CXCR4-directed [68Ga]Ga-PentixaFor PET/CT vs AVS performance in a diagnoStic randomized Trial Ultimately comparing hypertenSion outcome in primary aldosteronism

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This study has been transitioned to CTIS with ID 2024-512628-12-00 check the CTIS register for the current data. Primary objectives-To assess the concordance between [68Ga]Ga-PentixaFor PET/CT and AVS for identification and/or lateralization of APAs...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Adrenal gland disorders
Study type	Observational invasive

Summary

ID

NL-OMON49887

Source
ToetsingOnline

Brief title
CASTUS-Trial

Condition

- Adrenal gland disorders
- Endocrine neoplasms benign

Synonym
Aldosterone overproduction, Primary aldosteronis

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMW,PentixaPharm GmbH

Intervention

Keyword: [68Ga]Ga-Pentixafor PET/CT, Adrenal vein sampling, CXCR4, Primary aldosteronism

Outcome measures

Primary outcome

Step 1: Definitive uptake criteria of [68Ga]Ga-PentixaFor will be established and used in [68Ga]Ga-PentixaFor PET/CT. Lateralization results of [68Ga]Ga-PentixaFor PET/CT will be compared with lateralization results of AVS to assess concordance. In the Spartacus trial CT based management was compared with AVS based management, 50% of patients with both conclusive CT and AVS had concordant results (5). Based on the Spartacus trial results, we aim for a concordance of 50% between [68Ga]Ga-PentixaFor PET/CT and AVS results as compatible with possible non-inferiority of [68Ga]Ga-PentixaFor PET/CT compared to AVS after which we proceed to step 2.

Step 2: Patients with unilateral cause of PA will receive surgery based on AVS or [68Ga]Ga-PentixaFor PET/CT results. Patients with a bilateral cause of PA will receive antihypertensive medication. Both diagnostic methods will be compared by measuring the intensity of antihypertensive drugs used by the patients from both groups six months after diagnosis , expressed in daily defined doses (DDD). The daily defined dose is the assumed average maintenance dose per day for a drug used for its main indication in adults. For instance, 5

mg of amlodipine has a daily defined dose of 1, and so does 10 mg of lisinopril. If both drugs are taken together, the daily defined dose is 2. Daily defined dose in this way provides an estimation of intensity of drug use for the same indication and can be used to compare different patient populations.

Secondary outcome

Secondary objectives

Step 1:

- To establish definitive quantitative criteria of [68Ga]Ga-PentixaFor uptake in unilateral and bilateral PA for SUVs, liver-to-lesion ratio and lesion-to-contralateral ratio.
- In patients who receive unilateral adrenalectomy, compare quantitative data in PET/CT imaging between immunohistochemically (CYP11B2 and CXCR4 staining) diagnosed multinodular hyperplasia and solitary adenomas.
- To assess biochemical and clinical outcomes based on PASO criteria (2)

Step 2:

- To asses biochemical and clinical outcomes after adrenalectomy of [68Ga]Ga-PentixaFor PET/CT imaging vs AVS in subtyping patients with PA by using the PASO criteria for clinical and biochemical outcome measures (complete, partial or absent)
- To evaluate reproducibility of [68Ga]Ga-PentixaFor PET/CT by comparison of two [68Ga]Ga-PentixaFor PET/CT scans with an interval of 1-14 days in the first 10 patients undergoing [68Ga]Ga-PentixaFor PET/CT.

- To assess intra- and inter-reader agreement of [68Ga]Ga-PentixaFor PET/CT for subtyping for each imaging center.

- To analyze inter-observer agreement of [68Ga]Ga-PentixaFor PET/CT between the imaging centers in terms of subtyping.

- In patients who receive unilateral adrenalectomy, compare quantitative data in PET/CT imaging between immunohistochemically (CYP11B2 and CXCR4 staining) diagnosed multinodular hyperplasia and solitary adenomas.

- To perform cost effectiveness analysis of AVS versus [68Ga]Ga-PentixaFor PET/CT management.

- To evaluate quality of life as assessed by EQ-5D-5L questionnaire and the Short Form health survey (SF36) of [68Ga]Ga-PentixaFor PET/CT versus AVS management

- Determination of the rate of inconclusive results and/or failure of subtype diagnosis by [68Ga]Ga-PentixaFor PET/CT imaging or AVS.

- To assess safety and intolerability.

- To assess image quality of [68Ga]Ga-PentixaFor PET/CT imaging, using the SUVmean, SUVmax, and SUVpeak, lesion-to-liver ratio, contrast-to-noise ratio, and signal-to-noise ratio.

Study description

Background summary

Primary aldosteronism (PA) is the most frequent form of secondary hypertension. Correct diagnosis and targeted treatment of PA are essential because of high vascular morbidity associated with PA as compared to essential hypertension with comparable blood pressure levels. PA is usually caused by either a

unilateral aldosterone-producing adenoma (APA) or by bilateral adrenal hyperplasia (BAH). Distinction between APA and BAH is critical since the former may be cured by adrenalectomy, and the latter necessitates life-long medical therapy with mineralocorticoid receptor antagonists (MRA). The distinction between unilateral and bilateral PA can be made by adrenal vein sampling (AVS), as recommended by The Endocrine Society 2016 guideline (1). Since AVS is invasive, not widely available, dependent on skilled radiologists and costly, there is a need for an accurate, non-invasive functional imaging modality. Based on clinical data obtained in retrospective studies so far, it appears that a potentially suitable imaging modality for this purpose is [68Ga]Ga-PentixaFor PET/CT. We propose to perform an two-step trial, in which the first step consists of a prospective feasibility study of [68Ga]Ga-PentixaFor PET/CT scanning. When the concordance of [68Ga]Ga-PentixaFor PET/CT and AVS appears to be >50%, we will continue to the second step: a prospective, randomized diagnostic study comparing outcomes of AVS-based and [68Ga]Ga-PentixaFor PET/CT based management of patients with primary aldosteronism.

Study objective

This study has been transitioned to CTIS with ID 2024-512628-12-00 check the CTIS register for the current data.

Primary objectives
-To assess the concordance between [68Ga]Ga-PentixaFor PET/CT and AVS for identification and/or lateralization of APAs in patients with PA. (Step 1)
-To assess non-inferiority in terms of clinical outcomes of [68Ga]Ga-PentixaFor PET/CT imaging vs. AVS in subtyping of patients with PA randomized to either [68Ga]Ga-PentixaFor PET/CT imaging or AVS confirmed by the surrogate Standard of Truth (SoT) daily defined doses (DDD) in patients after 6 months follow-up. (Step 2)

Secondary objectives
Step 1:
- To establish definitive quantitative criteria of [68Ga]Ga-PentixaFor uptake in unilateral and bilateral PA for SUVs, liver-to-lesion ratio and lesion-to-contralateral ratio.
- In patients who receive unilateral adrenalectomy, compare quantitative data in PET/CT imaging between immunohistochemically (CYP11B2 and CXCR4 staining) diagnosed multinodular hyperplasia and solitary adenomas.
- To assess biochemical and clinical outcomes based on PASO criteria (2)

Step 2:
- To asses biochemical and clinical outcomes after adrenalectomy of [68Ga]Ga-PentixaFor PET/CT imaging vs AVS in subtyping patients with PA by using the PASO criteria for clinical and biochemical outcome measures

(complete, partial or absent)
- To evaluate reproducibility of [68Ga]Ga-PentixaFor PET/CT by comparison of two [68Ga]Ga-PentixaFor PET/CT scans with an interval of 1-14 days in the first 10 patients undergoing [68Ga]Ga-PentixaFor PET/CT.
- To assess intra- and inter-reader agreement of [68Ga]Ga-PentixaFor PET/CT for subtyping for each imaging center.
- To analyze inter-observer agreement of [68Ga]Ga-PentixaFor PET/CT between the imaging centers in terms of subtyping.
- In patients who receive unilateral adrenalectomy, compare quantitative data in PET/CT imaging between immunohistochemically (CYP11B2 and CXCR4 staining) diagnosed multinodular hyperplasia and solitary adenomas.
- To perform cost effectiveness analysis of AVS versus [68Ga]Ga-PentixaFor PET/CT management.
- To evaluate quality of life as assessed by EQ-5D-5L questionnaire and the Short Form health survey (SF36) of [68Ga]Ga-PentixaFor PET/CT versus AVS management
- Determination of the rate of inconclusive results and/or failure of subtype diagnosis by [68Ga]Ga-PentixaFor PET/CT imaging or AVS.
- To assess safety and intolerability.
- To assess image quality of [68Ga]Ga-PentixaFor PET/CT imaging, using the SUVmean, SUVmax, and SUVpeak, lesion-to-liver ratio, contrast-to-noise ratio, and signal-to-noise ratio.

Study design

Two-step design in which step one is a two-center, single arm and open label study, followed, conditionally on the results of step one, by a five-center, prospective, two-armed, diagnostic randomized controlled trial.

Intervention

[68Ga]Ga-PentixaFor PET/CT

Study burden and risks

The extra burden of participation in the first step consists of a tracer injection and a PET/CT scan. The risks associated with a peptide injection in the microdose range are low. Adverse reactions have not been observed. Effective radiation dose of 150 +/- 50 MBq [68Ga]Ga-PentixaFor will be approximately 2.3 mSv, which is an acceptable dose.

In the second step, patients randomized to PET/CT will not undergo AVS. Those patients receive 3.4 mSv in totaal for the PET/CT.
The first 10 patients the subpopulation undergoing PET/CT twice (in order to assess reproducibility) receive 6.8 mSv in total for both PET/CTs. Both doses

are acceptable according to the NFU guidelines.

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

- The patient has a diagnosis of primary aldosteronism, confirmed by an elevated aldosterone/renin ratio (ARR) and an intravenous salt-loading test (according to the Endocrine Society guidelines)(1)
- Patients who fall in the *grey area* according to the Endocrine Society guidelines (1), will be discussed with all site investigators before inclusion to reach consensus on the diagnosis before inclusion.
- Age over 18 years at time of consent
- Signed informed consent

Exclusion criteria

- Refusal by the patients to undergo AVS, [68Ga]Ga-PentixaFor PET/CT, CT, or adrenalectomy
- Suspicion of familial hyperaldosteronism type 1, type 2, type 3 or type 4
- Suspicion of adrenocortical carcinoma
- Severe comorbidity potentially interfering with treatment or health-related quality of life
- Requirement of medication interfering with the study protocol
- Any medical condition present that in the opinion of the investigator will affect patients* clinical status.
- Pregnancy or lactation
• Estimated glomerular filtration rate (eGFR) kleiner dan 40 ml/min/1.73m²

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-02-2022
Enrollment:	228
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	[68Ga]Ga-PentixaFor
Generic name:	PentixaFor

Ethics review

Approved WMO Date:	14-12-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-01-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-01-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-03-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 28682
Source: NTR
Title:

In other registers

Register	ID
EU-CTR	CTIS2024-512628-12-00
EudraCT	EUCTR2021-003460-27-NL
CCMO	NL78206.091.21
Other	NL9625