A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men with Non-Metastatic (M0) Castration-Resistant Prostate Cancer

Published: 23-07-2013
Last updated: 19-09-2024

This study has been transitioned to CTIS with ID 2023-509221-47-00 check the CTIS register for the current data. To demonstrate superiority in the metastasis-free survival (MFS) of men with high risk NM-CRPC treated with apalutamide versus...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Prostatic disorders (excl infections and inflammations)
Study type	Interventional

Summary

ID

NL-OMON54510

Source
ToetsingOnline

Brief title
SPARTAN

Condition

- Prostatic disorders (excl infections and inflammations)

Synonym
Non-Metastatic Castration-Resistant Prostate Cancer, non-spread Castration-Resistant Prostate Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Aragon Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Aragon Pharmaceuticals

Intervention

Keyword: ARN-509, Multicenter, Non-Metastatic Castration-Resistant Prostate Cancer, second-generation anti-androgen

Outcome measures

Primary outcome

Metastasis-Free Survival (MFS)

Secondary outcome

Secondary Endpoints

* Time to Metastasis (TTM)

* PFS

* Time to symptomatic progression

* Overall survival (OS)

* Time to initiation of cytotoxic chemotherapy

Other Evaluations

* Health-related quality of life and prostate cancer-specific symptoms

* Type, incidence, severity, timing, seriousness, and relatedness of adverse

events and laboratory abnormalities

* PSA Response

* Time to PSA progression

* Population PK

* Assessment of ventricular repolarization

* Second progression-free survival (PFS2)

* Medical resource utilization (MRU)

Study description

Background summary

See protocol 24- Section 1. Background

Study objective

This study has been transitioned to CTIS with ID 2023-509221-47-00 check the CTIS register for the current data.

To demonstrate superiority in the metastasis-free survival (MFS) of men with high risk NM-CRPC treated with apalutamide versus placebo

Secondary Objective:
To compare the overall survival (OS) of men with high risk NM-CRPC treated with apalutamide versus placebo
To compare the time to symptomatic progression in men with high risk NM-CRPC treated with apalutamide versus placebo
To compare the time to initiation of cytotoxic chemotherapy in men with high risk NM-CRPC treated with apalutamide versus placebo
To compare the progression-free survival (PFS) of men with high risk NM-CRPC treated with apalutamide versus placebo
To compare the time to metastasis (TTM) in men with high risk NM-CRPC treated with apalutamide versus placebo
To evaluate the safety and tolerability of apalutamide

Other Objectives
To compare patient reported outcomes (PROs) of health-related quality of life and prostate cancer-specific symptoms in men with high risk NM-CRPC treated with apalutamide versus placebo
To evaluate the population pharmacokinetics (PK) of apalutamide
To evaluate the effect of apalutamide on ventricular repolarization in a subset of patients from selected clinical sites
To evaluate exploratory biomarkers predictive of response and resistance to apalutamide treatment

Study design

This is a randomized (2:1), multicenter, double-blind, placebo-controlled,

Phase III clinical trial evaluating the efficacy and safety of apalutamide versus placebo in men with high risk (M0) NM-CRPC, defined as PSA Doubling Time (PSADT) <= 10 months. Patients will be stratified based on: - PSADT: > 6 months vs. <= 6 months - Bone-sparing agent use: Yes vs. No - Loco-regional disease: N0 vs. N1 Patients will be followed for safety and efficacy as per the schedule of activities and will remain on study treatment until documented radiographic progression (development of distant metastases as assessed by blinded independent central review) or the development of unacceptable toxicity. Patients discontinuing treatment due to documented radiographic progression will enter the survival follow-up period, where they will be followed for the development of symptomatic progression and initiation of subsequent anti-cancer therapies (in particular, cytotoxic chemotherapy) every 4 months until death, loss of followup, or withdrawal of consent, whichever comes first. Patients discontinuing treatment prior to documented radiographic progression will also enter the survival follow-up period where they will continue to have scheduled disease assessments every 4 months until documented radiographic progression, and will be followed for the development of symptomatic progression and initiation of subsequent anti-cancer therapies (in particular, cytotoxic chemotherapy) every 4 months until death, loss of follow up, or withdrawal of consent, whichever comes first. At the time of study unblinding and in the event of a positive study result, all subjects currently receiving placebo will have the opportunity to receive active therapy with apalutamide.

Intervention

apalutamide/matched placebo tablets will be administered orally on a continuous daily dosing regimen, at a starting dose for apalutamide of 240 mg once daily (4 x 60-mg tablets). The only difference between apalutamide and its matched placebo is the absence of the active ingredient in the matched placebo.

Study burden and risks

At this time around 500 patients have been treated with apalutamide. Risks and side effects that may be possibly related to apalutamide include: Very Common (>10%) Fatigue Skin rash Joint pain (Arthralgia) Weight loss Fall Fracture Common (1- 10%) Itching Changes in thyroid function (Hypothyroidism) Increase in cholesterol Increase in triglycerides Very Rare (<1%) Seizure Seizures have been observed very rarely in subjects taking part in apalutamide studies. The doctor will confirm that the patient has no history of seizure and will check throughout the study that the patient is not taking other medications that can increase a risk of seizures. The patient must inform the doctor of all medications he is taking and any changes in medications. If the patient thinks he might have had a seizure, or convulsion, or have lost consciousness (passed out), he must let his doctor know right away. More than 1 in 10 patients have

developed a rash. Some rashes may need medical attention. The rash may be confined to one area of the body or may spread across the body. The patient must contact his doctor at the first sign of rash or any symptoms of rash (like itching) during the study. Rashes that are painful, blisters on or near the lips, eyes or genitals may need immediate evaluation by the doctor. The patient may be given medicines to apply to his skin or take by mouth to help the signs and symptoms of rash. Also the study medication may be temporarily held.

Contacts

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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Criterion modified per amendment. 1.2 Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features, with high risk for development of metastases, defined

as PSADT <= 10 months. PSADT is calculated using at least 3 PSA values obtained during continuous ADT. (see Section 5.1). 2. Criterion modified per amendment 2.1 Castration-resistant prostate cancer demonstrated during continuous ADT, defined as 3 PSA rises at least 1 week apart, with the last PSA > 2 ng/mL 3. Criterion modified per amendment 3.1. Criterion modified per amendment 3.2 Surgically or medically castrated, with testosterone levels of <50 ng/dL. If the patient is medically castrated, continuous dosing with GnRHa must have been initiated at least 4 weeks prior to randomization and must be continued throughout the study to maintain castrate levels of testosterone. 4. Criterion modified per amendment 4.1 Patients receiving bone loss prevention treatment with bone-sparing agents indicated for the treatment of osteoporosis at doses and dosing schedule appropriate for the treatment of osteoporosis (e.g., denosumab [Prolia®], zoledronic acid [Reclast®]) must be on stable doses for at least 4 weeks prior to randomization. 5. Criterion modified per amendment 5.2 Patients who received a first generation anti-androgen (e.g., bicalutamide, flutamide, nilutamide) must have at least a 4-week washout prior to randomization AND must show continuing disease (PSA) progression (an increase in PSA) after washout. 6. Criterion modified per amendment 6.2 At least 4 weeks must have elapsed from the use of 5-α reductase inhibitors (e.g., dutasteride, finasteride), estrogens (irrespective of dose used), and any other anti-cancer therapy prior to randomization, including chemotherapy given in the adjuvant/neoadjuvant setting (e.g., clinical trial) 7. At least 4 weeks must have elapsed from major surgery or radiation therapy prior to randomization 8. Age >= 18 years 9. Eastern Cooperative Oncology Group (ECOG) Performance Status grade 0 or 1 10. Resolution of all acute toxic effects of prior therapy or surgical procedure to Grade 1 or baseline prior to randomization 11. Criterion modified per amendment 11.1 Criterion modified per amendment 11.2 Adequate organ function as defined by the following criteria: * Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) <= 2.5 x upper limit of normal (ULN) * Total serum bilirubin <=1.5 x ULN. Total serum bilirubin >1.5 x ULN is allowed if Gilbert*s disease is documented prior to screening. * Serum creatinine <= 2 x ULN * Absolute neutrophil count (ANC) >= 1500/µL * Platelets >= 100,000/µL * Hemoglobin >= 9.0 g/dL o Administration of growth factors or blood transfusions will not be allowed within 4 weeks of the hematology labs required to confirm eligibility 12. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to randomization 13. Criterion modified per amendment 13.1 Willingness and ability to comply with scheduled visits, treatment plans, laboratory and radiographic assessments, and other study procedures, including ability to swallow large study drug tablets, the completion of patient reported outcomes questionnaires and long-term survival follow-up visits

Exclusion criteria

1. Criterion modified per amendment 1.1 Presence of distant metastases confirmed by blinded independent central review (BICR), including CNS and vertebral or meningeal involvement, or history of distant metastases. Exception: Pelvic lymph nodes <2 cm in short axis (N1) located below the iliac bifurcation are allowed 2. Symptomatic loco-regional disease requiring medical intervention, such as moderate or severe urinary obstruction or hydronephrosis, due to primary tumor (e.g., tumor obstruction of bladder trigone) 3. Prior treatment with second generation anti-androgens (e.g., enzalutamide) 4. Criterion modified per amendment 4.1 Prior treatment with CYP17 inhibitors (e.g., abiraterone acetate, orteronel, galerterone, ketoconazole, aminoglutethimide) 5. Prior treatment with radiopharmaceutical agents (e.g., Strontium-89), immunotherapy (e.g., sipuleucel-T), or any other investigational agent for NM-CRPC 6. Prior chemotherapy for prostate cancer, except if administered in the adjuvant/neoadjuvant setting 7. History of seizure or condition that may pre-dispose to seizure (e.g., prior stroke within 1 year prior to randomization, brain arteriovenous malformation, Schwannoma, meningioma, or other benign CNS or meningeal disease which may require treatment with surgery or radiation therapy) 8. Criterion modified per amendment 8.1 Criterion modified per amendment 8.2 Concurrent therapy with any of the following (all must have been discontinued or substituted for at least 4 weeks prior to randomization): * Medications known to lower the seizure threshold (for a complete list please see Appendix 5) * Herbal (i.e., saw palmetto) and non-herbal products (i.e., pomegranate) that may decrease PSA levels * Systemic (oral/IV/IM) corticosteroids. Short term use (<= 4 weeks) of corticosteroids during the study is allowed if clinically indicated, but it should be tapered off as soon as possible * Any other experimental treatment on another clinical trial * Agents indicated for the prevention of skeletal-related events in patients with solid tumors (e.g., denosumab [Xgeva®]) 9. Criterion modified per amendment 9.1 Criterion modified per amendment 9.2 History or evidence of any of the following conditions: - Any prior malignancy (other than adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission) within 5 years prior to randomization * Any of the following within 6 months prior to randomization:Severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g., pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias - Uncontrolled hypertension (systolic blood pressure >=160 mmHg or diastolic BP >=100 mmHg). Patients with a history of uncontrolled hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment. -Gastrointestinal disorder affecting absorption -Active infection, such as human immunodeficiency virus (HIV) - Any other condition that, in the opinion of the Investigator, would impair the patient*s ability to comply with

study procedures.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-12-2014
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NAP
Generic name:	ARN-509 (apalutamide)

Ethics review

Approved WMO

Date:	23-07-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	27-01-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-06-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-06-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-07-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	17-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-11-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-07-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-07-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-11-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-11-2015

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-09-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-10-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-04-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-05-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-11-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-02-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-02-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-03-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-09-2018
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-10-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-03-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	12-03-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-03-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-06-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-09-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-10-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-04-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-07-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-12-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-12-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-07-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-10-2022

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-10-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
EU-CTR	CTIS2023-509221-47-00
EudraCT	EUCTR2012-004322-24-NL
ClinicalTrials.gov	NCT01946204
CCMO	NL43395.060.13