently (≥5%) in the control than in the Lutathera group (all grades: 7.5% vs. 13.7% and grade ≥3: 7.5% vs. 13.7%).

No new AEs or major differences in SOCs/PT frequencies were seen in the re-treated or crossover subjects, which would need to be additionally mentioned. Considering the small size of both subpopulations, meaningful conclusion from the reported outcome are less roboust.

The incidence of **deaths** during the study was rather similar in both Lutathera (21.8%) and the control arms (19.2%). Most of these deaths occurred due to the disease under study (20.4% vs. 17.8%). Six on-treatment deaths were reported and was more frequent in the control arm (4 subjects; 5.5%) compared to 2 subjects (1.4%) in the Lutathera arm.

The incidence of **SAEs** was 20.4% in the Lutathera arm and 20.5% in the control arm. However, SAEs considered to be related to any study treatment by the Investigator were reported more frequently in the Lutathera arm vs. the control arm (5.4% vs. 1.4%). Small intestinal obstruction, a well known

dangerous disease complication was the only suspected SAE reported in >1% of subjects (2 subjects; 1.4%).

No additional clinically meaningful differences in **laboratory chemistry events** beside those already discussed above were observed between the Lutathera group vs. the Control group.

No major shifts from baseline were observed in the Karnofsky scale scores when compared to baseline in both treatment arms.

Analysis of the AE incidences across subgroups of age, gender, race and baseline creatinine clearance and between arms for each subgroup showed similar trends to those observed in the overall study population. The numerical differences that were observed among subgroups were not considered clinically meaningful, given the limited sample size of these subgroups and the number of events that led to these differences.

No new information about drug-drug and other interactions has been generated in support of this application; recommendations are described in the approved prescribing information.

Study discontinuation due to TEAEs in NETTER-2 occurred in four patients (2.7%). For the 3/147 (2.0%) subjects in the Lutathera arm the reasons were cardiac failure, small intestinal obstruction and thrombocytopenia, while 1/111 (0.7%) subject discontinued in the control arm (also due to small intestinal obstruction). Only the disease associated small intestinal obstruction events were Grade ≥3 events (probably not treatment related).

Thus, treatment discontinuation due to safety events were rare and at least partially not treatment related in NETTER-2.

The same is true regarding TEAEs leading to dose interruption or dose reduction.

In NETTER-1, discontinuation due to TEAE were reported in 9.0 % (10/111) of the Lutathera treated subjects. However, the lower dose discontinuation rate observed in NETTER-2 might also be at least partially the result of the meanwhile available experience with an already established product with the same underlying disease and improved management strategies for the handling of safety complications.

With respect to post-marketing safety data, no new validated signals indicating a different risk were detected since approval.

All risks are fully reflected in the Product information as well as in the updated approved current RMP.

Additional expert consultations

CHMP agreed to consult the SAG Oncology and ask the following question:

2. What is your view of the overall safety profile of Lutetium (^{177}Lu) oxodotreotide?

3. To what extent do PRRT-related toxicities, such as hematological and renal toxicities, secondary malignancies, secondary mutations and NET grade progression, raise a concern in this early setting?

Assessment of paediatric data on clinical safety

N/A

2.5.11. Conclusions on clinical safety

The safety profile of Lutathera observed in NETTER-2 was consistent with that observed in NETTER-1 and the Pooled datasets, as well as with the known safety profile of Lutathera in the GEP-NET population.

The overall safety profile of Lutathera in GEP-NET subjects is well characterized and remains consistent with that previously reported. No new or changing safety signals were identified. No new TEAEs were observed. Overall, the incidence rates for AESIs reported in NETTER-1 Lutathera group were consistently higher than those in NETTER-2. Insofar, these lower frequencies for most TEAEs might allow presuming a better tolerability of Lutathera in the newly diagnosed GEP-NET target population. However, improved clinical management due to the meanwhile large experience with Lutathera may have also contributed to this outcome.

Overall, Lutathera treatment appears to be tolerable and manageable in the applied indication. However, it is reminded that late renal and hematological toxicities and also secondary hematological malignancies (MDS and AML) are known risks of Lutathera@ as targeted radioligand therapy. There is also a risk for developing secondary mutations and NET grade progression which may lead to a decreased efficacy of other treatment options like target therapies or chemotherapy in later treatment lines.

2.5.12. PSUR cycle

No changes to the PSUR cycle are warranted.

2.6. Significance / Non-Conformity of paediatric studies

N/A

3. Risk management plan

The MAH submitted an updated RMP version 3.0 with this application. The proposed RMP changes were the following:

RMP v3.0 includes clinical data from the registration study NETTER-2 to support the addition of a new therapeutic indication for Lutathera.

3.1. Safety Specification

Epidemiology of the indications and target population

The section was changed to reflect extension of indications "Lutathera is indicated for the treatment of newly diagnosed, unresectable or metastatic, well-differentiated (G2 and G3), SSTR-positive, GEP-NETs in adults." The changes in this section are acceptable provided that the benefit - risk in new indication is positive.

Clinical trial exposure

Clinical trial exposure was updated with data obtained from NETTER-2 study and pooled data from ERASMUS MC, NETTER-1 and NETTER-2.

Populations not studied in clinical trials

Population not studied in clinical trials has not been changed. The editorial changes are acceptable.

Post-authorisation experience

No substantial changes were introduced. The data was updated up to DLP.

Additional EU requirements for the safety specification

No changes.

Potential for medication errors

Not applicable.

Potential for off-label use

Not applicable.

Specific paediatric issues

Not applicable.

Identified and potential risks

The safety concerns have not been changed. Characterization of the risks was updated with data from NETTER-2 study and pooled data.

3.2. Summary of the safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Renal dysfunction • Myelosuppression / cytopenias (immediate hematotoxicity) • Myelodysplastic syndrome / acute leukemia (late hematotoxicity) • Hepatotoxicity • Tumor lysis syndrome • Hormone release-induced crises • Hypogonadism, sexual dysfunction • Drug interaction with somatostatin/somatostatin analogues
Important potential risks	• Radiotoxicity, including occupational exposure and inadvertent exposure

Summary of safety concerns	
	• Secondary malignancies (solid tumors) • Embryo-fetal toxicity
Missing information	• Radiation exposure during breast feeding • Exposure in patients with renal impairment • Exposure in patients with severe hepatic impairment • Long-term safety data

Considering the data in the safety specification, the safety concerns listed above are appropriate.

3.3. Pharmacovigilance plan

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Study A-LUT-T-E02-402 (SALUS) Ongoing	Primary research-objective: • To assess the incidence and nature of potential long-term second primary malignancies, including solid tumors and hematological neoplasia, occurring over a 7-year follow-up period in patients with unresectable or metastatic, well-differentiated, SSTR positive GEP-NETs tumors. Secondary research-objectives: • To quantify the incidence of other important identified and potential risks specified in the lutetium (^{177}Lu) oxodotreotide RMP such as: renal dysfunction, myelosuppression/cytopenias, MDS, hypogonadism, sexual dysfunction, drug interaction with somatostatin/SAs, tumor cell lysis-related hormone release-induced crises, hepatotoxicity, radiotoxicity. • To detect potential new risks overall, and potential risks in patients under-represented in	Renal dysfunction Myelosuppression / cytopenias (immediate hematotoxicity) Myelodysplastic syndrome / acute leukemia (late hematotoxicity) Hepatotoxicity Tumor lysis syndrome Hormone release-induced crises Hypogonadism, sexual dysfunction Drug interaction with somatostatin/somatostatin analogues Radiotoxicity, including occupational exposure and inadvertent exposure Secondary malignancies (solid tumors) Embryo-fetal toxicity Radiation exposure during breast feeding Exposure in patients with renal impairment	Final study report submission	31-Dec-2028

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	the clinical trial, including elderly patients, patients with renal and liver impairment, reduced BM reserve, exposure in breast-feeding women, accidental fetal and child exposure. • To describe the patterns of drug utilization that may add knowledge about the safety of lutetium (^{177}Lu) oxodotreotide.	Exposure in patients with severe hepatic impairment Long-term safety data		

*Category 1 studies are imposed activities considered key to the benefit risk of the product.
Category 2 studies are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.
Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Overall conclusions on the PhV Plan

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are needed.

3.4. Risk minimisation measures

Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Renal dysfunction	**Routine risk communication** SmPC sections 4.2, 4.3, 4.4, 4.8 and 4.9 Package Leaflet (PL) sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Dose management guidance in case of renal toxicity is provided in the SmPC. Advice is given in the SmPC to concomitantly administer an amino acid solution containing the amino acids, L-lysine and L-arginine. Patients should be advised to empty their bladder frequently. Physicians are advised to assess renal function at baseline, during and at least for the first year after treatment; physicians are advised to assess renal function more frequently in case of renal-impaired patients with CrCl ≥ 40 ml/min is advised in the SmPC. Lutathera is contraindicated in kidney failure patients with CrCl < 30 mL/min.

	Treatment is not recommended in patients with CrCl < 40 mL/min at baseline. No dose adjustment is recommended for renally impaired patients with baseline creatinine clearance ≥40 mL/min. **Other routine risk minimization measures beyond the Product Information:** None
Myelosuppression / cytopenias (immediate hematotoxicity)	**Routine risk communication** SmPC sections 4.2, 4.4, 4.8 and 4.9 PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Dose management guidance is provided in the SmPC. Physicians are advised to monitor blood counts at baseline and during treatment and until resolution of any eventual toxicity. Treatment initiation not recommended in patients with severely impaired hematological function at baseline (except lymphopenia). **Other routine risk minimization measures beyond the Product Information:** None
Myelodysplastic syndrome / acute leukemia (late hematotoxicity)	**Routine risk communication** SmPC sections 4.4 and 4.8 PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Potential risks and/or predictive factors are provided in the SmPC. **Other routine risk minimization measures beyond the Product Information:** None
Hepatotoxicity	**Routine risk communication** SmPC sections 4.2, 4.4 and 4.8 PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Dose management guidance in case of hepatotoxicity is provided in the SmPC. Recommendation to monitor ALT, AST, bilirubin and serum albumin during treatment is provided in the SmPC. Physicians are advised for careful benefit-risk assessment in patients having baseline hepatic impairment. **Other routine risk minimization measures beyond the Product Information:** None
Tumor lysis syndrome	**Routine risk communication** SmPC sections 4.4 and 4.8 PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Guidance provided in the SmPC to assess renal function and electrolyte balance at baseline and during treatment. Physicians are advised to treat with increased caution patients with a history of renal insufficiency and high tumor burden. **Other routine risk minimization measures beyond the Product Information:**

	None
Hormone release-induced crises	**Routine risk communication** SmPC sections 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Physicians are advised to consider observation of patients by overnight hospitalization in some cases (e.g., patients with poor pharmacologic control of symptoms). Recommended treatments in case of hormonal crises are provided in the SmPC. **Other routine risk minimization measures beyond the Product Information:** None
Hypogonadism, sexual dysfunction	**Routine risk communication** SmPC section 4.6 PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients are recommended to have genetic consultation if they wish to have children after treatment. Cryopreservation of sperm or eggs can be discussed as an option to patients before the treatment. **Other routine risk minimization measures beyond the Product Information:** None
Drug interaction with somatostatin/somatostatin analogues	**Routine risk communication** SmPC sections 4.4 and 4.5 PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation is provided in the SmPC that administration of long-acting SAs should be avoided within 30 days prior to the administration of this medicinal product. If necessary, patients may be treated with short-acting SAs up to 24 hours preceding Lutathera administration. **Other routine risk minimization measures beyond the Product Information:** None
Important potential risks	
Radiotoxicity, including occupational exposure and inadvertent exposure	**Routine risk communication** SmPC sections 4.4, 4.6, 4.9, 6.6, 11 and 12 PL sections 1, 2 and 3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Detailed radioprotection measures are provided in the SmPC. **Other routine risk minimization measures beyond the Product Information:** Legal status: Lutathera can be administered only by persons authorized to handle radiopharmaceuticals in designated clinical settings.
Secondary malignancies (solid tumors)	**Routine risk communication** SmPC section 4.4 PL section None

	Routine risk minimization activities recommending specific clinical measures to address the risk: None **Other routine risk minimization measures beyond the Product Information:** None
Embryo-fetal toxicity	**Routine risk communication** SmPC sections 4.3 and 4.6 PL sections 2 and 3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** The use of Lutathera is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded due to the risk associated with the ionizing radiation. Physicians are advised to exclude pregnancy by using an adequate/validated test. Pregnant women should be advised of the risk to a fetus. Male and female patients are advised to avoid the pregnancy during treatment with Lutathera and for a minimum of the following 6 months after the end of the treatment. **Other routine risk minimization measures beyond the Product Information:** None
Missing information	
Radiation exposure during breast feeding	**Routine risk communication** SmPC section 4.6 PL sections 2 and 3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation is provided in the SmPC to avoid the breast-feeding during treatment. If treatment with Lutathera during breast feeding is necessary, the child must be weaned. **Other routine risk minimization measures beyond the Product Information:** None
Exposure in patients with renal impairment	**Routine risk communication** SmPC sections 4.2, 4.3, 4.4 and 4.8 PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Treatment with Lutathera in patients with severe kidney failure with CrCl < 30 mL/min is contraindicated. Treatment with Lutathera in patients with CrCl < 40 mL/min at baseline is not recommended. **Other routine risk minimization measures beyond the Product Information:** None
Exposure in patients with severe hepatic impairment	**Routine risk communication** SmPC sections 4.2, 4.4 and 4.8 PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients with severe hepatic impairment should only be treated with Lutathera after careful benefit-risk assessment. **Other routine risk minimization measures beyond the Product Information:**

	None
Long-term safety data	**Routine risk communication** SmPC section 4.8 PL section None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None

Additional risk minimisation measures

Patient Guide

Objectives:

Increasing patients' awareness on the risk of radiotoxicity by occupational exposure and inadvertent exposure to peptide receptor radionuclide therapy, and providing information concerning the necessary precautions to take to limit unnecessary exposure to themselves and the people around them.

Rationale for the additional risk minimization activity:

There is a need to provide information to patients concerning the necessary precautions to take to limit unnecessary radiation exposure to themselves and the people around them.

Target audience and planned distribution path:

A patient guide is prepared nationally, in line with the key safety messages defined in the RMP. The patient guide is distributed to centers where Lutathera is expected to be used. In these centers, the patient who receive Lutathera should receive this guide.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness of additional risk minimization measure is assessed by number of reports, seriousness/severity and outcome of Radiotoxicity, including occupational exposure and inadvertent exposure over time and presented in the PSUR.

- ***Summary of risk minimization measures***

Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Renal dysfunction	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.4, 4.8 and 4.9 PL sections 2 and 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31Dec2028)
Myelosuppression / cytopenias (immediate hematotoxicity)	**Routine risk minimization measures:** SmPC sections 4.2, 4.4, 4.8 and 4.9 PL sections 2 and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None	**Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)
Myelodysplastic syndrome / acute leukemia (late hematotoxicity)	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)
Hepatotoxicity	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8 PL sections 2 and 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)
Tumor lysis syndrome	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)
Hormone release-induced crises	**Routine risk minimization measures:** SmPC sections 4.4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)
Hypogonadism, sexual dysfunction	**Routine risk minimization measures:** SmPC section 4.6 PL section 2 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)
Drug interaction with somatostatin/somatostatin analogues	**Routine risk minimization measures:** SmPC sections 4.4 and 4.5	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	PL section 2 **Additional risk minimization measures:** None	**Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)
Important potential risks		
Radiotoxicity, including occupational exposure and inadvertent exposure	**Routine risk minimization measures:** SmPC sections 4.4, 4.6, 4.9, 6.6, 11 and 12 PL sections 1, 2 and 3 **Additional risk minimization measures:** Patient guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)
Secondary malignancies (solid tumors)	**Routine risk minimization measures:** SmPC section 4.4 PL section None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)
Embryo-fetal toxicity	**Routine risk minimization measures:** SmPC sections 4.3 and 4.6 PL sections 2 and 3 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)
Missing information		
Radiation exposure during breast feeding	**Routine risk minimization measures:** SmPC section 4.6 PL sections 2 and 3 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)
Exposure in patients with renal impairment	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.4 and 4.8 PL sections 2 and 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Exposure in patients with severe hepatic impairment	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8 PL sections 2 and 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)
Long-term safety data	**Routine risk minimization measures:** SmPC section 4.8 PL section None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study A-LUT-T-E02-402 (SALUS) (Final report submission: 31-Dec-2028)

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.5. Elements for a public summary of the RMP

The elements for a public summary of the RMP do not require revision following the conclusion of the procedure:

3.6. Annexes

The annexes have been updated appropriately.

3.7. Overall conclusion on the RMP

☒The changes to the RMP would be acceptable, provided that all major and other concerns will be resolved.

4. Changes to the Product Information

As a result of this variation procedure, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated and included additions needed due to include the newly applied indication. The Package Leaflet (PL) is

updated accordingly.

4.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

As stated by the Applicant "given that the proposed changes to the Lutathera PL are not significant and were already tested in a previous user consultation of the Lutathera PL a new user consultation is not deemed necessary."

5. Benefit-Risk Balance

5.1. Therapeutic Context

Lutathera® (also known as [177Lu]Lu-DOTA-TATE or 177Lu-DOTA0-Tyr3-octreotate; USAN: lutetium Lu 177 dotatate; INN: lutetium (177Lu) oxodotreotide; hereinafter referred to as Lutathera in this document) is a tumour-targeted radioligand therapy (RLT) approved in 40 countries worldwide for the treatment of somatostatin receptor (SSTR)-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults [PSUR 20-Dec-2021 to 19-Dec-2022].

The purpose of this variation is to assess the submitted evidence for the administration of Lutathera as first-line treatment in patients with newly diagnosed, SSTR-positive, advanced GEP-NET.

This SCE is based on the key efficacy results from the Phase III NETTER-2 study (also known as CAAA601A22301) with data cut-off date of 20-Jul-2023 and includes also data from a second OS interim analysis (data cut-off date: 24-May-2024).

5.1.1. Disease or condition

GEP-NETs are a rare, heterogeneous group of neoplasms that arise from the diffuse endocrine system. The prevalence and incidence of GEP-NETs appears to be rising steadily (Das, Dasari 2021). In Europe, the incidence of GEP-NETs based on the national and regional registries has increased over the last two decades from 2.5/100,000 population (van der Zwan et al 2013) to 3.35 - 6.22/100,000 population (Alwan et al 2020, Genus et al 2019, Grundmann et al 2023, Thiis-Evensen, Cetinkaya 2023, Gudmundsdottir et al 2019). In the USA, the estimated incidence rate of GEP-NETs increased from 1.05 (95% CI: 0.9, 1.21) per 100,000 persons in 1975 to 5.45 (95% CI: 5.31, 5.61) per 100,000 persons in 2015 (Xu et al 2021). Overall, the estimated prevalence of GEP-NETs in the recent studies in the EU, Norway, and USA ranged from 31 per 100,000 individuals to 63 per 100,000 individuals, depending on region and duration of prevalence period (Thiis-Evensen, Cetinkaya 2023, Dasari et al 2017).

The historical classification of GEP-NETs is based on the embryonic origin of the tumour site, i.e., foregut, midgut and hindgut tumours (Cives, Strosberg 2018). However, in a more recent and clinically relevant WHO classification system, distinction is made between well-differentiated NETs (previously designated as carcinoid tumours) and poorly differentiated neuroendocrine carcinomas (Klöppel 2017, WHO 2019). Well-differentiated GEP-NETs express SSTR, specifically subtype 2 (SSTR2), in high abundance and are further differentiated by grades (G1, G2, and G3) with differing Ki67 index (i.e., <3%, 3-20%, and >20%, respectively).

GEP-NET patients with early-stage disease are often asymptomatic or present with poorly defined symptoms and consequently, at the time of confirmed diagnosis, a significant percentage of GEP-NET patients have advanced disease and hepatic metastases.

5.1.2. Available therapies and unmet medical need

Clinical management in patients with advanced GEP-NET typically involves a multi-modal approach including surgery, liver-targeted therapy, radiotherapy and medical treatment with chemotherapy, targeted therapies, peptide receptor radionuclide therapy (PRRT, a commonly used term for RLTs specifically targeting peptide receptors), and somatostatin analogues (SSAs) (Pavel et al 2020, Shah et al 2021).

For newly diagnosed patients with advanced GEP-NETs, only a few approved treatment options exist, and there is no universally accepted standard of care therapy. In addition, approved therapies in the first-line setting have limited application because they are only indicated in specific subsets of GEP-NET patients (octreotide long-acting release (LAR) for midgut tumours or tumours of unknown origin and for symptomatic control of functional GEP-NETs (Sandostatin LAR SmPC 2022); lanreotide for G1 and G2 GEP-NETs with Ki67 <10% (Somatuline Autogel SmPC 2023); and streptozocin in combination with 5-fluorouracil for symptomatic G1 and G2 pancreatic NET) (Zanosar SmPC 2022).

Other approved therapeutic options are limited to the progressive population and use in newly diagnosed patients occurs off-label, following treatment guideline recommendations.

Furthermore, there is limited robust data available for the efficacy of first-line treatments in newly diagnosed patients with high grade GEP-NETs. Clinical data is mainly limited to G1/G2 tumours or comes from small non-randomized studies. For high grade (G3) GEP-NETs, there is a lack of prospective trials evaluating systemic therapy, and there is considerable controversy regarding the choice of first-line therapy and beyond (Sonbol, Halfdanarson 2019, Sorbye et al 2019). Targeted therapy in G3 NET is not well established, while platinum-based chemotherapy has shown efficacy regarding ORR comparable to that in NETTER-2. Considering the substantial heterogeneity in the published studies and uncertainties, an investigator's best choice control arm instead of the questionable octreotide therapy would also have been an option for G2 and G3 GEP-NETs in the Rapporteur's view. However, the MAH clarified

Overall, most of the medicinal products approved for GEP-NET have limited application because they are only approved for use in sub-populations of GEP-NET patients.

There remains a high unmet medical need in G2/G3 GEP-NETs as well as in the first-line treatment for advanced GEP-NET.

5.1.3. Main clinical studies

The ongoing NETTER-2 study is a Phase III, multicenter, stratified, open-label, randomized, comparator-controlled study comparing treatment with Lutathera plus octreotide LAR 30 mg (Lutathera arm) to treatment with high-dose octreotide LAR 60 mg (control arm) (Figure 8).

The study population consisted of subjects with newly diagnosed, SSTR-positive, well-differentiated G2 (Ki67 index ≥ 10% to ≤ 20%) or G3 (Ki67 index > 20% to ≤ 55%), advanced (metastatic or locally advanced, inoperable) GEP-NETs. Overall, approximately 222 subjects were planned to be randomized in a 2:1 ratio to Lutathera arm or control arm. Randomization was stratified by tumour grade (G2 or G3) and tumour origin (pancreatic NET (pNET) or other origin).

The study consists of a screening phase, a treatment phase, an optional cross-over (for subjects in the control arm) or re-treatment phase (for subjects in the Lutathera arm), and a follow-up phase.

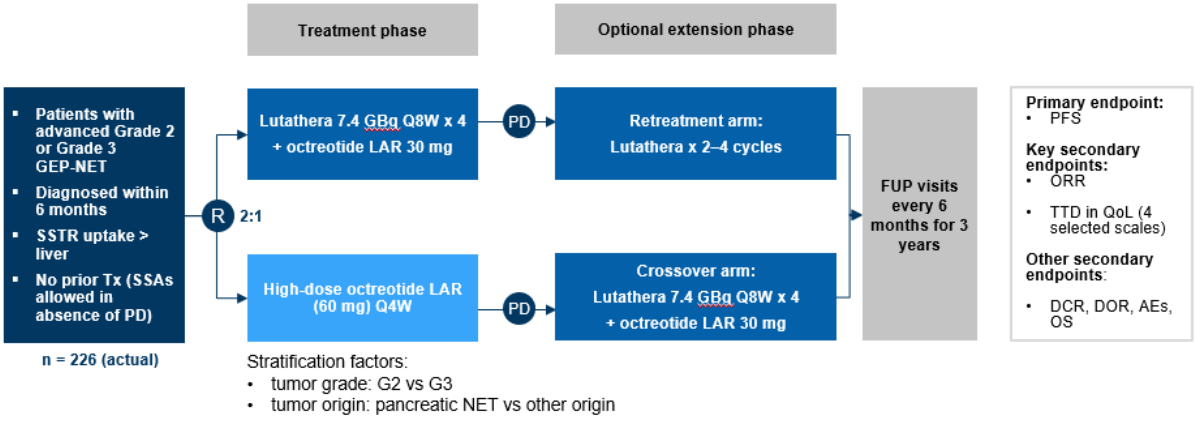
The treatment regimens are as follows:

- Lutathera arm: Lutathera 7.4 GBq/200 mCi × 4 cycles every 8 ± 1 weeks (cumulative dose: 29.6 GBq/800 mCi) plus octreotide long-acting 30 mg every 8 weeks during Lutathera treatment and every 4 weeks after last Lutathera treatment.
- Control arm: high-dose octreotide long-acting 60 mg every 4 weeks

The main purpose of the NETTER-2 study was to determine if treatment in the Lutathera arm prolongs PFS in subjects with newly diagnosed SSTR-positive, G2 and G3 advanced GEP-NET when compared with treatment in the control arm.

The primary efficacy and safety analyses of the study were planned after approximately 99 PFS events (99 centrally confirmed disease progressions or death events) had occurred.

Figure 8. Study design of NETTER-2



GEP-NET: gastroenteropancreatic neuroendocrine tumour; SSTR: somatostatin receptor; SSA: somatostatin analogue; PD: progressive disease; LAR: long-acting release; Q8W: every 8 weeks; Q4W: every 4 weeks; G: grade; GBq: Giga Becquerel; FUP: follow-up period; PFS: progression-free survival; ORR: objective response rate; TTD: time to deterioration; QoL: quality of life; DCR: disease control rate; DOR: duration of response; AE: adverse event; OS: overall survival Source: [NETTER-2-Figure 9-1]

The primary endpoint was PFS centrally assessed by blinded Independent Review Committee (IRC) according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. The key secondary endpoints included ORR as per central review by blinded IRC according to RECIST v1.1, and the time to deterioration (TTD) in the selected scales from the European Organization for Research and Treatment of Cancer (EORTC) as well as Quality of Life Questionnaires (QLQ-C30): Global Health Status, Diarrhea, Fatigue, and Pain.

Other secondary efficacy endpoints included disease control rate (DCR), duration of response (DOR), and overall survival (OS).

The primary endpoint (PFS) and key secondary endpoints (ORR and TTD) were tested in a hierarchical fashion to protect the type I error rate. The order of the hypothesis testing was PFS, then ORR, followed by TTD for Global Health Status, Diarrhea, Fatigue, and Pain. OS is not included in this testing.

5.2. Favourable effects

The study met its primary objective demonstrating statistically significant and clinically meaningful benefit of treatment in the Lutathera arm over control arm on PFS based on central review, with an estimated 72% risk reduction of progression or death (stratified HR 0.276; 95% CI: 0.182,0.418; stratified log-rank p <0.0001). The median PFS was 22.8 months (95% CI: 19.4, NE) in the Lutathera arm vs. 8.5 months (95% CI: 7.7, 13.8) in the control arm.

Multiple supportive and sensitivity analyses demonstrated the observed PFS benefit was robust and consistent across relevant prognostic categories.

- Results of the PFS analysis per Investigator assessment were consistent with an estimated 77% reduction in the risk of progression or death (stratified HR 0.234; 95% CI: 0.158, 0.347).
- The overall concordance rate between PFS by central review and by Investigator assessment (event vs. censored observations) was 85.4% in the Lutathera arm and 80.0% in control arm.
- Homogeneity and consistency of the PFS benefit of Lutathera arm over control arm were evident across all subgroups assessed, including the stratification factors (tumour grade: grade 2 and grade 3, and tumour origin: pNET vs. other origin).

The study met also the key secondary objective for ORR. Lutathera was associated with improved rates of ORR per central review (43%; 95% CI: 35.0, 51.3) vs. control arm (9.3%; 95% CI: 3.8, 18.3) (p= <0.0001) corresponding to an adjusted odds ratio for stratification factors of 7.81 (95%CI: 3.32, 18.40; p-value <0.0001).

Complete response was observed in 8 subjects (5.3%) in the Lutathera arm compared to none in the control arm according to the outcome in the central review.

5.3. Uncertainties and limitations about favourable effects

There is no established positive impact on overall survival (OS) in the NETTER-2 study, which was included as an "other secondary endpoint" not included in the hierarchical testing.

As of the data cut-off date, a total of 70 deaths were recorded (51 (33.8%) in the Lutathera arm and 19 (25.3%) in the control arm. The median follow-up time from the randomization date to date of OS event or censoring was 26.3 months for the Lutathera arm versus 25.6 months for the control arm. The median OS was 43.3 months (95% CI: 37.3, NE) in the Lutathera arm and was not estimable in the control arm. The observed hazard ratio (HR) was 1.25 (95% CI: 0.74, 2.13).

As the clinical interpretation of the hazard ratio is generally not straightforward, additional effect measures need to be considered for B/R evaluation such as difference in proportion of progression-free patients at fixed time points. Using the Restricted Mean Survival Time (RMST) method, there was no notable difference between the study arms in mean survival time restricted to 24 months: 21.3 months (95% CI: 20.5, 22.2) in the Lutathera arm vs. 21.4 months (95% CI: 20.0, 22.8) in the control arm with a p-value of 0.9578.

The hierarchical testing strategy in NETTER 2 to control the type 1 error, does not reflect fully the clinical relevance of the endpoints. Notably, no confirmatory conclusions for overall survival will be possible (whereby it is acknowledged that the possibility to cross over will anyway hamper the interpretation of overall survival). Therefore, it remains uncertain, whether the first line treatment applied will result also to an overall survival benefit as shown for the already approved indication.

Considering that no clear evidence supports the suggestion that high-dose octreotide provides superior disease control relative to standard-dose octreotide, it seems that SSAs alone are inappropriate for

patients with higher grade 2 or 3 tumours with a high tumour burden or symptoms related to tumour growth, especially in pancreatic tumours. This assumption is in line with the finding that about one third of the control arm subjects need to cross over due to disease progression relatively early, which might have contributed to the clear PFS prolongation in the Lutathera arm. Moreover, other treatments are available. Investigator's best choice would have been an appropriate control arm.

Also, in contrast to the approved advanced GEP-NET population investigated in NETTER-1, no significant difference in quality of life was observed between the treatment arms in the TTD for Global health status with a stratified HR (95% CI) of 0.856 (0.570, 1.283) in the NETTER-2 trial. The median TTD times (95% CI) were 13.2 months (8.8, 17.2) and 8.6 months (5.8, 14.0), in the Lutathera and control arm respectively. Similarly, no significant difference was observed between the treatment arms in the TTD for diarrhoea (stratified HR (95% CI); 0.877 (0.555, 1.386)), fatigue (stratified HR (95% CI); 0.998 (0.695, 1.432)) and pain (stratified HR (95% CI); 0.918 (0.623, 1.351)). Although this outcome does not prove any improved QoL from the Lutathera treatment, but may indicate at least a small positive trend, it is acknowledged that at least Lutathera treatment does not significantly deteriorate the subjects QoL, which may be seen as a surrogate for relatively good tolerability of the additional treatment.

More than 50 % of the Ki67 > 20 % tumours included in the trial are located in the pancreas. Since in this population the degree of SSTR positivity appears to be partially significantly lower according literature, the efficacy of high dose 60 mg Octreotid treatment in the control arm may be challenged as ineffective in subjects with pGEP-NETs.

5.4. Unfavourable effects

The overall safety and tolerability profile of Lutathera observed in the pivotal NETTER-2 study was consistent with known safety profile of Lutathera in advanced GEP-NET patients as reported from NETTER-1 and ERASMUS trial. The incidence of AEs (irrespective of causal relationship) was similar between the two arms (Lutathera vs. control arms). Most common all grade and grade ≥3 AEs by PT irrespective of causality, occurring with a greater frequency (≥10% difference for all grades) among subjects in the Lutathera arm vs. control arm include:

- anemia (all grades: 19.7% vs. 6.8% and grade ≥3: 0.7% vs. 1.4%)
- platelet count decreased (all grades: 17.0% vs. 5.5% and grade ≥3: 1.4% vs. 0)
- alopecia (all grades: 15.0% vs. 1.4% and grade ≥3: 0 vs. 0)
- lymphocyte count decreased (all grades: 10.9% vs. 0 and grade ≥3: 5.4% vs. 0)
- platelet count decreased (all grades: 17.0% vs. 5.5% and grade ≥3: 1.4% vs. 0)

Most common all grade and grade ≥3 AEs by PT related to study treatment occurring with a greater frequency (≥10% difference for all grades) among subjects in the Lutathera arm vs. control arm during the randomized treatment period include:

- nausea (all grades: 20.4% vs. 2.7% and grade ≥3: 0.7% vs.0%)
- alopecia (all grades: 13.6% vs. 0% and grade ≥3: 0% vs. 0%)
- anemia (all grades: 13.6% vs. 0% and grade ≥3: 0% vs. 0%)
- platelet count decreased (all grades: 12.9% vs. 0% and grade ≥3: 0% vs. 0%)
- WBC count decreased (all grades: 12.2% vs. 0% and grade ≥3: 2.0% vs. 0%)
- lymphocyte count decreased (all grades: 10.2% vs. 0 and grade ≥3: 4.8% vs. 0%)

Incidence of SAEs was 20.4% and 20.5% in the Lutathera arm and control arm, respectively. SAEs considered to be related to any study treatment by the Investigator were reported more frequently in the Lutathera arm vs. the control arm (5.4% vs. 1.4%). Small intestinal obstruction was the only suspected SAE reported in >1% of subjects (2 subjects; 1.4%).

The incidence of deaths during the study was similar in both Lutathera arm (21.8%) and the control arms (19.2%). Most of these deaths occurred due to the disease under study (20.4% vs. 17.8%). Six on-treatment deaths were reported and was more frequent in the control arm (4 subjects; 5.5%) compared to 2 subjects (1.4%) in the Lutathera arm.

AEs requiring dose reduction of any study treatment in the randomized treatment period were similarly reported in Lutathera (2%) and control (1.4%) arms.

Similar rate of AEs leading to dose interruption was reported in both Lutathera and control arms (15.6% and 15.1%).

In the Lutathera arm, AESI related to immediate hematotoxicity were observed in 20.4% subjects (grade ≥3 13.6%) including grade ≥3 lymphocyte count decreased (8 subjects; 5.4%), grade ≥3 lymphopenia (4 subjects; 2.7%), grade ≥3 decreased neutrophil count (3 subjects; 2.0%), grade ≥3 decreased white blood cell count (3 subjects; 2.0%), grade ≥3 decreased platelet count (2 subjects; 1.4%), grade ≥2 thrombocytopenia (5 subjects; 3.4%), grade ≥3 anemia (1 subject; 0.7%). One subject in the control arm had grade 4 anemia.

Nephrotoxicity was observed in 8.8% subjects in Lutathera arm compared to 5.5% in the control arm.

Secondary haematological malignancy (myelodysplastic syndrome) was observed in 1 subject in the Lutathera arm at the time of primary analysis DCO. Cumulatively, there were 4 events of secondary hematological malignancies (3 MDS cases among them one progressed to AML) in 3 subjects (2%) during the NETTER-2 study after a median follow-up time of 26.3 months in the Lutathera arm.

AESIs of cardiovascular and electrolyte disorders were reported less frequently in the Lutathera arm (7.5%) compared to the control arm (13.7%).

Haematological abnormalities (almost all types) were more frequent on Lutathera arm, due to mechanism of action of Lutathera. No differences were observed between grade ⩾3 worsening haematological abnormalities from baseline in both the treatment arms, except for incidences of decreased lymphocytes (38.1% vs. 2.7%).No clinically meaningful differences in the occurrence of biochemical abnormalities were observed between the Lutathera and control arms.

No major shifts from baseline were observed in the Karnofsky scale scores when compared to baseline in both treatment arms.

Lower incidences of nausea (27.2%) and vomiting (14.3%) were reported in the study than in NETTER-1.

Analysis of the AE incidences across subgroups of age, gender, race, and values of baseline creatinine clearance and between arms for each subgroup showed similar trends to those observed in the overall study population.

Based on the limited information at the time of data cutoff, AE profile observed in the crossover and the retreatment period appear less informative, but was similar to that observed in the randomized treatment period.

5.5. Uncertainties and limitations about unfavourable effects

It is not excluded that early aggressive treatment in well-differentiated tumours like the applied GEP-NETs may increase the risk for developing secondary mutations which decrease efficacy of other treatment options in later treatment lines.

For Lutathera as a therapeutic radiopharmaceutical, safety data collection should not be restricted to the current prognosis but should represent patients with improved prognosis and extended life expectancy.

This applies in particular for the current application of extension of indication. The Applicant should discuss and propose details for the performance of a long-term safety follow-up trial (PASS, Cat. 3) in adult patients with newly diagnosed unresectable or metastatic, well-differentiated (G2 and G3), somatostatin receptor-positive GEP-NETs.

5.6. Effects Table

Table 27. Effects Table for Lutathera in for the treatment of newly diagnosed, unresectable or metastatic, well-differentiated (G2 and G3), SSTR-positive GEP-NETs in adults. (20. July 2023)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Progression free survival (RECIST1.1)	months	22.8 months	8.5 months	Treatment arm includes also crossover from control to treatment allow, stratified log-rank p-value <0.0001	stratified HR 0.276; 95% CI: 0.182, 0.418; stratified log-rank p-value <0.0001)
ORR	Objective Response Rate	%	43% (95% CI: 35.0,51.3)	9.3% (95%CI: 3.8, 18.3)	Crossover allowed p-value <0.0001	corresponding to an adjusted odds ratio for stratification factors of 7.81 (95%CI: 3.32, 18.40; p-value <0.0001)
TTD	Time to deterior-ation QoL	N (%)	79 (52.3)	33 (44.0)	Not statistical significant (p-value: 0.2222)	Log-rank test (one-sided) Stratified p-value: 0.2222
DCR	Disease control rate by central review	%	89.4%, (95% CI: 83.4, 93.8)	66.7%, (95% CI: 54.8, 77.1)	Overlap of CIs	
OS	Overall survival (Deaths)		51/151 (33.8)	19/75 (25.3)	immature at the time of data cut-off	
CR	Complete Response		8 (5.3)	0		
PR	Partial Response		57 (37.7)	7 (9.3)		
SD	Stable Disease		72 (47.7)	42 (56.0)		
Unfavourable Effects						

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
TEAES	All Grade (Grade⩾3	%	92.5(35.4	94.5(27.4)	As reported	CSR/SCS
SAEs		%	20.4	20.5	As reported	CSR/SCS
Deaths	During treatment phase	N(%)	2 (1.4)	4(5.5)	As reported	CSR/SCS
Discontinuation	All Grade (Grade≥3	%	2.0 (0.7)	9.0 (2.7)	As reported	CSR/SCS
Anaemia	All Grade (Grade≥3)	%	19.7(0.7)	6.8 (1.4)	As reported	CSR/SCS
Fatigue	All Grade (Grade≥3)	%	19.7(0)	17.8 (0)	As reported	CSR/SCS
Asthenia	All Grade (Grade≥3)	%	19.0(0.7)	12-3 (0)	As reported	CSR/SCS
Thrombocytopenia	All Grade (Grade≥3)	%	4 (5.5)	5.5 (0)	As reported	CSR/SCS
Alopecia	All Grade (Grade≥3)	%	1 (1.4)	1.4 (0)	As reported	CSR/SCS
Lympho-penia	All Grade (Grade≥3)	%	6.1 (2.7)	0 (0)	As reported	CSR/SCS
Nephro-toxicity	All Grade (Grade≥3)	%	8.8%	5.5%	As reported	CSR/SCS

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

A clinically meaningful and statistically significant benefit in PFS based on the central radiology review was observed with a median PFS of 22.8 months in the Lutathera arm vs. 8.5 months in the control arm and HR of 0.276 (95% CI: 0.182,0.418; stratified log-rank p <0.0001) favouring the Lutathera arm versus the control arm was observed in the new indication for the treatment of newly diagnosed, unresectable or metastatic, well-differentiated (G2 and G3), SSTR-positive, GEP-NETs in adults. The effect on PFS was consistent across relevant predefined subgroups and thus robust.

The efficacy outcome regarding the primary endpoint was supported by the key secondary endpoint of ORR, which was statistically superior in the Lutathera arm (43%; 95% CI: 35.0, 51.3) compared to the control arm (9.3%; 95% CI: 3.8, 18.3) and odds ratio for stratification factors of 7.81 (95%CI: 3.32, 18.40; p-value <0.0001). Notably, complete response was observed in 8 subjects (5.3%) in Lutathera arm and none in the control arm.

With respect to the other key secondary endpoint time to deterioration of main symptoms (TTD) and the other secondary endpoints, no statistically significant benefit was reported.

In particular, overall survival (OS) data immature at the time of cutoff-date and not in favour for Lutathera: 51 subjects (33.8%) in the Lutathera arm died compared with 19 subjects (25.3%) in the control arm after a median follow-up time from the randomisation date to date of OS event or censoring of 26.3 months for the Lutathera arm versus 25.6 months for the control arm. While median OS was 43.3 months (95% CI: 37.3, NE) in the Lutathera arm, it was still not estimable in the control arm. Thus, the observed hazard ratio (HR) was 1.25 (95% CI: 0.74, 2.13). The high rate of cross- over (48%) and the early occurrence of this cross-over (at median time of 10 months) has confounded the OS data. Considering that due to the 2:1 randomisation and the crossover of 48% of the control arm

subjects only few subjects remain in the control arm, it appears very likely that reliable OS will remain missing.

The treatment of Lutathera was associated with a safety profile that is generally consistent with the known safety profile of Lutathera. Most of the events were transient and reversible. The concomitant use of 2.5% Lys-Arg amino acid solution led to a lower rate of nausea and vomiting incidences as compared to those reported in the NETTER-1 study, where complex amino acid solutions with higher osmolality were used. Analysis of AESIs of immediate haematotoxicity, secondary haematological malignancies, nephrotoxicity and cardiovascular events showed no change in the characterization of the risks compared to previous results observed in NETTER-1 trial, which led to approval of the already approved.

Overall, Lutathera® treatment appears to be tolerable and manageable in the applied indication. Only some OCs regarding more information on several details as mentioned in the discussion need further clarification with respect to safety. However, it is reminded that late haematotoxicities and secondary haematological malignancies (MDS and AML) are known risks of Lutathera@ as targeted radioligand therapy. There is also a risk for developing secondary mutations which may lead to a decreased efficacy of other treatment options like target therapies or chemotherapy in later treatment lines.

5.7.2. Balance of benefits and risks

While the NETTER-2 study is positive on its primary endpoint PFS, starting aggressive treatment early in selected patients with a high tumour burden comes with potential risks of haematological and renal toxicities, secondary malignancies, secondary mutations and NET grade progression. Therefore, in the absence of an established positive impact on OS, the applicant is requested to justify a positive B/R balance.

5.7.3. Additional considerations on the benefit-risk balance

CHMP agreed to consult the SAG Oncology and ask the following question:

1. Given the lack of an established overall survival (OS) benefit for Lutetium (^{177}Lu) oxodotreotide in the NETTER-2 study, is early initiation of treatment justified in selected patients with a high tumor burden based on its impact on progression-free survival (PFS) and response rates?
2. What is your view of the overall safety profile of Lutetium (^{177}Lu) oxodotreotide?
3. To what extent do PRRT-related toxicities, such as hematological and renal toxicities, secondary malignancies, secondary mutations and NET grade progression, raise a concern in this early setting?

5.8. Conclusions

The overall B/R of Lutathera is currently negative.

5.9. Update of the Product information

As a result of this variation procedure, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated and included additions needed due to include the newly applied indication. The Package Leaflet (PL) is updated accordingly.

Reference is made to the PI with Rapp's comments.

5.9.1. User consultation

In accordance with Articles 59(3) and 61(1) of Directive 2001/83, a consultation with the target patient population regarding the readability of the Package Leaflet (PL) for Lutathera® 370 MBq/mL solution for infusion was conducted as part of the initial Marketing Authorization Application, for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEPNETs) in adults.

It is acknowledged that the results of the user consultation with target patient groups submitted in April 2016, demonstrated that the PL is written in clear and user-friendly language, meeting the criteria for readability as set out in the Guideline on the readability of the labeling and package leaflet of medicinal products for human use (v1, 12 January 2009).

With this type II variation submission a new therapeutic indication for the treatment of newly diagnosed, unresectable or metastatic, well-differentiated (G2 and G3), somatostatin receptor-positive GEP-NETs adult patients. The new information proposed in the PL included in this type II variation maintains the currently approved layout/structure and format. Specifically, the following key information remain the same as for the currently approved PL for Lutathera:

• Section 5 'How Lutathera is stored'

• Section 6 'Contents of the pack and other information'

The proposed changes are limited to the following sections:

• Section 1 'What Lutathera is and what it is used for' includes a revision of the current approved indication in order to reflect the newly proposed indication (i.e., mainly deletion of the statement "and do not respond any more to your current treatment")

• Section 2 'What you need to know before Lutathera is used' includes minor editorial changes to improve the language.

• Section 3 'How Lutathera is used' includes minor editorial changes to improve the language.

• Section 4 'Possible side effects' includes revisions in alignment with proposed changes in Section 4.8 of the EU SmPC. Adverse drug reactions (ADR) in lay language's term are deleted or reorganized based on the updated ADR frequency. Some revisions on the lay language description and/or additional editorial revisions are included to improve the language.

As per the European Commission`s Readability Guideline, "for changes to existing marketing authorisations, the need for user consultation covers in principle situations where significant changes are made to the package leaflet, either through a variation or a procedure according to Article 61(3) of Directive 2001/83/EC". Given that the proposed changes to the Lutathera PL are not significant and were already tested in a previous user consultation of the Lutathera PL a new user consultation is not deemed necessary in the Rapporteur's view.

6. References

Alwan H, La Rosa S, Andreas Kopp P, et al (2020)] Incidence trends of lung and gastroenteropancreatic neuroendocrine neoplasms in Switzerland. Cancer Med; 9(24):9454-61.

[Cives M, Strosberg JR (2018)] Gastroenteropancreatic neuroendocrine tumours. Cancer J Clin; 68(6):471-87.

[Das S, Dasari A (2021)] Epidemiology, Incidence, and Prevalence of Neuroendocrine Neoplasms: Are There Global Differences? Curr Oncol Rep; 23(4):43.

[Dasari A, Shen C, Halperin D, et al (2017)] Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumours in the United States. JAMA Oncol; 3(10):1335-42.

[Eads JR, Halfdanarson TR, Asmis T, et al (2023)] Expert consensus practice recommendations of the North American Neuroendocrine Tumour Society for the management of high grade gastroenteropancreatic and gynecologic neuroendocrine neoplasms. Endocr Relat Cancer; 30(8):e220206.

[Genus TSE, Bouvier C, Wong KF, et al (2019)] Impact of neuroendocrine morphology on cancer outcomes and stage at diagnosis: a UK nationwide cohort study 2013-2015. Br J Cancer; 121(11):966-972.

[Grundmann N, Voigtländer S, Hakimhashemi A, et al (2023)] Site-specific trends in gastroenteropancreatic neuroendocrine neoplasms in Bavaria, Germany. Cancer Med; 12(19):19949-58.

[Gudmundsdottir H, Möller PH, Jonasson JG, et al (2019)] Gastroenteropancreatic neuroendocrine tumours in Iceland: a population-based study. Scand J Gastroenterol; 54(1):69- 75.

[Klöppel G (2017)] Neuroendocrine neoplasms: dichotomy, origin and classifications. Visc Med; 33(5):324-30.

[Lutathera SmPC (2024)] Lutathera 370 MBq/ml solution for infusion. Summary of product characteristics. Advanced Accelerator Applications, Rueil-Malmaison, France. Revised May 2024.

[Lutathera USPI (2024)] Lutathera (lutetium Lu 177 dotatate) injection. US Prescribing Information. Advanced Accelerator Applications USA, Inc, NJ. Revised April 2024.

[Pavel M, Oberg K, Falconi M, et al (2020)] ESMO Guidelines Committee. Gastroenteropancreatic neuroendocrine neoplasms: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol; 31(7):844-60.

[Sandostatin LAR SmPC (2022)] Sandostatin LAR 10 mg powder and solvent for suspension for injection. Summary of product characteristics. Novartis Ireland Limited, Dublin, Ireland. Revised July 2022.

[Shah MH, Goldner WS, Benson AB, et al (2021)] Neuroendocrine and adrenal tumours, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw; 19(7):839- 68.

[Somatuline Autogel SmPC (2023)] Somatuline Autogel 60 mg, solution for injection in a prefilled syringe. Summary of product characteristics. Ipsen Pharmaceuticals Limited, Dublin, Ireland. Revised August 2023.

[Sonbol MB, Halfdanarson TR (2019)] Management of well-differentiated high-grade (G3) neuroendocrine tumours. Curr Treat Options Oncol; 20(9):74.

[Sorbye H, Baudin E, Borbath I, et al (2019)] Unmet needs in high-grade gastroenteropancreatic neuroendocrine neoplasms (WHO G3). Neuroendocrinology; 108(1):54-62.

[Strosberg J, El-Haddad G, Wolin E, et al (2017)] NETTER-1 Trial Investigators. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumours. N Engl J Med; 376(2):125-35.

[Thiis-Evensen E, Boyar Cetinkaya R (2023)] Incidence and prevalence of neuroendocrine neoplasms in Norway 1993-2021. J Neuroendocrinol; 35(4):e13264.

WHO (2019) World Health Organization Classification of tumours, digestive system tumours, Fifth Edition, Volume 1. ISBN:978-92-832-4499-8. (available upon request)

[van der Zwan JM, Trama A, Otter R, et al (2013)] Rare neuroendocrine tumours: results of the surveillance of rare cancers in Europe project. Eur J Cancer; 49(11):2565-78.

[Xu Z, Wang L, Dai S, et al (2021)] Epidemiologic trends of and factors associated with overall survival for patients with gastroenteropancreatic neuroendocrine tumours in the United States. JAMA Netw Open; 4(9):e2124750.

[Zanosar SmPC (2022)] Zanosar 1 g, powder for concentrate for solution for infusion. Summary of product characteristics. Esteve Pharmaceuticals S.A.S., Montrouge, France. Revised October 2022.