# A novel method to improve the detection of cancer and metastases by peptide scanning under the protection of enzyme inhibitors: PepProtect 1

Published: 12-10-2017
Last updated: 12-04-2024

1.To monitor the safety and tolerability of racecadotril in combination with 111In-DOTA-MG112.To study in patients whether the neutral endopeptidase (NEP) inhibitor racecadotril improves the in vivo stability of the radiopeptide 111In-DOTA-MG11

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Endocrine neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON44441

**Source**
ToetsingOnline

**Brief title**
PepProtect 1

### Condition

- Endocrine neoplasms malignant and unspecified

**Synonym**
medullary cancer of the thyroid, medullary carcinoma of the thyroid

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Erasmus MC, Universitair Medisch Centrum Rotterdam

**Source(s) of monetary or material Support:** Ministerie van OC&W,Stichting Coolsingel

## Intervention

**Keyword:** enzyme inhibitor (neutral endopeptidase), in vivo stabilization, medullary thyroid carcinoma, peptide scintigraphy (SPECT/CT)

## Outcome measures

### Primary outcome

1. To monitor the safety and tolerability of racecadotril in combination with

111In-DOTA-MG11; adverse events will be monitored according to international

standards, CTCAE 4.03

2. To study in patients whether the neutral endopeptidase (NEP) inhibitor

racecadotril improves the in vivo stability of the radiopeptide

111In-DOTA-MG11; percentage intact radiopeptide, 10 min. after injection, will

be measured

### Secondary outcome

1. To study whether the tumour uptake of 111In-DOTA-MG11 is

improved in parallel with the improved in vivo stability of 111In-DOTAMG11

by racecadotril protection.

2. To explore the sensitivity of [racecadotril-protected] 111In-DOTAMG11

scintigraphy (planar and SPECT/CT) to detect medullary thyroid

cancer lesions

# Study description

### Background summary

One of the key issues for the success of using peptide-tracers in patients for

diagnosis and therapy is the stability of the compounds. Unfortunately, most labeled peptides are very unstable in the physiology of the human body, being degraded by enzymes. Peptides, including radiopeptides, can be chemically modified to improve stability against enzymatic breakdown, but subsequent evaluation to reveal candidates of choice remains challenging, as stabilization often interferes with receptor affinity.
Recently, a radically different approach has been developed; we have demonstrated a highly effective method to improve the stability of peptide-tracers in the blood stream. In mouse models this method leads to unprecedented enhancement of tumor uptake without impairing background clearance. With a single co-injection of a suitable enzyme inhibitor we stabilized circulating peptide-tracers, significantly increasing their supply and binding to receptors on the tumor cells and impressively amplifying tumor-to-background ratios. This exciting strategy exploits our recent findings that one single enzyme: neutral endopeptidase (NEP, EC 3.4.24.11, neprylysin) is a major player in the in vivo degradation of a wide array of peptide-tracers

## Study objective

1.To monitor the safety and tolerability of racecadotril in combination with 111In-DOTA-MG11
2.To study in patients whether the neutral endopeptidase (NEP) inhibitor racecadotril improves the in vivo stability of the radiopeptide 111In-DOTA-MG11

## Study design

The study is a phase I single center, open clinical trial

## Intervention

Patients will twice undergo a scan with 111-In-DOTA-MG11, once at baseline without racecadotril and once with racecadotril, as intended intervention.

## Study burden and risks

-Patients will undergo 2 days of investigations at *baseline-2* visit (injection, scanning and blood samples); 1 day of investigations at *baseline-1* visit (oral racecadotril, observation, 1 blood sample); 2 days of investigations at *intervention* visit (oral racecadotril, injection, scanning, blood samples). One follow-up visit is planned; in conjunction with a regular outpatient visit.
-The risk of undesirable effects is minimal; minor, self-limiting side-effects of short duration are expected ([hypotension, tachycardia, nausea, dizziness] similar to the side effects from the Pentagastrin® test)
-Radiation burden is expected to be in the range of 11 mSv for a single 200 MBq 111In-DOTA-MG11 administration (analoguous to other known hydrophilic

111In-radiopeptides). For 2 visits, with associated low-dose CT in SPECT/CT scans, the total radiation burden for a patient in this study will be in the range of 27 mSv. This is within category IIIb, according to the recent NCRD publication *Human Exposure to Ionising Radiation for Clinical and Research Purposes: Radiation Dose & Risk Estimates*. This is justified, as the benefits of the study are aimed directly at: *directly related to saving lives or mitigating serious diseases in the future*, which is a category IIIb justification.
-Potential direct benefits: improved diagnosis/staging of MTC may lead to improved, personalized treatment strategy for some individual MTC patients, with possible better prognosis and/or less chance of unnessary/futile surgery procedures.
-Potential future benefits: the (successful) protection of radioloabelled DOTA-MG11 may be further developed and applied for PET/CT imaging (using Ga-68), or for peptide targeted radiation therapy (e.g. using Lu-177).
-Potential future benefits: the principle of protecting naturally instable radiopeptides may aid in developing other instable radiopeptides, aimed at other forms of cancer (e.g. breast, prostate) into practice as useful clinical tools.

## Contacts

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## Trial sites

### Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Related to the medullary cancer of the thyroid:
1. Histologically documented medullary cancer of the thyroid (MTC), or with elevated tumour marker (serum calcitonin) after previous treatment(s) for MTC
Related to the patient:
2. Life expectancy of more than 6 months.
3. WHO performance status 0 or 1
4. Male or female patients aged >18 years without upper age limit.

## Exclusion criteria

1. Patients requiring treatment of the tumour urgently, before assessments required for the study can be completed.
2. Pregnancy or breast feeding. Negative pregnancy test is required in female patients with child-bearing potential.
3. Impaired renal function (eGFR <60 mL/min/1.73 m2)
4. Impaired liver function (cirrhosis, grade B of the Child-Pugh classification; or hepatic enzyme levels >3x upper limit of normal)
5. Known allergy or hypersensitivity to gastrin analogues or any of the components of the study medications.
6. Any use of NEP-inhibitors within 30 days prior to the study; any use of experimental medication or other medication that potentially interfere with racecadotril or In111-DOTA-MG11.
7. Any use of ACE inhibitors within 3 days of racecadotril administrations.

# Study design

## Design

**Study type:** Interventional

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |

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|---|---|
| Primary purpose: | Diagnostic |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-11-2017 |
| Enrollment: | 12 |
| Type: | Anticipated |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Hidrasec |
| Generic name: | Racecadotril |
| Product type: | Medicine |
| Brand name: | nvt |
| Generic name: | 111-In-DOTA-MG11 |
| Registration: | Yes - NL outside intended use |

## Ethics review

Approved WMO

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|---|---|
| Date: | 12-10-2017 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

Approved WMO

| | |
|---|---|
| Date: | 04-12-2017 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

## Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2017-003469-93-NL |
| CCMO | NL63101.078.17 |