Amsterdam, 21 May 2026
EMA/134444/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Deqtynet

International non-proprietary name: copper (64Cu) oxodotreotide

Procedure No. EMEA/H/C/006608/0000

Note

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

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List of abbreviations

AE	Adverse Event
ATSM	Diacetyl-bis (N4-methylthiosemicarbazone)
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical study report
CT	Computed tomography
Cu	Copper
DOTA	1,4,7,10-tetraazacyclodecane- 1,4,7,10-tetraa
DOTATATE	DOTA-Tyr3-octreotate
DOTANOC	DOTA-1-Nal-3-octreotide
DOTATOC	DOTA-Tyr3-octreotide
DTPA	Diethylenetriaminepentaacetic acid
EE	Efficacy evaluable
EMA	European Medicines Agency
EOS	End of Synthesis
FDG	Fluorodeoxyglucose
FN	False negative
FNR	False negative rate
FP	False positive
FPR	False positive rate
Ga	Gallium
GCP	Good Clinical Practice
GEP	Gastro-entero-pancreatic
GFR	Glomerular filtration rate
GI	Gastrointestinal
HEK	Human embryonic kidney
IGF	Insulin-like growth factor
In	Indium
ITD	Intent to diagnose
IV	Intravenous
LCNEC	Large cell neuroendocrine carcinoma
Lu	Lutetium
MBq	Megabecquerel
mCi	Millicurie
ME	Market Exclusivity
mGy	Milligray
MPC	Murine podocyte cell
MR	Magnetic resonance
MRI	Magnetic resonance imaging
mSv	Millisievert
NEC	Neuroendocrine carcinoma
NEN	Neuroendocrine neoplasm
NET	Neuroendocrine tumour
NDA	New drug application
NOAEL	No observable adverse effect level
NPV	Negative predictive value
OC	Octreotide
OME	Orphan Market Exclusivity
PD	Pharmacodynamics
PET	Positron emission tomography
PFA	Progression free survival
PK	Pharmacokinetic

PPV	Positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
PRRT	Peptide receptor radiotherapy
RMP	Risk management plan
SCLC	Small cell lung cancer
SD	Standard deviation
SE	Standard error
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SOT	Standard of truth
SPECT	Single photon emission computed tomography
SRI	Somatostatin receptor imaging
SRIF	Somatotropin Release Inhibiting Factor
SRS	Somatostatin receptor scintigraphy
SST	Somatostatin
SSTR	Somatostatin receptor
SUV	Standardised uptake value
TEAE	Treatment emergent AE
TN	True negative
TP	True positive
TSH	Thyroid-stimulating hormone
US	Ultrasonographic
USA	United States of America
Y	Year

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	DEQTYNET
Active substance	Copper (^{64}Cu) oxodotreotide
INN or common name	Copper (^{64}Cu) oxodotreotide
Applicant	Cis Bio International Saclay 306 Route Nationale P. O. Box 32 91192 Gif Sur Yvette Cedex FRANCE
EMA product number	EMEA/H/C/006608
ATC code and pharmacotherapeutic group	V09IX15
Pharmaceutical form(s) and strength (s)	Solution for injection 37 MBq/ml
Packaging	vial (glass)
Package size(s)	1 vial
Route of administration	Intravenous use
Device or diagnostic	Not applicable
Orphan designation	Yes
Orphan indication status confirmed	Yes
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	N/A
Legal basis	Article 8.3 of Directive 2001/83/EC
Final indication	This medicinal product is for diagnostic use only. DEQTYNET is indicated for positron emission tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated neuroendocrine tumours (NETs) excluding neuroblastomas.
New active substance status	Applied for

1.2. Protocol assistance

The applicant did not seek Protocol assistance from the CHMP.

1.3. Eligibility to the centralised procedure

The applicant Cis Bio International submitted on 28 February 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for DEQTYNET (Copper (^{64}Cu) oxodotreotide), through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the CHMP on 30 May 2024.

The applicant applied for the following indication: "…in adult patients for positron emission tomography (PET) for the localization of somatostatin receptor positive neuroendocrine neoplasms (excluding neuroblastomas)".

1.4. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies and bibliographic literature substituting/supporting certain test(s) or study(ies).

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision(s) P/0301/2024 on the granting of a (product-specific) waiver for "diagnosis of neuroendocrine tumours (excluding neuroblastoma)".

1.6. Information on orphan market exclusivity

DEQTYNET was designated as an orphan medicinal product EU/3/22/2727 on 09/12/2022 in the following condition: Diagnosis of neuroendocrine neoplasms.

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure: SomaKit TOC.

1.6.2. Derogation(s) from market exclusivity applicable to similar orphan products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application contained a report addressing the derogations laid down in Article 8(3) of the Regulation (EC) No 141/2000, in particular based on the following claims:

- That the holder of the marketing authorisation for the original orphan medicinal product (SomaKit TOC) is unable to supply sufficient quantities of the medicinal product (Article 8(3)(b) of the Regulation (EC) No. 141/2000) and
- That the applicant can establish in the application that the medicinal product, although similar to the orphan medicinal product already authorised (SomaKit TOC), is safer, more effective or

otherwise clinically superior (Article 8(3)(c) of Regulation (EC) No 141/2000).

1.7. Applicant's request(s) for consideration

1.7.1. New active substance status

The applicant requested the radiopharmaceutical substance Copper (^{64}Cu) dotatate to be considered as a new active substance as it is a constituent not previously authorised in a medicinal product in the European Union.

1.7.1.1. CHMP recommendation on new active substance status

Based on the review of available data, it is considered that this radiopharmaceutical substance, is a new active substance as it is a constituent of a medicinal product not previously authorised within the European Union.

1.8. Patient experience data

Table 1. Patient experience data relevant to the application

Patient experience data submitted with this application				***Section where discussed (if applicable)***
☐	Patient experience data submitted by the applicant:			
	☐	Clinical outcome assessments (COAs) such as		
		☐	Patient-reported outcomes (PRO)	
		☐	Other	
	☐	Patient preference studies		
	☐	Observational studies/RWD designed to capture patient experience data		
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)		
	☐	Other (please specify)		
☒	Other patient experience data not submitted by the applicant but considered in this evaluation:			
	☒	Input informed from participation in meetings or public hearings with patient stakeholders		A patient representative was invited to the Oral explanations that were held during the February and April CHMP plenaries.
	☐	CHMP early dialogue with patient organisations		
	☐	Third party interventions from patients and patient groups		
	☐	Other (e.g. medical literature, summaries/analysis from patient engagement activities - please specify)		

1.9. Steps taken for the assessment of the product

The rapporteur and Co-rapporteur appointed by the CHMP were:

CHMP Rapporteur:	Daniela Philadelphy
CHMP Co-rapporteur:	Nicolas Beix

The application was received by the EMA on	28 February 2025
The procedure started on	27 March 2025
The CHMP rapporteur's first assessment report was received on	16 June 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	18 June 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	30 June 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	24 July 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	08 October 2025
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	18 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	11 December 2025
The applicant submitted the responses to the CHMP list of outstanding issues on	23 January 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	12 February 2026
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	24 February 2026
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	26 February 2026
The applicant submitted the responses to the CHMP list of outstanding issues on	20 March 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	08 April 2026
SAG experts were convened to address questions raised by the CHMP on the limitations of the pivotal trial. The CHMP considered the views of the SAG as presented in the minutes of this meeting.	14 April 2026
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	21 April 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Deqtynet on	21 May 2026
The CHMP adopted a report on similarity of SomaKit TOC on (see appendix on similarity)	21 May 2026

The CHMP adopted a report on derogations applicable to similar orphan products for SomaKit TOC (see appendix on derogations)	21 May 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see appendix on NAS)	21 May 2026

1.10. CHMP outcome

1.10.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this report.

1.10.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.10.2.1. Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Deqtynet is similar to SomaKit TOC within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. See the appendix on similarity.

1.10.2.2. Derogation(s) from market exclusivity applicable to similar orphan products

The CHMP by consensus is of the opinion that pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000 the following derogations laid down in Article 8(3) of Regulation (EC) No 141/2000 do not apply:

- the holder of the marketing authorisation for SomaKit TOC is unable to supply sufficient quantities of the medicinal product and/or
- the applicant could establish in the application that the medicinal product, although similar to SomaKit TOC, is safer, more effective or otherwise clinically superior (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) for the same therapeutic indication (see appendix on derogations).

See the appendix on derogation(s) from market exclusivity applicable to similar orphan products.

1.10.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Deqtynet for PET imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated neuroendocrine tumours (NETs), excluding neuroblastomas, is favourable. However, the CHMP considers Deqtynet to be similar to SomaKit TOC, for the same therapeutic indication, and considers that none of the derogations regarding orphan market exclusivity apply. Therefore, the CHMP recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product.

Furthermore, following the review of the available data in the context of the applicant's claim of new

active substance status, the CHMP position at the time of this report is reflected in appendix 4.

1.10.3.1. Divergent position(s)

Divergent position(s) to the majority recommendation on benefit/risk is appended to this report.

2. Introduction

2.1. Therapeutic context

Neuroendocrine neoplasms (NENs) are a genetically diverse spectrum of solid tumours arising from the secretory cells of the neuroendocrine system that produce peptides causing characteristic hormonal syndromes. NENs can be clinically symptomatic (i.e., 'functioning'), or silent, (i.e., 'nonfunctioning') (Öberg 2011). In general, all NENs are considered malignant, although their growth rate and overall aggressiveness vary significantly. Only paragangliomas are considered benign according to the ICD-10 classification (D3A Benign neuroendocrine tumours).

Epithelial well-differentiated neoplasms, composed of tumour cells that faithfully retain the morphological and molecular features of normal neuroendocrine cells, are defined as **neuroendocrine tumors (NETs)**, a non-committal definition implying a potential for metastasis; proliferation-based grading systems in three tiers (G1, G2, and G3) are proposed for prognostic stratification and have proven effective and reliable in the respiratory and digestive systems.

Epithelial poorly differentiated neoplasms, composed of cells with severe cellular atypia and severely deranged molecular/genetic profiles but broadly retaining neuroendocrine markers, are defined as **neuroendocrine carcinomas (NECs)**. NECs are by default high grade and are subclassified as small or large cell types (SCNEC, LCNEC). NECs are also rare compared to NETs (Rindi et al., 2022).

NENs occur mostly in the gastrointestinal tract and this group of tumours is referred to as gastro-entero-pancreatic NETs (GEP-NETs). NETs can, however, also occur in other tissues, such as thymus, lung, and other uncommon sites such as ovaries, heart and prostate. Regardless of their primary site, NENs share histological, immunohistochemical and ultrastructural features (Raut et al., 2006; Ramage et al., 2005).

Most well-differentiated NENs express somatostatin receptors (SSTR) on their cell surface, which forms the basis for SSTR imaging and therapy. Somatostatin receptor PET/CT and PET/MRI have become fundamental tools in detecting and stratifying endocrine tumour differentiation (Hope 2017, Pavel 2020).

2.2. Aspects of development

The Clinical Development Program for DEQTYNET includes the following three studies:

- RMX-17-22: Phase 1 open-label, dose-ranging study conducted in patients with NETs
- NETMedix Denmark Study (Retrospective Analysis): Phase 2, open-label, comparative study for the detection of SSTR expressing NETs
- RMX-18-22: Phase 3, open-label, single-arm, single-centre study for the detection of SSTR expressing NETs

2.3. Description of the product

The product consists of a somatostatin receptor (SSTR)-targeting peptide complex (i.e. dotatate) that is radiolabelled with the isotope Copper-64 (^{64}Cu). ^{64}Cu-dotatate binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSTR2). It binds to cells that express somatostatin receptors including malignant neuroendocrine cells, which overexpress SSTR2 receptors. Copper (^{64}Cu) is a positron (β+) emitting radionuclide with an emission yield that allows PET imaging.

^{64}Cu-dotatate has been approved in the US since 2020 under the name Detectnet. The approved indication is "for use with positron emission tomography (PET) for localization of somatostatin positive neuroendocrine tumors (NETs) in adult patients."

The initially proposed indication in the current application was "in adult patients for positron emission tomography (PET) for the localization of somatostatin receptor positive neuroendocrine neoplasms (excluding neuroblastomas)"

The recommended activity to be administered was 148 MBq by a single intravenous injection.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection required.

2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection required.

2.4.3. Good clinical practice (GCP) inspection(s)

No inspection required.

3. Quality aspects

3.1. Introduction

The finished product is presented as a solution for injection containing 37 MBq/ml of Copper ^{64}Cu dotatate as active substance at the date and time of calibration.

Other ingredients are: sodium acetate trihydrate (E262), gentisic acid, sodium ascorbate (E301), and water for injections.

The product is available in a type I glass vial, closed with a chlorobutyl stopper and an aluminium seal. This is placed into a lead container.

3.2. Active substance

The active substance is Copper (^{64}Cu) dotatate.

It is synthetised using a chemical precursor, dotatate as a TFA (trifluoroacetic acid) salt, which is

radiolabelled with the radionuclide ^{64}Cu.

The information related to the active substance is presented as described below:

Radioactive chemical precursor: Copper (^{64}Cu) chloride is described in a module 3.2.S.

Non-radioactive chemical precursor: Dotatate (as TFA salt), is described in an ASMF and information related to the applicant's part is provided in a module 3.2.S.

Radiolabelled active substance: Copper (^{64}Cu) dotatate is described in a separate module 3.2.S. Due to its radioactive nature the active substance is not isolated. The synthesis of the active substance and its formulation into the finished product are part of an automated continuous process which does not allow isolation and testing of the pure active substance.

Thus, the active substance section in this report includes three different sections.

3.2.1. Radioactive chemical precursor [Copper (^{64}Cu) chloride]

3.2.1.1. General information

The chemical name of the radioactive chemical precursor is Copper (^{64}Cu) chloride. It has the molecular formula $^{64}CuCl_2$, a molecular mass of 134.83 and the following structure:

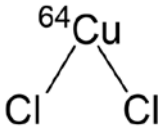


Figure 1: Structure of Copper (^{64}Cu) chloride

The precursor is a salt of a chemical element and is characterised through the use of gamma spectroscopy to confirm the radionuclide identity and thus elemental identity. The oxidation state is inferred from the behaviour of the salt and the available knowledge with respect to non-radioactive copper chloride solutions.

Copper (^{64}Cu) chloride is a radionuclide precursor solution. The radionuclide ^{64}Cu has a half-life of 12.7 hours. The decay scheme for ^{64}Cu has been provided. It decays to stable ^{64}Ni by β+emission or by electronic capture. It also decays to stable ^{64}Zn by β- emission.

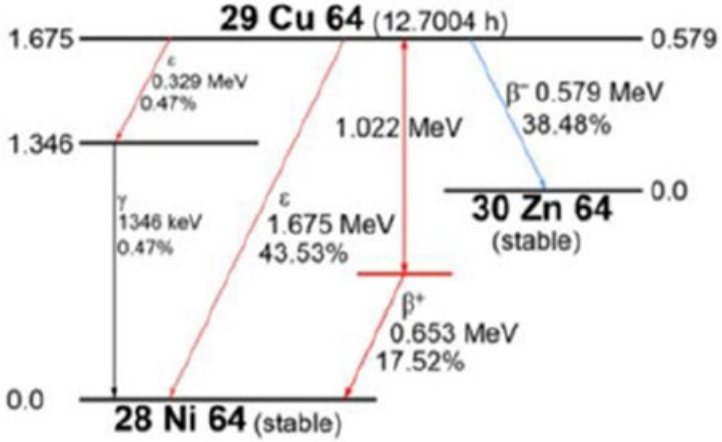


Figure 2: Simplified Decay Scheme of Copper 64

The general information on the radioactive precursor Copper (^{64}Cu) chloride is considered sufficient.

3.2.1.2. Manufacture, characterisation, and process controls

Sufficient information has been provided regarding the GMP standards of the manufacturing site.

Copper (^{64}Cu) chloride is manufactured in four main steps using well defined starting materials with acceptable specifications.

Copper (^{64}Cu) chloride is produced by a nuclear reaction, meaning that the target is bombarded with protons, with emission of neutrons, producing the radionuclide ^{64}Cu.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the precursor and its impurities are in accordance with the EU guideline on radiopharmaceuticals.

Potential and actual impurities were well discussed with regards to their origin and characterised. The potential formation and fate of various radionuclide impurities has been adequately described and is acceptable.

The commercial manufacturing process for the radioactive precursor was developed in parallel with the clinical development program. The process has not changed; the development was conducted at one facility and was then transferred to the proposed commercial manufacturer. The manufacturing process at the two sites is identical, except for the certain changes made to the cyclotron operating parameters. The differences in parameters are acceptable, and the quality of the precursor is considered to be equivalent.

The radioactive precursor is packaged in 15 ml sterile pyrogen-free vials made of Type I glass and topped with chlorobutyl rubber stoppers and an aluminium crimp seal. The materials are generally known to be resistant to radiolysis and have been used with other commercially available radiopharmaceutical products and radionuclides.

3.2.1.3. Specification

The specification for the radioactive precursor includes tests for appearance (visual), radionuclidic identification (gamma spectrometry), radionuclidic purity (gamma spectrometry), specific radioactivity (ICP-OES), radioactive concentration (gamma spectrometry) and elemental impurities (ICP-OES).

The specification for copper (^{64}Cu) chloride is appropriate for a radioactive precursor, and relevant parameters have been specified with appropriate acceptance criteria defined.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis data for three commercial batches of copper (^{64}Cu) chloride have been provided. The results are within the specifications and consistent from batch to batch.

3.2.1.4. Stability

Copper (^{64}Cu) chloride is not stored due to the relatively short half-life of ^{64}Cu. The radionuclidic solution is used the same day as the production day.

3.2.2. Non-radioactive chemical precursor [Dotatate]

3.2.2.1. General information

The chemical name of the non-radioactive chemical precursor is 2,2',2''-(10-(2-((*R*)-1-((4*R*,7*S*,10*S*,13*R*,16*S*,19*R*)-13-((1*H* indol-3-yl)methyl)-10-(4-aminobutyl)-4-((1*S*,2*R*)-1-carboxy-2 hydroxypropylcarbamoyl)-16-(4-hydroxybenzyl)-7-((*R*)-1 hydroxyethyl)-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17 pentaazacycloicosan-9-ylamino)-1-oxo-3-phenylpropan-2 ylamino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7 triyl)triacetic acid. It is often referred to as dotatate or oxodotreotide. It is present as the TFA salt and has the molecular formula $C_{65}H_{90}N_{14}O_{19}S_2.C_2HF_3O_2$. It has a molecular mass of 1,435.6 and the following structure:

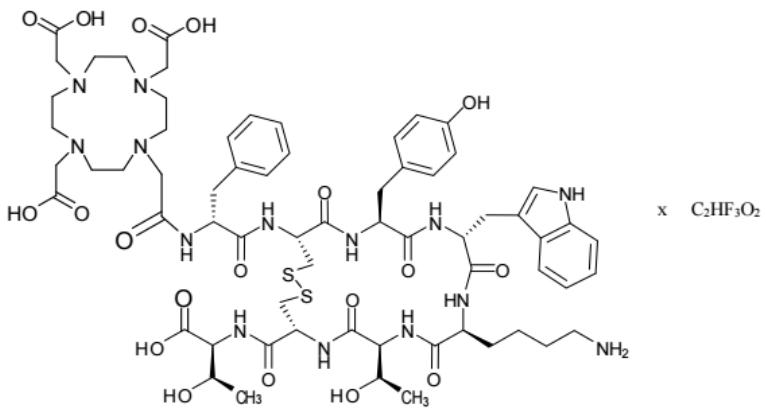


Figure 3: Structure of dotatate

Dotatate is a cyclic octapeptide with a covalently bound chelator. The molecule is cyclised through a disulfide bridge between the SH groups of the cysteines.

The structure was confirmed by performing the following tests: NMR, FTIR, tandem mass spectrometry analysis (MS-MS sequencing), MALDI-TOF mass spectrometry, amino acid analysis, determination of the enantiomeric purity of amino acids, determination of specific optical rotation of the peptide, and ion/gas chromatography for counter ion determination. The cyclisation/oxidation process and the resulting cyclic product can be verified by a shift in the retention time between the linear and cyclic form (RP-HPLC), mass reduction in the cyclic peptide (mass spectrometry) and iodoacetamide labelling of linear dotatate.

Dotatate is a white to off white powder freely soluble in water. It is not hygroscopic.

The precursor exhibits stereoisomerism due to the presence of ten chiral centres. Enantiomeric purity is controlled routinely by GC-MS (Ph. Eur.) in the specifications. Polymorphism is not considered relevant since it is dissolved prior to incorporation into the finished product.

3.2.2.2. Manufacture, characterisation, and process controls

Detailed information on the manufacture of the non-radioactive precursor has been provided in the

restricted part of the ASMF and it was considered satisfactory.

Sufficient information has been provided regarding the GMP standards of the site.

The non-radioactive precursor is manufactured in six main steps using well defined starting materials with acceptable specifications.

The packaging materials comply with relevant and Ph. Eur. requirements and satisfactory specifications have been presented.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the non-radioactive precursor and its impurities is acceptable. Potential and actual impurities were well discussed with regards to their origin and characterised.

3.2.2.3. Specification

The non-radioactive chemical precursor specification includes tests for appearance (visual), identification (MS-MS sequencing, MS, IR and amino acid analysis by GC), enantiomeric purity (GC-MS), peptide content by amino acid analysis (GC), net peptide content (GC), assay (RP-HPLC), purity (RP-HPLC), impurities (RP-HPLC), residual solvents (GC), counter ion content (ion chromatography, GC), water content (GC), bacterial endotoxins (Ph. Eur.), and microbial contamination (Ph. Eur.).

The proposed specification is acceptable; it has been set in accordance with the principles of the Ph. Eur. general monograph for chemical precursors for radiopharmaceutical preparations. The proposed limits are in line with the compendial requirements.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards for assay and impurities testing has been presented.

Batch analysis data from 18 commercial batches of the precursor were provided. The results are within the specifications and consistent from batch to batch.

3.2.2.4. Stability

Stability data from 12 commercial scale batches of the bulk precursor packaged in PETG bottles stored for up 36 months under long term conditions (-20 °C ± 5 °C) were provided. Data from 3 commercial scale batches of the aliquoted precursor packaged in borosilicate glass vials stored for up to 24 months under long term conditions were also provided. In addition, considerable supportive stability data was provided including from a larger glass vial size stored for up to 60 months under the same long term conditions. This provided data is considered representative of the results for the proposed glass vials considering the same packaging materials and consistent stability results provided.

Accelerated stability studies were conducted for 3 commercial scale batches of the proposed aliquots stored for 24 months at 5 °C ± 3 °C. A temperature excursion study (25 °C ± 2 °C / 60 % RH ± 5 % RH) was also conducted for 12 months on one commercial scale batch, and a stress temperature study (40 °C ± 2 °C / 75 % RH ± 5 % RH) was conducted for 1 month.

The following parameters were tested: appearance, identification, counter ion content, water content, net peptide content, peptide purity, impurities, bacterial endotoxins, and microbial contamination.

Under long term & accelerated conditions, no significant changes or trends were noted. In the temperature excursion study, a decrease in peptide purity was noted at the later time-points however

this parameter remained within specification. In the stress temperature study, it was similarly noted that peptide purity began to decrease but remained within specification for the duration of the study.

Further stress testing studies using acidic, basic, oxidising and oxidising/basic conditions were performed on one batch. Results of the study showed that the chemical precursor remained stable in solution under strong acidic conditions but is unstable under all other investigated conditions.

Photostability testing following the ICH guideline Q1B was performed on one batch. Based on the results of the study, the peptide purity of the chemical precursor decreased after exposure to light indicating that it is photolabile.

The stability results indicate that the precursor stored in PETG bottles or bulk aliquots is sufficiently stable. The stability results justify the proposed retest period of 36 months at -20 °C ± 5 °C in PETG bottles protected from light, and a retest period of 60 months at -20 °C ± 5 °C for the proposed aliquots stored protected from light.

3.2.3. Active substance – Copper (^{64}Cu) dotatate

3.2.3.1. General information

The chemical name of copper (^{64}Cu) dotatate is 2-[4-[2-[[(2*R*)-1-[[(4*R*,7*S*,10*S*,13*R*,16*S*,19*R*)-10-(4-aminobutyl)-4-[[(1*S*,2*R*)-1-carboxy-2-hydroxypropyl]carbamoyl]-7-[(1*R*)-1-hydroxyethyl]-16-[(4-hydroxyphenyl)methyl]-13-(1H-indol-3-ylmethyl)-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentazacycloicos-19-yl]amino]-1-oxo-3-phenylpropan-2-yl]amino]-2-oxoethyl]-10-(carboxylatomethyl)-7-(carboxymethyl)-1,4,7,10-tetrazacyclododec-1-yl]acetate;copper 64. It has the molecular formula $C_{65}H_{88}CuN_{14}O_{19}S_2$ and a relative molecular mass of 1497.5. The structure is as follows:

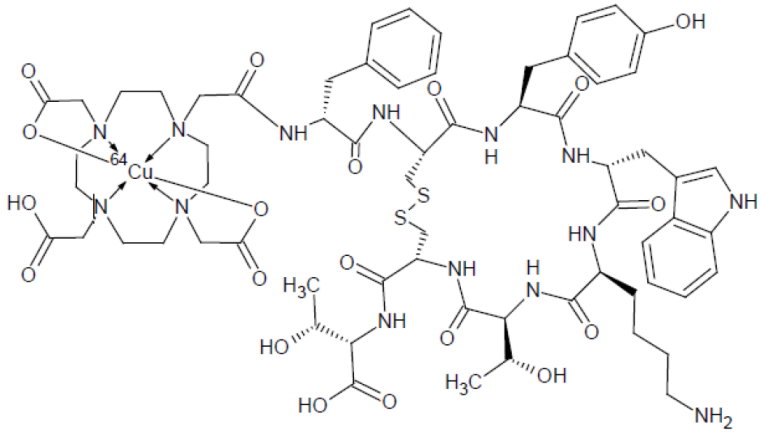


Figure 4: Structure of Copper (^{64}Cu) dotatate

The structure of the active substance has been elucidated by HPLC & LC-MS analysis. Comparisons were also performed analysing the active substance with non-radioactive copper bound to dotatate.

The radioactive active substance is produced as an aqueous concentrated bulk solution. Due to its radioactive nature, the active substance is not isolated. The synthesis of the active substance and its formulation into the finished product are part of an automated continuous process which does not allow isolation and testing of the active substance.

The synthesis of the active *s*ubstance is a complexation reaction between copper (^{64}Cu) and dotatate. This reaction does not have any impact on the chiral centres of the dotatate peptide. The characterisation

of the chiral centres is performed during the production of the non-radioactive chemical precursor. The solid state properties of the active substance are not relevant as it is present in solution.

3.2.3.2. Manufacture, characterisation, and process controls

Sufficient information has been provided regarding the GMP standards of the manufacturing site.

The non-radioactive precursor is manufactured in three main steps using the non-radioactive chemical precursor dotatate and the radioactive chemical precursor copper (^{64}Cu).

The synthesis, radiolabelling, and transfer are performed using an automated synthesiser. The solutions are prepared and transferred to the reactor and radiolabelling then takes place. In the final step, the radiolabelled active substance is transferred to the dispensing cell and immediately manufactured into the finished product.

The information provided on the manufacturing process and the process parameters is sufficient, as the process is an automated continuous process.

3.2.3.3. Specification

The synthesis of the active substance and its formulation into the finished product are part of an automated continuous process which does not allow for isolation and testing of the pure active substance. Therefore, specifications, associated analytical procedures, relevant method validation, batch analyses data and justification of specifications are available only for the finished product.

3.2.3.4. Stability

As the active substance is synthesised with an automated unit through a continuous process leading to the finished product without isolation of any intermediates stability data is only relevant for the finished product.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

The finished product is a sterile isotonic solution for injection. It is a clear, colourless to yellow solution presented in a multidose vial containing between 1 ml and 4 ml. The volume of solution to be administered can range from 0.2 ml to 4 ml per dose.

Radioactive concentration at calibration date and time is set at 37 MBq/ml, which corresponds to an amount of radioactivity per vial between 37 MBq and 148 MBq. Natural decay of the radionuclide is a property of any radiopharmaceutical, whether it is produced industrially or in-house. Consequently, specific activity, total radioactivity, and radio concentration (volumetric activity) of the finished product change over time.

The finished product is developed as a ready to use radiopharmaceutical solution for injection. The process and formulation is based on a continuous automated process in which the active substance is never isolated, held or released. The entire process is performed using a synthesis unit and a dispensing system.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards where this is applicable. There are no novel excipients used in the finished product formulation. For gentisic acid, a suitable in-house specification has been provided to ensure appropriate quality. The excipients are commonly used in radiopharmaceutical preparations, and their compatibility was confirmed based on the finished product stability results.

The quality development of the product built on prior knowledge and the following critical quality attributes (CQAs) were identified by the applicant during development:

The continuous process was developed with reference to the identified CQAs above with focus on the solution preparation, radiolabelling, and formulation manufacturing steps. The information gained during development was used to inform the selected process parameters and controls for the commercial process. The proposed commercial process was further developed from the process used for the clinical batches; the same general steps are maintained with accommodations for equipment and the calibration time differences. The changes introduced have been presented in sufficient detail and have been justified. The manufacturing processes and associated finished products are considered comparable.

The applicant investigated potential methods of sterilisation, and it was determined that terminal sterilisation was not feasible for the product. Significant degradation was observed upon exposure of the solution to the temperatures that are relevant for enabling such terminal sterilisation. For this reason, a method based on sterile filtration and aseptic processing was selected.

The primary packaging is a type I glass vial with a chlorobutyl rubber stopper and an aluminium crimp seal. The materials comply with Ph. Eur. requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. A lead container is used as part of the secondary packaging to provide radiation protection.

3.3.2. Manufacture of the product and process controls

The finished product is manufactured at CIS Bio International, 306 Route Nationale, Bp 32 Saclay, 91192 Gif-sur-Yvette, France. For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The finished product manufacturing process consists of four main steps: dilution, sterile filtration, filling & packaging. The process is considered to be a non-standard manufacturing process.

The manufacturing process and in-process controls have been sufficiently described.

Process validation data from three commercial scale validation batches of the finished product manufactured at the proposed manufacturing site were provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Appropriate information was also provided concerning media fill simulations for the aseptic processing steps and concerning the validation of the sterile filters.

3.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form; appearance (visual), identification (gamma ray spectrometry, HPLC), pH (Ph. Eur.), sodium ascorbate content (potentiometric titration), gentisic acid content (HPLC), impurities (HPLC), radiochemical purity (HPLC), radionuclidic purity (gamma ray spectrometry), radioactive concentration (ionisation chamber), apparent specific activity (HPLC), bacterial endotoxins (Ph. Eur.), and sterility (Ph. Eur.).

The proposed specifications are considered appropriate for this radiopharmaceutical dosage form and the relevant limits are appropriately set and justified.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. are well within specifications.

3.3.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 55 hours after the synthesis at 40 °C ± 2 °C in an upside-down position were provided. The batches of medicinal product were identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Stability studies for radiopharmaceuticals do not need to be in compliance with ICH guidelines and nuclear decay is an intrinsic property of these products which often necessitates a short shelf life.

Samples were tested for appearance, pH, impurities, radiochemical purity, endotoxins and sterility. The analytical procedures used are stability indicating.

Under the conditions tested, no specific trends or out of specification results were noted, radiochemical purity remains acceptable and impurities remain below the specification limits. The stability data obtained demonstrates the absence of interaction between the finished product and the container closure system.

The applicant also investigated the impact of multiple piercings of the stoppers in order to simulate potential use in a nuclear medicine service. The data provided indicate no impact from up to 10 piercings of the stoppers.

Based on available stability data, the proposed shelf-life of 55 hours following manufacture and 2 hours after final calibration are acceptable. A lead shielded container is provided to protect from radiation and radiopharmaceuticals should be stored in accordance with national regulation on radioactive materials.

3.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

3.4. Discussion and conclusions on quality aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. From a quality point of view, the current application is approvable.

4. Non-clinical aspects

4.1. Introduction

The Applicant did not conduct any non-clinical studies. The data on non-clinical pharmacology, efficacy and safety is obtained from published literatures sources.

4.2. Analytical methods

The Applicant did not perform any non-clinical studies, therefore no discussion on analytical methods is included in this report.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

The pharmacology of radiolabelled DOTATATE has been evaluated in *in vitro* binding assays, as well as *in vivo* in tumour-bearing mouse models. ^{68}Ga-DOTATATE showed high binding affinity to SSTR2 in the low nanomolar concentration range (IC_{50} for hSST2 was 0.2 ± 0.04 nM (Reubi 2000). Additionally, another study showed that ^{64}Cu-DOTATATE was readily internalised into SST-2 expressing HEK cells, with 20% of the radioactivity externalised to the medium within 2 hours (Rylova 2018).

4.3.1.2. Secondary pharmacodynamics

There is no specific data on the secondary pharmacology of ^{64}Cu-DOTATATE. However, the applicant provided bibliographic literature regarding potential off-target effects of somatostatin synthetic analogues (SSAs).

Antiproliferative effects

SSAs were initially developed for the symptomatic control of neuroendocrine tumours due to their anti-secretory effect. However, further studies confirmed that SSAs also have a positive impact on the progression-free survival (PFS) in pancreatic and non-pancreatic NETs due to their antiproliferative effect (Gomes-Porras 2020). *In vitro* and *in vivo* studies confirmed that SSAs can induce cytostasis or apoptosis, particularly via SSTR2, with downstream signalling through SHP-1 phosphatase, inhibition of VEGF, IGF and suppression of tumour angiogenesis via modulation of nitric oxide (NO) production (Dasgupta 2004, Rai 2015).

Hormonal and gastrointestinal effects

SSAs are reported to inhibit a broad range of hormones, including growth hormone, insulin, glucagon, pancreatic polypeptide, GIP, gastrin, TSH, VIP and secretin. They also affect GI motility, gallbladder emptying and gut transit times (Harris 1994).

Glucose metabolism, insulin and glucagon secretion

In animal studies, somatostatin analogues like octreotide and pasireotide alter insulin and glucagon secretion, leading to transient changes in blood glucose (Schmid 2012).

While primarily used for imaging and therapy, radiolabelled SSAs still activate somatostatin receptor–mediated pathways (Eychenne 2020, Vitali 2021) and therefore can elicit above-mentioned effects. Specifically, for DOTATATE, effects on glucose homeostasis and hormonal effects are expected to be minimal due to its very high (almost exclusive) affinity to SSTR-2. Hormonal effects and effects on glucose homeostasis are mediated equally also (or exclusively in some cases, e.g. for insulin secretion) by SSTR-1 and 5 (He 2009, Strowski 2003, Amisten 2013).

4.3.1.3. Safety pharmacology

No data were provided.

4.3.1.4. Pharmacodynamic drug interactions

No data were provided.

4.3.2. Pharmacokinetics

4.3.2.1. Absorption

Not applicable. DEQTYNET solution for injection is a radiolabelled receptor-targeted diagnostic product, which is administered by a single intravenous injection.

4.3.2.2. Distribution

Results of three published biodistribution studies were provided by the applicant.

In mouse xenograft models, ^{64}Cu-DOTATATE showed rapid clearance from the blood. In Balb/c nude mice inoculated subcutaneously with 3.5 x 10^6 tumorigenic A427-7 cells, the tumour-to-background uptake ratio of ^{64}Cu-DOTATATE was initially high, but dropped thereafter until 24 h post-injection (Paterson 2014). PLI, PET, and *ex vivo* radiotracer distribution studies in a mouse pheochromocytoma (MPC)-mCherry allograft model revealed strong ^{64}Cu-DOTATATE accumulation in tumours of control animals but only weak accumulation in blood and muscles, as well as in visceral organs such as liver, kidneys, and pancreas (Ullrich 2016). In *in vivo* biodistribution study in female Balb/c nude mice bearing HEK-hsst-2 xenografts tumour uptake of ^{64}Cu-DOTATATE was rapid in the first hour (20.6 ± 3.7%IA/g) and decreased in the following hours (2.8 ± 0.3%IA/g left after 24 hours) (Rylova 2018). ^{64}Cu-DOTATATE showed relatively high accumulation and long retention of activity in some organs, including liver, pancreas, stomach and intestine at 1 hour post injection. Blocking experiments confirmed the receptor-mediated uptake of ^{64}Cu-DOTATATE in the tumour and SST-2-positive organs.

4.3.2.3. Metabolism

A study by Liu (2017), which evaluated both *in vitro* and *in vivo* stability of ^{177}Lu-DOTATATE, reports an excellent *in vitro* stability, with >96% radiochemical purity within 240 h incubation at room temperature. It also reports good *in vivo* stability with a radiochemical purity collected in urine (BALB/c mice) of >90% within 240 h post-injection. A fast metabolism of ^{177}Lu-DOTATATE was reported in a human study by Lubbernik (2020). The fraction of intact ^{177}Lu-DOTATATE in plasma was reported to decrease rapidly to 23% ± 5% (mean ± SD) at 24 h and 1.7% ±0. 9% at 96 h after injection.

4.3.2.4. Excretion

No non-clinical data on excretion was provided. Further pharmacokinetic data on ^{64}Cu-DOTATATE was generated in human studies. See 5.2.2 Pharmacokinetics of this overview.

4.3.2.5. Pharmacokinetic drug interactions

A variety of SST analogues, some with high affinity and selectivity to somatostatin receptor subtypes, have been synthesised and developed and a competitive binding of somatostatin and its analogues to somatostatin receptors, and may therefore interfere with the efficacy of ^{64}Cu-DOTATATE. See 5.2.2 Pharmacokinetics of this report.

4.3.2.6. Other pharmacokinetic studies

Not applicable.

4.4. Toxicology

No toxicity studies with ^{64}Cu-DOTATATE, nor with ^{68}Ga-DOTATATE or unlabelled DOTATATE were submitted.

4.4.1. Single-dose toxicity

No data available.

4.4.2. Repeat-dose toxicity

No data available.

4.4.3. Genotoxicity

No data available.

4.4.4. Carcinogenicity

According to the applicant, long-term carcinogenicity studies can be waived according to ICH S1A guideline, as the proposed product is used neither continuously for at least 6 months, nor repeatedly in an intermittent manner.

4.4.5. Developmental and reproductive toxicity

The applicant notes that radiation emitted from the radioactive nuclide is known to be genotoxic and radiopharmaceutical administration to pregnant women exposes the embryo/foetus to radiation. Similarly, administration to breastfeeding women exposes the child to radiation. However, the applicant considered that as ^{64}Cu-DOTATATE is used to diagnose a potentially life-threatening condition, an absolute contraindication for use in pregnant and breastfeeding women is not applicable. See section 5.4.6 Safety in special populations of this report.

4.4.6. Toxicokinetics and exposure margins

No data provided.

4.4.7. Local tolerance

No data on intravenous irritancy was provided.

4.4.8. Other toxicity studies

In order to compensate for the lack of non-clinical data, Quantitative structure-activity relationship (QSAR) data was generated using different software suites.

Acute toxicity

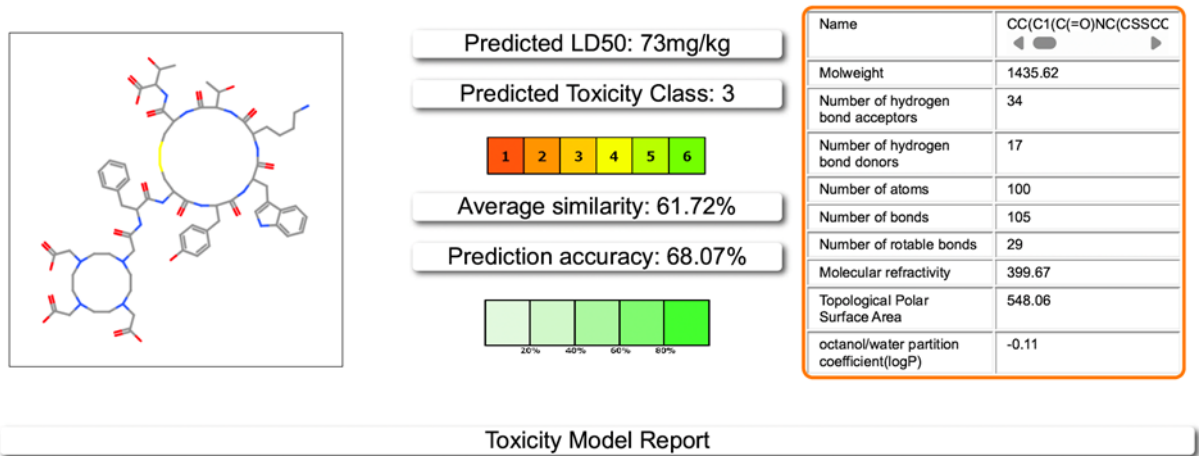
Acute toxicity is the most relevant toxicological endpoint, as the proposed product is a diagnostic agent that is only used as a single dose.

Two SAR tools were used to assess the acute toxicity (calculated as LD_{50}), ProTox 3.0 and QSAR Toolbox. The results are presented below.

ProTox 3.0 prediction

The predicted Lethal Dose 50% (LD_{50}) for the compound is 73 mg/kg and is categorized as acute toxicity class 3 according to the Globally Harmonized System (GHS) (Figure 9). The prediction raised flags for neurotoxicity, respiratory toxicity and immunotoxicity. However, this prediction suite does not allow for a quantitative prediction of individual specific organ toxicity endpoints.

Figure 5. ProTox 3.0 prediction for acute toxicity



QSAR Toolbox prediction

The predicted value of LD_{50} is 187 mg/kg (Figure 10). However, the prediction is based on only 2 values and therefore not considered strong enough to be scientifically valid.

Figure 6. QSAR Toolbox prediction for acute toxicity

Target information

Structural information	Numerical identifiers	Chemical names
SMILES: C[C@@H](O)[C@H](NC(=O)[C@@H]1CSSC[C@H](NC(=O)[C@@H](Cc2ccccc2)NC(=O)CN2CCN(CC(O)=O)CCN(CC(O)=O)CCN(CC(O)=O)CC2)C(=O)N[C@@H](Cc2ccc(O)cc2)C(=O)N[C@H](Cc2c[nH]c3ccccc23)C(=O)N[C@@H](CCCCN)C(=O)N[C@@H]([C@@H](C)O)C(=O)N1)C(O)=O  Structure	CAS#: 177943-88-3 Other: N/A	Dotatate

Prediction summary

Predicted endpoint: Human Health Hazards -> Acute Toxicity -> LD50
Predicted value: 187 [mg/kg] (equal to 0.00013 [mol/kg])
Data gap filling method: Read-across analysis

Repeat-dose toxicity

Repeated dose toxicity results are difficult to simulate in an *in silico* environment, as there is little high-quality data available in consulted databases. Nevertheless, a quantitative prediction has been done with QSAR Toolbox (Figure 11).

QSAR Toolbox prediction

There is not enough robust data in the databases to allow the prediction of a No observed adverse effect level (NOAEL).

Due to very limited information for similar molecules in the database, the simulated No observed effect level (NOEL) used information from different test species (mouse, rat, monkey), as well as from different routes of administration (oral, intraperitoneal, intravenous).

The NOEL was predicted using a read-across analysis. The molecule was profiled using general mechanistic and endpoint-specific profilers and categorised based on structure similarity (50-60%). The read-across used data from 437 chemicals with 132 chemicals having experimental data. 4 closest neighbours were considered for the quantification. The calculation option was set to "Minimal", which ensures that the minimal value is considered in case of multiple options.

The predicted NOEL is 0.25 mg/kg. The simulation was set to be as conservative as possible, to ensure a significant safety margin. This NOEL represents a dose level that is several orders of magnitude higher

(0.0143 µg per dose versus 250 µg/kg NOEL) than the expected dose level used in humans.

Figure 7. QSAR Toolbox prediction for repeat-dose toxicity

Target information		
Structural information SMILES: C[C@@H](O)[C@H](NC(=O)[C@@H]1CSSC[C@H](NC(=O)[C@@H](Cc2ccccc2)NC(=O)CN2CCN(CC(O)=O)CCN(CC(O)=O)CCN(CC(O)=O)CC2)C(=O)N[C@@H](Cc2ccc(O)cc2)C(=O)N[C@H](Cc2c[nH]c3ccccc23)C(=O)N[C@@H](CCCCN)C(=O)N[C@@H]([C@@H](C)O)C(=O)N1)C(O)=O  Structure	**Numerical identifiers** CAS#: 177943-88-3 Other: N/A	**Chemical names** Dotatate

Prediction summary
Predicted endpoint: Human Health Hazards -> Repeated Dose Toxicity -> NOEL
Predicted value: 0.25 [mg/kg bdwt/d]
Data gap filling method: Read-across analysis

Genotoxicity

The applicant emphasizes that the genotoxicity studies are not recommended for radiopharmaceuticals, as the radioligand is known to be genotoxic and the underlying (potential) genotoxicity of the carrier molecule is considered irrelevant. This is especially true for diagnostic radiopharmaceuticals, which are only administered as a single micro-dose.

Nevertheless, two SAR predictions were performed, and both delivered a negative result:

QSAR Toolbox prediction

The prediction is performed by means of a read-across analysis and based on 9 closest neighbours. The result is negative (Figure 12).

Figure 8. QSAR Toolbox prediction for genotoxicity

Target information		
Structural information SMILES: C[C@@H](O)[C@H](NC(=O)[C@@H]1CSSC[C@H](NC(=O)[C@@H](Cc2ccccc2)NC(=O)CN2CCN(CC(O)=O)CCN(CC(O)=O)CCN(CC(O)=O)CC2)C(=O)N[C@@H](Cc2ccc(O)cc2)C(=O)N[C@H](Cc2c[nH]c3ccccc23)C(=O)N[C@@H](CCCCN)C(=O)N[C@@H]([C@@H](C)O)C(=O)N1)C(O)=O  Structure	**Numerical identifiers** CAS#: 177943-88-3 Other: N/A	**Chemical names** Dotatate

Prediction summary
Predicted endpoint: Human Health Hazards -> Genetic Toxicity -> in Vitro -> Bacterial Reverse Mutation Assay (e.g. Ames Test) -> Gene mutation
Predicted value: Negative [Gene mutation I]
Data gap filling method: Read-across analysis

T.E.S.T. prediction

The prediction using the Consensus method, yielded a negative result with a high concordance (0.9), sensitivity (0.75) and specificity (1.0) (Figure 13). The consensus method uses an average value of the predicted endpoint from 4 other methodologies (hierarchical method, single-model method, group contribution method and nearest neighbour method).

Figure 9. T.E.S.T prediction for genotoxicity

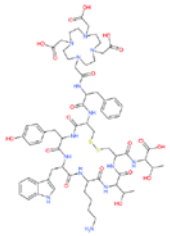
Predicted Mutagenicity for C_QVFLVLMYXXNJDT-UHFFFAOYSA-N from Consensus method

Prediction results

Endpoint	Experimental value	Predicted value
Mutagenicity value	N/A	0,29
Mutagenicity result	N/A	Mutagenicity Negative

Individual Predictions

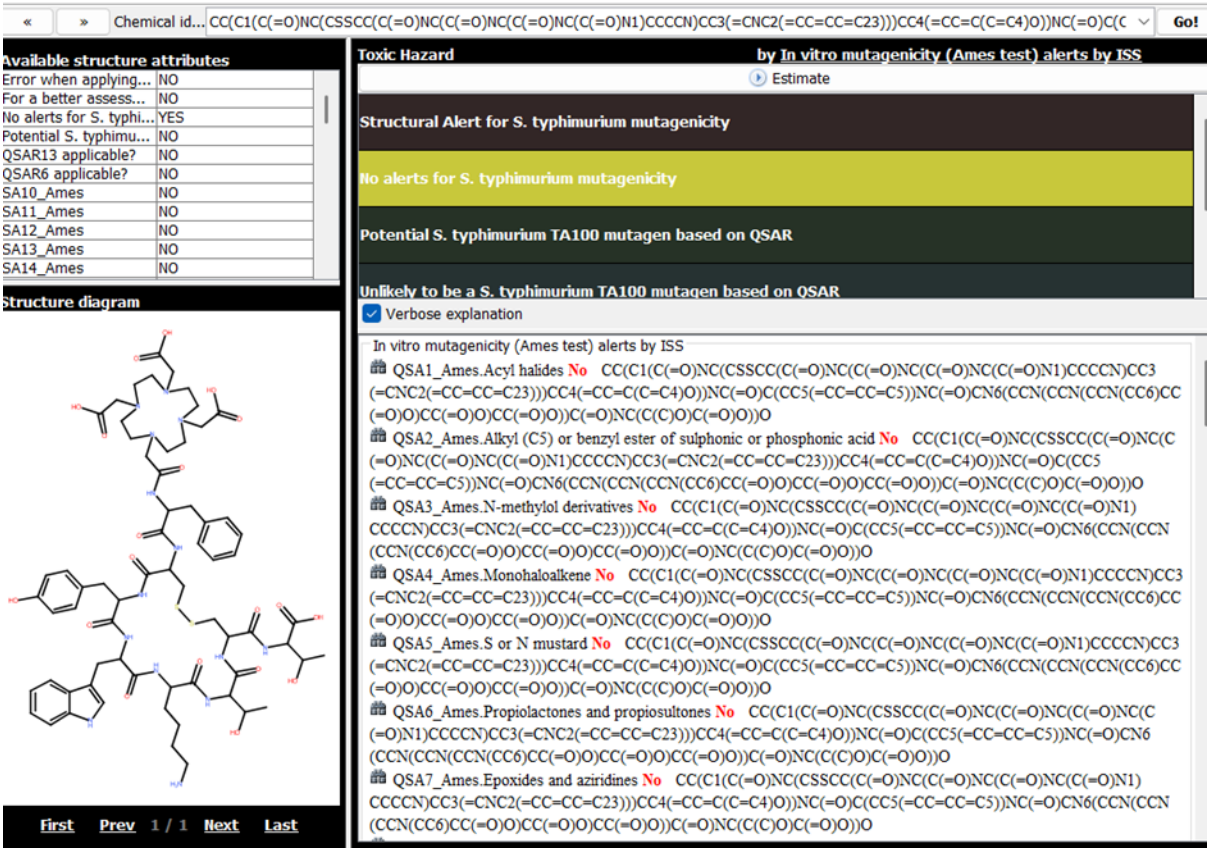
Method	Predicted value
Hierarchical clustering	-0,08
Nearest neighbor	0,67



ToxTree prediction

There were no alerts for *S.typhimurium* mutagenicity based on the Benigni-Bossa rulebase; this is a decision tree for estimating carcinogenicity and mutagenicity by discriminant analysis and structural rules (Figure 14). A module for ToxTree was developed by the Joint Research Centre's European Chemicals Bureau and is considered to be a well-established prediction tool.

Figure 10. ToxTree prediction for genotoxicity



4.4.9. Ecotoxicity/environmental risk assessment

Table 2. Summary of main study results: Phase I

Substance (INN/Invented Name):	(^{64}Cu)Cu-dotatate ((^{64}Cu) oxodotreotide)		
CAS-number (if available):	1426155-87-4		
PBT/vPvB screening			
Study type	***Test protocol***	***Result***	***Conclusion***
Bioaccumulation potential-log Kow	OECD107	-2.99 at pH N/A	Potential PBT: N
PBT/vPvB assessment			
PBT/vPvB statement:	Dotatate is considered to be not PBT, nor vPvB.		

Phase I			
Parameter	***Value***	***Unit***	***Conclusion***
PEC_{sw}, default	0,000454	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			N

$PEC_{surfacewater}$ for ^{64}Cu-dotatate is below the action limit of 0.01 µg/L. Consequently, a Phase II risk assessment is not required.

A bioaccumulation potential is not indicated based on the log K_{ow} < 4.5. A definitive PBT/vPvB assessment is not required.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Pharmacology

DOTATATE is an 8 amino acid long octapeptide (called octreotide) with a covalently bound DOTA bifunctional chelator radiolabelled with ^{64}Cu, a positron and beta-emitter with a long half-life of over 12 hours. The positron emission has a low energy of 0.653MeV, which enables the production of high-resolution images somatostatin receptor-expressing neuroendocrine neoplasms. The pharmacology of ^{64}Cu-DOTATATE has been characterised in the published literature with *in vitro* binding assays, as well as *in vivo* in tumour-bearing mouse models. High binding affinity in the low nanomolar concentration range makes the product a suitable candidate for a diagnostic radiopharmaceutical. Additionally, ^{64}Cu-DOTATATE is readily internalised into SST-2 expressing HEK cells, with 20% of the radioactivity externalised to the medium within 2 hours. Overall, the ^{64}Cu-DOTATATE has a high affinity for SST-2 receptors and is therefore a suitable radiopharmaceutical option for the diagnostics of SST-2 expressing tumours.

Relevant information is also available in the public domain regarding potential off-target effects of somatostatin synthetic analogues (SSAs). SSAs have a positive impact on the progression-free survival (PFS) in pancreatic and non-pancreatic NETs due to their antiproliferative effect. *In vitro* and *in vivo* studies confirmed that SSAs can induce cytostasis or apoptosis, particularly via SSTR2, with

downstream signalling through SHP-1 phosphatase, inhibition of VEGF, IGF and suppression of tumour angiogenesis via modulation of NO production. Hormonal and gastrointestinal effects include inhibition of a broad range of hormones, including growth hormone, insulin, glucagon, pancreatic polypeptide, GIP, gastrin, TSH, VIP and secretin. Effects on GI motility, gallbladder emptying and gut transit times have been reported. In animal studies, somatostatin analogues like octreotide and pasireotide alter insulin and glucagon secretion, leading to transient changes in blood glucose. The effects of dotatate on glucose homeostasis and hormonal effects are expected to be minimal due to its very high (almost exclusive) affinity to SSTR-2 while these effects are mediated equally or even exclusively by SSTR-1 and SSTR-5.

No data on safety pharmacology studies for ^{64}Cu-DOTATATE or any other DOTA-based tracer were provided by the applicant. This was considered acceptable as such studies are not relevant for radioactively labelled somatostatin receptor agonist administered by intravenous route as a single low dose.

Pharmacokinetics

Based on published literature studies, ^{64}Cu-DOTATATE has relatively high accumulation and long retention of activity in organs, including liver, pancreas, stomach and intestine at one hour post injection. Blocking experiments confirmed the receptor-mediated uptake of ^{64}Cu-DOTATATE in the tumour and SST-2-positive organs.

No own metabolism studies were performed by the applicant. There is conflicting data available in published literature regarding the *in vivo* stability of oxodotreotide (DOTATATE). A study by Liu (2017), which evaluated both *in vitro* and *in vivo* stability of ^{177}Lu-DOTATATE, reports an excellent *in vitro* stability, with >96% radiochemical purity within 240 h incubation at room temperature. It also reports good *in vivo* stability with a radiochemical purity collected in urine (BALB/c mice) of >90% within 240 h post-injection. A fast metabolism of ^{177}Lu-DOTATATE was reported in a human study by Lubbernik (2020). The fraction of intact ^{177}Lu-DOTATATE in plasma is reported to decrease rapidly to 23% ± 5% (mean ± SD) at 24 h and 1.7% ±0. 9% at 96 h after injection. The clinical implications of these findings are still unclear; however, the applicant argues that the reported metabolism of ^{177}Lu-DOTATATE at 24 h and 96 h after injection in human is likely irrelevant for ^{64}Cu-DOTATATE, which is injected 1 to 3 hours prior to PET imaging. This assumption is supported.

PK interaction studies are not relevant for the radioactively labelled somatostatin receptor agonist, which is administered by intravenous route as a single low dose. However, the Applicant concludes that a variety of SST analogues, some with high affinity and selectivity of somatostatin receptor subtypes, have been synthesised and developed and a competitive binding of somatostatin and its analogues to somatostatin receptors may interfere with the efficacy of ^{64}Cu-DOTATATE.

Toxicology

DOTATATE is a molecule that is being used in clinical practice since 2017 (2016 in the United States, also for diagnostic purposes), with extensive post-marketing experience. There has not been any safety issue reported plausibly related to unlabelled DOTATATE.

It has been reported that small structural changes in the radioligand molecule such as the introduction of a metal replacement of one metal by another, may provoke alteration in the binding affinity for selected SSTR subtypes and may have an impact on the quality and safety. Consequently, the most relevant toxicity study should use either the non-radioactive product labelled with a stable isotope, when possible, or the decayed product which are more representative of what will be administered to humans than the alone non-radioactive part.

In accordance with EMA/CHMP/SWP/686140/2018, carcinogenicity and reproductive toxicity studies can be waived since the radiation emission of radiopharmaceuticals is causing well known DNA damage with consequences for carcinogenicity and reproductive toxicity. In addition, ^{64}Cu-DOTATATE is intended for single diagnostic use only. It is agreed with the applicant that an absolute contraindication for use in pregnant and breastfeeding women should not be imposed as ^{64}Cu-DOTATATE is intended to be used to diagnose a potentially life-threatening condition.

Concerning the lack of local tolerance data, the post-marketing experience from Detectnet (^{64}Cu-DOTATATE injection approved in the US since 2020) is considered sufficient.

In line with the 3R goals to eliminate unnecessary and unethical testing of chemicals on animals, the applicant conducted a structure-activity relationship (SAR) evaluation of DOTATATE, using 4 different (Q)SAR approaches and literature data to simulate not only the genotoxicity, but also two main toxicity endpoints, NOEL and LD_{50}. The applicant concluded that acute toxicity is the most relevant toxicological endpoint, as the proposed product is a diagnostic agent that is only used as a single dose. This is agreed with. Using Protox 3.0 The predicted LD_{50} for the compound is 73 mg/kg and is categorised as acute toxicity class 3 according to GHS.

While some uncertainties remain regarding LD_{50} predictions of DOTATATE, negative results for genotoxicity using two SAR prediction tools are considered reliable.

The ProTox prediction raised flags for DOTATATE-related neurotoxicity, respiratory toxicity and immunotoxicity. The Applicant explains that ProTox prediction does not allow for a quantitative prediction of individual specific organ toxicity endpoints. However, this *in silico* assessment estimated high probability for respiratory toxicity (0.92) and immunotoxicity (0.95). To assess the relevance of these findings the Applicant made a comprehensive literature search to review any relevant data from human real-word exposure that would suggest a potential for respiratory or immunotoxicity caused by DOTATATE (either unlabeled or cold compound, e.g. labelled with ^{175}Lu) (results not shown). Additionally, review of pharmacovigilance data from Eudravigilance was conducted by performing a search in EudraVigilance data analysis system (EVDAS) (results not shown). The lack of relevant findings indicates that the respiratory toxicity and immunotoxicity signals for DOTATATE predicted *in silico* by the ProTox platform do not warrant any additional safety measures.

No discussion about the excipients used in the product was provided by the applicant. However, this can be accepted since the excipients used in solution for injection are commonly used in pharmaceutical preparations. Gentisic acid, which acts as a stabilizer, is present in many plants and as potential antioxidant is used in pharmaceutical formulations. Two other excipients, sodium acetate trihydrate and sodium ascorbate are added to buffer and stabilize the solution.

^{64}Cu-DOTATATE is unlikely to represent a risk for the environment following its prescribed usage in patients and no further risk assessment is required.

4.5.2. Conclusions

The Applicant has not conducted any non-clinical studies. The submitted data on non-clinical pharmacology, efficacy and safety was obtained from published literatures sources. Overall, considering the non-clinical safety data from *in vitro*, *in vivo* and *in silico* (QSAR) studies and from clinical studies performed at this time, an extended single dose toxicity study is not ethically justified.

Overall, from a non-clinical perspective, the submitted data support the granting of a marketing authorisation. Therefore, the current application is considered approvable from a non-clinical point of view.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Study RMX-17-22 started on 04/01/2018 and ended on 28/02/2018. It enrolled 12 patients. Study RMX-18-22 started on 22/01/2018 and ended on 02/12/2018. It enrolled 63 patients.

Both studies were conducted at the same single site: Excel Diagnostics and Nuclear Oncology Center 9701 Richmond Ave. Houston, TX 77042, US. The FDA performed GCP inspection between May 4,2020 and May 8, 2020.

No routine inspection has been requested by the CHMP. Based on the review of clinical data, the CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier (see section 2.4.3).

5.1.2. Tabular overview of clinical trials

Table 3. Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 1					
RMX-17-22	Prospective, open-label, Single-dose, Dose-ranging Study with a 2 day follow-up	^{64}Cu-DOTATATE i.v. bolus injection of 3-5 mCi (111-185 MBq)	Adult patients with prior history of pathologically confirmed neuroendocrine tumour	**Primary**: To identify the lowest amount of administered radiotracer dose of ^{64}Cu-DOTATATE that provides diagnostic quality PET-CT image, coincident with the as low as reasonably achievable (ALARA) principle **Secondary**: To assess the effect of radiotracer (^{64}Cu-DOTATATE) dose on PET-CT image quality	12 patients in total, 4 patients per dose cohort
Phase 2					
NETMedix Denmark Trial (retrospective analysis Pfiefer, 2015)	Retrospective analysis, open-label, single center, single-dose, comparative	^{64}Cu-DOTATATE: i.v. injection of 183-232 MBq 111In-Octreotide: i.v. injection of	Patients with histologically verified neuroendocrine tumour	**Primary**: To investigate whether ^{64}Cu-DOTATATE PET scan findings had the ability to diagnose somatostatin receptor-positive NETs (^{64}Cu-DOTATATE vs SOT) **Secondary**: To evaluate the positive predictive value (PPV), negative predictive value (NPV), and accuracy of ^{64}Cu-DOTATATE PET scan findings relative to the Standard of Truth (SOT)	112 patients

		181-268 MBq			
Phase 3 Diagnostic confirmatory					
RMX-18-22	Open-label, Single-dose, Single-arm, 2-day follow-up	^{64}Cu-DOTATATE_ i.v. bolus injection of 4.0 mCi ± 10% (148 ± 10% MBq)	Patients with prior history of pathologically confirmed neuroendocrine tumours or suspected NETs and healthy subjects	**Primary**: To assess the performance (sensitivity and specificity) of ^{64}Cu-DOTATATE PET-CT imaging in subjects with known or suspected NETs, when comparing individual reader results to a SOT for each subject. **Secondary**: To characterize the predictive value of ^{64}Cu-DOTATATE PET-CT imaging when comparing an imaging reader-majority rule determination to the SOT for each subject and also when the comparison was performed on an individual reader basis. To evaluate the imaging performance (sens/spec) of ^{64}Cu-DOTATATE when comparing an imaging reader-majority rule determination to the SOT for each subject. To evaluate the imaging performance of ^{64}Cu-DOTATATE to determine if subjects had metastatic or local disease as compared to the SOT. **Exploratory:** To evaluate PK and identify any major ^{64}Cu moieties other than intact parent drug, free ^{64}Cu, and known radiolysis byproducts of the parent drug.	63 subjects (59 enrolled in this study and additional 4 from RMX-17-22) 30 healthy subjects 33 patients with confirmed/suspected NET

5.2. Clinical pharmacology

The pharmacokinetics of ^{64}Cu-DOTATATE were evaluated as exploratory objective in the Phase 3 study "RMX-18-22". For a detailed discussion of the study design please refer to section 5.3.2 "Main study". Furthermore, the applicant provided a literature review of the clinical pharmacology data of ^{64}Cu and DOTATATE, as well as related radiotracers to further substantiate the metabolism of the proposed radiochemical (^{64}Cu-DOTATATE).

5.2.1. Methods

RMX-18-22 Study:

Sample Collection and Preparation at the Clinical Site

Preparation A: 1 mL of sample (plasma or urine) was delivered to a scintillation vial in 'bulk' 'as is' from the Sponsor. All samples were evaluated with the NaI radiometric detector and a µCi value was calculated based on the calibration of the instrument.

Analytical methods

The analytical method was a reverse phase HPLC procedure for the separation and identification of $^{64}CuCl_2$, ^{64}Cu-DOTATATE and other impurities (radiolysis by products) by Gamma detection and

additional UV detection to determine DOTATATE content (both free and metal bound DOTATATE) in ^{64}Cu-DOTATATE.

A detailed description of the method (SOP) was provided by the applicant.

According to the SOP, the method was able to separate excipients (ascorbate, acetate, gentrisic acid) from potential impurities and the active substance (^{64}Cu-DOTATATE).

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The clinical pharmacokinetics (PK) of ^{64}Cu-DOTATATE were evaluated in a patient subset of the Phase 3 study "RMX-18-22" population supplemented by studies from public literature.

Six NET patients from the PK sub-study of RMX-18-22 were selected based on their clinical status and their interest in participation. Ages ranged from 42–73 years, heights 165–193 cm, and weights 58–127 kg. The subset included four males and two females; four participants were White and two Black/African American, all non-Hispanic/Latino. Tumour origins included the rectum, pancreas (2 patients), lung (2 patients), and small intestine. Pathology descriptions comprised two carcinoids, two well-differentiated NETs, one atypical carcinoid, and one metastatic small intestine NET. Tumour grades ranged from G2 to G3, with Ki-67 proliferation indices between 4.8% and 40%. Prior treatments varied and included surgery, somatostatin analogues (lanreotide, octreotide), chemotherapy, multiple forms of radiotherapy (EBRT, SBRT, PRRT, SIRT), and targeted therapies (everolimus, sunitinib). Two patients were receiving ongoing treatment with lanreotide.

148±10% MBq (4.0±10% mCi) of the study drug was administered as an intravenous bolus injection. Blood samples were analysed at 1, 10, 30, 60, and 120 minutes. Urine samples were analysed in three intervals post- injection of the study drug; 0-60 minutes, 60-120 minutes, and 120-360 minutes.

5.2.2.2. Evaluation and qualification of models

Not applicable.

5.2.2.3. Absorption

This medicinal product is administered intravenously and is immediately and completely bioavailable.

5.2.2.4. Distribution

Data from literature:

Pfeifer et al., 2012:

In the first-in-man study with ^{64}Cu-DOTATATE (193–232 MBq), in which 14 patients with a history of NETs underwent both PET-CT with ^{64}Cu-DOTATATE and SPECT-CT with the standard imaging agent Octreoscan ((111In)pentetreotide), tissue radioactivity concentrations for normal organs and lesions were quantified, and standardised uptake values (SUVs) were calculated for the early (1 h) and delayed (3 h) scans. The data from five patients were used to assess the radiation dose.

On the basis of SUV quantitation, tracer accumulation was classified in the following 3 categories: high, moderate, and faint. High accumulation of ^{64}Cu-DOTATATE was seen in the pituitary (averaged

SUVmax +/- SEM at 1 h and 3 h, 19.0 +/- 2.6 and 19.4 +/- 3.3, respectively), adrenal glands (21.1 +/- 3.1 and 27.8 +/- 3.6, respectively), kidneys (21.3 +/- 2.5 and 19.9 +/- 2.0, respectively), renal pelvis, and urinary bladder. Moderate to high uptake was observed in the liver (11.3 +/- 0.8 and 13.6 +/- 0.8, respectively) and spleen (17.8 +/- 1.8 and 18.0 +/- 1.8, respectively). The salivary glands showed faint to moderate uptake in 12 of 14 patients. In two patients, moderate tracer accumulation was observed in the thyroid gland, with a diffuse distribution pattern in one patient and a focal pattern in the other. SUVmax of the early and delayed images remained relatively stable (variability ≤ 20%) for tissues that had known high physiologic SSTR density and did not take part in tracer or activity excretion (i.e., pituitary, adrenals, and spleen). The same was true for most lesions. Conversely, higher time-dependent intra-patient variability for SUVmax was observed for the kidneys, corresponding with urinary tracer excretion as demonstrated by activity accumulation in the renal pelvis and urinary bladder seen only on the early and delayed images. As a possible sign of hepatobiliary excretion, an increase in SUVmax from the 1 h to the 3 h scan in normal liver tissue ranged from 10% to 65% among patients. This finding was in line with visible activity localised to the gallbladder on 3 h images, which was not apparent on images from the early acquisition. Images of the late scan (24 h) were characterised by activity washout from most organs and lesions, whereas activity retention in the liver and activity accumulation in the intestines became apparent. No activity was visible in the renal collecting system or urinary bladder at the late time point.

The dose calculations yielded an effective dose of 0.0315 mSv/MBq. Apart from the pituitary gland, which was estimated to receive an absorbed dose of 0.19 mGy/MBq, the liver was the organ with the highest absorbed dose (0.16 mGy/MBq), followed by the kidneys (0.14 mGy/MBq).

A high and quite stable SUVmax for lesions on both early (1 h) and delayed (3 h) images suggests a high rate of tracer internalisation and a low dissociation rate of ^{64}Cu-DOTATATE from SSTRs during this time interval.

Johnbeck et al., 2017

The study by Jonhbeck et al (2017) provides a comparison of SUVmax in tumour lesions for ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC in 59 NET patients, and evaluates background SUVmax and tumour to background ratio for both tracers (results not shown).

Other studies

Beauregard 2012	^{68}Ga-DOTA-octreotate 133–307 MBq	- Tumour sequestration, body habitus and urinary excretion inversely influence all healthy tissue uptake values
Larsson 2012	Lu-[DOTA0, Tyr3]-octreotate (^{177}Lu-octreotate) 3.5-8 GBq	- In the individual patient, the mean deviation of all subsequent kidney doses compared to that of the first administration was 1% (SD = 19%) and 5% (SD = 23%) for the right and left kidneys, respectively. - Large inter-individual variations in kidney dose were found (0.33-2.4 Gy/GBq) following a therapeutic dose, demonstrating the need for patient-specific dosimetry and treatment planning.
Kashyap 2013	^{177}Lu-DOTA-octreotate (LuTate) 6–12 GBq (with concomitant 5FU as radiosensitizer)	- The greatest renal exposure to circulating radiopeptide occurs in the first 1 – 2 h after injection.

		- No significant change in GFR and no grade 3 or 4 nephrotoxicity after induction peptide receptor chemoradionuclide therapy.
Hicks 2016	Cu-64 MeCOSAR-octreotate (CuSARTATE) 200 MBq	- High retention of activity in lesions and the spleen with SUVmax increasing slightly from a mean of 48.6 to 52.2 (P = NS) in the most intense lesion and SUVmean decreasing slightly from 19.6 to 18.7 (P= NS) in spleen from 1 to 24hr. - Between these time-points there was washout from liver and kidneys with SUVmean falling from 6.4 to 2.6 (p<0.0001) and 14.7 to 10.8 (p<0.001), respectively. - The spleen was the critical non-target tissue.
Lubberink 2020	^{177}Lu-DOTATATE 6.0-7.4 GBq	- Plasma–to–whole-blood ratio was constant and similar across patients and time points at around 1.65, indicating that all blood radioactivity was contained in plasma rather than blood cells. - Free ^{177}Lu-DOTATATE in plasma was 87% ± 2% immediately after infusion, decreasing to 82% ± 3% at 4 h after injection, 23% ± 5% at 24 h after injection, and 1.7% ± 0.9% at 96 h after injection.

A comparison of absorbed doses for the most commonly used tracers and for ^{64}Cu-DOTATATE in the most exposed organs and the effective doses for the whole body was provided by the applicant and is shown in the table below.

Table 4. Absorbed Doses in the Most Exposed Organs and the Effective Doses of Somatostatin Receptor Tracers

Organ/dose	**^{68}Ga-DOTANOC**	**^{68}Ga-DOTATOC**	**^{68}Ga-DOTATATE**	**^{64}Cu-DOTATATE**	**^{111}In-DTPAOC**	**^{111}In-DOTATOC**
Kidneys (mGy/MBq)	0.09	0.22	0.09	0.14	0.47	0.50
Liver (mGy/MBq)	0.03	0.07	0.05	0.16	0.07	0.05
Spleen (mGy/MBq)	0.07	0.24	0.28	0.12	0.36	0.47
Bladder (mGy/MBq)	0.08	0.07	0.13	0.04	0.19	0.16
Effective dose (mSv/MBq)	0.02	0.02	0.03	0.03	0.05	0.05
Typical administered dose (MBq)	120-200	120-200	120-200	180-220	111-222	140-200
Radiation burden at a typical dose (mSv)	2.0-3.3	2.8-4.6	3.0-5.1	5.7-6.9	5.6-11.1	7.0-10.0

Note: Unknown source

5.2.2.5. Metabolism

Study RMX-18-22:

The applicant reported that there was no free-^{64}Cu found in the patient blood and urine samples analysed by HPLC. The spiked product samples did not demonstrate a radiometric signal increase over that of the standard and did not yield any usable product information.

According to the applicant, radiometric metabolites are not anticipated for this product, and it is not known where in the chromatographic analysis method these potential metabolites may elute. Potential radiolysis products are expected to elute between 0.8 and 1.4 Relative Retention Time to the ^{64}Cu-DOTATATE product. Nevertheless, the LC fraction collection window of 6 to 10 minutes, specific to the ^{64}Cu-DOTATATE and potential radiolysis peak(s), does not allow for discrimination between the product and potential radiolysis or metabolite products when evaluating the 'LC fraction' patient samples.

According to the applicant, bioanalytical assays were, thus, unable to characterise the PK of the product beyond the data collected due to the low dose of ^{64}Cu-DOTATATE administered in the clinical studies (4 mCi). Analysis of additional information such as intact parent drug, free ^{64}Cu and ^{64}Cu moieties was extremely challenging if not impossible, according to the applicant, due to the half-life of ^{64}Cu (12.7 hours) and the very low levels of radioactivity that were present in the blood. Therefore, there are no additional, useful PK data available.

Literature:

The applicant's literature search results did not reveal specific metabolites of ^{64}Cu-DOTATATE in clinical studies.

However, conflicting data is available in published literature regarding the *in vivo* stability of oxodotreotide (DOTATATE). A study by Liu (2017), which evaluated both *in vitro* and *in vivo* stability of ^{177}Lu-DOTATATE, reports an excellent *in vitro* stability, with >96% radiochemical purity within 240 h incubation at room temperature. It also reports good *in vivo* stability with a radiochemical purity collected in urine (BALB/c mice) of >90% within 240 h post-injection.

On the other hand, a fast metabolism of ^{177}Lu-DOTATATE was reported in a human study by Lubberink (2020). The fraction of intact ^{177}Lu-DOTATATE in plasma is reported to decrease rapidly to 23% ± 5% (mean ± SD) at 24 h and 1.7% ±0. 9% at 96 h after injection. Earlier studies showed that DOTATATE is likely not metabolised; however, these new data could indicate that ^{177}Lu-labeled fragments/metabolites could be cleared from the tumours or other somatostatin receptor–expressing cells. These metabolites subsequently appear to be removed from the body by hepatic clearance and not by renal excretion, explaining the lack of radioactive metabolites found in urine.

5.2.2.6. Elimination

Study RMX-18-22

An activity value for all of the study samples was calculated and plotted. The sample activity level was decay-corrected back to the patient dosing time.

Blood recovery

Blood recovery was calculated utilizing Nadler's formula (by Nadler et al. 1962) for the total blood volume which depends on the patient's weight and height.

Table 5. ^{64}Cu-dotatate blood recovery

64Cu-DOTATATE: Blood Recovery								
Patient ID	Patient weight (Kg)	Patient Height (cm)	Blood Volume	Injected Activity (mCi)	Blood Activity Experimental (uCi/mL)[1]	Measured Blood Activity Recovery at 120 min	Calculated Blood Activity Recovery at 120 min	Blood TIA 0-2 hr
[redacted]	79.5	176	5147	4.16	0.06	7.4%	7.5%	0.28
[redacted]	127.3	193	7330	4.30	0.04	6.8%	6.8%	0.35
[redacted]	80.9	175	5178	4.22	0.03	3.7%	3.0%	0.23
[redacted]	63.6	178	4733	4.26	0.04	4.4%	4.2%	0.19
[redacted]	58.2	165	3702	3.96	0.15	14.0%	14.6%	0.48
[redacted]	81.8	167	4554	4.26	0.05	5.3%	5.3%	0.31

1 - at 120min

The blood activity concentration measured at 1, 10-, 30-, 60- and 120-min post-injection were converted to percent injected dose, plotted at a function of time and fitted with a bi-exponential function (see section 5.2.2.7 Dosimetry, below).

Interpolation of this function at x min provided the calculated blood recovery calculated as the percent of injected activity in the blood at this time.

The average calculated blood recovery at 1 min is 72.3 +/- 6.4 %. At 120 minutes, the average calculated blood recovery is 6.9 % and the Time-integrated activity (TIA) in the blood for the 0-2 hour period is 0.31 +/- 0.10 h.

Urine dose recovery

Urine samples were normalised to the patient's urine output volume.

Table 6. ^{64}Cu-dotatate Urine Dose Recovery (decay corrected back to dosing time)

Patient ID	Patient Dose Level (mCi)	Urine (mCi)	% Recovery at 6 hours	Total Urine Output (g)	Average Dose Level per mL Urine (mCi/mL)
[redacted]	4.16	1.7	40.87	1765	9.63E-04
[redacted]	4.30	1.2	27.91	965	1.24E-03
[redacted]	4.22	1.3	30.81	2055	6.33E-04
[redacted]	4.26	0.7	16.43	375	1.87E-03
[redacted]	3.96	1.5	37.88	525	2.86E-03
[redacted]	4.26	0.8	18.78	995	8.04E-04

The urine recovery demonstrates that between 16% to 40% of the dose was excreted into the urine and recovered over the 6-hour study time frame. The structure of the dotatate product leads to a binding to the megalin receptor in the kidneys (Vegt 2011). Greater recovery is anticipated by the applicant with a longer study time frame. A higher dose recovery is also anticipated by the Applicant if dosing is combined with a kidney flush with an amino acid to bind the megalin receptors prior to dosing.

Other studies

Anderson 2001	^{64}Cu-TETA-octreotide	- ^{64}Cu-TETA-octreotide was rapidly cleared from the blood.

	107–130 MBq	- 59.2% +/- 17.6% of the injected dose was excreted in the urine - Absorbed dose measurements indicated that the bladder wall was the dose-limiting organ.
Esser 2006	^{177}Lu-DOTA-ocreotate 3.7 GBq	- Radioactivity in the blood decrease to less than 10% injected activity within the first 3h - Cumulative excreted activity in urine: 71% within 24h
Beauregard 2012	^{68}Ga-DOTA-octreotate 133–307 MBq	- Tumour sequestration, body habitus and urinary excretion inversely influence all healthy tissue uptake values - Since ^{68}Ga-DOTA-octreotate is filtered by glomeruli and then partially reabsorbed in proximal convoluted tubule (Vegt et al., 2010), it may be advisable to decrease the dose in patients with poor renal function in a therapy setting.
Kashyap 2013	^{177}Lu-DOTA-octreotate (LuTate) 6–12 GBq (with concomitant 5FU as radiosensitizer)	- LuTate blood clearance obeyed a biexponential model. The initial clearance half-time was measured at 20.8 min. Approximately 88 % of blood activity was cleared within 2 h (initial tissue uptake). After 4 h, clearance slowed with measurements indicating a long-term biological half-life of 12.9 h. *

5.2.2.7. Dosimetry

A dosimetry table based on organ time-integrated activity (TIAs) reported by Pfeifer et al. (2012) was provided by the applicant, incorporating updated urinary excretion and blood clearance data from the RMX-18-22 study. Specifically, the bladder content and left-ventricle TIAs were recalculated using total activities collected in urine (excreted) and blood time activity data, respectively.

Urine excretion:

The collected urine total activity was plotted as a function of time and fitted for each patient with an uptake function of the form (A(t) = A0(1 - exp(- A1 t)), where A0 is the filling fraction and A1 is the filling rate constant related to the bladder filling half-life by the relation ln(2)/A1.

The filling fraction and filling half-life was then entered in the MIRD bladder voiding model built in OLINDA/EXM software along with a voiding interval of 2 hour to yield the bladder content time-integrated activity (residence time), as done by Laforest et al. 2023. The fitted function was also integrated to infinity, incorporating physical decay, to give the total urine TIA, and the excreted activity expressed as TIA excreted as the difference between the integral to infinity TIA and the MIRD bladder TIA (calculated at void interval of 2hr).

The table below contains the integral in urine for all patients, along with the MIRD bladder residence time (@ 2 hr void interval) and the excreted in urine expressed in terms of TIA. Based on this data, the average urinary bladder contents TIA is thus 0.38 +/- 0.13 MBq h/MBq, as opposed to the reported value of 0.11 MBq h/MBq in Pfeifer et al. paper.

Table 7. Cumulative collect urine data TIA, modelled Bladder content TIA with the assumption of 2h void interval and excreted activity expressed as TIA

Patient ID	Urine Integral	MIRD void (@2hr)	Urine Excreted
[redacted]	6.385	0.456	5.93
[redacted]	4.794	0.438	4.36
[redacted]	5.316	0.456	4.86
[redacted]	2.586	0.201	2.38
[redacted]	5.739	0.486	5.25
[redacted]	3.187	0.228	2.96
Average(hr)	4.67	0.38	4.29
Stdev	1.49	0.13	1.37

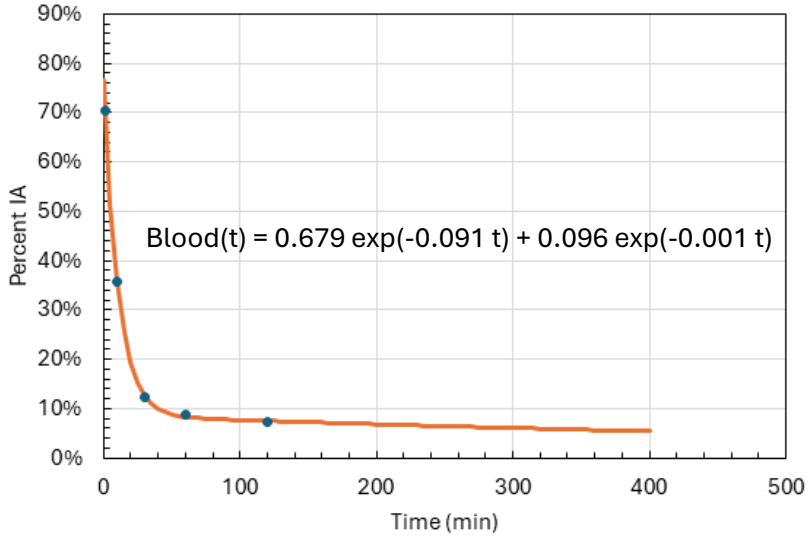
Blood activity:

The RadioMedix report also contains the blood activity concentration at 1, 10-, 30-, 60- and 120-min post-injection. An example of Blood percent injected activity where the total blood volume per patient is estimated using the Nadler's formula (Nadler et al., 1962) is plotted in the graph below for one patient and fitted with two-exponential functions. Integration to infinity of this function gives the blood time-integrated activity (or residence time).

The effective blood clearance rate constant is also presented in this table. It is customary to associate a fraction of the blood TIA to the left ventricle of heart content which is a dosimetric source organ.

The left ventricle volume was taken as 454 mL and 347 mL in males and females, respectively, as per ICRP-106.

Figure 11. Blood time activity data expressed as percent injected activity using total blood volume calculated using the Nadler's formula (for one patient) along with bi-exponential



Using this volume and the total blood volume per patient as calculated from the Nadler's formula, an average heart content TIA of 0.04 +/- 0.02 MBq h/MBq was calculated. Values for individual patients are listed in the figure below.

Figure 12. Blood time activity data expressed as percent injected activity using total blood volume calculated using the Nadler's formula (for the first patient) along with bi-exponential

	Heart Content	
Patient ID	**TIAC(hr)**	**Blood Effective HFL**
[redacted]	0.07	5.57
[redacted]	0.03	1.23
[redacted]	0.02	0.67
[redacted]	0.03	1.65
[redacted]	0.07	1.32
[redacted]	0.03	1.25
Average(hr)	0.04	1.95
Stdev	0.02	1.80

According to these modifications, the organ TIA of Pfeifer et al (first column in the table below) are modified as follow:

Table 8. Organ TIA of Pfefer et al, 2012 and revised organ TIA accounted for new urine collection data and excretion.

Organs	Mean (MBq h/MBq)	Mean (MBq h/MBq)
Adrenals	0.0265	0.0265
GallBladder	0.015	0.015
Lower large intestine contents	0.0974	0.0974
Small intestine contents	0.523	0.523
Kidneys	0.478	0.478
Liver	3.33	3.33
Muscle	4.23	4.23
Pancreas	0.094	0.094
Red Marrow	0.359	0.359
Spleen	0.24	0.24
Urinary Bladder Content	0.11	0.38
Heart content	-	0.04
Excreted in urine	-	4.26
Remainder	**7.23**	4.25

The most important differences are the bladder content TIA and the TIA associated to the remainder of the body.

The urine data in the RadioMedix report a much higher excreted urine activity and thus in consequence, reduces the activity associated to the remainder of the body, as constrained by the fact that the sum of all TIA must be equal to the half-live of the radionuclide/ln(2), or 18.3 hour for ^{64}Cu.

Revised Dosimetry

The revised TIA values from the table above were entered into OLINADA/EXM for Cu-64 using the human adult anthropomorphic phantom. The organ doses along with the Effective Dose (ED) are reported in the table below.

Table 9. Organ radiation dose comparison with the results of Pfeifer et al and the revised dosimetry

Target Organ	Dose (mGy/MBq)	@2h void Dose (mGy/MBq)
Adrenals	1.37E-01	1.36E-01
Brain	1.27E-02	7.79E-03
Breasts	1.32E-02	8.89E-03
Gallbladder wall	3.96E-02	3.52E-02
Lower large intestine wall	4.32E-02	3.91E-02
Small intestine wall	6.55E-02	6.07E-02
Stomach wall	1.93E-02	1.45E-02
Upper large intestine wall	2.18E-02	1.71E-02
Heart wall	1.86E-02	1.66E-02
Kidneys	1.39E-01	1.38E-01
Liver	1.61E-01	1.60E-01
Lungs	1.67E-02	1.22E-02
Muscle	1.90E-02	1.77E-02
Ovaries	1.92E-02	1.49E-02
Pancreas	9.27E-02	9.11E-02
Red marrow	2.66E-02	2.29E-02
Osteogenic cells	3.35E-02	2.41E-02
Skin	1.22E-02	8.28E-03
Spleen	1.15E-01	1.13E-01
Testes	1.36E-02	9.63E-03
Thymus	1.49E-02	1.03E-02
Thyroid	1.41E-02	9.47E-03
Urinary bladder wall	3.70E-02	8.54E-02
Uterus	1.89E-02	1.54E-02
Total body	2.50E-02	2.08E-02
Effective dose (mSv/MBq)	3.15E-02	3.02E-02

After re-calculation, the radiation doses to the organs for which activity was measured in the original Pfeifer paper appear broadly similar, with the exception of the bladder wall dose, which has increased from 0.0369 mSv/MBq to 0.0854 mSv/MBq. After re-calculation, the unmeasured organs such as brain, breasts and thyroid have somewhat lower organ dose. This can be explained by the fact the

unmeasured activity assigned to the remainder of the body is lower in these new estimates since the urine excretion data lead to lower remainder of the body TIA activity, which in turns lead to lower irradiation of these organs.

5.2.2.8. Dose proportionality and time dependency

Dose proportionality does not appear to be of significant relevance since only a single dose is considered which will be administered once for diagnostic purpose.

5.2.2.9. Pharmacokinetics in the target population

Not applicable

5.2.2.10. Special populations

No studies in special populations were conducted for this application.

Breast-feeding women:
There are several publications available that report specific information on lactation cessation necessity, but none of those contains information for ^{64}Cu. Nevertheless, there is one case report available that investigated the excretion of DOTATATE (radiolabelled with ^{68}Ga) into breast milk.

Forwood 2016	68Ga-DOTA-Octreotate (DOTATATE) 200 MBq	- Case report of prominent breast tissue uptake - Breast milk sample from the patient at 90 minutes postinjection was assayed in a gamma counter and shown to have a concentration of 5.6 Bq/g per MBq - The advice to mothers should be to withhold breastfeeding for 4 hours, then discard whatever can be expressed and feed again once the milk returns.

Since no specific data is available for ^{64}Cu-DOATATE, the applicant suggests taking a conservative approach and include a window of 10 physical half-lives (10 x 12.7h), which, considering the exponential decay, should result in 99.9% of the radioisotope being eliminated (ACMUI 2018).

Impaired renal and hepatic function:

Pharmacokinetics in patients with renal or hepatic impairment have not been studied.

Please refer to the literature on renal elimination listed in section 5.2.2.6. Elimination (e.g., Larsson et al., 2012; Beauregard et al., 2012; Kashyap et al., 2013).

Other special populations:

The influence of gender, ethnicity, weight and age was not specifically addressed in any of the currently available publications on ^{64}Cu-DOTATATE. However, there is data available for DOTATATE, radiolabeled with different radionuclides (mainly ^{68}Ga and ^{177}Lu).

Elderly:

Since the elimination of DOTA-based tracers is mainly renal, it is plausible to expect that in elderly patients, with a declining renal function, could result in a slower elimination. General pharmacokinetic literature reports that renal clearance (normalized to body weight) decreases by approximately 1% annually during adulthood, with increased variability among the elderly. Comprehensive literature

reviews report reduced clearance and elevated serum concentrations in older adults, contributing to heightened drug sensitivity and risk of adverse effects (Perruca et al. 2007 and Ngcobo et al. 2025).

Age, gender, BMI, body weight, percentage of body water, SSTR2 expression:

In a study with ^{68}Ga-DOTATAE it was evaluated how age, gender and body mass index (BMI) impact the kidney uptake. The comprehensive analysis showed that only BMI is a significant confounder; increasing BMI was associated with an increasing renal radiotracer uptake, which could be explained partly with larger organ mass in larger patients. Age and gender did not significantly impact the uptake (Lee et al. 2021; non-peer-reviewed poster).

Since DOTATATE is a hydrophilic molecule with a small volume of distribution and does not partition into adipose tissue, the Applicant states that body weight itself might be a poor predictor of distribution; it is lean body mass that is expected to be a better predictor than BMI (Pai et al. 2020, Malan et al. 2022 and Barras et al. 2017).

Further to this observation, the applicant proposes that the distribution is therefore expected to be significantly different in persons with a higher percentage of body water, such as children.

In a study by Filizoglu et al. 2025, the biodistribution of ^{68}Ga-DOTATATE was evaluated in children and compared to previous reports in adults. The study revealed significant differences in the physiological bio-distribution of ^{68}Ga-DOTATATE between pediatric and adult subjects. Of note, these variations were mainly attributable to developmental differences, including the differing levels of somatic and metabolic activity in these organs and the variations in somatostatin receptor expression or hepatic metabolism with age.

Similarly, persons with a lower percentage of body water (e.g., females) might have a lower volume of distribution. However, based on the results from the study by Lee et al. 2021 (non-peer-reviewed poster), the applicant estimates the difference not to be clinically relevant.

In a PBPK model, developed and published by Siebinga et al.2021, the inter-individual variability of ^{68}Ga-DOTATATE organ distribution was solely linked to the variability in SSTR2 expression and differences in administered peptide amounts.

Ethnicity:

There is no information published on how ethnicity impacts the PK of any radiopharmaceutical. However, theoretical influences (based on body composition and renal function differences between ethnic groups) can be hypothesized.

East Asian populations often have lower average BMI but higher body fat percentage at a given BMI compared to Caucasian populations (Wang et al. 1994). African populations may have higher lean body mass compared to Europeans at similar BMIs (Wagner et al. 2000). For hydrophilic molecules like DOTATATE, these differences may cause small shifts in plasma concentration and Vd, but no published clinical evidence has shown any measurable impact on the performance of any radiopharmaceutical. On average, African Americans tend to have higher measured GFR values compared with Caucasians at the same serum creatinine (Eneanya et al. 2019 and Velasco et al. 2021). Asian populations may have lower average GFR compared to Caucasians. This was observed in a predominantly Indian cohort of predominantly vegetarians. Some individuals exhibited values classified as Stage 3 chronic kidney disease despite being generally healthy. This suggests that lower GFR may be physiologically normal within certain Asian populations (Kumar et al. 2019, Kitiyakara et al. 2012 and Kumar et al. 2018).

The applicant expects these differences to be modest and usually normalized in clinical dosing through adjustment for renal function rather than ethnicity per se.

Regarding the diagnostic performance of the tracer, theoretically, a differential expression pattern among ethnic groups could be significant. However, no scientific data could be identified that would imply such a difference, yet.

Paediatric population:

There is no relevant use of copper (^{64}Cu) dotatate in the paediatric population.

On 16 August 2024 a product specific PIP waiver was granted by EMA for copper (^{64}Cu) oxodotreotide, (EMEA-003610-PIP01-24). The waiver was granted for all subsets of the paediatric population on the condition: *Diagnosis of neuroendocrine tumours (excluding neuroblastoma)*.

5.2.2.11. Pharmacokinetic interaction studies

5.2.2.11.1. PK drug-drug interactions

The applicant did not conduct pharmacokinetic interaction studies, but provided some literature data.

Literature:

"Cold" somatostatin analogues (SSAs)

Both ^{64}Cu-DOTATATE and "cold" somatostatin (SST) analogues bind to receptor subtype 2 (SSTR2). This common molecular target of the medication and the tracer could reduce the specific PET signal by simple competition or by evoking internalisation of SSTR2.

For a comprehensive review and meta-analysis of this topic, see Wang et al. (2023), which includes literature up to March 2022. Notably, Chahid et al. (2023) published additional findings not covered in that review.

These studies indicate that SSA administration appears not to impair lesion detection, and in some cases leads to reduced background uptake (e.g., in liver and spleen), without compromising tumour visualization. These effects are thought to arise from distinct pharmacodynamic mechanisms: it has been postulated that unlabelled SSAs have negligible effect on tumour lesion uptake due to the high density of SSTR2 in neuroendocrine tumours, which allows sufficient receptor availability even in the presence of receptor saturation. In contrast, normal tissues such as liver and spleen express lower levels of SSTR2, and are more easily saturated by the cold peptide, leading to reduced background uptake.

Moreover, differences in receptor internalization and recycling may further contribute with tumours showing faster receptor re-expression compared to normal tissues, enhancing contrast over time.

These findings suggest that strict discontinuation of SSAs prior to imaging may not be necessary, and that a more individualized approach is appropriate.

Glucocorticoids

Some studies have demonstrated that glucocorticoids may downregulate SSTR2 expression, which could theoretically affect the binding and imaging characteristics of radiolabelled somatostatin analogs, including ^{64}Cu-DOTATATE.

Findings by Lam et al. (1993) and Pivonello et al. (2022, 2025) indicate that sustained glucocorticoid exposure may attenuate SSTR2 expression, with possible consequences for radiotracer uptake and lesion detectability. However, the majority of these effects have been observed in pituitary corticotroph tumors or Cushing-related NETs. Whether such downregulation is relevant in other NET populations or

at the low peptide masses used in diagnostic imaging (e.g., ~50 µg or less) is currently unconfirmed. At present, there is no direct evidence that short-term exposure to therapeutic glucocorticoids at clinically relevant doses significantly reduces SSTR2 expression in NET patients undergoing diagnostic PET imaging according to the Applicant.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

At the chemical concentrations used for diagnostic examinations, this medicinal product does not appear to have pharmacodynamic activity.

^{64}Cu-DOTATATE binds to cells that express SSTR including malignant cells, which overexpress SSTR2 (Görges 2001). ^{64}Cu is a beta+ emitting radionuclide with an emission yield that allows PET imaging (Lewis 1999).

^{64}Cu-DOTATATE has 3 main components, namely the somatostatin analogue octreotate, the chemical linker DOTA (tetraxetan) and the positron emitter ^{64}Cu.

DOTATATE shows good binding to SSTR-positive tumours in animal models (de Jong 1998). Reubi et al. reported a 9-fold increase biding to SSTR2, the receptor with the highest expression in most NENs, for DOTATATE as compared to DOTATOC (Reubi 2000).

5.2.3.2. Primary and secondary pharmacology

The relationship between copper (^{64}Cu) dotatate plasma concentrations and successful imaging was not explored in clinical trials.

At the chemical concentrations used for diagnostic examinations, this medicinal product does not appear to have any pharmacodynamic activity.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

Please refer to section 5.2.2.11. Pharmacokinetic interactions studies.

5.2.3.4. Genetic differences in PD response

Please refer to the section discussing different SSTR subtype expression patterns.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Drug-exposure-response and PK/PD approaches were not studied/provided by the applicant.

5.2.5. Dose selection and therapeutic window

Please refer to section 5.3.1. Dose response below.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Pharmacokinetics:

The applicant evaluated clinical pharmacokinetics (PK) of 64Cu-DOTATATE in a patient subset of the Phase 3 study "RMX-18-22" population, providing relevant data on radiotracer elimination, supplemented by studies from public literature.

Six NET patients from the PK sub-study of RMX-18-22 were selected based on their clinical status and their interest in participation. Considering the small size of the PK sub-set (n=6), demographic and baseline data appear roughly comparable with characteristics of the overall (safety) study population.

Overall, the amount and quality of PK data is deemed scarce and of poor quality. Nevertheless, since the radiotracer is administered only once, the dose is considerably lower than a therapeutic dose, and the condition is rare and malignant. The PK package is considered sufficient to conclude on essential PK aspects.

Distribution:

The study *by Pfeifer et al., 2012* used higher administered activities (193–232 MBq) compared to the recommended posology (148 MBq). Nevertheless, it is considered relevant for studying tracer distribution, as this difference in administered activity is expected to have no or very limited impact on distribution.

The size of the PK study population in this study is very small (n=5). However, in the context of a rare disease such as NETs, and considering that the distribution results are qualitatively consistent with those reported in other literature studies, the study is still considered useful for informing the dosimetry of the product (see topic below).

Physiological uptake of ^{68}Ga-DOTATATE tended to decrease with increasing tumour sequestration, increasing body size (lean body weight and body surface area), and increasing urinary elimination after injecting NET patients with different doses of ^{68}Ga-DOTATATE (Beauregard et al., 2012). According to Kashyap et al., 2013, the blood clearance of a high, therapeutic dose of ^{177}Lu-DOTATATE obeyed a biexponential model (first half-life of 20.8 min and second half-life of 12.9 h). Although the data for these radiotracers likely cannot be directly compared to ^{64}Cu-DOTATATE, general trends may still be extrapolated to ^{64}Cu-DOTATATE.

Metabolism:

In Study RMX-18-22, HPLC analysis of blood and urine samples showed no free-^{64}Cu, though the claim is questionable due to poor HPLC plot quality. The clinical impact of trace elements (free ^{64}Cu, ^{64}Ni, and ^{64}Zn) is probably negligible due to their low concentration in the tracer (ICH GL (Q3D (R2))). There is no consensus in the scientific community if DOTATATE yields metabolites.

Since the related ^{177}Lu-DOTATATE was considered to have a low probability of causing significant metabolism- or transporter-mediated interactions, the lack of dedicated PK interaction studies for ^{64}Cu-DOTATATE is acceptable.

Elimination:

Blood recovery: In study RMX-18-22, radioactivity in blood declined in the six patients selected for PK analysis from study RMX-18-22. Upon request, the applicant re-calculated the blood recovery post-injection using Nadler's formula (Nadler et al., 1962). The revised analysis yielded a mean blood

recovery of 72.3% ± 6.4% after 1 min. At 120 min post-injection, the average calculated blood recovery was 6.9 % and the Time-integrated activity (TIA) in the blood for the 0-2-hour period was 0.31 +/- 0.10 h. In one patient with a higher body weight (127 kg), the estimated blood recovery was lower compared to the other 5 patients. This patient also had a delayed Cmax (10 min) despite the i.v. administration.

Renal elimination: In study RMX-18-22, approximately 16-40% of radioactivity (decay corrected back to dosing time) was excreted via urine within 6 hours.

Hepatic elimination: In study RMX-18-22, hepatic elimination via feces was not determined. Conflicting data on hepatic metabolism is available in published literature regarding the in vivo stability of oxodotreotide (DOTATATE).

In addition to RMX-18-22 data, the applicant provided literature references on elimination (Anderson 2001, Esser 2006, Beauregard 2012, Kashyap 2013). Overall, these references are considered relevant, although all cited studies investigated structurally similar, but not identical radiotracer analogues. Therefore, caution is needed when extrapolating to ^{64}Cu-DOTATATE.

Dosimetry:

As the assumed parameters used by Pfeifer et al., 2012, to generate the Absorbed Doses table (e.g., an estimated urinary excretion fraction of 10%, a biologic half-life of 1h, etc.) did not appear to be consistent with more recent results, such as those from study RMX-18-22, a revised dosimetry table was provided. This updated table is based on organ TIAs reported by Pfeifer et al. (2012), incorporating updated urinary excretion and blood clearance data from the study RMX-18-22. Specifically, the bladder content and left-ventricle TIAs were calculated using total activities collected in urine (excreted) and blood time activity data, respectively. This dosimetry table is considered acceptable.

Special populations:

No studies in special populations (renal or hepatic impaired patients, paediatric patients, etc.) were conducted for this application, which was considered acceptable. ^{64}Cu-DOATATE is intended for use in adults only. In clinical practice, the administered dose for PET imaging is often adjusted based on body weight and other patient's characteristics, as well as scanner sensitivity.

Breast-feeding: Forwood et al., 2016, described that breast milk sample from a patient at 90 minutes postinjection of 200 MBq ^{68}Ga-DOTATATE showed to have a concentration of 5.6 Bq/g per MBq administered. Given that ^{68}Ga has a significantly shorter physical half-life than ^{64}Cu (68 minutes vs. 12.7 hours), and in the absence of specific elimination data for ^{64}Cu-DOATATE, the applicant proposes a conservative clearance window of 10 physical half-lives (127 hours). This duration is expected to result in ≥99.9% elimination of the radioisotope, based on exponential decay principles (ACMUI, 2018). The applicant's conservative approach in this matter is endorsed.

Gender, ethnic factors, body weight, age/elderly: According to the applicant, the influence of gender, ethnicity, weight and age was not specifically addressed in any of the currently available publications on ^{64}Cu-DOTATATE. However, there is data available for DOTATATE, radiolabeled with different radionuclides (mainly ^{68}Ga and ^{177}Lu). A comprehensive analysis by Lee et al (2021) showed that BMI is a significant confounder. BMI was associated with an increasing renal radiotracer uptake. In addition, since the elimination of DOTA-based tracers is mainly renal, it is plausible to expect that in elderly patients, with a declining renal function, could result in a slower elimination. The applicant's summary of literature is considered informative.

Paediatric population: There is no relevant use of ^{64}Cu-DOTATATE in the paediatric population.

Drug-drug-interactions (DDI):

"Cold" somatostatin analogues (SSAs)

The applicant provided a literature review addressing the impact of somatostatin analogues (SSAs) on the biodistribution of radiolabelled somatostatin receptor tracers, including ^{64}Cu-DOTATATE. It is acknowledged that prior administration of SSAs appears not to reduce tumour uptake and may, in fact, enhance tumour-to-background contrast.

Glucocorticoids

The applicant provided three literature references (Lam et al., 1993; Pivonello et al., 2022; Pivonello et al., 2025) which demonstrate that glucocorticoids could in theory influence diagnostic ^{64}Cu-DOTATATE PK and imaging by inducing downregulation of SSTR2, via (a) endogenous hypercortisolism or (b) therapeutic short- and/or long-acting glucocorticoids even this has only been shown for pituitary corticotroph tumours or Cushing-related NETs.

Pharmacodynamics:

Mechanism of action:

The proposed mechanism of action is plausible. DOTATATE is an SSTR agonist and binds to SSTR2 with 3-4 magnitudes higher affinity that to other SSTR subtypes (Reubi et al., 2000). SSTR PET typically shows high uptake in well-differentiated or low-grade lesions and lower uptake in poorly differentiated or high-grade lesions.

Primary pharmacology

The relationship between copper (^{64}Cu) dotatate plasma concentrations and successful imaging was not explored in clinical trials by the applicant. At the chemical concentrations used for diagnostic examinations, this medicinal product does not appear to have any pharmacodynamic activity.

5.2.6.2. Conclusions

Since clinical pharmacology was only studied in six patients of study RMX-18-22, the applicant provided a review of relevant studies from the literature. Overall, even though the information is very limited, the data cover the parts considered most essential for PK and PD and are considered acceptable to support a marketing authorisation for Deqtynet.

5.3. Clinical efficacy

5.3.1. Dose response study

Before the Applicant conducted a dose response study RMX-17-22, there had already been investigational clinical experience with ^{64}Cu-DOTATATE from clinical trials conducted at the University of Copenhagen, Denmark. This experience has been described in two literature references (Pfeifer, 2012; Pfeifer, 2015) provided as supportive evidence (see section 5.3.4).

Study RMX-17-22

Study RMX-17-22 was a phase 1, open-label, single-dose, dose-ranging study to identify the lowest amount of administered dose to obtain a diagnostic quality ^{64}Cu- DOTATATE PET-CT Scan for Imaging Patients with Known Somatostatin Receptor-positive Neuroendocrine Tumors (NETs).

Objectives

The primary objective was to identify the lowest amount of administered radiotracer dose of ^{64}Cu-DOTATATE that provides diagnostic quality PET-CT image, coincident with the as low as reasonably achievable (ALARA) principle.

The secondary objective was to assess the effect of radiotracer (^{64}Cu-DOTATATE) dose on PET-CT image quality.

Study population

Patients with confirmed neuroendocrine tumours (NET) were eligible for the study. NET was to be confirmed either based on histology/biopsy report; or based on conventional imaging scans of affected area such as MRI and/or contrast enhanced CT and/or an FDG PET-CT scan and/or NaF PET-CT scan and/or OctreoScan® performed within 8 weeks prior to study date.

In total, 12 patients were planned to be recruited. All patients were recruited from one clinical site, Excel Diagnostics and Nuclear Oncology Center, US.

Dose levels

Dose levels were based on the work of Pfeifer (2012) and Pfeifer (2015). The mean dose of ^{64}Cu-DOTATATE given in Pfeifer, 2012, Pfeifer, 2015, study was 5.45 mCi. This dose was chosen by Pfeifer et al based on previous experience with SSTR PET imaging agents like ^{68}Ga-DOTATATE.

The rationale for the dose-ranging study is based on the ALARA (as low as reasonably achievable) principle. In this study, 3 dose levels were administered to 4 patients within three dose cohorts i.e. 3 mCi (111 MBq) ± 10%, 4 mCi (148 MBq) ± 10% and 5 mCi (185 MBq) ±10%. The study drug was administered as an i.v. bolus injection.

Patients were randomly assigned to one of the three dose levels based on the randomization list for the study.

Study assessments

A PET-CT image was acquired 60 ±15 minutes after injection of ^{64}Cu-DOTATATE. In order to determine the radiotracer dose effect on ^{64}Cu-DOTATATE PET-CT image quality, the images acquired at the clinical site were transferred to the sponsor. The sponsor performed blinding and randomisation of images.

The images were provided to three nuclear medicine physicians, blinded to the dose of the images. Images were reviewed qualitatively and a questionnaire was completed by each nuclear medicine physician independently.

All three readers assessed the image quality of each subject in the cohort and assigned a score according to the table below. The sponsor then unblinded the independent reader's assessment and calculated average score for each subject in the cohort.

The average scores (based on 3 readers) for each subject were entered in a database and the sum of all the subjects score of the given cohort was considered in selecting the dose level cohort that provides diagnostic quality image.

Table 10. Image technical assessment criteria for image quality assessment

No.	Image technical assessment criteria	Score
1	Inadequate: images look grainy with poor delineation of lesions.	0

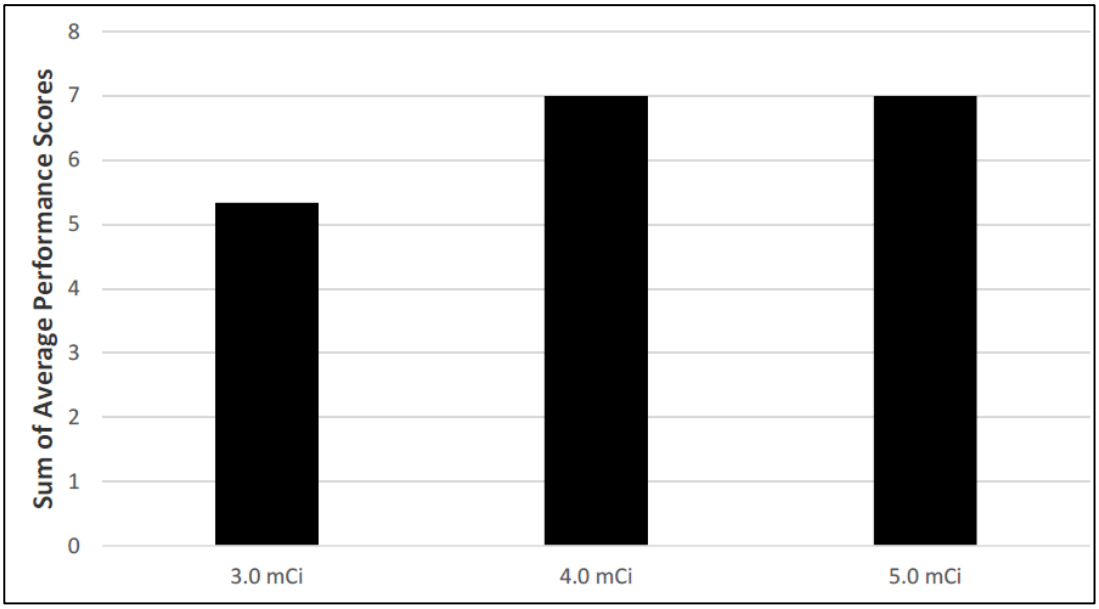
2	Questionable: images are clear but lesions delineation is suboptimal and small lesions (1 cm) are hard to assess	1
3	Acceptable: images are clear and large and small lesions delineation is possible	2

The lowest dose level cohort of radiotracer which met the quality performance score of ≥7 was to be selected for a future efficacy study.

Efficacy

The study yielded image quality scores for the three dose groups (3 mCi, 4 mCi and 5 mCi) of 5.333, 7.0 and 7.0, respectively.

Figure 13. Sum of Average Per Patient Image Quality Scores by Dose Group



5.3.2. Main study

5.3.2.1. Study RMX-18-22 (NCT03673943)

5.3.2.1.1. Study title: An Open-label, Single-dose, Single arm, Single-center Clinical Trial of ^{64}Cu-DOTATATE (NETMedix™) PET-CT Scan for Imaging Patients with Known or Suspected Somatostatin Receptor-positive Neuroendocrine Tumors (NETs)

5.3.2.1.2. Study design

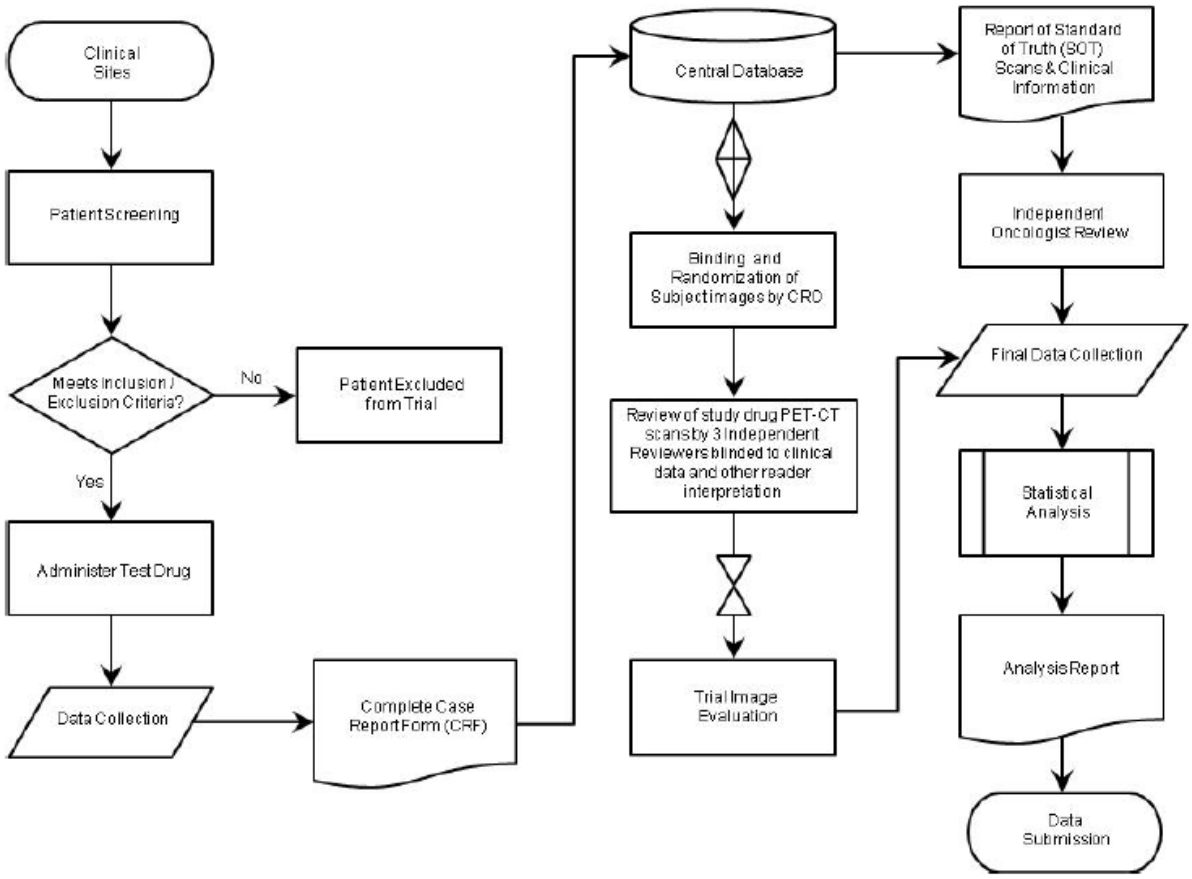
RMX-18-22 was an open-label, single-dose, single-arm, single-centre, non-comparative phase 3 study to assess imaging performance of ^{64}Cu-DOTATATE PET-CT versus standard of truth (SoT).

The group comparison was within-subject, i.e. ^{64}Cu-DOTATATE and the SoT were assessed in the same subject.

The duration of subject participation was from the time of signing the informed consent form through the 2-day post-injection visit.

For investigations of PK and safety, please refer to respective sections of this report.

Figure 14. Flow-chart of data collection, processing and interpretation



PET-CT Imaging

According to the study protocol, a PET-CT image was to be acquired 60 ±15 minutes after the injection of the ^{64}Cu-DOTATATE dose. Imaging was to be performed using a dedicated PET-CT unit; whole-body examinations (top of the skull to mid-thigh) were to be performed with the subject in a supine position. The time to acquire PET-CT images was defined differently in the SAP, however the applicant stated that the protocol was followed during the clinical study.

A non-contrast-enhanced CT scan for all examinations was to be performed using the CT exposure factors of 140 kVp and 80 mA in 0.5 s. With subject position maintained, a whole-body PET emission scan was to be performed covering an area identical to that covered by CT; scans were to be performed in 3-dimensional mode. All PET acquisitions were to be carried out in 3-dimensional mode (at least 5 minutes per bed position), over an approximately 30-minute scanning time. PET images were to be reconstructed using CT for attenuation correction and using ordered-subsets expectation maximization with 2 iterations and 24 subsets.

Imaging data interpretation

Standard of truth (SoT)

For patients, composite conventional imaging modalities as well as pathology results were to be used for detection of disease. Imaging modalities including anatomical imaging (CT and/or MRI) or functional imaging (NaF and/or ^{18}F-FDG and/or bone scan and/or Octreoscan) and collective information from these scans were used for assessment of disease.

For healthy volunteers, CT (acquired with contrast agent) component of the study drug (^{64}Cu-DOTATATE PET-CT) read by an independent radiologist blinded to PET image was to be used to further verify the volunteers as having a negative SoT.

A single independent oncologist was to perform a blinded assessment of patients' diagnoses based upon all non-investigational diagnostic data (including diagnostic imaging outlined above but excluding the ^{64}Cu-DOTATATE imaging) for determination of disease. Patients categorized as "Disease" were to be further categorized as "Localized" or "Metastatic" disease. The final decision on the SoT outcome was to be made by an oncologist.

Table 11. Criteria for standard of truth (SoT) determination

No.	SOT	Outcome
1	Confirmed histopathologically NET tumors, if not fully resected	Disease
2	At least one lesion identified by anatomical imaging (CT and/or MRI) or functional imaging ($Na^{18}F$ and/or ^{18}F-FDG and/or bone scan and/or Octreoscan) and consistent clinical data.	Disease
3	Healthy volunteers or patients with neither histological confirmation nor a lesion identified on anatomical imaging (CT and/or MRI) or functional imaging ($Na^{18}F$ and/or ^{18}F-FDG and/or bone scan and/or Octreoscan) and clinical data inconsistent for NET.	No Disease

Definition of SoT tests:

a. Pathological confirmation: A biopsy report confirming presence of histologically confirmed somatostatin receptor expressing neuroendocrine tumour. The test is true negative if histologically confirmed tumour has been fully resected with no evidence of disease throughout the body by other SOT tests, including clinical data.

b. Anatomical imaging (CT, MRI): A diagnostic CT or MRI report suggestive of abnormal tissue mass consistent with NET.

c. Functional imaging (18F-FDG and NaF and bone scan): Functional imaging report suggestive of metabolically active tumour/lesion on 18F-FDG scans. For positive lesions non-specific inflammatory/infectious lesions should be excluded. Negative FDG findings were not to rule out a NET lesion, since some low-grade NET lesions are not FDG avid. Lesions in skeletal system based on NaF PET/CT imaging or bone scan. Lesions identified on Octreoscan SPECT imaging scan.

If available, pathological confirmation (a) was to serve as a stand-alone SoT. If (a) was not available, anatomical (b) and/or functional imagining (c) were to be used.

^{64}Cu-DOTATATE PET/CT images

The PET-CT images acquired at the clinical site were to be transferred to the imaging contract research organization (CRO), including PET-CT images of 4 subjects from the selected dose cohort of Phase 1 study. The CRO was to perform blinding and randomisation of images and to provide the images to 3 independent nuclear medicine physicians, previously trained by the CRO to detect scintigraphic hot spot images associated with somatostatin receptors. These independent physicians were to categorize patients as "Disease" or "No Disease". If a patient is categorized as "Disease", the physicians were to further categorize patients as "Localized" or "Metastatic" disease. All three independent readers' assessments were to be recorded in the database and considered for final analysis. Ten percent of the images read were to be randomly selected for the assessment of intra-reader variability. Cases

selected for intra-reader variability were to be reintroduced to the independent reviewers no earlier than four weeks after the primary read.

^{64}Cu-DOTATATE PET-CT images vs SoT comparison

A comparison of independent image reviewer's assessment (^{64}Cu-DOTATATE PET-CT images) and independent oncologist's assessment (SoT) were to be made to categorize patients in true positive, true negative, false positive and false negative patients.

Treatment

The study drug is ^{64}Cu-DOTATATE, where ^{64}Cu (the tracer) is a positron-emitter, Octreotate (the peptide) is a somatostatin analogue, and DOTA (chelator) is a chemical chelator used to link ^{64}Cu to Octreotate.

^{64}Copper is a positron-emitting isotope with intermediate half-life (12.7 hours), produced in a cyclotron by bombarding proton beam to an enriched ^{64}Ni target to produce ^{64}Ni(p,n) ^{64}Cu nuclear reaction.

Table 12. Radiochemical characteristics of ^{64}Cu isotope

^{64}Cu physical half-life T½	Decay product	Maximum positron energy	Maximum linear range
12.7 hrs	^{64}Ni (61%) ^{64}Zn (39%)	0.66 MeV	1.0 mm

The ^{64}Cu-labelled radiopharmaceuticals were produced at a centralized production facility (RadioMedix Inc).

The study drug was to be administered as an i.v. bolus injection. Injection was to be given by hand directly into a 22 or 24 gauge catheter at a rate of 3-4 mL/min and the catheter was to be flushed with 3 ml of normal saline post-injection. The estimated radioactive dose was to be determined by measuring the amount of radioactivity in the syringe pre- and post-injection, using a calibrated radioisotope dose calibrator in accordance with the nuclear medicine department's SOPs. The difference in radioactivity before the injection and after injection was to be considered as the total injected dose.

There was a discrepancy between the SAP and the protocol regarding the following items: the dose of radioactivity, waiting time allowed for tracer distribution, and PET scan acquisition time. The SAP required an injection of 185-227 MBq (5.0-6.0 mCi) of ^{64}Cu-DOTATATE followed by a 20 minute PET scan beginning 50 minutes post-injection. The protocol required an injection of 148 ± 10% MBq (4.0 ± 10% mCi) of ^{64}Cu-DOTATATE followed by a 5 minute per bed position PET scan beginning 60 ± 15 minutes post-injection. According to the applicant, the protocol was followed during the clinical study. The dose 148 ± 10% MBq (4.0 ± 10% mCi) was also selected in the dose-ranging study RMX-17-22.

Subjects were advised to increase fluid intake at baseline and after image acquisition to maintain proper hydration throughout the study period and decrease radiation exposure to the urinary bladder. To enhance imaging, subjects were encouraged to void prior to study imaging, post-injection.

As a note, no comparator was used in this study. The ^{64}Cu-DOTATATE PET image results for each patient were compared to the results with the SoT to define diagnostic performance of ^{64}Cu-DOTATATE.

Randomisation and blinding

^{64}Cu-DOTATATE PET/CT images

The interpretation of the Cu-DOTATATE PET/CT images was performed by three independent nuclear medicine physicians. All readers independently reviewed anonymized imaging datasets and were blinded to all clinical information, including patient identifiers, patient medical history, laboratory results, eligibility criteria, and the SoT imaging and associated interpretation.

Standard of truth (SoT)

The SoT was assigned retrospectively by a single independent oncologist who was not involved in patient enrolment or clinical care, and who was blinded to the PET image interpretation results. The independent oncologist was provided with a curated clinical data package, which included pathology result, non-study imaging reports (e.g., CT, MRI, FDG PET-CT, NaF PET-CT, bone scan, Octreoscan, Ga-DOTATATE PET-CT), medical history, physical examination findings, and clinical information used for eligibility, as well as any additional relevant clinical information (e.g. follow-up imaging (CT, MRI, PET), histopathology, or relevant laboratory markers (e.g., Chromogranin A, serotonin)) that became available after enrolment but before database lock.

Patient population

RMX-18-22 was performed at a single centre in the US (Excel Diagnostics and Nuclear Oncology Center in Houston, Texas).

Sample size calculation

The study was powered with respect to the co-primary endpoints of sensitivity and specificity. In order to have at least a 80% chance of showing that the sensitivity was at least 0.70 and the specificity was at least 0.60 **a sample of 63 subjects was needed**, divided among n1 = 42 SoT positive subjects and n2 = 21 SoT negative subjects. This sample size was derived under the assumptions that the readers were viewing the same images and that their reads were correlated at r = 0.70 and that the true Sensitivity and Specificity are each 0.90. The study was powered at 90% for each subtest to give the overall study 80% power. This sample size was determined by Monte Carlo simulation with the parameter values given above. The simulation used 5000 replications: the standard error of the estimated power was no more than 0.6%. To satisfy the sample size requirements for each endpoint a total of n=63 subjects was needed, allocated in a 2:1 (Positive:Negative) ratio. These calculations assumed a one-sided α=0.025 level of significance and that the data came from a binomial distribution.

The study was therefore planned to recruit a total of 59 subjects, including both healthy volunteers and patients with confirmed or suspected neuroendocrine tumours (NETs). The efficacy analysis was planned to include 63 subjects, 59 subjects from this phase 3 trial and 4 patients from the selected dose cohort of the phase 1 Study RMX-17-22.

Key inclusion criteria:

Patients

1. Subjects of either sex, aged ≥18 years.
2. Meet *at least one* of the following criteria:
    a. Confirmed or suspicion of NET based on histology/ biopsy report.

b. Confirmed or suspicion of NET based on conventional imaging scans of affected area such as MRI AND/OR contrast enhanced CT AND/OR an FDG PET-CT scan AND/OR NaF PET-CT scan AND/OR OctreoScan® AND/OR clinical symptoms performed within 8 weeks prior to study date.

Healthy volunteers (HV)

1. Healthy male or female subjects age ≥18 years of age included,
2. Subject in good health as determined by absence of clinically significant abnormalities determined by a full medical history, physical examination, vital signs and clinical laboratory tests.

Patients and HV

1. Recent blood test results (within 4 weeks pre-dose) as follows: WBC: >2 x 109/L; Haemoglobin: >8.0g/dL; Platelets: >50 x 109/L; ALT, AST, AP: ≤5 times ULN; Bilirubin: ≤3 times ULN; Serum creatinine: <170 µmol/L

Key exclusion criteria:

1. Therapeutic use of any somatostatin analogue, including Sandostatin LAR (within 28 days) and Sandostatin (within 2 days) prior to study imaging. If a subject is on Sandostatin LAR, a wash-out period of 28 days is required before the injection of the study drug.
2. History or presence of significant haematological abnormalities or immunodeficiency or any condition that might compromise the immune system (infection, vaccination), of any aetiology as indicated by clinically significantly abnormal values of following hematologic parameters (platelets, haemoglobin, WBC count and ANC).
3. Acute or chronic clinically significant conditions such as uncontrolled congestive heart failure (rule out with MUGA scan, if suspected), liver or kidney dysfunction, uncontrolled hypertension
4. Participation in other clinical research trials involving evaluation of other investigational treatments within 30 days prior to enrolment and/or unwilling to allow at least one week before participation in another drug trial following the current study.

5.3.2.1.3. Objectives and estimands

Primary objective

The primary objective was to assess the performance (sensitivity and specificity) of ^{64}Cu-DOTATATE PET-CT imaging in subjects with known or suspected NETs, by comparing individual reader results to the standard of truth (SoT) for each subject.

The co-primary endpoints were sensitivity and specificity of ^{64}Cu-DOTATATE PET-CT imaging when each imaging reader's subject-level result is compared to a SOT for the subject, with primary endpoint success defined as the same two out of three readers having sensitivity and specificity results exceeding the specified thresholds (>70% for sensitivity and >60% for specificity).

The following two-way table was to be utilized to compute sensitivity, specificity, NPV, PPV, and accuracy:

Table 13. Data collected to compute sensitivity, specificity, NPV, PPV and accuracy

		SOT Reference Standard	
		Disease	No Disease
^{64}Cu-DOTATATE Scan Result	Disease	TP	FP
	No Disease	FN	TN

Based on the above table, the co-primary effectiveness endpoints were to be computed as follows:

- sensitivity = TP/(TP + FN)
- specificity = TN/(TN + FP)

Estimand for the primary objective

The applicant has not defined an estimand for the primary objective.

Upon request, the applicant provided a table of estimand attributes according to the ICH E9 (R1) addendum on estimands. Intercurrent events (ICEs) were handled as follows: for the ICE of receiving treatment between evaluation of SoT and PET scan and PET scan being evaluated outside the scheduled window a treatment policy strategy was applied. For the ICE of an image not being evaluable a principal stratum strategy was applied, restricting the analysis to patients for whom the scans were evaluable (evaluable by all readers for majority read).

Statistical methods for estimation and sensitivity analysis on primary endpoint

Analysis Sets

All efficacy analyses were conducted in the efficacy evaluable (EE) population. The EE population consisted of all subjects who were enrolled in the phase 3 study and 4 subjects from the selected 4.0 mCi dose cohort of the Phase 1 study having the following characteristics:

- had an established SoT;
- were injected with ^{64}Cu-DOTATATE; and
- had an image read result using ^{64}Cu-DOTATATE by three independent readers.

Statistical Analyses

The co-primary endpoints of sensitivity and specificity were calculated on a by-reader basis. The individual results were aggregated.

The co-primary endpoints were estimated as point estimates and 95% confidence intervals calculated with the score method.

The following two hypotheses were tested for the coprimary endpoints:

- Ha0: Sensitivity ≤ 70% vs Ha1: Sensitivity > 70%

and

- Hb0: Specificity ≤ 60% vs Hb1: Specificity > 60%

Each hypothesis test was conducted at the one-sided alpha level of 0.025. The sensitivity and specificity were calculated on a by-reader basis. Success was to be declared if two of the three independent readers achieve sensitivity and specificity significantly over the threshold. That is, the same two out of three readers must achieve success upon sensitivity and specificity.

Secondary objectives

Secondary objectives:

- To characterize the predictive value of ^{64}Cu-DOTATATE PET-CT imaging when comparing an imaging reader-majority rule determination to the SoT for each subject and also when the comparison is performed on an individual reader basis.
- To evaluate the imaging performance (sensitivity and specificity) of ^{64}Cu-DOTATATE when comparing an imaging reader-majority rule determination to the SoT for each subject.
- To evaluate the imaging performance of ^{64}Cu-DOTATATE to determine if subjects have metastatic or local disease as compared to the SoT.

Secondary endpoints:

- majority of readers sensitivity and specificity
- majority of readers positive predictive value (PPV) and negative predictive value (NPV);
- majority of readers accuracy;
- individual reader sensitivity and specificity in distinguishing between localized and metastatic disease;
- majority read sensitivity and specificity in distinguishing between localized and metastatic disease;
- individual reader accuracy, PPV, and NPV.

Table 14. Data collected to compute sensitivity, specificity, NPV, PPV and accuracy

		SOT Reference Standard	
		Disease	No Disease
^{64}Cu-DOTATATE Scan Result	Disease	TP	FP
	No Disease	FN	TN

Based on the above table, the endpoints were to be computed as follows for the respective Cu-DOTATATE results and SOT corresponding to the endpoint:

- positive predictive value (PPV) = TP/(TP + FP)
- negative predictive value (NPV) = TN/(TN + FN)
- accuracy = (TP + TN) / (TP + TN + FP + FN)

Estimands for the secondary objectives

The applicant has not defined estimands for the secondary objectives.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

The secondary endpoints were estimated as point estimates and 95% confidence intervals calculated with the score method. Sensitivity, specificity, PPV, NPV and accuracy are defined as above.

Tertiary objective

Tertiary objective:

- To evaluate the intra-reader and inter-reader agreement.

Tertiary endpoints:

- intra-reader agreement
- inter-reader agreement

Estimand for the tertiary objective

The applicant has not defined estimands for the secondary objectives.

Statistical methods for estimation and sensitivity analysis on the tertiary estimands

For each reader pair (Readers 1&2, Readers 1&3, and Readers 2&3), a Cohen's Kappa along with a 95% confidence interval on Cohen's Kappa was computed. A Generalized Fleiss Kappa and associated 95% confidence interval were computed to assess overall agreement among the 3 readers. Intra-reader variability was assessed using the n=10 randomly chosen study images that are re-read by the readers. Cohen's Kappa was computed for each reader on the pairs of re-reads.

5.3.2.1.4. Results

Participant flow and numbers analysed

Table 15. Subject disposition

	Overall
Screen Failure	2
Enrolled	66
Completed	63 (95.5%)
Early Termination (Withdrawal)	3 (4.5%)
Reason for Early Termination (Early Withdrawal)	
Death	0 (0.0%)
Adverse Event	0 (0.0%)
Lost to Follow Up	0 (0.0%)
Withdrawal of Subject Consent	3 (4.5%)
Investigator Discretion	0 (0.0%)
Protocol Deviation	0 (0.0%)
Sponsor Discretion	0 (0.0%)
Other	0 (0.0%)

Treatment compliance

A total of 63 subjects were injected with a mean dose of 4.11 mCi of ^{64}Cu-DOTATATE. A total of 62 subjects received a dose of 4 mCi ± 10% of ^{64}Cu-DOTATATE. One healthy subject received a total injected dose of 3.5756 mCi of ^{64}Cu-DOTATATE.

Deviations from study plan

Intra-reader variability: Intra-reader variability was planned to be assessed using n=10 randomly chosen study images that were re-read by the readers. This was interpreted to mean n=10%, thus n=7 randomly chosen study images were ultimately re-read by the readers.

Standard of truth: ^{68}Ga-DOTATATE PET-CT reports were included in the clinical data package that was presented to the independent oncologist in order to establish the SoT as ^{68}Ga-DOTATATE is the new gold standard for somatostatin receptor positive NET tumours. The revised SoT was therefore defined as follows: confirmed or suspicious NET disease by histology or conventional anatomical and/or functional imaging modalities including but not limited to magnetic resonance imaging (MRI), computed tomography (CT), F-18 FDG PET-CT, F-18 NaF bone PET-CT, bone scintigraphy, and/or Octreoscan®, and/or ^{68}Ga-DOTATATE PET-CT. This SoT was the SoT used in the analysis.

Baseline data

Table 16. Demographics and baseline characteristics - EE population

Characteristic	Overall (N = 63)
Age (years), n	
Mean (SD)	54.37 (15.65)
Median (min, max)	54.00 (25.0, 82.0)
Height (**cm**), n	
Mean (SD)	171,8 (11,5)
Median (min, max)	172,72 (147,3., 199,8)
Weight (**kg**), n	
Mean (SD)	83,9 (20,8)
Median (min, max)	80,73 (51,7,148,3)
Gender, n (%)	
Male	28 (44.4%)
Female	35 (55.6%)
Race, n (%)	
American Indian or Alaska Native	0 (0.0%)
Asian	2 (3.2%)
Black or African American	6 (9.5%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)
White	54 (85.7%)
Other	1 (1.6%)
Ethnicity, n (%)	
Hispanic or Latino	11 (17.5%)
Not Hispanic or Latino	52 (82.5%)
Unknown	0 (0.0%)
Not Reported	0 (0.0%)

The trial population (n=59; excluding 4 patients from the phase 1 RMX-17-22 study) consisted of:

- 21 healthy volunteers,
- 5 subjects with suspected NETs or pheochromocytoma,
- 33 patients with known NETs or pheochromocytoma.

Table 17. Baseline disease characteristics

[*Healthy volunteers and subjects with suspected disease with no information were excluded from this table*]

Subject ID #	Subject Category	Tumor Origin	*Pathology Description*	Grade[1]	Ki67 (%)	Prior Treatment	Ongoing Treatment
[redacted]	Suspicious/ Pheo	Adrenal Gland	*Pheochromocytoma*			Surgery	
[redacted]	Patient/NET	Pancreas	*Intermediate Diferentiated NET*	G2	4		
[redacted]	Patient/NET	Pancreas	*Well Differentiated NET*	G3	22		
[redacted]	Patient/NET	Rectum	*Well Differentiated NET (grade II)*	G2	(2-10)		
[redacted]	Patient/NET	Pancreas	*Well Differentiated NET*	G1	(2-3)	Octreotide LAR/Surgery/TACE/CHT	Octreotide LAR
[redacted]	Patient/NET	Small Intestine	*Well Differentiated NET*	G1	2	Surgery/TACE/EBRT	
[redacted]	Patient/NET	Pancreas	*Metastatic Pancreatic NET with extensive degeneration*		NA		
[redacted]	Patient/NET	Pancreas	*Carcinoma with Neuroendocrine Differentiation*		NA	CHT/EBRT	
[redacted]	Patient/NET	Pancreas	*Well Differentiated NET*	G1	(1-2)		
[redacted]	Patient/NET	Colon	*Well Differentiated NET*		NA	Lanreotide LAR	
[redacted]	Patient/NET	Pancreas	*Well Differentiated NET*	G1	2,4	Surgery/TACE/Octreotide LAR	
[redacted]	Patient/NET	Unknown	*Well Differentiated Low Grade NET*		NA	Lanreotide LAR	
[redacted]	Patient/NET	Small Intestine	*Carcinoid Tumor*		NA	Surgery/TACE/Octreotide/Octreotide LAR	
[redacted]	Patient/NET	Unknown	*Metastatic NET*		NA		
[redacted]	Patient/NET	Rectum	*Carcinoid*	G1	(1-2)	Surgery/EBRT	
[redacted]	Patient/NET	Small Intestine	*Well Differentiated NET*		NA	Octreotide LAR	

[redacted]	Patient/NET	Small Intestine	*Well Differentiated NET*	G1	2	TACE/Surgery/Lanreotide	Lanreotide*
[redacted]	Patient/NET	Colon	*NET*	G2	6	Surgery	
[redacted]	Patient/NET	Small Intestine	*Low Grade*		NA		
[redacted]	Patient/NET	Pancreas	*Well Differentiated Low Grade NET*	G1	<3	Surgery	
[redacted]	Patient/Pheo	Adrenal Gland	*Pheochromocytoma*	G1	1	Surgery	
[redacted]	Patient/NET	Rectum	*Carcinoid*		NA	Surgery	
[redacted]	Patient/NET	Pancreas	*Well Differentiated NET*	G2	4,8	SIRT/TACE/Surgery/Lanreotide/Sunitinib	
[redacted]	Patient/NET	Lung	*Carcinoid*	G2	5	Surgery/EBRT/CHT/Lanreotide	Lanreotide*
[redacted]	Patient/NET	Colon	*Well Differentiated NET*	G1	<2	Surgery	
[redacted]	Patient/NET	Unknown	*Metastatic High Grade NET*	G3	100	Surgery	
[redacted]	Patient/NET	Pancreas	*Moderately Differentiated Metastatic Neuroendocrine Carcinoma*			Octreotide/Denosumab/PRRT	
[redacted]	Patient/NET	Lung	*Atypical Carcinoid*	G3	(30-40)	EBRT/CHT/SBRT/PRRT/Lanreotide/Denosumab	
[redacted]	Patient/NET	Pancreas	*Well Differentiated NET*	G2	5	Surgery/Octreotide/Everolimus	
[redacted]	Patient/NET	Small Intestine	*Small Intestine Metastatic NET*	G2	18	Surgery/Lanreotide LAR/PRRT	Lanreotide LAR*

Subject ID #	Subject Category	Tumor Origin	*Pathology Description*	Grade[1]	Ki67 (%)	Prior Treatment	Ongoing Treatment
[redacted]	Patient/NET	Rectum	*Well Differentiated NET*	G2	(3-20)	Surgery/Lanreotide/EBRT/PRRT	
[redacted]	Patient/NET	Pancreas	*NET*	G1	2	CHT/Octreotide LAR/PRRT	CHT/Octreotide LAR*
[redacted]	Patient/NET	Pancreas	*Well Differentiated NET*	G2	9	Surgery/TACE/SIRT/CHT/RF/Octreotide LAR/PRRT	CHT/Octreotide LAR*
[redacted]	Patient/NET	Colon	*Well Differentiated NET*	G1	<3	Surgery/SBRT/CHT/TACE/SIRT/PRRT	

[1]Classification based on Ki-67 values

NET=neuroendocrine tumour, Pheo=pheochromocytoma, CHT= chemotherapy, EBRT= external beam radiation therapy, SBRT=single beam radiation therapy, TACE=trans arterial chemo embolization, SIRT= selective internal radiation therapy, PRRT=pepetide receptor radionuclide therapy, RF=radiofrequency

* Washout period of 2 and 28 days before the imaging for short- and long-acting somatostatin analogues was kept

Outcomes and estimation

Co-primary endpoints

Table 18. Summary of Individual Reader Results for ^{64}Cu-DOTATATE PET Imaging Versus SOT – EE Population (N=63)

Reader	Parameter	Estimate (95% CI)	Reader passes Sensitivity and Specificity hypotheses?
Reader 1	sensitivity	0.9091 (0.7567, 0.9808)	Yes
	specificity	0.9333 (0.7793, 0.9918)	Yes
Reader 2	sensitivity	0.9091 (0.7567, 0.9808)	Yes
	specificity	0.8000 (0.6143, 0.9229)	Yes
Reader 3	sensitivity	0.9091 (0.7567, 0.9808)	Yes
	specificity	0.9000 (0.7347, 0.9789)	Yes

Ancillary analyses

The applicant was requested to provide an estimate for the diagnostic performance (sensitivity and specificity) of an average rater evaluating an average subject, by fitting two logistic regression models for cases and controls as determined by SoT to all available data and reporting the estimated marginal means (LS-means) of sensitivity and specificity. The models include both rater and subject as random or fixed effects and use Firth correction, since the occurrence of perfect separation is likely.

The sensitivity for an average rater evaluating an average patient was estimated, using LS-means, to be **0.8254** (95% CI: 0.7405, 0.8868). The specificity for an average rater evaluating an average patient was estimated, using LS-means, to be: **0.8156** (95% CI: 0.7244, 0.8815).

There were uncertainties regarding the inclusion, in the reference standard (SoT), of other diagnostic agents sharing the same mode of action as ^{64}Cu-DOTATATE. The use of alternative somatostatin analogues within the SoT was therefore further examined. The applicant clarified that no patients had ^{68}Ga-DOTATATE images included in their reference standard. However, some patients had Octreoscan images incorporated into the composite reference. To address this, a subgroup analysis excluding these patients was provided (see table below).

Table 19. Subgroup Analysis excluding patients with SSTR imaging agents in SoT

Reader	Parameter	Efficacy Evaluable (EE) Population		Subgroup analysis: Excluding 10 patients with SSTR imaging agents in SoT	
		n	Estimate (CI**)	n	Estimate (CI**)
R1	Sensitivity	33	0.91 (0.76, 0.98)	24	0.92 (0.73, 0.99)
R1	Specificity	29	0.97 (0.82, 0.99)	29	0.93 (0.77, 0.99)
R2	Sensitivity	33	0.91 (0.76, 0.98)	24	0.88 (0.68, 0.97)
R2	Specificity	30	0.80 (0.61, 0.92)	29	0.79 (0.60, 0.92)
R3	Sensitivity	33	0.91 (0.76, 0.98)	24	0.92 (0.73, 0.99)
R3	Specificity	30	0.90 (0.73, 0.98)	29	0.90 (0.73, 0.98)
Average rater	Sensitivity	0.8254 (95% CI: 0.7405–0.8868)			
Average rater	Specificity	0.8156 (95% CI: 0.7244–0.8815)			
Average rater	Sensitivity			0.825 (95% CI: 0.723, 0.895)	
Average rater	Specificity			0.813 (95% CI: 0.720, 0.881)	

The sensitivity for an average reader evaluating an average patient was estimated, using LS-means, to be 0.8254 (95% CI: 0.7405–0.8868).
The specificity for an average reader evaluating an average patient was estimated, using LS-means, to be 0.8156 (95% CI: 0.7244–0.8815).

Secondary endpoints

Table 20. ^{64}Cu-DOTATATE PET Majority Read Imaging Versus Standard of Truth Two-Way Table – EE Population (N=63)

		Standard of Truth		
Method of Evaluation		**Disease**	**No Disease**	**Total**
^{64}Cu-DOTATATE Scan Results	**Disease**	30	1	31
	No Disease	3	28	31
	Total	33	29	62

Table 21. Summary Statistics for ^{64}Cu-DOTATATE Majority Read Imaging Versus Standard of Truth – EE Population (N=63)

	Summary Statistics		
Parameter	**Estimate**	**95% CI**	**p-Value**
Sensitivity[a]	0.9091	(0.7643, 0.9686)	0.0042
Positive Predictive Value	0.9677	(0.8381, 0.9943)	
Specificity[b]	0.9655	(0.8282, 0.9939)	<0.0001
Negative Predictive Value	0.9032	(0.7510, 0.9665)	
Accuracy	0.9355	(0.8455, 0.9746)	

CI=Confidence Interval
[a] One sided α=0.025 test of H_{a0}:Sens $\leq$0.70 vs. H_{a1}:Sens>0.70
[b] One sided α=0.025 test of H_{b0}:Spec $\leq$0.60 vs. H_{b1}:Spec>0.60

The above analysis was adapted to provide Clopper-Pearson confidence intervals. The estimate and 95% Clopper-Pearson CIs for the majority read are as follows: Sensitivity – 0.9091 (0.7567, 0.9808); Specificity - 0.9655 (0.8224, 0.9991).

Table 22. Individual Reader Summary Statistics for ^{64}Cu-DOTATATE PET Imaging Versus SOT – EE Population (N=63)

Reader	Parameter		
	PPV	NPV	Accuracy
1	0.9677	0.9032	0.9355
2	0.8333	0.8889	0.8571
2	0.9091	0.9000	0.9048

Readers who identified an image as positive were asked to further classify the disease as localized or metastatic. Sensitivity and specificity were determined relative to the SOT.

Table 23. Majority Read Classification of Localized and Metastatic Disease – EE Population (N=63)

Majority of Readers Classification	Standard of Truth		Sensitivity	Specificity
	Localized Disease (N=5)	Metastatic Disease (N=28)		
Localized Disease	2 (40.0%)	0 (0.0%)	1.0000	1.0000
Metastatic Disease	0 (0.0%)	28 (100.0%)		

Additional 3 patients were initially labelled as having localized disease according to SoT. However, this was attributed to an error in the SoT central read by one oncologist, as these patients initially had primary tumour but it was resected. The SoT for these patients was updated to 'not disease'.

Tertiary endpoints

Table 24. Summary of Inter-Reader Agreement for Assessment of ^{64}Cu-DOTATATE Imaging – EE Population (N=63)

Reader Pair	n	Kappa (SE)	95% CI on Kappa
1 vs. 2	62	0.7419 (0.0844)	(0.5764, 0.9074)
1 vs. 3	62	0.8710 (0.0623)	(0.7489, 0.9930)
2 vs. 3	63	0.7123 (0.0883)	(0.5392, 0.8855)
Overall	63	0.7664 (0.0732)	(0.6229, 0.9099)

SE=Standard Error
CI=Confidence Interval

Table 25. Summary of Intra-Reader Agreement of ^{64}Cu-DOTATATE PET Imaging – EE Population (N=63)

		Summary Statistics	
Reader	Parameter	Estimate	95% CI
1	Kappa	1.0000	(1.0000, 1.0000)
	Uncorrected Agreement	1.0000	(0.5904, 1.0000)
2	Kappa	0.5333	(0.0596, 1.0000)
	Uncorrected Agreement	0.7143	(0.2904, 0.9633)
3	Kappa	1.0000	(1.0000, 1.0000)
	Uncorrected Agreement	1.0000	(0.5904, 1.0000)

CI=Confidence Interval

Pre-defined and post-hoc subgroup analyses

No pre-defined subgroup analyses were performed.

5.3.3. Clinical studies in special populations

No clinical studies in special populations have been performed.

5.3.4. Supportive studies

5.3.4.1. NETMedix Denmark Trial

This was a retrospective analysis of a study of the use of ^{64}CU-DOTATATE for the detection of somatostatin receptor-positive neuroendocrine tumours (NETs).

The study results were previously published (Pfeifer et al., 2012, 2015), see below.

5.3.4.1.1. Study Design of Pfeifer et al 2015

The study that generated the data was an open-label, single-center, single-dose, comparative study using DOTATATE peptide labelled with the ^{64}Cu tracer to assess diagnostic performance versus existing technologies based on ^{68}Ga and ^{111}In labels on somatostatin receptor binding peptides. Subjects were recruited from among patients referred for ^{111}In-Octreotide scanning. At the time of the study, this was the routine examination method for NET diagnostics in Denmark.

Study population

Patients were to be enrolled in a prospective study from mid-2008.

Patients with neuroendocrine tumours from the gastro-enteropancreatic system, thymus and bronchi were expected to be enrolled according to the inclusion and exclusion criteria:

Inclusion criteria

- Histologically verified neuroendocrine tumour of gastroenteropancreatic or pulmonary origin of all grades
- Referred for In-111-octreotide scan

Exclusion criteria

- Below 18 years of age
- Pregnancy/lactation
- Unable to understand "Patient Information"
- Low performance status (based on WHO Performance status), excluded if score >3)
- Chemotherapy or radiation therapy within 5 weeks prior to the scintigraphy

Blinding

Readers of the PET/CT and SPECT/CT images were blinded and did not have access to other clinical information, including patient history. The PET/CT and SPECT/CT were analysed separately by two different teams consisting of two experienced interpreters and the members of both teams remained the same throughout the study. The two teams were masked to the images and readings of the other team.

Description of the trial intervention

Patients with neuroendocrine tumours received the routinely performed ^{111}In-Octreotide SPECT/low-dose CT scan and also a contrast enhanced CT scan and a ^{64}Cu-DOTATATE PET/CT scan. The 3 examinations were performed in random order, with the shortest time possible between scans and within a maximum of 60 days. Scan dosing was:

^{111}In-Octreotide: 181-268 (mean, 218) MBq.

^{64}Cu-DOTATATE: 183-232 (mean, 202) MBq.

Identity of investigational products

^{64}Cu-DOTATATE was produced in house. The labeling efficiency was greater than 95% as determined with radio-reversed-phase high-performance liquid chromatography. The specific activity was 4.78 MBq/nmol.

^{111}In-Octreotide was purchased from Covidien and prepared in accordance with the instructions of the manufacturer.

Study assessments

Efficacy

The efficacy results of the analysis of ^{64}Cu-DOTATATE vs ^{111}In-Octreotide were published (Pfeifer et al., 2015). The retrospective study report covers the analysis of ^{64}Cu-DOTATATE vs SoT.

Study objectives

The primary objective of the study was to investigate whether ^{64}CU-DOTATATE PET scan findings have the ability to diagnose somatostatin receptor-positive NETs.

Assessment of the primary objective was based on the sensitivity and specificity of ^{64}Cu-DOTATATE PET scan findings in detecting the presence of somatostatin receptor-positive NETs relative to the Standard of Truth (SoT) (see below for details of SoT determination.)

The secondary objectives of the study were to evaluate the positive predictive value (PPV), negative predictive value (NPV), and accuracy of ^{64}Cu-DOTATATE PET scan findings relative to the SoT.

Primary Efficacy Variables

The co-primary endpoints of the study are the sensitivity and specificity of ^{64}Cu-DOTATATE based on the SoT.

Secondary Efficacy Variables

The secondary effectiveness endpoints of the study were:

- positive predictive value (PPV)
- negative predictive value (NPV)

- accuracy
- False negative rate (FNR)
- False positive rate (FPR)

Statistical methods

Sample Size – original study Pfeifer et al 2015

According to the original study protocol the study was powered with respect to the primary endpoint of sensitivity.

In order to demonstrate a 10% better sensitivity (90% vs 80%) for the new method with a type I error (α) of 5% and a type II error (β) of 30% n=45 patients were needed. To account for possible drop outs, 60 patients were to be enrolled to obtain at least 45 patients having all 3 scans performed.

Types of Analyses – retrospective analysis

The objectives of the statistical analysis were to demonstrate better sensitivity and specificity than the current diagnostic standards (taken to be 80% and 60%, respectively).

Unless otherwise stated, all hypothesis tests were conducted at the one-sided α=0.025 level of significance.

Missing Data Conventions

In the statistical analysis of the primary effectiveness endpoints of the study, only subjects with evaluable endpoints will be used in the statistical analysis, i.e., a complete case analysis.

The data analyses were to be conducted using SAS© Software, Version 9.4 or higher.

Efficacy Analysis

Primary Efficacy Variables

The following two-way table was utilized to compute sensitivity, specificity, NPV, PPV, and accuracy:

	SOT Reference-Disease	SOT Reference-No Disease
^{64}Cu-DOTATATE Scan Result Disease	TP	FP
^{64}Cu-DOTATATE Scan Result No Disease	FN	TN

Based on the above, the co-primary endpoints were to be computed as follows:

- sensitivity = TP/(TP + FN)
- specificity = TN/(TN + FP)

The following two hypotheses were to be tested at the end of the study relative to the co-primary endpoints:

Ha0: Sensitivity ≤ 80% vs Ha1: Sensitivity > 80%

and

Hb0: Specificity ≤ 60% vs Hb1: Specificity > 60%

Each hypothesis test was to be conducted at the one-sided α = 0.025 level of significance. Point estimates of sensitivity and specificity were to be calculated along with two-sided 95% confidence intervals using the score method.

Secondary Efficacy Variables

Based on the table presented above, the secondary endpoints were computed as follows:

- NPV = TN/(TN + FN)
- PPV = TP/(TP + FP)
- FNR = FN/(TN + FN)
- FPR = FP/(FP + TP)
- accuracy = (TP + TN)/(TP + TN + FP + FN)

Point estimates of the NPV, PPV, and accuracy were calculated along with 95% confidence intervals using the score method with continuity correction.

Standard of Truth

A condition of enrolment in the trial was a histopathologically confirmed diagnosis of a somatostatin receptor positive neuroendocrine tumour. Some subjects had had the primary tumour resected and follow-up therapy (radiation or chemotherapy) and were recruited when receiving a routine follow-up scan. Some patients who were positive on the ^{64}Cu-DOTATATE received further follow-up surgery, biopsy or imaging. Thus, the standard of truth was established as follows:

- A patient who is negative on both the CT scan and the ^{111}In-Octreoscan SPECT scan is negative for the disease;
- A patient who is positive on either of the referenced scans is positive;
- A patient whose tumour was confirmed as NET via biopsy, surgical resection, or follow-up imaging using somatostatin receptor based imaging modalities (other than ^{64}Cu-DOTATATE) is positive.

5.3.4.1.2. Results NETMedix Denmark Trial

Participant flow and numbers analysed

Eligible patients had histopathologically confirmed NETs of gastroenteropancreatic or pulmonary origin of all grades. They were enrolled in the study from October 6th 2009 to May 5th 2011. Follow-up ended on November 15th 2014 for evaluation of discrepant imaging findings. Patients were followed for 42-60 months.

A total of 124 patients were screened, out of this 112 were enrolled and all the 112 completed both the ^{64}Cu-DOTATATE and ^{111}In-Octreotide scans.

Baseline data

This study was conducted at a single research institution in Denmark.

Table 26. Demographics

Demographic Variable	Statistic	All ITD Patients
Age (years)	N	112
	Mean (SD)	61.6 (10.85)
	Median (Min, Max)	63.0 (30, 84)
Gender	Female n (%)	49 (43.8%)
	Male n (%)	63 (56.3%)

Max=maximum; Min=minimum; SD=Standard Deviation

Outcomes and estimations

Primary efficacy results

There were no false positives recorded (FPR=0.0000) for imaging with ^{64}Cu-DOTATATE relative to the Standard of Truth. One false negative was recorded (FNR=0.0100). Of note, imaging of this patient with ^{111}In-Octreotide also yielded a false negative. In total, ^{64}Cu-DOTATATE demonstrated a specificity of 1.0000 in identifying those patients without disease (12/12). ^{64}Cu-DOTATATE demonstrated a sensitivity of 0.9900 in identifying those patients positive for a NET (99/100).

Table 27. ^{64}Cu-DOTATATE PET imaging versus standard of truth two-way table ITD population (n=112)

		Standard of Truth		
Method of Evaluation		**Disease**	**No Disease**	**Total**
^{64}Cu-DOTATATE Scan Results	**Disease**	99	0	99
	No Disease	1	12	13
	Total	100	12	112

Table 28. Summary statistics for ^{64}Cu-DOTATE imaging versus standard of truth ITD population (n=112)

	Summary Statistics		
Parameter	**Estimate**	**95% CI**	**p-Value**
Sensitivity[a]	0.9900	(0.9455, 0.9982)	<0.0001
False Negative Rate	0.0100	(0.0018, 0.0545)	
Specificity[b]	1.0000	(0.7575, 1.0000)	0.0022
False Positive Rate	0.0000	(0.0000, 0.2425)	

[a] One sided α=0.025 test of H_{a0}:Sens $\leq$0.80 vs. H_{a1}:Sens>0.80
[b] One sided α=0.025 test of H_{b0}:Spec $\leq$0.60 vs. H_{b1}:Spec>0.80

**Assessor's note to footnote b: Hb1:Spec should read >0.60*

All 12 patients who were negative to disease had a history of NET confirmed by histopathology and had undergone procedures such as surgery, radio frequency ablation, and treatment with peptide receptor radionuclide therapy. The study scan (^{64}Cu-DOTATATE) was performed to assess any residual disease.

Five cases were negative for disease on CT and ^{111}In-Octreotide and positive for disease on ^{64}Cu-DOTATATE. All five patients had a history of NET confirmed by histopathology and had undergone treatment procedures such as surgery and radio frequency ablation. The study scan (^{64}Cu-DOTATATE) was performed to assess any residual disease. The patients were followed up by biopsy, other somatostatin receptor imaging (SRI) modality (111In-octreotide and 68Ga-DOTATOC), or additional imaging performed (CT, MR or US).

Secondary efficacy results

The probability of disease being present given a positive result with ^{64}Cu-DOTATATE (PPV) was 1.000. The probability of disease being absent given a negative result with ^{64}Cu-DOTATATE (NPV) was 0.9231. In this study, imaging with ^{64}Cu-DOTATATE had an accuracy of 0.9911.

Table 29. Summary statistics for ^{64}Cu-DOTATATE imaging versus standard of truth ITD population (n = 112)

	Summary Statistics	
Parameter	**Estimate**	**95% CI**
Positive Predictive Value	1.0000	(0.9626, 1.0000)
Negative Predictive Value	0.9231	(0.6669, 0.9863)
Accuracy	0.9911	(0.9512, 0.9984)

CI=Confidence Interval

5.3.4.2. Diagnostic performance data from published literature

Pfeifer 2012

Study design:

This was a first-in-human study to support the clinical use of ^{64}Cu-DOTATATE for SRI. In a prospective setup, 14 patients with a history of neuroendocrine tumours underwent both PET/CT with ^{64}Cu-DOTATATE and SPECT/CT with the routine imaging agent ^{111}In-diethylenetriaminepentaacetic acidoctreotide (^{111}In-DTPA-OC).

Extent of exposure:

Fourteen (14) patients were exposed to ^{64}Cu-DOTATATE and received a single intravenous injection of 193-232 MBq. Patients also received a single intravenous injection of 197-227 MBq ^{111}In-DTPA-OC.

Efficacy assessments:

PET/CT and SPECT/CT images were analysed separately by 2 different teams consisting of 2 experienced readers. The 2 teams were masked to the images and readings of the other team. The absolute number of lesions per organ system was obtained with a numeric limitation of 10 lesions per organ and 30 positive findings for lymph nodes per patient.

Subject disposition:

Fourteen patients with histopathologically confirmed NETs were enrolled in the study. The study group consisted of 13 patients with gastroenteropancreatic NETs and 1 patient with a known mutation in the multiple endocrine neoplasia type I gene, who was diagnosed with a bronchogenic NET 10 years earlier.

Patient characteristics:

Table 30. Patient characteristics in the study by Pfeifer (2012)

Patient No.	Tumour origin	Age and sex	Ki67 (%)	Syndrome	TNM	Metastases	^{18}F-FDG
1	Cecum	58, M	NA	Carcinoid	IV	Carcinomatosis	Positive
2	Duodenum	50, F	1	Gastrinoma	R0	No	Negative
3	Unknown	44, M	5	Carcinoid	IV	Peritoneum	NA
4	Ileum	62, M	3	None	R1	No	NA
5	Ileum	63, M	3	Carcinoid	IV	LN	Negative
6	Unknown	40, F	5	Carcinoid	IV	Liver	Negative
7	Pancreas	72, M	7	None	IV	Liver, bone	NA
8	Jejunum	51, F	3	Carcinoid	IV	Liver, breast	Negative
9	Unknown	81, M	10	Carcinoid	IV	Liver, peritoneum	Positive
10	Ileum	64, M	1	None	IV	LN	NA
11	Unknown	64, M	4	Carcinoid	IV	Liver	Positive
12	Ileum	72, M	10	Carcinoid	IV	Liver, bone, LN	NA
13	Bronchogenic	44, F	5	Carcinoid	IV	Lungs, LN	Positive
14	Unknown	76, M	7	Carcinoid	IV	Liver	Positive

R0 resection = complete resection, no microscopic residual tumour
R1 resection = microscopic residual tumour
LN=lymph node
NA=not available

Efficacy results:

In an organ-based comparison of the 2 SRI modalities, ^{64}Cu-DOTATATE PET detected additional lesions in 6 of 14 patients (43%). All lesions detected on ^{111}In-DTPA-OC SPECT were also detected on ^{64}Cu-DOTATATE PET. In 5 patients, the additional lesions were localised in organs or organ systems not previously recognised as metastatic sites: lung lesions (patient 1), a single-bone metastasis and hepatic lesions (patient 8), bone metastases and lymph nodes (patient 9), peritoneal carcinomatosis (patient 12), pancreatic and pulmonary lesions (patient 13), and a brain metastasis and a single-bone lesion (patient 14). All foci detected by ^{64}Cu-DOTATATE PET but not by ^{111}In-DTPA-OC SPECT were retrospectively assessed as being true-positive lesions, with the exception of the bone lesions in patients 9 and 14. Thus, in 6 patients, one or more of the additional lesions found by PET were confirmed. ^{64}Cu-DOTATATE PET revealed in general more lesions (n>219, including 98 lymph nodes) than conventional SRI (n>105, including 29 lymph nodes). A common feature of nearly all additionally discovered lesions was their diminutive size.

Table 37 provides an overview of the results from the findings of the 2 SRI modalities, co-registered diagnostic CT, and follow-up imaging.

Table 31. Number and localisation of lesions detected by different imaging methods (Pfeifer 2012)

Patient no.	^{111}In-DTPA-OC SPECT	^{64}Cu-DOTATATE PET	CT	Follow-up[1]
1	Peritoneal carcinomatosis, bones (1), lymph nodes (8)	Peritoneal carcinamatosis, bones (>10), lymph nodes (>30) + lungs (6)*	Peritoneal carcinomatosis, bones (1), lymph nodes (>25), lungs (1)*	
2	Negative	Negative	Negative	
3	Large solitary peritoneal soft-tissue mass (1)	Large solitary peritoneal soft-tissue mass (1)	Large solitary peritoneal soft-tissue mass (1)	
4	Negative	Negative	Negative	
5	Lymph nodes (9)	Lymph nodes (>30)	Lymph nodes (10)	
6	Liver (6), large solitary peritoneal soft-tissue mass (1)	Liver (>10), large solitary peritoneal soft-tissue mass (1)	Liver (2)	
7	Pancreas (1), liver (>10), bones (5)	Pancreas (1), liver (>10), bones (>10)	Pancreas (1), liver (>10), bones (1)	
8	Breasts (>10), large solitary peritoneal soft-tissue mass (1), lymph nodes (1)	Breasts (>10), large solitary peritoneal soft-tissue mass (1), lymph nodes (19) + liver (>10)* + bones (1)*	Breasts (>10), large solitary peritoneal soft-tissue mass (1), lymph nodes (12) + liver (2)*	Bones*
9	Liver (1), large solitary peritoneal soft-tissue mass (1)	Liver (1), large solitary peritoneal soft-tissue mass (1) + bones (3)** + lymph nodes (2)*	Liver (1)	Lymph nodes*
10	Lymph nodes (8)	Lymph nodes (10)	Lymph nodes (4)	
11	Liver (>10)	Liver (>10)	Liver (10)	
12	Ileum (1), liver (>10), bones (4), lymph nodes (2)	Ileum (1), liver (>10), bones (7), lymph nodes (6) + peritoneal carcinomatosis*	Ileum (1), liver (>10), lymph nodes (4)	Peritoneal carcinomatosis*
13	Lymph nodes (1), thyroid gland (1)	Lymph nodes (1), thyroid gland (1) + pancreas (3)* + lungs (4)*	Lymph nodes (3), + lungs (10)*	Pancreas*
14	Liver (1), large solitary peritoneal soft-tissue mass (1), peritoneal carcinomatosis	Liver (1), large solitary peritoneal soft-tissue mass (1), peritoneal carcinomatosis + brain (1)* + bones (1)*	Liver (1), large solitary peritoneal soft-tissue mass (1), peritoneal carcinomatosis	Brain*

[1]Confirmation by follow-up with VT (co-registered, stand-alone).
*Additional findings detected by PET method.
**Bone lesions in patients 9 and 14 have not yet been confirmed
If lesions were known from previous investigations, confirmation was not demanded. Besides abdominal SPECT, thoracic SPECT was performed in patients 1, 5, 7, 8, 10, 11, 13 and 14. Numbers are given in parentheses.

Pfeifer 2015

Study Design:

This published report was utilised in the retrospective analysis of the NETMedix Denmark Trial. See section 5.3.4.1 for further details.

Patients were recruited from among patients referred for ^{111}In-DTPA-OC scanning. Patients received three imaging modalities:

- ^{64}Cu-DOTATATE PET/CT scan

- Diagnostic CT scan (preferably contrast-enhanced, unless contraindicated)
- ^{111}In-DTPA-OC SPECT/low-dose CT scan

Extent of exposure:

All 112 patients were injected with ^{64}Cu-DOTATATE. A mean (SD) dose of 202.2 (10.00) MBq of ^{64}Cu-DOTATATE was delivered. Doses ranged from 183 MBq to 232 MBq.

Efficacy assessments:

See Section 5.3.4.1. for details on image evaluation.

Comparisons between the 2 methods were performed on the basis of patients, organs, and lesions. Sensitivity, specificity and accuracy were calculated on a patient basis.

The McNemar test for paired proportions with continuity correction was applied to compare ^{64}Cu-DOTATATE and ^{111}In-DTPA-OC at the patient level. The 95% confidence intervals for sensitivity, specificity, accuracy, and predictive values were computed using the adjusted Wald method. A sign test was used to explore differences in lesion detection rates between the 2 SRI modalities. Two-sided P values of less than 0.05 were considered statistically significant.

Patient characteristics:

Table 32. Patient characteristics (adapted from Pfeifer 2015)

Characteristic	**Number (percentage)**
Male:Female	63:49 (56%:44%)
Mean age (years)	62
Site of primary tumour	
Lung carcinoid	9 (8%)
Unknown primary site	23 (21%)
Stomach	1 (1%)
Small intestine	49 (44%)
Pancreas	19 (17%)
Cecum/appendix	6 (5%)
Rectum	2 (1.5%)
Biliary tract (extrahepatic)	2 (1.5%)
Oesophagus	1 (1%)
Functional status	
Functioning	40 (36%)
Nonfunctioning	72 (64%)
Grading	
G1	31 (28%)
G2	70 (62%)
G3	9 (8%)

Efficacy Results:

Patient-Based Comparison

One hundred twelve (112) patients underwent ^{64}Cu-DOTATATE PET and ^{111}In-DTPA-OC SPECT, and contrast-enhanced diagnostic CT in the inclusion period of 19 months. In 100 of the 112 NEN patients, residual or recurrent disease was established on the basis of previous clinical evaluation, CT, and SRI within the scope of this study and prospective follow-up. Accordingly, 12 patients were negative for disease and of these 12, 8 were expectedly negative as they were newly operated on with removal of the known pathologic focus/foci and referred for evaluation of possible residual disease.

Eighty-seven patients (87) were congruently positive on both ^{64}Cu-DOTATATE PET and ^{111}In-DTPA-OC SPECT scans. Ten patients with proven residual or recurrent disease were identified only by ^{64}Cu-DOTATATE PET, leading to 97 true-positive ^{64}Cu-DOTATATE PET cases and 87 true-positive ^{111}In-DTPA-OC SPECT cases. ^{111}In-DTPA-OC SPECT was false-negative in 13 patients, whereas ^{64}Cu-DOTATATE PET was false-negative in 3 patients. Two of these three matching false-negative cases comprised patients with high-grade (G3) pancreatic NETs with liver metastases and Ki-67 indices of 40% and 30%, respectively. The third patient had been diagnosed with a bronchopulmonary carcinoid with a mitotic count of 1 and liver metastases. No false-positive results for either SRI modality were seen on a patient basis. Accordingly, sensitivity for ^{64}Cu-DOTATATE and ^{111}In-DTPA-OC was 97% and 87%, respectively. The comparison of diagnostic sensitivity, specificity, accuracy, positive predictive value, and negative predictive value and their 95% confidence intervals are shown below.

Table 33. Comparison of diagnostic performance of ^{64}Cu-DOTATATE and ^{111}In-DTPA-OC

Parameter	^{64}Cu-DOTATATE	^{111}In-DTPA-OC
Sensitivity	97% (92%-99%)*	87% (79%-92%)*
Specificity	100% (96%-100%)	100% (96%-100%)
Accuracy	97% (92%-99%)*	88% (81%-93%)
Positive predictive value**	100% (97%-100%)	100% (96%-100%)
Negative predictive value**	80% (54%-94%)	48% (30%-67%)

*P = 0.017; ^{64}Cu-DOTATATE vs. ^{111}In-DTPA-OC (McNemar test for paired proportions)
** At prevalence of disease of 89%.
Numbers in parentheses are 95% confidence intervals calculated using adjusted Wald method

Five of the 10 patients with residual or recurrent NETs, which were revealed only by ^{64}Cu-DOTATATE PET, had liver metastases. Of 112 included patients, bone metastases were present in 38 cases (34%) of which PET detected 36 and CT the remaining 2. All SPECT-positive cases were also PET-positive. In contrast, of the 36 PET-positive cases, 13 cases (29%) were SPECT-negative.

Organ-Based Comparison

An organ-based analysis yielded concordant findings in 72 (64%) patients—that is, that both ^{111}In-DTPA-OC and ^{64}Cu-DOTATATE PET consistently showed no lesions or consistently revealed at least 1 lesion for all organs/regions of the patient. In 40 of the 112 patients (36%), ^{64}Cu-DOTATATE PET detected lesions in additional organs/regions. There did not seem to be a difference in performance between the 2 SPECT scanners used, because there were 6 of the 21 patients (29%) scanned using the VG Hawkeye with discrepant findings in comparison to 34 of the 91 patients (37%) scanned using the Precedence scanner with discrepant findings. In some patients, 2 or more additional organ involvements were identified by PET, giving a total of 58 additional organ involvements found on PET com- pared with SPECT. During the 42–60 mo of follow-up, the additional organ involvements identified on PET were confirmed to be true-positive in 35 of the 40 patients.

The most common discrepant finding was lymph node metastases. Thus, in 14 of the 40 discrepant cases, no lymph node metastases were present on SPECT whereas PET identified up to 11 lymph node

metastases. Only in two of the 40 patients did SPECT identify more than five lymph node metastases whereas PET revealed more than 5 lymph node metastases in 13 cases.

In 11 patients, no liver lesions were present on SPECT whereas PET identified up to 20 liver metastases. In three of these 11 patients, the liver metastases were also not evident on CT, but all 3 were later confirmed to be true-positive lesions. In general, for all 40 discrepant cases, PET identified at least as many and often more lesions than both SPECT and CT. All lesions detected on ^{111}In-DTPA-OC SPECT were also detected on ^{64}Cu-DOTATATE PET. In 10 of the 40 cases, no lesions were detected by SRS and in five of these patients, the CT scans were also negative.

Lesion-Based Comparison

In total, 1,213 lesions were detected by ^{64}Cu-DOTATATE PET in comparison to 603 lesions detected by ^{111}In-DTPA-OC SPECT. Of the 112 patients, 21 (19%) were scanned on the VG Hawkeye scanner, and in agreement with this, 123 (20%) of the 603 lesions detected by ^{111}In-DTPA-OC were identified using the VG Hawkeye scanner. In 28 patients (25%), PET and SPECT identified the same number of lesions; in 52 patients (46%), PET identified 1–9 more lesions than SPECT; and in 32 patients (29%), PET identified 10 or more additional lesions than SPECT.

The most frequent finding was liver metastases, for which 468 lesions were present on PET, compared with 320 on SPECT. The clearest difference was the detection rate of bone metastases for which 208 lesions were found on PET, compared with 90 on SPECT.

Johnbeck 2017

Study Design:

This was a prospective, open-label, single-center, study to compare on a head to-head basis the diagnostic performance of ^{64}Cu-DOTATATE with that of ^{68}Ga-DOTATOC in NET patients. Sixty patients, of whom 59 were evaluable, were prospectively enrolled in this study and were followed up for 2 years to determine whether discrepant lesions were true or false. The inclusion criteria were primary staging or restaging. A PET/CT scanner was used for both patient scans and the CT component was of diagnostic quality. Both PET/CT scans were performed within 1 week of each other (1-5 days apart).

Extent of exposure:

Fifty-nine (59) patients were exposed to ^{64}Cu-DOTATATE and received a single intravenous injection of 200 MBq. Patients also received a single intravenous injection of 150 MBq ^{68}Ga-DOTATOC.

Efficacy assessments:

A team with a nuclear medicine specialist and a radiologist evaluated the images in consensus. All lesions on the ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC scans were compared, and discordant additional lesions were noted for each of the scans. Lesion sites were divided into regions or groups: liver, pancreas, intestines, lung, bones, lymph nodes, carcinomatosis, and other (ovaries, mamma, soft tissue, and other less common regions). The number of PET-positive lesions (≤20) in each region was counted, and the SUVmax of one concordant lesion in each region was noted. Clinical follow-up was more than 2 years. Discordant lesions were controlled by comparison to all available later images of the patients (68Ga-DOTATOC PET/CT, CT, and MR) to verify the lesions as true- or false-positive findings. For comparison of discrepant lesions using different PET tracers in the same patient, the McNemar test for paired proportions correct for continuity was used. The probability that a discordant observation was found by ^{64}Cu-DOTATATE was reported with the exact binomial confidence interval. The t test for paired samples was used to compare SUVmax for the two scans and to compare the TBRs.

Subject disposition:

Fifty-nine patients were enrolled from the Departments of Clinical Endocrinology and Gastrointestinal Surgery in the Neuroendocrine Tumour Center of Excellence at Rigshospitalet, Copenhagen.

Patient characteristics:

Table 34. Patient characteristics (adapted from Johnbeck 2017)

Characteristic	**Number (percentage)**
Male:Female	35:24 (59%:41%)
Mean age (years)	61
Site of primary tumour	
Small intestine	35 (59%)
Pancreas	11 (19%)
Colon	5 (9%)
Lung	2 (3%)
Other	3 (5%)
Unknown	3 (5%)
Grading	
G1	12 (20%)
G2	40 (68%)
G3	0

Efficacy results:

In total, 701 PET-positive lesions were found by both tracers (concordant lesions), whereas an additional 68 lesions were found by only one tracer (discordant lesions).

^{64}Cu-DOTATATE found 42 discordant lesions, and 33 of these were confirmed during follow-up to be true-positive. ^{68}Ga-DOTATOC found 26 discordant lesions, and 7 were confirmed to be true-positive. Thus, ^{64}Cu-DOTATATE found more true-positive discordant lesions than ^{68}Ga-DOTATOC (33 additional lesions vs. 7, $P < 0.001$). Of the true-positive discordant lesions, 83% were revealed by ^{64}Cu-DOTATATE but on 17% by ^{68}Ga-DOTATOC.

Table 41 shows the comparison of concordant and true-positive discordant lesions found by concurrent ^{64}Cu-DOTATATE and 68Ga-DOTATOC in the 59 patients with NENs.

Table 35. Comparison of concordant and true-positive discordant lesions (Johnbeck 2017)

Region	Concordant lesions	True-positive on ^{64}Cu-DOTATATE	True-positive on ^{68}Ga-DOTATOC	P	Probability that discordant lesion was found by ^{64}Cu-DOTATATE[2]
Liver	298	7	3	0.34	0.70 (0.67-0.93)
Lymph nodes	222	6	2	0.29	0.75 (0.35-0.98)
Bones	102	11	2	0.02	0.85 (0.55-0.98)
Lung	3	0	0	NA	NA
Pancreas	10	1	0	1.00	1.00 (0.05-1.00)
Intestines	26	0	0	NA	NA
Carcinomatosis	25	7	0	0.02	1.00 (0.59-1.00)
Other[1]	15	1[2]	0	1.00	1.00 (0.05-1.00)
Total	701	33	7	<0.001	0.83 (0.67-0.93)

[1] Breast (10), ovary (2), adrenal gland (1), soft tissue (3).
[2] Data are estimate followed by 95% CI in parentheses. NA = not applicable

On a *per-patient* analysis, discrepant lesions between the ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC scans were found in 22 patients. Follow-up confirmed that in 13 of 14 patients, ^{64}Cu-DOTATATE PET/CT was TP for additional lesions. Three of the 8 patients with additional lesions found by ^{68}Ga-DOTATOC PET/CT, were confirmed to be TP on follow-up. The additional lesions in the remaining 5 patients were not found on later imaging (^{68}Ga-DOTATOC PET/CT, CT, or MR) and thus were considered FP.

Although additional TP lesions were found in 13 patients by ^{64}Cu-DOTATATE PET/CT and in 3 patients by ^{68}Ga-DOTATOC PET/CT, the sensitivity to diagnose NET disease in a patient was 100% (95% CI, 93%–100%), the specificity was 90% (95% CI, 56%–100%), the positive predictive value was 98% (95% CI, 90%–100%), and the NPV was 100% (95% CI, 66%–100%) on both scans because concordant lesions were also found in all patients with additional lesions.

5.3.4.3. Impact on diagnostic thinking based on published reports

Carlsen 2020, Carlsen 2021 – prognostic value

These articles relate to the role of the ^{64}Cu-DOTATATE diagnostic tests as a predictor of disease outcomes.

Given that overexpression of SSTRs in patients with NENs is used for both diagnosis and treatment, Carlsen et al, investigated the potential association between the ^{64}Cu-DOTATATE uptake with SRI and overall survival (OS) and profession-free survival (PFS) in NENs patients. The studies reported an association between tumour SSTR density, as visualized with ^{64}Cu-DOTATATE PET/CT SRI, and PFS, but not with OS. The accuracy in predicting PFS for the individual patient was modest. Assessment of the lowest, rather than the highest, lesion uptake increased prognostication by ^{64}Cu-DOTATATE.

5.3.4.4. Impact on patient management based on published reports

Pfeifer 2012, Pfeifer 2015, Johnbeck 2017

Please refer to Section 5.3.4.2 for a description of the studies.

More lesions detected by ^{64}Cu-DOTATATE compared to ^{68}Ga-DOTATOC and ^{111}In-DTPAOC. ^{64}Cu-DOTATATE found more TP discordant lesions than ^{68}Ga-DOTATOC

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

Analyses across trials have been provided upon request.

Input data and methods

Data from four studies was included in the meta-analyses. Patient counts were extracted from study reports/published manuscripts as follows:

- RMX-18-22 Study Report (Majority Reader counts): 30 true positives, 3 false negatives, 28 true negatives and 1 false positive.
- NetMedix Denmark Study Report: 99 true positives, 1 false negative, 12 true negatives and 0 false positives.
- Johnbeck (2017) published manuscript: 49 true positives, 0 false negatives, 9 true negatives and 1 false positive.

Two random effects meta-analyses were conducted using the metafor package in R (v4.8-0), one for sensitivity and one for specificity. Logit transformed proportions and variances were calculated for each study from the true positive and true negative counts, using the escalc function. Unadjusted random-effects meta-analytic models were then fitted to this transformed data using the rma function with a restricted maximum likelihood (REML) estimator. Results were back transformed to the original scale using the transf.ilogit function.

Results

The pooled patient-based estimate of sensitivity was: 0.97 (95% CI: 0.89, 0.99)

The pooled patient-based estimate of specificity was: 0.94 (95% CI: 0.82, 0.98)

5.3.6. Overall discussion and conclusions on clinical efficacy

5.3.6.1. Discussion

Indication and clinical programme

The initially proposed indication for Deqtynet (64Cu-DOTATATE) was: "*in adult patients for positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine neoplasms (excluding neuroblastomas)*".

To support this application, a single phase 3 clinical study (RMX-18-22) was submitted as main evidence, supported by one retrospective analysis, the NETMedix trial, based on a previously published study (Pfeifer 2015), and 3 published literature reports (Pfeifer 2012, Pfeifer 2015 and Johnbeck 2017). In addition, results from a dose-range study (RMX-17-22) were submitted.

Dose-response study

A dose ranging phase 1 study (RMX-17-22) was conducted, where 3 dose levels were investigated: 3 mCi (111 MBq)±10%, 4 mCi (148 MBq)±10% and 5 mCi (185 MBq)±10%. Since 4mCi and 5mCi yielded similar results regarding the image quality, the lower of the two doses was selected for the phase 3 trial based on ALARA (as low as reasonably achievable) principle. The proposed dose (activity) to be administered is 148 MBq. However, the administered activity may be adjusted to the patient's characteristics, the type of PET camera used, and the acquisition mode. Nevertheless, the applicant is

recommended to investigate optimizing radiation activity based on patient characteristics, the type of PET camera used and acquisition mode in the post-marketing (**REC**)**.**

Clinical setting/diagnostic question

The precise clinical setting at the time of the referral for SSTR imaging was not systematically collected either in the pivotal trial or in the retrospective NETMedix Denmark trial. Somatostatin receptor PET imaging has a wide range of applications in neuroendocrine tumours (NETs), e.g. initial staging after histologic diagnosis of NETs, localization of primary tumours in known metastatic disease but unknown primary, staging before planned surgery, monitoring etc. (Hope 2017). Given the diverse clinical settings a PET scan can be used in, and the rarity of the disease, it may not be feasible to estimate ^{64}Cu-DOTATATE diagnostic performance in a sufficient number of patients in each clinical setting in all disease subtypes.

Main study RMX-18-22

Design

RMX-18-22 was an open-label, single-dose, single-arm, single-centre, non-comparative phase 3 study to assess imaging performance of ^{64}Cu-DOTATATE PET-CT versus standard of truth (SoT).

The **primary objective** was to assess the diagnostic performance (sensitivity and specificity) of ^{64}Cu-DOTATATE PET-CT imaging in subjects with known or suspected NETs (HV were also included), by comparing the results to the SoT for each subject. The diagnostic performance was assessed at subject level (subject has a disease yes/no). The group comparison was within-subject, i.e. ^{64}Cu-DOTATATE and the SoT were assessed in the same subject.

The inclusion of HVs is acceptable for the evaluation of diagnostic performance at the subject level, as they represent true negative cases. However, the restriction of the inclusion criteria to patients with NETs is seen critically in light of the aforementioned differences between NETs and NECs. Consequently, the extrapolation of the observed diagnostic performance from patients with NETs to patients with NECs cannot be readily assumed.

When the investigational agent is developed as an alternative or improvement over existing diagnostic agents, comparative studies (superiority or non-inferiority) are requested where both investigation agent and selected comparator are compared to the SoT (CPMP/EWP/1119/98/Rev. 1). **No comparator** was included in Study RMX-18-22. Nonetheless, it is deemed sufficient to estimate the diagnostic performance with respect to the standard of truth/reference standard, also considering the shared mechanism of action with SomaKit TOC, both being somatostatin receptor agonists with high affinity to SSTR2. Also, a direct comparison against another diagnostic with the same mode of action may only allow the conclusion that both diagnostics can detect the same false-positive/negative lesions. This was also supported by the SAG input (see SAG minutes in section 9.6.3 of this report).

Comparative performance of ^{64}Cu-DOTATATE is informed by literature reports, which, despite some methodological weaknesses provide reassurance that diagnostic performance of Deqtynet is not inferior to that of ^{68}Ga-edotreotide (^{68}Ga-DOTATOC), even though no formal hypothesis was tested (see later).

The pivotal study was conducted in a **single centre** in the US (Excel Diagnostics and Nuclear Oncology Center), which raises concerns regarding external validity. Although the limitations of a single-centre design are partially mitigated by the use of a blinded, independent central review involving multiple readers, thereby reducing site specific interpretation bias, residual bias may persist due to potential variations in referral patterns and clinical management across different regions. Notwithstanding their limitations, the **supportive studies conducted at an additional centre in Denmark** also

demonstrate high per-patient diagnostic performance (see later) and provide additional **reassurance** regarding the concerns associated with the single centre design of the pivotal study.

^{64}Cu-DOTATATE PET image results for each patient were compared against the SoT. SoT was comprised of different imaging modalities - anatomical (e.g. CT and/or MRI) and functional (e.g. NaF and/or ^{18}F-FDG and/or bone scan and/or Octreoscan) - as well as biopsy/histopathology report, biomarkers and clinical signs and symptoms. Imaging modalities have generally lower sensitivity and specificity compared to the histopathology report, which is considered the most reliable and widely accepted SoT. Therefore, the **composite SoT** including different imaging modalities, each with different respective sensitivity and specificity, is rather seen as surrogate SoT or reference standard. The absence of an objective and standardized method of establishing the SoT (resulting in varying SoT composition across subjects) is an important methodological weakness, since the final decision (disease/no disease, localized/metastatic) was made by a **single oncologist** based on collective data, introducing potential bias due to subjective interpretation. Furthermore, the quantification of diagnostic accuracy of such variable SoT is challenging, which in turn impacts the interpretability of specificity and sensitivity results for ^{64}Cu-DOTATATE. For patients with no histopathology results, the determination of SOT is likely to have lower spec/sens introducing potential for misdiagnosis.

Furthermore, the **reference standard included imaging modalities closely related to Deqtynet** (somatostatin analogues, i.e., Octreoscan). In the confirmatory trials, the SoT should be established independently of the results of the investigational agent and of its comparator. The SoT should not include as a component any information obtained with the investigational agent or the comparator (CPMP/EWP/1119/98/Rev. 1). Since somatostatin analogues bind similarly to somatostatin receptors, even if minor differences may exist in the binding to somatostatin receptor subtypes, they are expected to detect/not detect same lesions: false-positive results with ^{111}In-pentreotide shared by ^{64}Cu-DOTATATE being classified as true positive, and false-negative results with ^{111}In-pentreotide shared by ^{64}Cu-DOTATATE being underevaluated. This raises concerns about independence of the diagnostic performance assessment and limits the reliability of diagnostic performance of DEQTYNET.

However, the **concerns** regarding the **bias associated with the SoT** are **alleviated by the study results** (see later).

The **co-primary endpoints** were **sensitivity and specificity** of ^{64}Cu-DOTATATE PET-CT imaging when each imaging reader's subject-level result was compared to a SOT for the subject.

The secondary endpoints were accuracy, positive predictive value (PPV) and negative predictive value (NPV), sensitivity and specificity in distinguishing between localized and metastatic disease. These endpoints were evaluated per reader and for majority of readers. Test reliability was evaluated by intra-reader and inter-reader agreement as tertiary endpoints.

Two hypotheses were tested for the co-primary endpoints: Ha0: Sensitivity ≤ 70% vs Ha1: Sensitivity > 70%, and Hb0: Specificity ≤ 60% vs Hb1: Specificity > 60%. Each hypothesis test was conducted at the one-sided alpha level of 0.025. The sensitivity and specificity were calculated on a by-reader basis. Success was to be declared if at least 2/3 independent readers achieve both sensitivity and specificity significantly over the thresholds. While the aggregation of by-reader results controls the Type I error rate under the assumption that the same hypothesis on one and the same underlying operating characteristics is tested three times, this might not hold true under inter-reader variability. The outlined success criterion evaluates the diagnostic performance adequately only under the assumption that all readers perform equally well for all participants. While unlikely, this procedure could declare success in cases where two readers perform well but one does not perform better than when randomly guessing. The applicant was asked to provide an estimate for the diagnostic performance of an

average rater evaluating an average subject. The details of this analysis and results are presented in the results section. The estimand definition describes the questions of interest well and is accepted.

In conclusion, the design of the main study does not fully align with all recommendations outlined in the Guideline on clinical evaluation of diagnostic agents. Nevertheless, several of these recommendations are considered preferable rather than mandatory and some limitations in study design are mitigated by the study results. Consequently, **the evidence generated in the pivotal study is considered sufficient to characterise the per-patient performance of Deqtynet.**

Results

As regards the discrepancy between the broad sought indication (NEN) and the study population restricted to patients with NETs only (subset of NEN), the Applicant argued that submitted studies used the term "NET" as a general term, which may not align with the newer classification and do not necessarily reflect only low or intermediate grade NETs, as the use of the general term "NEN" was introduced after the studies had already been finalized. Although the Applicant attempted to re-classify the RMX-18-22 study population according to the new WHO criteria and identified 3 potential cases, these could not unequivocally be identified as having NECs. As the majority of patients in the main study had NETs, and it could not be clearly established whether there were any NEC cases, due to the aforementioned differences between NETs and NEC, **the restriction of the indication to well-differentiated NETs was agreed**.

Furthermore, NENs arise from the diffuse neuroendocrine cell system and may occur at many different disease sites. Most frequently, NENs originate from the digestive system (approximately 2/3 of reported cases), referred to as "Gastro-enteropancreatic NETs (GEP-NETs)" (Pavel, 2020, Uhlig, 2024). Non-GEP NETs arise outside the GI tract and pancreas, with lung being the most common non-GEP site, and other anatomical sites are thymus, head and neck region, pituitary gland, adrenal medulla and paraganglia, genitourinary tract etc.

Most patients in the pivotal study had **G1 and G2 GEP-NETs**. Some literature suggests lower extent of SSTR2 expression on the tumour surface in G3 NETs compared to G1 and G2 NETs, leading to less effective uptake of the SSTR tracer, and consequently to lower detection rates on SSTR PET (Manneh-Kopp, 2022, Grawe, 2023). Literature data also suggest heterogeneous pattern of SSTR expression in some non-GEP NETs (e.g. metastatic lung NETs), with relatively few tumours showing high levels of uniform expression on SSTR PET/CT scans (Al-Toubah et al., 2023). However, SAG experts provided reassurance that the diagnostic performance is expected to apply across all disease grades and neuroendocrine tumours where the somatostatin receptor is *over-expressed*; and that limitation to G1-G2, and even GEP-NETs compared to all NETs, is considered unnecessary.

Consequently, **CHMP agreed to an indication of well-differentiated NETs**. Nevertheless, it should be taken into consideration that GEP-NETs tumours that do not over express somatostatin receptors may not be visualized.

The finally applied indication is as follows: *DEQTYNET is indicated for positron emission tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated neuroendocrine tumours (NETs) excluding neuroblastomas*.

Outcomes

The sensitivity was 0.9091 for all three readers. The specificity per reader ranged between 0.8000 and 0.9333. The lower bound of the 95% CIs for both co-primary endpoints were above predefined cutoffs for all 3 readers (sensitivity >70%, specificity >60%). As the predefined success criterion (2/3 readers meeting both criteria) was exceeded, the co-primary endpoints as defined by the applicant on subject-level diagnosis were met.

The sensitivity for an average rater evaluating an average patient was 0.8254 (95% CI: 0.7405, 0.8868). The specificity for an average rater evaluating an average patient was 0.8156 (95% CI: 0.7244, 0.8815).

False positives (FP): False positives can be due to physiological, osteoblastic and inflammatory activity or incidental. False positives may be seen in pancreas due to uncinate process, accessory spleen, splenunculi and splenosis following splenectomy. Active osteoblastic activity by virtue of osteoblasts expressing SSTR2 receptors, may also accumulate DOTATATE activity. Active inflammatory processes also demonstrate DOTATATE uptake; as activated white blood cells and in particular macrophages and leukocyte do express SSTR2 receptors. False positives are also possible with other tumours that express SSTR2 receptors (e.g. renal cell carcinoma) and in other non-cancerous pathologic conditions that express somatostatin receptors including thyroid disease (Malan 2022). Information regarding the risk for image misinterpretation has been highlighted as a potential risk of this medicine.

Based on majority reads, the probability of disease being present given a positive result with ^{64}Cu-DOTATATE (positive predictive value, PPV) was 0.9677; the probability of disease being absent given a negative result (negative predictive value, NPV) was 0.9032. Based on individual reads, PPV ranged from 0.8333 to 0.9677; and NPV ranged from 0.8889 to 0.9032. These predictive values need to be considered in the context of a clinical setting where most enrolled patients had confirmed disease and should not be transferred to another clinical setting. The majority of readers determined that imaging with ^{64}Cu-DOTATATE had an accuracy of 0.9355. Per individual reader, the accuracy ranged from 0.8571 to 0.9355.

With regard to the **uncertainties associated with the inclusion of other somatostatin analogues into the reference standard**, the applicant clarified that no patient had in practice ^{68}Ga-DOTATATE as a part of their composite reference standard, and provided a subgroup analysis excluding patients with Octreoscan images included in the composite reference standard. This subgroup analysis yielded similar point estimates as the original analysis and the success criteria as defined by the applicant i.e., 2/3 readers having sensitivity >70% and specificity >60%, were met. Also, in the analysis requested by the CHMP, i.e., per average rater evaluating an average subject, which was considered more relevant compared to 2/3 readers, the pre-defined criteria were met in this subgroup. The results of this subgroup analysis provide reassurance that the inclusion of another somatostatin analogue in the reference standard did not substantially influence the results and alleviate concerns regarding independence of the diagnostic performance assessment.

Furthermore, the potential bias due to subjective interpretation by a single oncologist responsible for making the final decision on the SoT is mitigated by the comprehensive source documentation, the availability of **histopathology results** for all patients with confirmed disease and the fact that most patients had metastatic disease. **These results alleviate the aforementioned uncertainties regarding the SoT/reference standard (at the study design level).**

In the main study, the diagnostic performance of Deqtynet was estimated at a *subject level (i.e. patient had disease Y/N)* for the primary analysis. If more than one lesion can be detected in an individual, test performance has to be expressed both in relation to an overall individual (per patient basis) and to lesions detected and/or organs or sites involved (per lesion or per site basis) (CPMP/EWP/1119/98/Rev. 1). Considering the proposed clinical utility of Deqtynet (staging and re-staging) the clinical question to be answered is not only whether the patient has the disease or not, but to evaluate the *extent of disease and localization* of SSTR-overexpression. Therefore, lesion and organ-/region-based analyses are considered relevant for the proposed clinical utility of Deqtynet. **The absence of diagnostic performance data at the lesion and organ level is considered a limitation of the pivotal study**.

The applicant proposed an exploratory **re-analysis of the existing data from the pivotal study** to provide sensitivity and specificity results on a ***per organ/region basis*** and *sensitivity of "index" lesions*, in addition to a new analysis on a per patient basis, to be submitted **post-authorisation**. The reference standard would be determined by two new, independent oncologists, utilizing the same dataset that was provided to the original SoT oncologist. On the other hand, the value of the proposed index lesion analysis is questionable as only a restricted and pre-selected subset of lesions would be evaluated, which increases the risk of bias. While considered relevant, the **per-lesion analysis is challenging**, as somatostatin analogues have higher sensitivity compared to conventional imaging (CT, MRI), and the gold standard, i.e histopathology, is likely not available for each lesion, which in turn impacts the interpretability of specificity and sensitivity results. The re-analyses proposed by the applicant (organ/region-based and lesion-based) were discussed with the SAG (see SAG minutes in section 9.6.3 of this report). Although considered informative, the SAG did not regard these analyses as critical for concluding on the B/R of Deqtynet. Consequently, the CHMP agreed that these re-analyses could be provided post-authorisation (**REC**).

At this stage, the supportive literature studies provide evidence on Deqtynet's diagnostic performance at an organ- and lesion level in addition to the subject level, all of which suggest good diagnostic performance (see below), and is considered sufficient to conclude on the B/R.

Supportive studies

The administered activity in the literature was higher compared to the activity in the pivotal study and that recommended for Deqtynet (mean ~200 MBq vs 148 MBq, respectively; mean [range]: 207 [193–232] MBq Pfeifer 2012, 202 [183-232] MBq Pfeifer 2015; 200 [no range stated] MBq Johnbeck 2017). However, this does not preclude the use of data from the literature studies to bridge the missing information from the pivotal study, as reassured by SAG-O (see SAG minutes in section 9.6.3 of this report). According to the SAG experts, PET scanner technology has more impact on image quality than minor differences in administered activity.

In addition, ^{64}Cu-DOTATATE that was used in the literature reports was produced in house as described in Pfeifer et al., 2012 (*vs* the central production of the commercial product subject to this application). There are some differences in used excipients and product specifications between the product used in the literature and the intended commercial product. The resulting impact remains unclear but may be negligible. The specifications for dotatate and related substance were tighter for Deqtynet.

The **NETMedix Denmark trial** is a retrospective analysis of published results from an open-label, single-centre, single-dose study (Pfeifer et al., 2015) that enrolled patients with histopathologically confirmed NETs. The retrospective analysis evaluated diagnostic performance parameters on a per-patient basis, which are in line with regulatory guidance (CPMP/EWP/1119/98/Rev. 1).

The chosen heterogenous composite SoT (concordance among baseline imaging modalities and clinical follow-up of discrepant findings) is a source of bias but as only patients with histopathologically confirmed disease were eligible, the impact on estimates on a per-patient basis may be contained.

The study population evaluated in the NETMedix Denmark Trial and literature reports consisted of patients with a confirmed (history) of NETs, with different anatomical origins of the primary tumour, including a small number of non-GEPs and G3 NETs, which is a relevant population. Hence, diagnostic performance estimates are applicable to patients with confirmed disease or disease history and well-differentiated NETs.

The primary efficacy analysis yielded a sensitivity estimate of 0.9900 (95% CI: 0.9455, 0.9982) and a specificity estimate of 1.00 (95% CI: 0.7575, 1.00). However, uncertainties regarding the use of the composite SOT remain. The PPV (1.00 [95% CI 0.9626, 1.000] and NPV (0.9231 [95% CI 0.6669,

0.9863]) are supportive to inform the impact on diagnostic thinking but are less valuable outside the evaluated clinical setting due to the dependency of the disease prevalence.

Despite the study facing some limitations, results are deemed as supportive evidence for the per-patient diagnostic performance of ^{64}Cu-DOTATATE in a larger sample size.

The published study by **Pfeifer et al., 2012** reported lesion detection rate of ^{64}Cu-DOTATATE PET/CT in comparison to ^{111}In-DTPA-octreotide SPECT in 14 patients with a history of NETs, overall suggestive of a better per-lesion detection with ^{64}Cu-DOTATATE PET.

The same comparison was evaluated in **Pfeifer et al., 2015** but in a larger cohort. While the study size of this study (N=112) is a strength, the above outlined uncertainties regarding heterogenous composite SoT are a limitation, especially for per-lesion performance. Further, PET/CT scans were not evaluated by independent readers. However, study findings on the comparative performance are in concordance with the already known better sensitivity of SSTR PET imaging in comparison to ^{111}In-DTPA-octreotide SPECT, which is also applicable to ^{64}Cu-DOTATATE. The detection of *additional organ-involvement* in approximately 1/3 of patients with a confirmed history of NET is deemed clinically relevant.

The **Johnbeck et al 2017** report is a head-to-head comparison between ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC, which is the most relevant comparator as it represents current clinical practice (ESMO guideline on GEP-NETs) and is approved in the EU (SomaKit TOC). According to the authors, the study enrolled patients for primary staging and restaging.

In total, 701 lesions were detected by both PET tracers (i.e. concordant lesions) in 37 out of 59 patients (63%). Of the 40 true-positive lesions that were discordant between PET tracers, 33 (82.5%) were found by ^{64}Cu-DOTATATE and 7 (17.5%) by ^{68}Ga-DOTATOC, which was reported as statistically significant. No overall lesion detection rate was reported. However, when considering all reported lesions that were confirmed in the study (701 concordant lesions and 40 discordant lesions, out of which 33 and 7 were detected only by ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC, respectively), the following can be deduced: ^{64}Cu-DOTATATE detected 734/741 lesions (99.1%) and ^{68}Ga-DOTATOC detected 708/741 lesions (95.6%).

These results indicate that numerically more lesions are detected with the Cu tracer in comparison to the Ga tracer. However, the clinical relevance of this numerical trend for the patient remains unclear as impact on patient management was not evaluated. Precise staging or an earlier detection of lesions in a follow-up setting, if additional organ involvement can be shown, would be clinically valuable. However, detecting another lesion in an already known metastatic site may not necessarily pose additional important information and can also further depend on the affected anatomical region (e.g. different liver segments). It seems that all but one patient with a soft tissue lesion, only detected on a ^{64}Cu-DOTATATE scan, had additional concordant lesions in affected anatomical sites. Patients with discordant lesions had additional lesions with concordant findings. Thus, the diagnostic performance of ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC on a per-patient analysis was identical (sensitivity: 100% [95% CI: 93%–100%]; specificity: 90% [95% CI: 56%–100%]).

The technical performance as regards the tumour to background ratio (TBR) was comparable between the two PET tracers in evaluated anatomical sites.

Reported per-lesion results are deemed challenging to interpret as regards clinical impact for the patient. In addition, lesions were verified based on agreement with the comparator rather than a reference standard and a heterogenous composite SoT was employed for discordant lesion verification at follow-up. Nevertheless, methodological challenges pertaining to lesion-based analyses are acknowledged. With regard to image analysis, the uncertain degree of reader blinding, the paired

image analysis by 1 reader-team and the different diagnostic quality of the CT component between PET scans are an additional source of bias. Overall, the Johnbeck study provides some reassurance that the diagnostic performance of ^{64}Cu-DOTATATE is not inferior to ^{68}Ga-DOTATOC.

Notwithstanding the limitations of the literature reports, these are overall considered sufficiently reassuring that Deqtynet adequately performs at an organ- and lesion-level, despite the lack of any product-specific estimates from the pivotal study beyond the patient level.

Impact on patient management and diagnostic thinking

Although not directly evaluated, the impact on patient management, could be indirectly inferred based on more detected lesions with respect to comparators. ^{64}Cu-DOTATATE detected numerically more lesions compared to ^{68}Ga-DOTATOC in one literature report (Johnbeck 2017). Whether reported trends in lesion detected impacted patient management and outcome was not evaluated in Johnbeck 2017. The clinical impact of a potential higher lesion detection rate depends on the clinical setting and additional anatomical findings and is thus, not straight forward to deduce. Precise staging or an earlier detection of lesions in a follow-up setting could impact patient management, especially if additional organ involvement can be shown. However, detecting more lesions (even if statistically significant) for an anatomical region that is already identified as metastatic site may not necessarily have implications on patient management (as also mentioned in Pfeifer et al., 2015, Hope et al., 2018) and may depend on the anatomical location (e.g. different segments on liver involvement). No additional discussion on patient management or a quantification thereof was provided.

Additionally, per-lesion estimates are limited by an overarching uncertainty regarding the stronger reliance on a surrogate SoT and are thus, more prone to bias.

The applicant has not provided data of impact on diagnostic thinking (higher probability of correct diagnosis after the test than before the test or change in diagnosis) or impact on patient management for ^{64}Cu-DOTATATE.

It is agreed that the role of SSTR PET imaging in refining staging and disease extent is *in general* well established and recognised in international clinical guidelines (ENETS; EANM/SNMMI; NCCN), which consider SSTR PET/CT a key tool for diagnostic work-up and disease characterisation in NETs.

Considering similar principal molecular structure and similar mechanism of action with SomaKit TOC, similar diagnostic performance as SomaKit TOC based on literature study reports (limitations are acknowledged), it is considered reasonable to assume that the impact on diagnostic thinking and patient management would be similar and no dedicated investigation of Deqtynet's impact on patient management and diagnostic thinking is deemed necessary.

5.3.6.2. Conclusions on the clinical efficacy

Deqtynet has demonstrated satisfactory diagnostic performance in PET imaging of well-differentiated NETs that over express somatostatin receptors on a *per-patient basis*.

Considering the proposed clinical utility of Deqtynet (staging and re-staging) the clinical question to be answered is not only whether the patient has the disease or not, but to evaluate the extent of disease and localization of SSTR-overexpression. Therefore, lesion and organ-/region-based analyses are considered relevant for the proposed clinical utility of Deqtynet. These analyses are available from the literature reports and suggest good diagnostic performance, which is considered sufficient for the B/R evaluation.

5.4. Clinical safety

Please refer to the table of studies in section 5.3.2

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The safety of ^{64}Cu-DOTATATE was evaluated based on safety data from 4 studies:

- **RMX-17-22** - Complete safety data from the Phase 1, open-label, study in patients
- **RMX-18-22** - Complete safety data from the open-label, pivotal, Phase 3 study in patients
- **NETMedix Denmark Study** Retrospective Analysis (reanalysis of data from Pfeifer et al., 2015)– Safety data from the Phase 2, open-label, comparative study in patients
- **Pfeifer 2012** – Supportive safety information from the literature

A tabular summary of the description of clinical studies in the development program for ^{64}Cu-DOTATATE contributing to safety is provided inthe table below. More detailed descriptions are provided in section 5.3 of this report.

Moreover, a published abstract by Kjaer (2019) was provided as a supportive study, which reported safety experience with ^{64}Cu-DOTATATE in 500 consecutive patients at a single center in Denmark, including patients described in study from Pfeifer (2012 and 2015), and Johnbeck (2017). The authors reported no major side-effects in these 500 patients, although safety monitoring measures were not specified.

Table 36. Description of Clinical Studies in the Development Program for ^{64}Cu-DOTATATE Contributing to Safety

Study ID (Status) [Study Start]	**Number of Centres (Location) Number of Subjects [Planned / Enrolled]**	**Study Design and Primary Objective(s)**	**Test Product(s); Dosage Regimen; Route of Administration; Duration of Treatment**	**Number of Subjects and Population**	**Gender (M/F) Age Range**	**Safety Endpoints**
RMX-17-22 (Completed) [04-Jan-2018]	1 (US) [12/12]	Phase 1, prospective, open-label, single-dose, dose-ranging To identify the lowest amount of administered radiotracer dose of ^{64}Cu- DOTATATE that provides diagnostic quality PET-CT image, coincident with the as low as reasonably achievable (ALARA) principle	^{64}Cu-DOTATATE: Single intravenous bolus injection of 3 - 5 mCi (111-185 MBq); After intravenous injection, PET images were acquired 60 ± 15 minutes after administration.	12 patients with confirmed NEN disease	7/5 44-83 y	AEs Vital signs Clinical laboratory parameters ECG recordings
NETMedix Denmark Study Retrospective Analysis of Pfeifer, 2015 (Completed) [06-Oct-2009]	1 (Denmark) [112 / 112]	Retrospective analysis, open-label, single-center, single-dose, comparative To investigate whether ^{64}Cu-DOTATATE PET scan findings had the ability to diagnose somatostatin receptor- positive NENs (^{64}Cu-DOTATATE vs SOT)	^{64}Cu-DOTATATE: Intravenous injection of 183-232 MBq ^{111}In-Octreotide: Intravenous injection of 181-268 MBq After intravenous injection, PET images were acquired 60 minutes after administration	112 patients with histologically verified neuroendocrine tumour	63 / 49 30-84 y	Drug reactions and AEs

RMX-18-22 (Completed) [22-Jan-2018]	1 (US) [59 / 59]	Open-label, single-arm, single-center To assess the performance (sensitivity and specificity) of 64Cu-DOTATATE PET-CT imaging in subjects with known or suspected NENs, when comparing individual reader results to a standard of truth (SOT) for each subject	^{64}Cu-DOTATATE: intravenous bolus injection of 4.0 mCi ± 10% (148 MBq) After intravenous injection, PET images were acquired 60 ± 15 minutes after administration.	63 healthy subjects and patients with confirmed or suspicion of NEN disease (59 subjects enrolled plus 4 from Study RMX-17-22)	28 / 35 25-82 y	AEs Vital signs Clinical laboratory tests ECG recordings
Pfeifer, 2012 (Completed) [Published: Aug-2012]	1 (Denmark) [14 / 14]	Prospective, first-in-man, exploratory, open-label, comparative Evaluate the clinical performance of PET with ^{64}Cu-DOTATATE compared to SPECT with 111In-DTPA-octreotide with respect to lesion detection	^{64}Cu-DOTATATE: Intravenous injection of 193-232 MBq ^{111}In-DTPA-octreotide: Intravenous injection of 197-227 MBq After intravenous injection, PET images were acquired 1 hour, 3 hours, and 24 hours after administration	14 patients with history of NENs	10 / 4 40-80 y	AEs

F=female; M=male; U=units; y=years

RMX-17-22 (Open-label, dose-ranging study in patients)

Safety was monitored in this study as follows:

- AE monitoring: through 48 hours post-injection
- ECG recording: a continuous ECG recording supervised by study site staff at least 15 minutes prior to administration of the study drug and continuing for at least 30 minutes after administration. In addition, a 12 lead static ECG was performed by the study site staff within 60 minutes before and within 60 minutes following study drug administration.

- Vital signs (blood pressure, body temperature, respiratory rate and pulse rate): collected pre-dose (within 30min) and 5, 10, 30, 60 and at the time of discharge post ^{64}Cu-DOTATATE injection.
- Blood sample collection for clinical laboratory assessments (including haematology and clinical chemistry): within 30 minutes pre-dose, within 2 hours and within 1-2 days post-dose

RMX-18-22 (Open-label, safety and efficacy study in patients and healthy subjects)

Safety was monitored in this study as follows:

- AE monitoring: through 48 hours post-injection
- ECG recording: a continuous ECG recording supervised by study site staff at least 15 minutes prior to administration of the study drug and continuing for at least 30 minutes after administration. In addition a 12 lead static ECG was performed by the study site staff within 60 minutes before and within 60 minutes following study drug administration.
- Vital signs (blood pressure, body temperature, respiratory rate and pulse rate): collected pre-dose (within 30min) and 5, 10, 30, 60 and at the time of discharge post ^{64}Cu-DOTATATE injection.
- Blood sample collection for clinical laboratory assessments (including haematology and clinical chemistry): within 30 minutes pre-dose, within 2 hours and within 1-2 days post-dose.

In studies RMX-17-22 and RMX-18-22 adverse events were collected pre-dose within one hour before, and post-dose within 2 hours after ^{64}Cu-DOTATATE injection. Follow-up phone calls were conducted to collect AEs at 24 hours and 48 hours after ^{64}Cu-DOTATATE injection administration (at 24 hours only in study RMX-17-22).

NETMedix Denmark Study (Retrospective analysis of an open-label, comparative study in patients)

Safety was monitored in this study as follows:

- AE monitoring: monitored for adverse or clinically detectable pharmacologic events during participation in the study as part of routine clinical practice.

Pfeifer 2012 (Study from published literature)

Safety was monitored in this study as follows:

- AE monitoring: monitored for adverse or clinically detectable pharmacologic events during participation in the study as part of routine clinical practice.

Safety Evaluations

Adverse Events

In clinical studies RMX-17-22, RMX-18-22, and the NETMedix Denmark study, an AE was defined as any unfavourable or unintended sign, symptom, or disease temporally associated with the use of study drug, regardless of causal relationship to study drug administration.

Treatment-emergent adverse event (TEAE) definitions were included in RMX-17-22 and RMX-18-22 as adverse events where start date and time was on or after the start date and time of the injection of study drug. If the AE had a missing start date or time, or if the injection start time was unknown, then the event was considered treatment emergent.

Severity Of Adverse Events

The intensity of each AE was categorised by the investigator as mild, moderate, or severe, using the following definitions:

- Mild: Events that were usually transient, required no special treatment, and did not interfere with the subject's daily activities.
- Moderate: Events that introduced some level of inconvenience or concern to the subject, and may have somewhat interfered with daily activities, but were usually ameliorated by simple therapeutic measures (may have included drug therapy).
- Severe: Events that were unacceptable or intolerable, significantly interrupted the subject's usual daily activity, and required systemic drug therapy or other treatment.

Causality Assessment

The investigator recorded the relationship of each AE to study drug in the subject's case report form (CRF) as definitely, probably, possibly, unknown, or not related.

Serious Adverse Events

A serious adverse event (SAE) was defined as any event that:

- Resulted in death;
- Was life-threatening;
- Resulted in persistent or significant disability/incapacity;
- Resulted in or prolonged an existing hospitalisation;
- Was a congenital anomaly/birth defect.

In addition, important medical events that may not have fallen into these categories could have been considered an SAE, if based upon appropriate medical judgment; they jeopardised the subject and required medical or surgical intervention to prevent one of the outcomes listed above.

Statistical Methods

Data from all subjects who received at least one injection of study drug are included in the safety analyses. For each study, these subjects are considered the Intent-to-diagnose (ITD) population.

Demographics: For RMX-17-22, RMX-18-22, and the NETMedix Denmark Study, the continuous demographic characteristics at screening (age, height, and weight) were summarised for all subjects in the safety population using descriptive statistics (mean, standard deviation, median, minimum, maximum, and number of non-missing observations). The categorical baseline characteristics (gender, race, ethnicity) were summarised for the ITD population using frequency counts and percentages.

Study Drug Exposure: For RMX-17-22 and the NETMedix Denmark Study, summary statistics (mean, standard deviation, n, minimum, maximum and median) were calculated for doses delivered. For RMX-18-22, summary statistics (mean, standard deviation, n, minimum, maximum and median) were computed on the wand counts on the dosing unit both pre and post injection and on the dose volume.

Adverse Events: The Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary was used to classify all TEAEs with respect to system organ class (SOC) and preferred term.

TEAEs were summarised by the total number and by the number and proportion of subjects reporting at least one occurrence of the TEAE. Frequencies of each TEAE were summarised by MedDRA preferred term within system organ class (SOC) and by severity, relation to study drug, and time of onset (before or after the initiation of study drug). Frequencies of each SAE were summarised by total

number, by the number and proportion of subjects reporting at least one occurrence of the SAE, and by MedDRA preferred term within system organ class (SOC).

Clinical Laboratory Results and Vital Signs: For RMX-17-22, for each lab parameter, the investigator reviewed the lab parameter values at each time point for each patient. In addition, for each lab parameter, the investigator reviewed the shift in lab parameter values from the baseline to each post dosing time point relative to the change in CTCAE (v4.0) scale scores. For RMX-18-22, for each quantitative clinical laboratory parameter, summary statistics on the raw and change from baseline values at each time point were calculated. If multiple pre-injection labs were recorded, then the results closest to imaging were used as baseline.

No clinical laboratory evaluations were collected in the NETMedix Denmark Study.

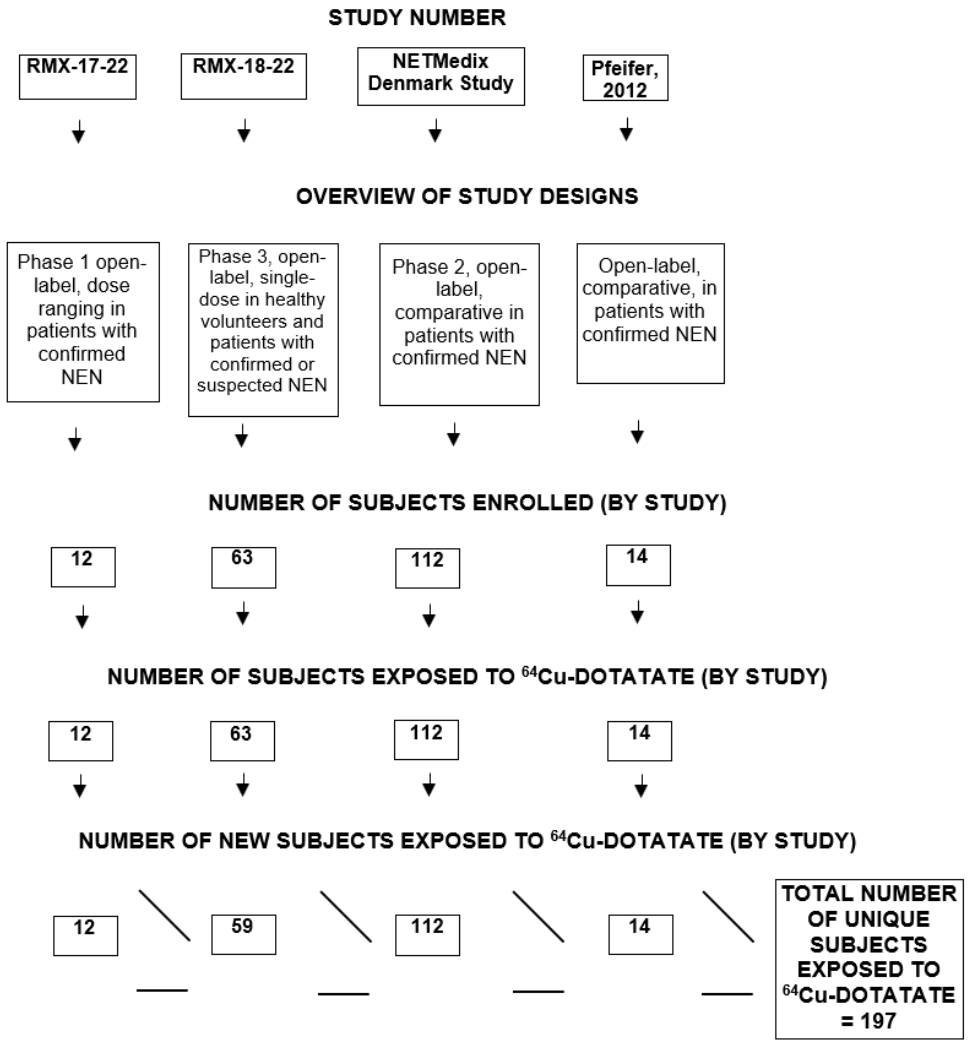
5.4.2. Patient exposure

The overall extent of exposure to ^{64}Cu-DOTATATE across the 3 studies in the Clinical Development Program and the supportive study in the literature is summarised in the figure below. All of the described studies are completed.

Four subjects from RMX-17-22 participated in RMX-18-22. Therefore, the total number of unique subjects exposed to ^{64}Cu-DOTATATE represents the sum of the number of "new" subjects in each study who had not received ^{64}Cu-DOTATATE in a prior study.

All studies were single dose; therefore, there have been 197 injections.

Figure 15. Overall Exposure to ^{64}Cu-DOTATATE across the Clinical Development Program Contributing to Safety



RMX-17-22 (Dose-Ranging in Patients)

Patients were randomly assigned to one of the three dose levels based on the randomisation list for the study, i.e. 3 (±10%) mCi, 4 (±10%) mCi, 5 (±10%) mCi. Each patient was administered a single intravenous bolus injection with intended radioactivity content according to their assigned group. The radioactivity/dose was measured before and after injection using a calibrated machine and recorded. The difference in radioactivity before and after the injection was considered to be the total dose administered. As shown in the Table below, all administered doses were within ±10% of the intended dose level.

Table 37. Extent of Exposure in Study RMX-17-22 (All Enrolled Population)

Subject Number	Cohort	Intended Dose (mCi)	Dose Administered (mCi)	DOTATATE Mass Dose Administered (µg)	Wait Time Between Injection and Imaging (hour:minutes)
[redacted]	1	3	3.1	18.04	1:02
[redacted]	1	3	3.13	22.96	1:07
[redacted]	1	3	3.04	21.63	0:56
[redacted]	1	3	3.1	19.57	1:02
[redacted]	2	4	4.3	38.25	0:50
[redacted]	2	4	4.37	33.66	1:08
[redacted]	2	4	4.35	30.60	0:58
[redacted]	2	4	3.8	22.24	1:08
[redacted]	3	5	5.28	42.64	1:06
[redacted]	3	5	5.18	33.21	1:01
[redacted]	3	5	5.39	29.87	1:08
[redacted]	3	5	5.36	32.96	1:00

RMX-18-22 (Healthy Subjects and Patients with NENs)

All 63 subjects were injected with a single dose of ^{64}Cu-DOTATATE. A mean (SD) dose of 4.11 (0.17) mCi of ^{64}Cu-DOTATATE was delivered. Doses ranged from 3.6 mCi to 4.4 mCi. The Table below provides a summary of ^{64}Cu-DOTATATE dose administration.

Table 38. Summary of ^{64}Cu-DOTATATE Dose Administration in Study RMX-18-22

	Mean	**SD**	**n**	**Min**	**Max**	**Median**
^{64}Cu-DOTATATE Delivered (mCi)	4.11	0.17	63	3.6	4.4	4.13
Mass dose of ^{64}Cu-DOTATATE Delivered (mcg)	17.48	6.27	63	8.5	38.3	16.10

NETMedix Denmark Study (Open-label, Comparative in Patients with NENs)

All 112 patients were injected with ^{64}Cu-DOTATATE. A mean (SD) dose of 202.2 (10.00) MBq of ^{64}Cu-DOTATATE was delivered. Doses ranged from 183 MBq to 232 MBq. The Table below provides a summary of ^{64}Cu-DOTATATE dose administration.

Table 39. Summary of ^{64}Cu-DOTATATE Dose Administration in NETMedix Denmark Study

	Mean	**SD**	**n**	**Min**	**Max**	**Median**
^{64}Cu-DOTATATE (MBq)	202.2	10.00	112	183	232	202.0

Max=maximum; Min=minimum; SD=Standard Deviation

Pfeifer 2012 (Open-Label Supportive Study in Literature in Patients with NENs)

In the Pfeifer, 2012 study, 14 patients received a single dose of ^{64}Cu-DOTATATE (193-232 MBq).

Extent of Exposure to ^{64}Cu-DOTATATE in Studies by Demographic Subsets

Exposure to ^{64}Cu-DOTATATE by Age

Table 40. Number of Subjects Exposed to ^{64}Cu-DOTATATE by Age Group and Study – Safety Population

Study, N	2-5 y	6-11 y	12-17 y	18-64 y	>64 y	Safety Population
RMX-17-22	0	0	0	8	4	12
RMX-18-22	0	0	0	42	17	59[a]
NETMedix Denmark Study	0	0	0	64	48	112
Pfeifer, 2012	0	0	0	10	4	14
Total, N	**0**	**0**	**0**	**124**	**73**	**197**

y=years; N= number of subjects

[a]Does not include 4 subjects from Study RMX-17-22, which were part of the total safety population for Study RMX-18-22

Exposure to ^{64}Cu-DOTATATE by Gender

Table 41. Number of Subjects Exposed to ^{64}Cu-DOTATATE by Gender and Study – Safety Population

Study, N	Male	Female	Safety Population
RMX-17-22	7	5	12
RMX-18-22	26	33	59[a]
NETMedix Denmark Study	63	49	112
Pfeifer, 2012	10	4	14
Total, N	**106**	**91**	**197**

y=years; N= number of subjects

[a] Does not include 4 subjects from Study RMX-17-22, which were part of the total safety population for Study RMX-18-22

Exposure to ^{64}Cu-DOTATATE by Race

Table 42. Number of Subjects Exposed to ^{64}Cu-DOTATATE by Race and Study – Safety Population

Study, N	White	Non-White	Safety Population
RMX-17-22	12	0	12
RMX-18-22	50	9	59[a]
Total, N	**62**	**9**	**71**

y=years; N= number of subjects

[a]Does not include 4 subjects from Study RMX-17-22, which were part of the total safety population for Study RMX-18-22

Demographic and Other Characteristics of Study Population

Table 43. Overall Demographic Profile of Subjects Exposed to ^{64}Cu-DOTATATE: by Study, Age, Gender, and Race

Demographic Parameter	RMX-17-22 N=12	RMX-18-22 N=63[a]	NETMedix Denmark Study	Pfeifer, 2012 N=14
Age (years) Mean ± SD Range	NA 44 - 83	54.37 ± 15.65 25 - 82	61.6 ± 10.85 30 - 84	NA 40 – 81
Sex, N (%) Female Male	5 (41.7%) 7 (58.3%)	35 (55.6%) 28 (44.4%)	49 (43.8%) 63 (56.3%)	4 (28.6%) 10 (71.4%)
Race, N (%) White/Caucasian Black/African American Hispanic/Latino Asian American Indian/ Alaska Native Other	12 (100.0%) 0 0 0 0 0	54 (85.7%) 6 (9.5%) 0 2 (3.2%) 0 1 (1.6%)[b]	NA	NA

N=number of subjects exposed to one or more doses of ^{64}Cu-DOTATATE in an individual study
NA=not available
[a]Four (4) subjects from Study RMX-17-22 are included as part of the total safety population for Study RMX-18-22
[b]One subject had a race of other-Latino recorded in error. This subject's race should have been set to missing and therefore the percentage of subjects with a race of Other would be 0% rather than 1.6% (n=1).
NOTE: Subjects may have been dosed with ^{64}Cu-DOTATATE in more than one study (see above).

RMX-17-22 (Dose-Ranging in Patients)

Table 44. Listing of Demographics and Baseline Characteristics (All Enrolled Population) for Study RMX-17-22

Cohort	Cohort Dose (±10%) mCi	Patient Number	Age (year)	Weight (lbs)	Height (inch)	Gender	Race	Ethnicity
1	3	[redacted]	[redacted]	[redacted]	[redacted]	F	White	Not Hispanic or Latino
1	3	[redacted]	[redacted]	[redacted]	[redacted]	M	White	Not Hispanic or Latino
1	3	[redacted]	[redacted]	[redacted]	[redacted]	F	White	Not Hispanic or Latino
1	3	[redacted]	[redacted]	[redacted]	[redacted]	M	White	Not Hispanic or Latino
2	4	[redacted]	[redacted]	[redacted]	[redacted]	M	White	Not Hispanic or Latino
2	4	[redacted]	[redacted]	[redacted]	[redacted]	F	White	Not Hispanic or Latino
2	4	[redacted]	[redacted]	[redacted]	[redacted]	F	White	Not Hispanic or Latino
2	4	[redacted]	[redacted]	[redacted]	[redacted]	M	White	Not Hispanic or Latino
3	5	[redacted]	[redacted]	[redacted]	[redacted]	M	White	Not Hispanic or Latino
3	5	[redacted]	[redacted]	[redacted]	[redacted]	M	White	Not Hispanic or Latino
3	5	[redacted]	[redacted]	[redacted]	[redacted]	M	White	Not Hispanic or Latino
3	5	[redacted]	[redacted]	[redacted]	[redacted]	F	White	Not Hispanic or Latino

RMX-18-22 (Healthy Subjects and Patients with NENs)

Table 45. Demographics and Baseline Characteristics (Safety Population) for Study RMX-18-22

Characteristic	Overall (N = 63[a])
Age (years), n	
Mean (SD)	54.37 (15.65)
Median (min, max)	54.00 (25.0, 82.0)
Height (in), n	
Mean (SD)	67.67 (4.54)
Median (min, max)	68.00 (58.0, 78.7)
Weight (lb), n	
Mean (SD)	185.75 (46.70)
Median (min, max)	178.00 (114.0, 327.0)
S, n (%)	
Male	28 (44.4%)
Female	35 (55.6%)
Race, n (%)	
American Indian or Alaska Native	0 (0.0%)
Asian	2 (3.2%)
Black or African American	6 (9.5%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)
White	54 (85.7%)
Other	1 (1.6%)
Ethnicity, n (%)	
Hispanic or Latino	11 (17.5%)
Not Hispanic or Latino	52 (82.5%)
Unknown	0 (0.0%)
Not Reported	0 (0.0%)

[a] Four (4) subjects from Study RMX-17-22 are included as part of the total safety population for Study RMX-18-22

NETMedix Denmark Study (Open-label, Comparative in Patients with NENs)

Table 46. Demographics for NETMedix Denmark Study

Demographic Variable	Statistic	All ITD Patients
Age (years)	N	112
	Mean (SD)	61.6 (10.85)
	Median (Min, Max)	63.0 (30, 84)
Gender	Female n (%)	49 (43.8%)
	Male n (%)	63 (56.3%)

Max=maximum; Min=minimum; SD=Standard Deviation

Pfeifer 2012 (Open-Label Supportive Study in Literature in Patients with NENs)

Table 47. Demographics: Pfeifer 2012 Study

Patient no.	Gender	Age
1	M	58
2	F	50
3	M	44
4	M	62
5	M	63
6	F	40
7	M	72
8	F	51
9	M	81
10	M	64
11	M	64
12	M	72
13	F	44
14	M	76

Prior and concomitant therapy

RMX-17-22 (Dose-Ranging in Patients)

Any concomitant medications being taken were obtained and recorded at the screening visit.

RMX-18-22 (Healthy Subjects and Patients with NENs)

All prior and concomitant medications taken by or administered to a subject in the safety population were collected from the 30 days prior to informed consent until completion/withdrawal from the study. Concomitant medications were coded using the WHO Drug Dictionary.

5.4.3. Adverse events

AEs summarised by the Applicant in the summary of clinical safety were treatment emergent; that is, AEs where start date and time was on or after the start date and time of the injection of study drug. If the AE had a missing start date or time, or if the injection start time was unknown, then the event was considered treatment emergent

A summary of treatment-emergent AEs (TEAEs) across the Clinical Development Program is provided in the Table below.

Table 48. Adverse Events Across the Clinical Development Program: Safety Population

Study	RMX-17-22	RMX-18-22	NETMedix Denmark Study		Pfiefer 2012
Study Drug	^{64}Cu-DOTATATE	^{64}Cu-DOTATATE	^{64}Cu-DOTATATE	^{111}In-Octreotide	^{64}Cu-DOTATATE
Number of treated subjects	12	63[a]	112	112	14
Number (%) of subjects with ≥1 TEAE All AEs Related AEs	 3 (25.0%) 0 (0%)	 5 (7.9%) 0 (0%)	 0 (0%) 0 (0%)	 0 (0%) 0 (0%)	 4 (28.6%) 4 (28.6%)
Total number of TEAEs All AEs Related AEs	 4 0	 9 0	 0 0	 0 0	 4 4
Number of deaths	0	0	0	0	0
Number (%) of subjects with treatment- emergent SAEs All SAEs Related SAEs	 0 0	 0 0	 0 0	 0 0	 0 0
Number (%) of subjects discontinued from study drug due to an AE	0	0	0	0	0

a) Four (4) subjects from Study RMX-17-22 are included as part of the total safety population for Study RMX-18-22

Analysis of Adverse Events

RMX-17-22 (Dose-Ranging in Patients)

Treatment-Emergent Adverse Events

A summary of the most commonly reported TEAEs (all and treatment-related) by SOC and preferred term is presented for subjects in RMX-17-22 in the table below. The ^{64}Cu-DOTATATE group includes the 12 patients who received ^{64}Cu-DOTATATE.

Three subjects reported a total of four adverse events observed during this study. Subject 1 reported flushing during the procedure and Subject 2 reported a headache during the procedure. At the 24 hour follow up phone call, Subject 3 reported syncope and Subject 2 reported neuropathy. The flushing and syncope were classed as unlikely to be related to the study drug by the investigator. The headache was classed as definitely not related to the study drug and the neuropathy was classed as probably not related to the study drug.

All events were mild in severity (CTCAE Grade 1) and all resolved without further follow up.

Table 49. Treatment-Emergent Adverse Events (All and Treatment- Related) by System Organ Class and Preferred Term (Reported in ≥1 Subject per SOC) – Safety Population (RMX- 17-22)

Safety population, N	**^{64}Cu-DOTATATE N=12**	
SOC **AE Preferred Term**	**All**	**Treatment-Related**
Number (%) of subjects with ≥1 TEAE	3 (25.0%)	0 (0%)
Nervous System Disorders	**3 (25.0%)**	**0 (0%)**
Headache	1 (8.3%)	0
Peripheral neuropathy	1 (8.3%)	0
Syncope	1 (8.3%)	0
Vascular Disorders	**1 (8.3%)**	**0 (0%)**
Flushing	1 (8.3%)	0

Four subjects in the 4.0 mCi dose group of Study RMX-17-22 were included in the analysis for the Phase 3 study (RMX-18-22). Two subjects in the 4.0 mCi dose group each reported one adverse event, which were included in Study RMX-18-22. One subject in the 5.0 mCi dose group reported two adverse events, which were not included in the analysis for Study RMX-18-22 (see Table below).

Table 50. Subjects Reporting Treatment-Emergent Adverse Events in Study RMX-17-22

Subject ID	**Dose (mCi)**	**Number of AE's**	**Adverse Event(s)**	**Safety Population**
[redacted]	4.0	1	Flushing	Included in RMX-18-22
[redacted]	4.0	1	Syncope	Included in RMX-18-22
[redacted]	5.0	2	Headache, neuropathy	Not included in RMX-18-22

RMX-18-22 (Healthy Subjects and Patients with NENs)

Treatment-Emergent Adverse Events

A summary of the most commonly reported TEAEs (all and treatment-related) by SOC and preferred term is presented for subjects who received ^{64}Cu-DOTATATE in RMX-18-22 in the Table below.

A total of 5 subjects (7.9%) experienced 8 adverse events that were determined to be probably not related to treatment with ^{64}Cu-DOTATATE. These adverse events included nausea, vomiting, headache, syncope, melanoderma, and flushing. One subject (1.6%) experienced an adverse event of hypertension that was determined to be definitely not related to treatment with ^{64}Cu-DOTATATE.

Table 51. Adverse Events by System Organ Class and Preferred Term (Reported in ≥1 Subject per SOC) – Safety Population (RMX-18-22)

Safety population, N	**^{64}Cu-DOTATATE N=63[a]**	
SOC **AE Preferred Term**	**All**	**Treatment-Related**
Number (%) of subjects with ≥1 TEAE	5 (7.9%)	0 (0)
Gastrointestinal Disorders	**3 (4.8%)**	**0 (0%)**
Nausea	1 (1.6%)	0
Vomiting[b]	2 (3.2%)	0
Nervous System Disorders	**2 (3.2%)**	**0 (0%)**
Headache	1 (1.6%)	0
Syncope	1 (1.6%)	0
Skin and Subcutaneous Tissue Disorders	**1 (1.6%)**	**0 (0%)**
Melanoderma	1 (1.6%)	0
Vascular Disorders	**3 (4.8%)**	**0 (0%)**
Flushing	2 (3.2%)	0
Hypertension	1 (1.6%)	0

[a] Four (4) subjects from Study RMX-17-22 are included as part of the total safety population for Study RMX- 18-22

[b] One subject reported two (2) episodes of vomiting, which are only counted once in this listing

A total of 4 subjects (6.3%) experienced 7 adverse events that were mild in severity and 2 subjects (3.2%) experienced 2 adverse events that were moderate in severity. There were no adverse events that were severe, life-threatening or disabling, or that resulted in death.

Adverse events that were mild in severity included nausea, vomiting, headache, melanoderma, and flushing. Adverse events that were moderate in severity included syncope and hypertension (see Table below).

Table 52. Subjects Reporting Treatment-Emergent Adverse Events in Study RMX-18-22

Subject ID	Number of AE's	Adverse Event(s)	Severity
[redacted]	1	Syncope	Moderate
[redacted]	1	Flushing	Mild
[redacted]	3	Headache Vomiting (2 episodes)	Mild Mild
[redacted]	2	Vomiting Hypertension	Mild Moderate
[redacted]	2	Nausea Melanoderma	Mild Mild

* Two subjects and were included from Study RMX-17-22

NETMedix Denmark Study (Open-label, Comparative in Patients)

Treatment-Emergent Adverse Events

For this study, routine clinical practice in tracking AEs was followed since both study drugs, ^{111}In-Octreotide and ^{64}Cu-DOTATATE (for local use at the Department of Clinical Physiology and Nuclear Medicine at Rigshospitalet) were approved agents at the study clinical site for the diagnosis of neuroendocrine tumours by the Danish Medicine Agency.

Patients were monitored for adverse events during their participation in the study as part of routine clinical practice. The Danish healthcare system requires that all adverse events must be filed electronically with the Danish authority. There were no adverse events or clinically detectable pharmacologic effects observed in this study.

Pfeifer 2012 (Open-Label Supportive Study in Literature in Patients)

There were no adverse or clinically detectable pharmacologic effects in any of the 14 subjects, except for 4 who experienced self-limiting nausea of seconds to a few minutes duration immediately after injection. The publication states that this side effect was probably due to the somatostatin analogue contained in the tracer.

A summary of the most commonly reported TEAEs (all and treatment-related) by SOC and preferred term is presented for subjects in the Pfeifer 2012 study in the Table below.

Table 53. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Pfeifer 2012)

N	^{64}Cu-DOTATATE N=14	
SOC **AE Preferred Term**	**All**	**Treatment-Related**
Number (%) of subjects with ≥1 TEAE	4 (28.6%)	4 (28.6%)
Gastrointestinal Disorders	**4 (28.6%)**	**4 (28.6%)**
Nausea	4 (28.6%)	4 (28.6%)

Table 54. Summary of AEs reported from clinical trials

Study	Number of included patients	AEs (n)	Frequency	Treatment related
RMX 17-22	12	Headache (1) Peripheral neuropathy (1) Syncope (1) Flushing (1)	8.3% 8.3% 8.3% 8.3%	0
RMX 18-22	63	Nausea (1) Vomiting (2) Headache (1) Syncope (1) Melanoderma (1) Flushing (2) Hypertension (1)	1.6% 3.2% 1.6% 1.6% 1.6% 3.2% 1.6%	0
Pfeifer 2012	14	Nausea (4)	28.6%	4

Overall Summary of Treatment-Emergent Adverse Events Among Subjects Exposed to ^{64}Cu-DOTATATE in Studies by Demographic Subsets

The majority of subjects exposed to ^{64}Cu-DOTATATE within each of these studies were between 18-64 years of age (Caucasian males). Thus, there are limitations to interpreting the influence of demographic factors on the overall incidence of subjects reporting a TEAE within these studies, and these analyses were not performed.

5.4.3.1. Adverse drug reactions

Table 55. Summary of ^{64}Cu-DOTATATE ADRs

MedDRA body system organ class	Adverse reactions	Frequency
Immune system disorders	Hypersensitivity reactions (including pruritus, urticaria, erythema, throat tightness, burning sensation, swelling face, eye swelling)	Not known*
Nervous system disorders	Syncope	Uncommon
	Headache	Uncommon
	Dizziness	Not known*
Cardiac disorders	Palpitations	Not known*
Vascular disorders	Hypertension	Uncommon
	Flushing	Uncommon
Respiratory and, thoracic and mediastinal disorders	Dyspnoeas	Not known*
Gastrointestinal disorders	Nausea	Common
	Vomiting	Common
	Diarrhoea	Not known*
	Eructation	Not known*
	Abdominal discomfort	Not known*
	Abdominal pain	Not known*
Skin and subcutaneous tissue disorders	Skin tightness	Uncommon
	Hyperhidrosis	Not known*
General disorders and administration site conditions	Chest pain, chest discomfort	Not known*
	Pain	Not known*

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

Adverse Events of Interest

There are no significant risks (identified or potential) associated with the use of radiolabelled receptor-targeted diagnostic products, including ^{64}Cu-DOTATATE.

Serious Adverse Events That Resulted in Death

There were no serious adverse events reported in any of the studies conducted with ^{64}Cu-DOTATATE.

Laboratory Adverse Events

No subjects in any study experienced a laboratory-related AE.

5.4.5. Discontinuation due to adverse events

No subjects in any study discontinued study drug (^{64}Cu-DOTATATE) due to an AE.

5.4.6. Safety in special populations

Intrinsic Factors

Analyses based on intrinsic factors were not performed due to the small number of adverse events reported. There were a total of 10 adverse events experienced by 6 subjects in studies RMX-17-22 and RMX-18-22 (total population of 71). All of these were considered unrelated to the study drug. In addition, there were no clinically significant changes in lab parameters or vital signs in both studies.

There were no subjects enrolled in the studies with renal or hepatic impairment, and there are no data available in the literature.

Extrinsic Factors

Analyses based on extrinsic factors were not performed.

Use in Pregnancy and Lactation

It is known that all radiopharmaceuticals, including ^{64}Cu-DOTATATE, have the potential to cause foetal harm as radionuclide procedures carried out on pregnant women also involve radiation dose to the embryo/foetus/child (DailyMed, 2025; International Atomic Energy Agency, n.d.). Since this is a well-characterised situation, no specific developmental toxicology studies were performed.

There are no studies with ^{64}Cu-DOTATATE in pregnant women to inform any drug- associated risks; however, all radiopharmaceuticals, including ^{64}Cu-DOTATATE, have the potential to cause foetal harm.

There is no information on the presence of ^{64}Cu-DOTATATE in human milk, the effect on the breastfed infant, or the effect on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ^{64}Cu-DOTATATE injection and any potential adverse effects on the breastfed child from ^{64}Cu-DOTATATE injection or from the underlying maternal condition.

No absolute contraindication is proposed, as the tracer is used to diagnose a potentially life-threatening condition.

Overdose

There is no information concerning overdose with ^{64}Cu-DOTATATE.

Drug Abuse

There is no anticipated potential for drug abuse with ^{64}Cu-DOTATATE.

Withdrawal and Rebound

There have been no withdrawal or rebound effects of ^{64}Cu-DOTATATE identified.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No safety concerns have been identified that would likely affect the ability to operate machinery or cause impairment of mental abilities.

5.4.7. Immunological events

Not applicable.

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

No studies examining potential drug interactions for ^{64}Cu-DOTATATE have been conducted. However, it is known that non-radioactive SST analogues competitively bind to the same SSTRs as 64Cu-DOTATATE. The concomitant use of such substances with ^{64}Cu-DOTATATE can cause a pharmacokinetic interaction. Thus, local clinical routine may require withdrawal of long- or short-acting SST analogues.

5.4.9. Vital signs and laboratory findings

Clinical laboratory

Clinical laboratory assessments (haematology and clinical chemistry) were performed for subjects who participated in Studies RMX-17-22 and RMX-18-22.

RMX-17-22 (Dose-Ranging in Patients)

Samples were collected from each patient at pre-dose, 30 minutes post dose, 2 hours post dose and 24-48 hours post dose in order to compute clinical laboratory parameters for each sample. The blood sample for 24-48 hours post dose was drawn outside of time point window for two patients, and one patient did not submit a blood sample for the 24-48 hours post dose time point.

The investigator noted no clinically significant changes in lab parameters (haematology and clinical chemistry).

RMX-18-22 (Healthy Subjects and Patients)

There were no clinically significant changes from baseline in mean serum chemistry or haematology values that occurred post-injection with ^{64}Cu-DOTATATE or at the Day 1-2 follow-up visit.

Of note, shift tables for creatinine presented a shift from a normal value at baseline to a high value at the Day 1-2 visit in 6 subjects (9.5%). Shift tables for glucose presented a shift from a normal value at baseline to a high value post-injection in 5 subjects (7.9%) and a shift from a normal value at baseline to a high value at the Day 1-2 visit in 13 subjects (20.6%). Shift tables for sodium presented a shift from a normal value pre-injection to a low value post- injection in 9 subjects (14.3%) which had resolved by the Day 1-2 visit.

Haematology

There were no shifts in haematology parameters in any subject that occurred post-injection ^{64}Cu-DOTATATE or at the Day 1-2 follow-up visit.

Clinical Chemistry

The incidence of shifts in creatinine, glucose and sodium is presented in the Table below for subjects with values that shifted from within the normal reference range at baseline to below the lower limit or above the upper limit of the normal range at any post-baseline time point. No clinically meaningful trends were observed for the 63 subjects who had both baseline and post-baseline creatinine, glucose and sodium evaluations.

Table 56. Creatinine, Glucose and Sodium: Incidence of Shifts From Baseline- to Post-Baseline (Normal to Abnormal) – Safety Population (RMX-18-22)

	^{64}Cu-DOTATATE	
Safety population, N	**63[a]**	
Subjects with baseline and post-baseline data, N	**63**	
Clinical Chemistry Parameter Shifts from baseline to post-baseline, N (%) [b]	**Post-injection**	**Day 1-2 post-injection**
Creatinine		
Normal to High	1 (1.6%)	6 (9.5%)
Normal to Low	0 (0%)	1 (1.6%)
Glucose		
Normal to High	5 (7.9%)	13 (20.6%)
Normal to Low	0 (0%)	0 (0%)

Sodium		
Normal to High	0 (0%)	1 (1.6%)
Normal to Low	9 (14.3%)	0 (0%)

[a] Four (4) subjects from Study RMX-17-22 are included as part of the total safety population for Study RMX- 18-22

[b] Laboratory assessments were performed within 2 hours post-injection and at Day 1-2 post injection.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vitals signs (blood pressure, heart rate, respiratory rate, and/or body temperature) were evaluated pre- and post-infusion in RMX-17-22 and RMX-18-22. In addition, ECG recordings were taken pre- and post-infusion in both studies.

RMX-17-22 (Dose-Ranging in Patients)

Vital signs were collected from pre-dosing to post dosing time points (5 minutes, 10 minutes, 30 minutes and 60 minutes post injection and at discharge). All changes in vital signs were evaluated by the investigator as to their clinical significance and qualification as an adverse event. There were no clinically significant changes in vital sign parameters for any of the patients enrolled in the trial.

ECG data were collected before and after dosing. The investigator examined the ECG values at each time point and the change in ECG parameters from pre to post dosing. The investigator noted changes or abnormalities in ECG parameters for four patients but all were judged as not clinically significant by the investigator.

RMX-18-22 (Healthy Subjects and Patients)

There were no clinically significant changes from baseline in mean vital signs occurring at 5-, 10-, 30-, or 60- minutes post-injection or at discharge. Mean systolic blood pressure was elevated at all time points from pre-injection to discharge and fluctuated from a mean low of 130.48 mmHg pre-injection to a mean high of 137.10 mmHg at 60 minutes post-injection. Upon discharge, the mean systolic blood pressure was 132.97 mmHg.

All subjects in studies RMX-17-22 and RMX-18-22 underwent a continuous ECG recording at least 15 minutes prior to administration of the study drug and continuing for at least 30 minutes after administration. In addition, a 12-lead static ECG was performed within 60 minutes before and within 60 minutes following study drug administration. All the ECG data were collected in digital format, analysed and reviewed (with manual over-read) by an independent physician to determine normal or abnormal and if abnormal, whether clinically significant or not significant. There were no shifts observed in ECG parameters from baseline to 1 hour post-injection of ^{64}Cu-DOTATATE.

5.4.10. Post-marketing experience

Based on analysis of the cumulative adverse events received from post marketing experience for Detectnet (^{64}Cu-DOTATATE approved in US since 03sep2020), and in consideration of the generalised hypersensitivity reactions associated with somatostatin receptor peptide agents described in correspondence received from the FDA, 'hypersensitivity reactions' was considered as an adverse reactions for ^{64}Cu-DOTATATE. Review of the available safety data up to 02sep2024 did not identify any new safety signals that change the safety profile of ^{64}Cu-DOTATATE.

5.4.11. In vitro biomarker test for patient selection for safety

Not applicable.

5.4.12. Overall discussion and conclusions on clinical safety

5.4.12.1. Discussion

5.4.12.1.1. Overall assessment of available safety data

Safety data base and patient exposure

The Applicant presents safety data from 3 clinical studies conducted in healthy volunteers and patients with confirmed or suspected NETs (RMX-17-22: n=12 patients; RMX-18-22: n=42 patients and n=21 HVs; NETMedix Denmark Study: n=112 patients;) and data from a literature study (Pfeifer 2012: n=14 patients) to support this application. Studies RMX-17-22, RMX-18-22 were conducted by the Applicant, the NETMedix Denmark trial is a retrospective reanalysis of data from Pfeifer 2015. ^{64}Cu-DOTATATE that was used in the literature reports (Pfeifer 2012, Pfeifer 2015) was produced in house as described in Pfeifer et al., 2012. However, no justification was provided that the product used in the literature reports is comparable to intended product subject to this application. Moreover, higher doses were applied in Pfeifer 2012 (183- 232 MBq) and Pfeifer 2015 (193- 232 MBq) compared to studies RMX-17-22 (111-185 MBq) and RMX-18-22 (148 MBq).

Detailed safety assessments and monitoring were performed in studies RMX-17-22 and RMX-18-22. While summary safety results were available from the NETMedix Denmark Study (Pfeifer 2015) and the literature reference Pfeifer 2012, the safety monitoring measures were not described in detail. Hence, study RMX-18-22 and study RMX-17-22 are regarded as the primary safety data for this submission.

It is noted that no cumulative safety summary including pooled safety data from all four studies was provided, only one table with pooled AEs and frequencies. Instead, safety data are reported by study, which hampers the safety assessment.

The study design and safety collection of studies RMX-17-22 and RMX-18-22 appear suitable and adequate for the outlined safety evaluations. Adverse events were collected pre-dose within 1 hour and post-dose within 2 hours of ^{64}Cu-DOTATATE injection, and at follow-up visits by phone at 48 hours.

The total number of unique subjects exposed to ^{64}Cu-DOTATATE throughout the four reported studies was 197 (21 HVs, 176 patients). All studies were single dose; therefore, there have been 197 injections.

The number of patients with suspected/confirmed NETs (n=176) exposed to study treatment is somewhat low but acceptable for such a rare condition (orphan indication). However, uncommon or rare AEs were not detected with a high probability. The safety follow up (48 hours after dosing) is also acceptable for evaluation of immediate effects of the single dose administration and is largely in line with the 'Guideline on clinical evaluation of diagnostic agents' (CPMP/EWP/1119/98/Rev. 1)

There is a risk of hypersensitivity and adverse events related to exposure to ionising radiation (induction of cancer and potential of hereditary defects).

According to GL (CPMP/EWP/1119/98/Rev. 1), *not only short-term but also long-term safety (when appropriate) should be properly assessed*. Based on Pfeifer 2012, the effective dose of ^{64}Cu-DOTATATE for an adult is approximately 4.7 mSv when the usual activity of 148 MBq is administered with the liver being the organ with the highest absorbed radiation dose (0.161 mGy/MBq), followed by the kidneys (0.139 mGy/MBq), adrenals (0.137 mGy/MBq) and spleen (0.115 mGy/MBq) (see Table 15 on Dosimetry). The proposed dose level of ^{64}Cu-DOTATATE is low compared to licensed radiotherapeutics (e.g. Lutathera: 4 infusions of 7 400 MBq each) and is comparable to commonly used diagnostic radiopharmaceuticals e.g. SomaKit TOC (effective dose 4.2 mSv), Locametz (effective dose 5.7 mSv),

Tauvid (effective dose 9.6 mSv) or gamma-emitting tracers ^{111}In-DTPAOC (effective dose 5.7–11.1 mSv) and ^{111}In-DOTATOC (effective dose 7.0–10.0 mSv). The Maximum Permissible Dose (MPD; upper limit of allowed radiation dose that one may receive without the risk of significant side effects) for physicians is 50 mSv per year (whole body), which is 10-fold higher than the radiation dose the patient receives with one ^{64}Cu-DOTATATE scan (Nicol 2018). In addition, the dose of the somatostatin analogue (octreotate) is not considered to have significant pharmacological effects apart from acute, temporary adverse events. The diagnostic dose of the somatostatin analogue (octreotate) will be used in a considerably lower quantity than the therapeutic dose of, e.g., octreotide.

Hence, it can be agreed with the Applicant that the risk of a mutagenic/carcinogenic event after exposure to a ^{64}Cu-DOTATATE scan, even if the scan is repeated, is considered low. Moreover, it is considered almost impossible to distinguish between radiation-induced tumours and the disease itself (NENs), since the disease is simultaneously a side effect, rendering long-term safety evaluations exceeding 48 hours not feasible.

Taken together, no major significant safety events are expected with the single ^{64}Cu-DOTATATE administration at the proposed dose level. Consequently, adverse reactions due to occupational and inadvertent exposure to ionising radiation are expected to occur with a low probability at the proposed dose level.

Most of the radiolabelled compounds are cleared through the kidneys and reabsorbed and partially retained in the proximal tubules, causing dose-limiting nephrotoxicity. To mitigate local dose accumulation the patient should be well hydrated before the start of the examination and urged to void before the examination and as often as possible during the first hours after the examination in order to reduce bladder radiation exposure.

While studies RMX-17-22 (n=12) and RMX-18-22 (n=63) where conducted each at a single center in the US, the NETMedix Denmark Study including 112 patients and the study by Pfeifer 2012 including 14 patients were conducted each at a single center in Denmark. Although the two RMX studies were conducted in the US, patients involved in the clinical development can be also considered representative of the European population, given that 126 patients were enrolled in Denmark.

Overall, all subjects exposed to ^{64}Cu-DOTATATE across the 4 studies were ≥18 years of age. The majority were male and in the white racial subset. Subject exposures by race are not available for the NETMedix Denmark and Pfeifer 2012 studies. No concern persists regarding the exposure by demographics. The Applicant did not discuss prior and concomitant therapies, no summaries were provided, only extensive subject listings are available from study RMX-17-22 and RMX-18-22. No information regarding concomitant medications is available from Denmark trial and Pfeifer 2012. The Applicant was requested to provide a summary of prior and concomitant therapies including pooled data from study RMX-17-22 and RMX-18-22 and discuss the safety impact of concomitant medications in conjunction with the administration of ^{64}Cu-DOTATATE. Special emphasis should be given on glucocorticosteroid administration and potential effects on image misinterpretation, as it has been shown that repeated administration of glucocorticosteroids prior to administration of ^{64}Cu-DOTATATE may cause insufficient SSTR2 expression for adequate visualisation of SSTR-positive NETs. Only a summary table on concomitant medications was provided for study RMX-17-22. For study RMX-17-22 and study RMX-18-22 a summary and discussion regarding glucocorticoid administration was provided. Image quality of PET scans in patients receiving glucocorticoids was reasonable.

Adverse Events

Adverse events (AEs) were reported by study, no cumulative safety summary over studies was provided. To be able to clearly identify AEs/ADRs including appropriate frequencies, the applicant was requested to provide a cumulative safety summary and table including pooled data of all four studies

included in the safety database (RMX-17-22, RMX-18-22, NETMedix Denmark trial, Pfeifer 2012). The Applicant stated that there was no specific pooling strategy due to the low number of AEs (19) and the lack of raw data from the published Pfeifer 2012 study. A table with all AEs with calculated frequency based on included patients was provided. No AEs were observed in the NETMedix Denmark study and in Pfeifer 4 patients experienced nausea. For the studies RMX-17-22 and RMX-18-22, two tables including AEs with severity grade and Investigator causality assessment were provided

A safety summary separated by patients with suspected/confirmed NETs (n=176) and healthy volunteers (n=21) was not provided, however, is not considered necessary as no AEs were reported in HVs.

There is no safety comparison between ^{64}Cu-DOTATATE and standard of truth (SoT) or other active comparators, since no active comparator was applied in studies RMX-17-22 and RMX-18-22. It appears, that patients were enrolled based on their SoT, i.e. according to the schedule of assessments, SoT images/reports within 8 weeks were accepted during screening. The interval between the acquisition of images used for SoT and PET-CT images with ^{64}Cu-DOTATATE was 8 weeks. AEs were collected 1 hour pre- and up to 48 hours post- ^{64}Cu-DOTATATE administration. Given that it is highly likely that safety events that appeared at/after ^{64}Cu-DOTATATE administration are indeed attributed to ^{64}Cu-DOTATATE, rather than to the SoT procedure.

Overall, ^{64}Cu-DOTATATE was well tolerated. The overall safety profile of ^{64}Cu-DOTATATE appears acceptable and in line with the safety profile of already licensed PET diagnostics.

No SAEs or deaths have been reported across the clinical development program. No subject discontinued study drug due to a TEAE in any study in the development program.

No AEs are considered of special interest or of particular clinical importance.

In the dose-finding Phase I study RMX-17-22, a total of 4 AEs were observed in 3/12 (25%) patients, i.e. flushing, syncope, headache and neuropathy. Headache was classified as definitely not related to the study drug (event started within 60 min before injection). Flushing and syncope were classified as unlikely to be related, and neuropathy was classed as probably not related to the study drug.

Considering safety events per dose (3mCi: n=0 TEAEs; 4mCi: n=2 TEAEs; 5mCi: n=2 TEAEs), a slight dose dependency could be suspected, however, due to the low sample size (total n=12; 4/dose arm), no firm conclusion can be drawn and could also be interpreted as chance finding.

All events were mild in severity - CTCAE Grade 1- and all resolved without further follow up. One event of syncope observed was severity CTCAE Grade 2.

One patient reported flushing 1 min after ^{64}Cu-DOTATATE injection which resolved after 3 mins. The patient had these episodes before due to NET (Carcinoid Syndrome), hence, the event was classified as unlikely related. Further information was provided on the flushing event with a “possible” related causality based on plausible time of onset and the presence of other potential causative factors.

In the Phase III study RMX-18-22, a total of 8 AEs were observed in 5/63 patients (7.9%), which were all assessed as probably not related to treatment. The AEs included nausea, vomiting, headache, syncope, melanoderma, and flushing. One subject (1.6%) experienced an AE of hypertension that was determined to be not related to ^{64}Cu-DOTATATE. The most common adverse events by MedDRA system organ class were gastrointestinal disorders (4.8%), nervous system disorders (3.2%), vascular disorders (3.2%), and skin and subcutaneous disorders (1.6%). All AEs were mild in severity except syncope and hypertension that were moderate in severity.

In the NETMedix Denmark study, no AEs or clinically detectable pharmacologic effects were observed. However, safety monitoring measures were not described in detail.

In Pfeifer 2012, 4 patients experienced a self-limiting 'nausea' event immediately after injection of seconds to a few minutes' duration. The authors attributed these events to the somatostatin analogue contained in the tracer. As for the NETMedix Denmark study, safety monitoring measures were not described in detail.

The influence of demographic factors on the overall incidence of subjects reporting a TEAE within the 4 studies was not provided. The Applicant considered outcomes of such an analysis not informative due to limitations of the interpretation. For studies RMX-17-22 and RMX-18-22 distribution of AE was provided by age range (<60 yoa, 60-75 yoa, >75 yoa) and more AEs were observed in the <60 y group. Although it is difficult to draw any further conclusions based on the small number of patients and AEs this is acknowledged, and no further concerns arise.

Risk of image misinterpretation

It is known that different primary tumours and metastases may express different amounts as well as different types of SSTR subtypes, and peptide ligands may bind differently to the five SSTR subtypes. Physiologically, several normal organs show an increased SSTR expression (spleen, liver, pituitary, thyroid, kidneys, adrenal glands, salivary glands, and pancreas), which means that these organs will be visible on a SSTR PET (Hope 2017, Rindi 2022). Hence, misinterpretation of images needs to be taken into account (CPMP/EWP/1119/98/Rev. 1).

Safety in special populations

Specific data for the safe use of ^{64}Cu-DOTATATE in special populations have not been provided.

The Applicant did not perform subgroup analyses of AEs for intrinsic factors (e.g. age, sex, race) due to the small number of adverse events reported. A subpopulation analysis by age was requested (see above).

No subjects with renal or hepatic impairment were enrolled in the studies and no data is available in the literature. However, increased radiation exposure and dose accumulation can be expected in these patients

It is known that all radiopharmaceuticals, including ^{64}Cu-DOTATATE, have the potential to cause foetal harm as radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus (DailyMed, 2025; International Atomic Energy Agency, n.d.). There is no data regarding the use of 64Cu-DOTATATE in pregnant and breast feeding women. However, as ^{64}Cu-DOTATATE is used to diagnose a potentially life-threatening condition, an absolute contraindication for use in pregnant (and breastfeeding) women is not applicable.

Considering certain reported safety events e.g. syncope, headache, nausea, vomiting, ^{64}Cu-DOTATATE may have a minor influence on the ability to drive and use machines.

Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies have been performed. It is known that cold (non-radioactive) SST analogues competitively bind to somatostatin receptors which may interfere with the efficacy of ^{64}Cu-DOTATATE. Certain long-acting SST analogues such as octreotide, lanreotide and pasireotide have been applied to treat indications caused by excessive release of growth hormone (acromegaly), or adrenocorticotropic hormone (Cushing's syndrome), and to treat carcinoid syndrome (Sun 2016). Since the concomitant use of such substances with ^{64}Cu-DOTATATE might cause pharmacokinetic interactions, withdrawal of long- or short-acting SST analogues may be considered in clinical routine.

In certain indications e.g. Cushing syndrome, the long-term exposure to endogenous hypercortisolism may down-regulate somatostatin receptor expression and negatively influence the results of

somatostatin receptor imaging with ^{64}Cu-DOTATATE. There is also evidence, that corticosteroids can induce down-regulation of SSTR2. Thus, repeated administration of glucocorticosteroids prior to administration of ^{64}Cu-DOTATATE may potentially cause insufficient SSTR2 expression for adequate visualisation of SSTR-positive NENs (see Pharmacology discussion in section 5.2.6).

Laboratory and other findings

In Studies RMX-17-22 and RMX-18-22, clinical laboratory assessments (haematology and clinical chemistry) were collected from each patient pre-dose, 30 minutes post dose, 2 hours post dose and 24-48 hours post dose. No clinically significant changes in lab parameters were reported in any of the studies. However, in study RMX-18-22 shifts in creatinine, glucose and sodium from normal at baseline to abnormal (below the lower limit or above the upper limit of the normal range) post-injection were reported in some patients. No clinically meaningful trends were observed.

There were no clinically significant changes in vital sign parameters (blood pressure, heart rate, respiratory rate, and/or body temperature) or ECG recordings (continuous ECG, 12-lead static ECG) for any of the patients enrolled in the trials.

Radiation protection

Regarding radiation protection, a discussion on the equivalent dose rate (EDR) at 1 meter from the patient following image acquisition with ^{64}Cu-DOTATATE was provided. The exposure rate is below the accepted thresholds of 25 µSv/h and there is no restriction for patient release.

Post marketing experience

Based on US post-marketing data with the licensed ^{64}Cu-DOTATATE (03 September 2020), 'hypersensitivity reactions' is considered an ADR for the product with symptoms including (pruritus, urticaria, erythema, throat tightness, burning sensation, swelling face, eye swelling, etc.

5.4.12.2. Conclusions on clinical safety

Overall, the presented safety data suggest that a single ^{64}Cu-DOTATATE administration is well tolerated, and the safety profile appears to be in line with the safety profile of already licensed PET diagnostics. The most common adverse events by MedDRA system organ class were gastrointestinal disorders (nausea, vomiting), nervous system disorders (headache syncope), vascular disorders (flushing, hypertension) and skin and subcutaneous disorders (melanoderma). No SAEs or deaths have been reported across the clinical development program. Concerning radiation exposure, the estimated effective dose from ^{64}Cu-DOTATATE is similar to that of other commonly used diagnostic radiopharmaceuticals, including those used for PET imaging of NET (e.g. SomaKit TOC).

Overall, the safety profile of 64Cu-DOTATATE is acceptable.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 57. Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

6.1.2. Discussion on proposed safety specification

The applicant has not included any safety concerns in the RMP. Given that the safety profile appears to be in line with that of already licensed PET diagnostics, and that the risks of the product would not require further characterization and could be adequately managed via routine pharmacovigilance activities, this approach is considered acceptable.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan

The applicant did not propose any routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

The applicant did not propose any additional pharmacovigilance activities.

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection have been proposed, which is endorsed in the absence of safety concerns in the RMP.

6.2.2.2. Additional pharmacovigilance activities

No additional pharmacovigilance activities have been proposed, which is endorsed in the absence of safety concerns in the RMP.

6.3. Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies have been proposed.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 58. Planned routine risk minimisation measures

Safety concern	**Routine risk minimisation activities**
None	Not applicable

The applicant did not propose any additional risk minimisation measures.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The routine risk minimisation measures are considered sufficient.

6.4.2.2. Additional risk minimisation measures

The applicant did not propose any additional risk minimisation measures. This is acceptable, in the absence of safety concerns in the RMP.

6.5. RMP summary and RMP annexes overall conclusion

The RMP Part VI is acceptable.

The RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 0.6 is acceptable. However, in view of the negative CHMP opinion, a RMP is not adopted at this stage.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

In light of the negative recommendation, the requirements for the Periodic Safety Update Reports submission are not applicable at this point in time.

8. Product information

Despite the conclusion of a positive benefit-risk balance for Deqtynet, given the absence of applicable derogations from market exclusivity and in view of the negative CHMP opinion, a satisfactory summary of product characteristics, labelling and package leaflet is not adopted at this stage.

8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

9. Benefit-risk assessment

9.1. Therapeutic context

The final claimed indication was: "for positron emission tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated neuroendocrine tumours (NETs) excluding neuroblastomas".

9.1.1. Disease or condition

Neuroendocrine neoplasms (NENs) are a genetically diverse spectrum of solid tumours arising from the secretory cells of the neuroendocrine system that produce peptides causing characteristic hormonal syndromes. NENs can be clinically symptomatic (i.e., 'functioning'), or silent, (i.e., 'nonfunctioning') (Öberg 2011). In general, almost all NENs are considered malignant, although their growth rate and overall aggressiveness vary significantly. Only paragangliomas are considered benign.

NENs include neuroendocrine tumours (NETs) and neuroendocrine carcinomas (NECs). NETs are generally well-differentiated (graded as G1, G2 and G3 based on proliferation), while NECs are poorly differentiated (by definition high-grade). These two classes of NENs reflect biologically and genetically two different diseases, with different levels of aggressiveness, prognosis and treatment options (Hope 2017, Rindi 2022). While well-differentiated NETs often exhibit high SSTR expression, particularly SSRT2, poorly differentiated NECs typically display lower to no SSTR expression (Rindi 2022). Consequently, NECs may not uptake the SSTR tracer as effectively, potentially leading to lower detection rates on SSTR PET. SSTR PET is often considered the primary imaging modality for assessing and staging well-differentiated NETs, whereas for poorly differentiated NECs, alternative imaging techniques like 18F-FDG PET, which detects metabolic activity, may be more sensitive (Hope 2017, Pavel 2020).

NENs occur mostly in the gastrointestinal tract and this group of tumours is referred to as gastro-entero-pancreatic NETs (GEP-NETs). NETs can, however, also occur in other tissues, such as thymus, lung, and other uncommon sites such as ovaries, heart and prostate.

The population of patients eligible for the diagnosis of the condition was estimated to be approximately 1 in 10,000 persons in the European Union per year, at the time the application for an orphan indication was made (EC Decision 9.12.2022, C(2022)9455).

9.1.2. Available therapies and unmet medical need

Many different imaging techniques are used in the diagnosis of NENs. Cross-sectional (anatomical) imaging modalities, such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) have been used to localize primary lesions and to stage the extent of the disease. Also, nuclear medicine plays an important role in the diagnostic work-up of NENs. The majority of NENs express somatostatin receptors (SSTR), which can be used as targets for radionuclide imaging. Several radiotracers comprising a somatostatin analogue chelated to a radioisotope have been developed for somatostatin receptor imaging. Imaging of somatostatin receptors in NENs was initially achieved by gamma-cameras using either conventional scintigraphy (2-D images) and single photon emission computed tomography (SPECT, 3-D images), with the radiotracers such as ^{111}Indium-pentetreotide (Octreoscan) or ^{99m}Tc-EDDA/HYNIC-TOC (Tektrotyd). However, SSTR scintigraphy presents some limitations that may decrease the diagnostic efficacy. This is mostly due to high physiological uptake such as in the liver as well as the lack of detection of smaller lesions.

Somatostatin receptor imaging (SRI) is considered the most sensitive imaging technique for the detection of neuroendocrine tumours (Pavel 2020, Rindi 2022).

SSTR imaging using PET tracers such as the ^{68}Ga-(DOTA)-conjugated peptides, offer higher spatial resolution and patient comfort due to earlier and shorter acquisition times compared to SPECT radiopharmaceuticals. PET/CT imaging with SSTR-analogues are indeed considered the gold standard of NENs imaging at present and should be performed whenever possible.

In the EU, the PET tracer ^{68}Ga-DOTATOC (^{68}Gallium edotreotide/SomaKit TOC) is approved for "*PET imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastro-enteropancreatic neuroendocrine tumours (GEP-NET) for localising primary tumours and their metastases".* ^{68}Ga-edotreotide (SomaKit TOC) has become a standard of care in the diagnostic process of patients with NET and its use is recommended in most international guidelines (NCCN 2022, Sundin 2017).

9.2. Main clinical studies

The main evidence on diagnostic performance of ^{64}Cu-DOTATATE comes from an open-label, single-dose, single-arm, single-centre, non-comparative phase 3 study (RMX-18-22) where imaging performance of ^{64}Cu-DOTATATE PET-CT was assessed versus standard of truth (SoT) which was comprised of different imaging modalities - anatomical (e.g. CT and/or MRI) and functional (e.g. NAF and/or ^{18}F-FDG and/or bone scan and/or Octreoscan) - as well as biopsy/histopathology report, biomarkers and clinical signs and symptoms. The study recruited healthy volunteers and patients with confirmed or suspected NET. Data from 63 subjects were analysed.

The **primary objective** was to assess the diagnostic performance (sensitivity and specificity) of ^{64}Cu-DOTATATE PET-CT imaging in subjects with known or suspected NETs, by comparing individual reader results to the SoT for each subject. Specificity and sensitivity were calculated on a per-subject basis.

The **clinical setting** was approximated based on patient's history. Most patients had metastatic disease and received prior therapy (e.g., surgery, chemotherapy, somatostatin analogues, PRRT), which likely corresponds to restaging or recurrence setting. Only few patients had confirmed disease with no prior treatment, corresponding to initial staging setting.

Most patients across all studies had G1 and G2 NETs (primarily GEP NETs).

In addition, literature data were submitted informing the *per-lesion* and *per-organ* diagnostic performance and providing comparative data with other SSTR imaging modalities (Pfeifer 2015, Johnbeck 2017).

9.3. Favourable effects

In study **RMX-18-22** the sensitivity was 0.9091 for all three readers. The specificity per reader ranged between 0.8000 and 0.9333. The lower bound of the 95% CIs for both co-primary endpoints were above predefined cutoffs for all 3 readers (sensitivity >70%, specificity >60%). As 3/3 readers met both criteria, exceeding the predefined success criterion (2/3 readers meeting both criteria), the co-primary endpoints as defined by the applicant on *subject-level* diagnosis were met. The analyses for an average rater evaluating an average patient yielded similar results; sensitivity was 0.8254 (95% CI: 0.7405, 0.8868) and specificity was 0.8156 (95% CI: 0.7244, 0.8815).

The positive predictive value (PPV) per reader ranged between 0.8333 and 0.9677. The negative predictive value (NPV) per reader ranged between 0.8889 and 0.9032. All readers demonstrated a level of accuracy ranging from 0.8571 to 0.9355.

Comparative diagnostic performance is informed by two literature reports (Pfeifer 2015 and Johnbeck 2017) indicating a numerically higher sensitivity in comparison to ^{111}In-DTPA-octreotide SPECT (97% [95% CI: 91%-99%] ^{64}Cu DOTATATE PET/CT and 87% [95% CI: 79%-92%] ^{111}In-octreotide SPECT) and a numerically comparable performance to ^{68}Ga-DOTATOC (identical sensitivity and specificity: 100% [95% CI: 93%–100%] and 90% [95% CI: 56%–100%], respectively) on a *per-patient* basis, supported by *per-organ* analyses. ^{64}Cu-DOTATATE showed a numerically higher value regarding lesion detection in comparison to ^{68}Ga-DOTATOC, as per Johnbeck et al 2017. No overall lesion detection rate was reported but considering all reported lesions that were confirmed in the study the following is deduced: ^{64}Cu-DOTATATE detected 734/741 lesions (99.1%) and ^{68}Ga-DOTATOC detected 708/741 lesions (95.6%).

9.3.1. Uncertainties and limitations about favourable effects

Diagnostic performance

In the pivotal study, ^{64}Cu-DOATATE PET image results were compared against the SoT. SoT included different anatomical and functional imaging modalities as well as biopsy/histopathology report, biomarkers and clinical signs and symptoms, varying across subjects. Therefore, the **variable composite SoT** including different modalities, each with different respective sensitivity and specificity, is rather seen **as surrogate SoT or reference standard**. The absence of an objective and standardized method of establishing the SoT is a methodological weakness. Also, the final decision (disease/no disease, localized/metastatic) was made by a **single oncologist** based on collective data, introducing potential bias due to subjective interpretation. The quantification of diagnostic accuracy of such variable SoT is challenging, which in turn impacts the interpretability of sensitivity and specificity results of Deqtynet. The potential bias due to subjective interpretation by a single oncologist and variable composite SoT is mitigated by the comprehensive source documentation, the availability of histopathology results for all patients with confirmed disease and the fact that most patients had metastatic disease. All these factors, along with the study results (high sens/spec) alleviate the uncertainties regarding the SoT/reference standard, at the study design level.

In the pivotal study, sensitivity and specificity were estimated at a subject level for the primary analysis. Considering the proposed clinical utility of Deqtynet (i.e. staging and restaging), the assessment of disease extent and localisation of SSTR overexpression is particularly relevant; however, **no data of the diagnostic performance on lesion and organ basis are available from the pivotal study.** Limited evidence at organ and lesion level has been provided from literature studies (Pfeifer 2015, Johnbeck 2017), which is considered reassuring.

9.4. Unfavourable effects

Study RMX-18-22 (n=42 patients and n=21 HVs) and study RMX-17-22 (n=12 patients) are regarded as the primary safety data for this submission.

No SAEs or deaths have been reported across the clinical development program. No subject discontinued study drug due to a TEAE in any study in the development program.

In the dose-finding Phase I study **RMX-17-22**, a total of 4 AEs were observed in 3/12 (25%) patients, i.e. flushing, syncope, headache and neuropathy. Headache was classified as definitely not related to the study drug. Flushing and syncope were classified as unlikely to be related, and neuropathy was classed as probably not related to the study drug. All events were mild in severity, and all resolved without further follow up. No event was reported in the 3mCi dose group, and 2 AEs each were reported in the 4mCi and 5mCi dose arms.

In the Phase III study **RMX-18-22**, a total of 8 AEs were observed in 5/63 patients (7.9%), which were all assessed as probably not related to treatment. The AEs included nausea, vomiting, headache, syncope, melanoderma, and flushing. The most common adverse events by MedDRA system organ class were gastrointestinal disorders (4.8%), nervous system disorders (3.2%), vascular disorders (3.2%), and skin and subcutaneous disorders (1.6%). All AEs were mild in severity except syncope and hypertension that were moderate in severity.

There is a risk of hypersensitivity and adverse events related to exposure to ionising radiation (induction of cancer and potential of hereditary defects).

9.4.1. Uncertainties and limitations about unfavourable effects

No subjects with renal or hepatic impairment were enrolled in the studies and no data is available in the literature.

It is known that all radiopharmaceuticals, including ^{64}Cu-DOTATATE, have the potential to cause foetal harm as radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. There is no data regarding the use of ^{64}Cu-DOTATATE in pregnant and breast-feeding women.

9.5. Effects table

Table 59. Effects Table for Deqtynet in PET imaging of somatostatin receptor overexpression in adult patients with well-differentiated NETs

Effect (short description)	*Treatment*	*Control*	*Uncertainties/ Strength of evidence*	*Ref*
Favourable effects				
Diagnostic performance	**^{64}Cu-DOTATATE 148 MBq**	**n.a**		
Sensitivity for an average rater evaluating an average patient subject-level (95% CI)	**0.8254** (0.7405, 0.8868)		**SoE:** prospective study, pre-defined success **Unc:** bias due to lack of an objective and standardized method of establishing the SoT	RMX-18-22
Specificity for an average rater evaluating an average patient subject-level (95% CI)	**0.8156** (0.7244, 0.8815)		**SoE:** prospective study, pre-defined success **Unc:** bias due to lack of an objective and standardized method of establishing the SoT	RMX-18-22
Unfavourable effects				
Adverse event (%)	**^{64}Cu-DOTATATE**	**n.a.**		
Nausea (2%)				
Vomiting (1%)				
Hypersensitivity reactions			**Unc:** derived from spontaneous reporting, frequency not known	

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence.

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

Technical performance

PET/CT scans using ^{64}Cu-DOTATATE yielded images of acceptable quality. The inter- and intra-reader agreement was high.

Diagnostic performance

In the pivotal study (RMX-18-22), the sensitivity for an average rater evaluating an average patient was 0.8254 (95% CI: 0.7405, 0.8868). The specificity was 0.8156 (95% CI: 0.7244, 0.8815).

The design of the pivotal study does not fully align with all recommendations outlined in the Guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev. 1). Nevertheless, the study design allows for determination of diagnostic performance on patient level.

Considering the proposed clinical utility of Deqtynet (i.e. staging and restaging), the assessment of disease extent and localisation of SSTR overexpression is particularly relevant. In this regard, the availability of per-region/per-organ data from the literature is reassuring (Pfeifer 2015, Johnbeck 2017).

^{64}Cu-DOTATATE was able to detect well-differentiated (G1 and G2) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) with high sensitivity and specificity. GEP-NETs represent the most prevalent subgroup of neuroendocrine neoplasms (NENs), and their incidence is increasing. Accurate detection in this population is therefore clinically valuable.

Although there are theoretical concerns that diagnostic performance may vary in G3 and non-GEP NETs due to heterogeneous SSTR expression and despite the limited number of patients with these tumour types studied with ^{64}Cu-DOTATATE, its mechanism of action suggests that diagnostic performance is likely to be consistent across disease grades and NETs that overexpress somatostatin receptors. This is supported by the SAG's opinion and relevant clinical guidelines. Consequently, the indication 'well-differentiated neuroendocrine tumours" is considered acceptable.

Safety

Administration of a single dose of ^{64}Cu-DOTATATE for PET diagnostic did not indicate any safety events of major concern and clinical safety appears to be in line with the safety profile of already licensed PET diagnostics. Concerning radiation exposure, ^{64}Cu-DOTATATE, is associated with a higher internal radiation burden for the patient, with effective dose being approximately 1.5-fold higher than that of other commonly used diagnostic radiopharmaceuticals, including those used for PET imaging of NET (e.g. SomaKit TOC).

9.6.2. Balance of benefits and risks

Diagnostic performance has been sufficiently characterised in well-differentiated NETs at the patient level. Considering the proposed clinical utility (i.e. staging and restaging), data beyond the patient level (i.e. at the organ and/or lesion level) are relevant to evaluate the extent of disease and localisation of SSTR overexpression. Although the performance of Deqtynet at a per-lesion and per-organ/region basis has not been compared against the SoT and is subject to uncertainties, and while acknowledging inherent challenges associated with lesion-based analyses, such information is available from supportive literature studies. These data are sufficiently reassuring that Deqtynet performs

comparably to already approved ^{68}Ga-DOTATOC at the organ/region and lesion level. Considering the totality of data, Deqtynet has demonstrated acceptable diagnostic performance in well-differentiated neuroendocrine tumours (NETs).

The safety database is small but acceptable in the context of the rare disease.

Thus, the overall BR balance is positive.

9.6.3. Additional considerations on the benefit-risk balance

9.6.3.1. Questions posed to additional experts

Upon request from the Committee for Human Medicinal Products, a SAG Oncology meeting was convened on 14 April 2026 to answer the following questions:

1. Is a lesion-based analysis necessary for evaluating the diagnostic performance of Deqtynet or would an organ/region-based analysis be sufficient? Please elaborate the rationale for your position.

The SAG agreed that in general there is no gold standard method except histopathology for "standard of truth (SoT)" in identifying GEP-NET manifestations. In practice, conventional imaging is generally used as SoT, with well-known limitations (dimensions, especially for nodes; CT-negative/PET-positive lesions often observed at bone level). Despite these limitations, the SAG agreed that taking overall knowledge about these agents and available clinical experience into account, the per patient analysis presented may provide sufficient information to conclude favourably on the diagnostic performance to inform treatment decisions for staging or re-staging, even in the absence of formal proof against histopathology SoT. This diagnostic performance is relevant for clinical decisions based on anatomical presence of disease, organ involvement, extent of disease, rather than number of individual lesions.

Diagnostic performance based on individual lesions analysis could provide additional information that may be useful in certain situations, e.g., follow-up of individual lesions over time and management of oligometastatic disease.

2. Will the proposed organ/region-based analysis (as currently planned), deliver relevant and sufficient data on the diagnostic performance of Deqtynet for meaningful use in the clinical setting in which it is intended to be used (i.e., staging and re-staging)?

The SAG agreed that the additional planned organ/region-based analysis would not likely provide additional critical information compared to the per patient analysis. The analysis presented and available information seem sufficient to establish the diagnostic performance in the intended use.

3. Please comment on the likely impact of the higher activity used in literature studies (mean ~200 MBq vs 148 MBq proposed in the PI and used in the pivotal study) on the diagnostic performance, and to what extent the results from literature can be extrapolated to Deqtynet when used as proposed in the product information.

The dosing information provided in the proposed product information seems adequate and in line with the activity administered for diagnostic purposes in this setting. The differences in administered activity do not seem likely to have any relevant impact on the diagnostic performance, based on current experience, mechanistic arguments, and given the higher sensitivity of current PET scanners. There are no particular challenges due to the change in activity administration in terms of translating the results from the literature to the proposed Deqtynet product information.

4. When evaluating and describing the diagnostic performance of Deqtynet in terms of sensitivity and specificity, is it relevant to compare it against another diagnostic agent with the same Mode of Action, or is it sufficient to evaluate its performance with respect to the standard of truth as defined in the pivotal study?

Establishing the diagnostic performance based on "standard of truth" is generally sufficient.

While the CT/MRI findings used as SoT in the pivotal study cannot be considered a definitive SoT, the approach used seems acceptable and widely used in clinical practice. The practical challenges of conducting studies using a definitive "standard of truth" test (histological confirmation) of individual lesions are acknowledged.

Currently, the pivotal study based on a comparison to MRI/CT and the supportive active-comparative study presented (Johnbeck et al., 2017) seem sufficient to establish the diagnostic performance of Deqtynet. In terms of relative performance compared to ^{68}Ga-DOTATOC, the conclusion of a greater number of lesions detected and the practical advantages in terms of scanning window seemed relevant.

Additional comments

The SAG discussed the proposed indication for Deqtynet and questioned the need to specify tumour grade in the indication, which may not always be available at the time of intended clinical use. It is understood that mention of tumour grade may reflect the GEP-NET population included in the clinical studies. However, while useful to confirm presence of the disease in the clinical study, grade would not be a necessary disease characteristic for the intended use of the product in a real-world setting.

In fact, the SAG highlighted that the diagnostic performance is expected to apply across all disease grades and neuroendocrine tumours where the somatostatin receptor is over-expressed. In this sense, the limitation to G1-G2, and even GEP-NET compared to all NET, was considered unnecessary from the point of view of diagnostic performance, and for peptide receptor radionuclide therapy treatment planning. Restricting patient access to the product may be inappropriate because the clinical workflow typically delays definitive grade assessment to a point later than when the diagnostic agent is ordinarily expected to be used.

One SAG member also highlighted that possible differences of DEQTYNET with respect to 68GA DOTATOC have not been formally established based on a randomized trial. However, other members pointed out that a comparative study would not address the aforementioned limitations in the absence of a definitive SoT for either group. In this sense, even a randomized trial would only provide limited information.

9.7. Benefit-risk conclusions

The B/R balance is positive.

However, since the CHMP does not agree with any of the derogations from market exclusivity applicable to the similar orphan product (SomaKit TOC), pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, a positive CHMP opinion cannot be adopted for Deqtynet (see section 1.10.2). Consequently, the CHMP adopts a negative opinion for this medicinal product.

10. Appendices

Divergent position(s) to the majority recommendation

APPENDIX

DIVERGENT POSITION DATED 21 May 2026

The undersigned members of the CHMP did not agree with the CHMP's conclusion of a positive benefit-risk balance for DEQTYNET (copper (64Cu) oxodotreotide) in the following indication:

This medicinal product is for diagnostic use only.

DEQTYNET is indicated for positron emission tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated neuroendocrine tumours (NETs) excluding neuroblastomas.

The reasons for the divergent opinion are as follows:

The pivotal study RMX-18-22 was an open-label, single-dose, single-arm, single-centre study with patient-based analysis against a composite standard of truth (SoT), without an active comparator. The study has methodological limitations which preclude a robust demonstration of diagnostic performance and clinical utility. In particular:

- the study predominantly included patients with already confirmed metastatic disease, which questions the external validity and generalisability of the findings;
- the composite SoT lacked adequate lesion matching between histopathology and PET findings and relied on limited supporting documentation for SoT determination;
- the reported results were primarily based on patient-level analyses, while reliable assessment at organ-/region-level and lesion-level, relevant for localisation of primary tumours and staging, was not sufficiently established.

The extrapolation beyond GEP-NETs, particularly to tumour subtypes with heterogeneous somatostatin receptor expression, further adds to these uncertainties. While certain methodological limitations of the pivotal study may be acceptable in the context of a rare disease, the broader indication beyond GEP-NETs, including tumour entities with higher prevalence, would have warranted more comprehensive clinical evidence.

Therefore, we cannot conclude on a positive benefit-risk balance for DEQTYNET.

CHMP Members expressing a divergent opinion:

Janet König

Jan Müller-Berghaus