A Randomized, Double-blind, Placebo-controlled Phase 3 Study of JNJ56021927 in Subjects with High-risk, Localized or Locally Advanced Prostate Cancer Receiving Treatment with Primary Radiation Therapy

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Primary ObjectiveTo determine if JNJ-56021927 plus gonadotropin releasing hormone (GnRH) agonist in subjects with high-risk, localized or locally advanced prostate cancer receiving primary radiation therapy (RT) results in an improvement of...

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

Summary

ID

NL-OMON53090

Source
ToetsingOnline

Brief title
56021927PCR3003 or ATLAS study

Condition

- Prostatic disorders (excl infections and inflammations)

Synonym
prostate cancer or high- risk Localized or Locally Advanced PC

Research involving

Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: door de opdrachtgever

Intervention

Keyword: ARN-509, JNJ-56021927, Prostate cancer, radiation therapy

Outcome measures

Primary outcome

EFFICACY EVALUATIONS/ENDPOINTS

To assess for distant metastasis, bone scan and chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) are required at the time of BCF (Phoenix definition, 2 ng/mL increase in PSA over nadir) and will continue as outlined in the Time and Events Schedule until documented distant metastasis by BICR or death. All clinically indicated unscheduled imaging must be reviewed by BICR. The primary endpoint of the study is MFS. The secondary endpoints are the time to local-regional recurrence, time to CRPC, time to distant metastasis, and OS.

Where possible, a PET scan must also be performed utilizing a prostate cancer-specific tracer such as, for example, PSMA-targeting tracer, 18F-fluciclovine, or 11C-choline. Conventional imaging must continue every 6 months (±4 weeks) until documented distant metastasis by BICR or death. PET will be performed and repeated at the same interval as conventional imaging

until either the PET scan reveals distant metastases per local review, or BICR of conventional imaging indicates distant metastasis, whichever occurs first. In the event that the PET scan reveals distant metastases and the BICR of conventional imaging does not, conventional imaging must be continued every 6 months until distant metastasis are seen by BICR.

The PROs included in this study are the FACT-P and the EQ-5D-5L. These questionnaires will be completed at the time points specified in the Time and Events Schedule.

Secondary outcome

PHARMACOKINETIC EVALUATIONS

Population PK assessments will be performed on approximately 750 subjects. Pre-dose blood samples for population PK will be collected as described in the Laboratory Manual.

BIOMARKER EVALUATIONS

Archival formalin-fixed paraffin-embedded (FFPE) tumor blocks or slides will be collected from all subjects consenting to genomic research to evaluate expression of high-risk markers and molecular classifiers such as OncotypeDx. Androgen-receptor splice variant 7 (AR-V7) expression and ARF876L levels will be evaluated.

Duration of medical care encounters, duration of hospitalization, the number and type of diagnostic and therapeutic tests and procedures, and outpatient medical encounters and treatments will be collected and may be used to conduct exploratory economic analyses.

Study description

Background summary

JNJ-56021927 (also referred to as ARN-509) is an orally available, non-steroidal selective antagonist of the androgen receptor (AR). JNJ-56021927 directly antagonizes the binding of androgen to the ligand-binding domain of the AR, impairing nuclear translocation and DNA binding. JNJ-56021927 binds the AR with 5-fold greater affinity than the first-generation anti-androgen bicalutamide. JNJ-56021927 is currently being developed for the treatment of both hormone-sensitive and castration-resistant prostate cancer (CRPC).

Patients with high- or very high-risk, localized or locally advanced prostate cancer include those with Gleason scores >=8, clinical stage >=cT2c (disease in both or extension outside of the lobes), high baseline PSA (>=20 ng/mL), or involvement of regional nodes. These patients are more likely to develop metastatic disease than are low- or intermediate-risk patients.

Patients with high-risk localized or locally advanced prostate cancer who undergo primary radiation therapy (RT) for the treatment of prostate cancer are commonly older and have more comorbidities than those who undergo radical prostatectomy. Although these patients have a significant prostate cancer-specific mortality risk, they may also have a high risk of mortality from other causes within 10 years of the diagnosis. Algorithms such as the Charlson Comorbidity Index (CCI), which is based on age and other comorbidities, may be utilized to select patients who will have a low 10-year probability of death from competing causes. Combined, the protocol-defined high-risk disease selection criteria and a >10-year life expectancy (based on the CCI) will identify those who are most likely to derive benefit from primary RT and long-term androgen deprivation therapy (ADT).

Multiple studies have shown that the addition of long-term ADT (gonadotropin

releasing hormone [GnRH] agonist +/- anti-androgen) to RT delays disease progression (ie, local-regional recurrence or distant metastasis) and prolongs survival. Thus, the National Comprehensive Cancer Network (NCCN, category 1) and European Association of Urology (EAU Level 1b) recommend RT combined with 2 or 3 years of ADT. Despite the use of ADT in combination with RT, metastatic progression and prostate cancer-related death still occur frequently in patients with high-risk disease. Therefore, high-risk, localized and locally advanced prostate cancer represents a serious clinical problem with currently unmet treatment needs.

Prostate cancer cells depend on AR signaling for DNA repair after damage from irradiation and the addition of a GnRH agonist plus a first generation anti-androgen, bicalutamide to RT improves outcomes. Therefore, it is hypothesized that a more complete AR blockade with the AR antagonist, JNJ-56021927, plus GnRH agonist will further delay time to distant metastasis and prostate cancer-related death in patients with high-risk localized or locally advanced prostate cancer receiving RT.

Study objective

Primary Objective
To determine if JNJ-56021927 plus gonadotropin releasing hormone (GnRH) agonist in subjects with high-risk, localized or locally advanced prostate cancer receiving primary radiation therapy (RT) results in an improvement of metastasis-free survival (MFS) evaluated by blinded independentcentral review (BICR)

Secondary Objectives
-To characterize the safety profile of JNJ-56021927 plus GnRH agonist in subjects with high-risk, localized or locally advanced prostate cancer receiving primary RT
-To determine if JNJ-56021927 plus GnRH agonist in subjects with high-risk, localized or locally advanced prostate cancer receiving primary RT results in an improvement of:
o Event-free survival
o Time PSA progression
o Overall survival (OS)
o Time to distant metastasis
o Time to next local or systematic treatment
o MFS by conventional or PET imgaging.

Other Objectives
-To determine if JNJ-56021927 plus GnRH agonist in subjects with high-risk, localized or locally advanced prostate cancer receiving primary RT delays the development of:
o Skeletal-related events (SREs)

o Disease progression-related pain
o Biochemical failure (BCF)
o Progression/ relapse on or after the next line of treatment
o Time to local-regional recurrence
o Time to castration-resistant prostate cancer (CRPC)
- To evaluate the effect of JNJ-56021927 plus GnRH agonist in subjects with high-risk, localized or locally advanced prostate cancer receiving primary RT on the normalization of testosterone
- To evaluate the effect of JNJ-56021927 plus GnRH agonist in subjects with high-risk, localized or locally advanced prostate cancer receiving primary RT on patient relevant outcomes including symptoms, function, and health-related quality of life
- To characterize the population pharmacokinetics (PK) of JNJ-56021927
- To demonstrate the cost benefit of JNJ-56021927 plus GnRH agonist compared with GnRH agonist in subjects with high-risk, localized or locally advanced prostate cancer receiving primary RT
- To evaluate the effect on PSA response of JNJ-56021927 plus GnRH agonist compared with GnRH agonist in subjects with high-risk, localized or locally advanced prostate cancer receiving primary RT
- To evaluate potential biomarkers predictive of response and resistance to JNJ-56021927 treatment
- To determine the proportion of patients with no PSA progression at 12,24,26, and 48 months
- To determine the proportion of patients with no evidence of disease (NED) at 4 years
- To determine the proportion of patients developing androgen receptor (AR) resistance based upon clinical, pathological, or molecular markers.

Study design

This is a randomized, double-blind, placebo-controlled, multicenter study of JNJ-56021927 plus GnRH agonist compared with GnRH agonist in subjects with high-risk, localized or locally advanced prostate cancer receiving primary RT. All subjects will receive active treatment with a GnRH agonist and primary RT as standard of care. Approximately 1,500 subjects will be randomly assigned in a 1:1 ratio to receive JNJ-56021927 or control. Randomization will be stratified by Gleason score (7 or >=8), N0 or N1, brachytherapy boost (yes or no), and region (NA, EU, or Other Countries).

The study will include a Screening Phase, Treatment Phase, a Posttreatment Phase and a Long-term Follow-up Phase.

The Screening Phase will allow for assessment of subject eligibility, demographics, PSA, and testosterone up to 35 days prior to randomization.

The Treatment Phase will include 30 cycles of therapy (each cycle is 28 days).

All subjects will receive GnRH agonist therapy throughout the Treatment Phase:
- Neoadjuvant to primary RT (2, 28-day cycles [Cycle 1, Day 1; C1D1 to C2D28])
o Investigational group will receive JNJ-56021927 plus bicalutamide placebo daily
o Control group will receive bicalutamide plus JNJ-56021927 placebo daily
- Concurrent with primary RT (2, 28-day cycles [C3D1 to C4D28])
o Investigational group will receive JNJ-56021927 plus bicalutamide placebo daily
o Control group will receive bicalutamide plus JNJ-56021927 placebo daily
- Adjuvant to primary RT (26, 28-day cycles [C5D1 to C30D28])
o Investigational group will receive JNJ-56021927 daily
o Control group will receive JNJ-56021927 placebo daily

The Posttreatment Phase will begin after a subject completes the Treatment Phase and the
End-of-Treatment Visit. The Posttreatment Phase will continue until documented distant metastasis by BICR, death, lost to follow-up, withdrawal of consent or termination of the study by the sponsor, whichever occurs first.

The Long-term Follow-up Phase will begin after a subject completes the Posttreatment Phase and End-of-Posttreatment Phase Visit. The Long-term Follow-up Phase will continue until death, lost to follow-up, withdrawal of consent or termination of the study by the sponsor, whichever occurs first.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study. The IDMC will review the safety and efficacy data during the study and make recommendations as to the further conduct of the study.

Intervention

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study. The IDMC will review the safety and efficacy data during the study and make recommendations as to the further conduct of the study.

Study burden and risks

Safety evaluations will include adverse events (AEs) (incidence, intensity, and type), vital sign measurements, clinical laboratory test results, and limited physical examinations.

Contacts

Public
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Scientific
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Breda 4837 DS
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Age >=18 years
- Indicated and planned to receive primary radiation therapy for prostate cancer
-Histologically confirmed adenocarcinoma of an intact prostate, and 1 of the following at
diagnosis:
• Gleason score >=8 and >=cT2c stage per AJCC 8th Edition
• Gleason score 7, PSA >=20 ng/mL, and >=cT2c stage per AJCC
- Charlson comorbidity index (CCI) <=3
- An Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) grade of 0 or 1
- Adequate liver function: aspartate aminotransferase (AST), alanine aminotransferase (ALT), <2 x upper limit of normal (ULN) and total bilirubin <1.5 x ULN
- Participants who are sexually active (even men with vasectomies) and willing to use a condom and agree not to donate sperm during the trial
- Signed, written, informed consent
- Be able to swallow whole study drug tablets

Exclusion criteria

- Presence of distant metastasis, including pelvic nodal disease below the iliac bifurcation >2 cm in the short axis
- Prior treatment with GnRH analogue or antiandrogen or both for >3 months prior to randomization
- Bilateral orchiectomy
- History of pelvic radiation
- Prior systemic (eg, chemotherapy) or procedural (eg, prostatectomy, cryotherapy) treatment for prostate cancer
- History of seizure or condition that may predispose to seizure (including, but not limited to prior stroke, transient ischemic attack or loss of consciousness <=1 year prior to randomization* brain arteriovenous malformation* or intracranial masses such as schwannomas and meningiomas that are causing edema or mass effect)
- Prior treatment with enzalutamide, abiraterone acetate, orteronel, galeterone, ketoconazole, aminoglutethimide, estrogens, megestrol acetate, and progestational agents for prostate cancer
- Prior treatment with radiopharmaceutical agents (eg, strontium 89) or immunotherapy (eg, sipuleucel-T) for prostate cancer
- Prior treatment with systemic glucocorticoids <=4 weeks prior to randomization or is expected to require long-term use of corticosteroids during the study
- Use of 5-alpha reductase inhibitors (eg, dutasteride, finasteride) <=4 weeks prior to randomization
- Use of any investigational agent <=4 weeks prior to randomization
- Current chronic use of opioid analgesics for >=3 weeks for oral or >= 7 days for non-oral formulations
- Major surgery <=4 weeks prior to randomization
- Current or prior treatment with antiepileptic medications for the treatment of seizures
- Gastrointestinal conditions affecting absorption
- Known or suspected contraindications or hypersensitivity to JNJ-56021927, bicalutamide or GnRH agonists or any of the components of the formulations
- Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject

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:	Recruitment stopped
Start date (anticipated):	10-07-2017
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ARN-509
Generic name:	nap
Product type:	Medicine
Brand name:	Casodex
Generic name:	Bicalutamide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	13-01-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	04-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	23-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-10-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-05-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2019

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-08-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	23-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-07-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-09-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-10-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-11-2022
Application type:	Amendment
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	EUCTR2015-003007-38-NL
CCMO	NL55777.078.15