



Clinical trial results:

PROVENT: A randomised, double blind, placebo controlled feasibility study to examine the clinical effectiveness of aspirin and/or Vitamin D3 to prevent disease progression in men on active surveillance for prostate cancer

Summary

EudraCT number	2014-001784-13
Trial protocol	GB
Global end of trial date	31 December 2019

Results information

Result version number	v1 (current)
This version publication date	16 December 2020
First version publication date	16 December 2020

Trial information

Trial identification

Sponsor protocol code	ISRCTN91422391
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Additional study identifiers

ISRCTN number	ISRCTN91422391
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	5 Walden Street, London, United Kingdom, E1 2EF
Public contact	Trial CI - Mr. Greg Shaw, Centre for Cancer Prevention, QMUL, +44 (0)20 3594 267, gregshaw@nhs.net
Scientific contact	Trial CI - Mr. Greg Shaw, Centre for Cancer Prevention, QMUL, +44 (0)20 3594 267, gregshaw@nhs.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2019
Global end of trial reached?	Yes
Global end of trial date	31 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research objective for this study is to demonstrate the acceptability and feasibility of recruiting to a randomised chemoprevention study of standard (300mg) or low dose (100mg) aspirin vs. placebo and/or Vitamin D3 vs. placebo in patients enrolled on an active surveillance programme for prostate cancer.

Protection of trial subjects:

Helicobacter pylori (H. pylori) has been shown to be a causative factor in GI bleeding, so all participants were tested for this at randomisation as a precaution. Patients were allowed to start their study medication, including aspirin/placebo aspirin, prior to obtaining the result of this test, as patients are not normally tested for this infection before commencing aspirin therapy and the maximum aspirin dose in this study is very low. Patients who tested positive were prescribed a course of proton pump inhibitors (PPIs) and antibiotics if they wished to continue on the study. GPs were informed. Once treated, there was no requirement to retest for this infection (as per NICE guidelines).

As a precaution, patients are advised to stop the aspirin/placebo tablets 7 days prior to prostate biopsy, or any other planned surgery. Patients will be reminded about this in the clinic, and this information is also included in the PIS and Diary Cards. There is no need to stop the Vitamin D3/placebo IMP prior to surgery.

Serum calcium levels will be checked at baseline and 6 monthly intervals. Administration of the Vitamin D3/placebo may be delayed if a participant experiences symptoms of hypercalcaemia.

Dyspepsia has been shown to be a risk factor for NSAID GI bleeding. Therefore, should new dyspeptic symptoms arise, or a gastrointestinal bleed occur (melaena, haematemesis, decreased haemoglobin) during the course of the study, then treatment with aspirin/aspirin placebo should cease immediately and permanently, and the patient will withdraw from the study.

In addition, administration of IMP will be discontinued if the patient develops a condition requiring treatment with a prohibited concomitant therapy, a condition which, in the judgement of the investigator, adversely affects the participant's safety, compliance or ability to complete evaluations and/or If the investigator concludes that this course of action is in the participant's best interests.

Background therapy:

N/A

Evidence for comparator:

Aspirin is a common Non-Steroidal Anti-Inflammatory Drugs (NSAID) used for analgesia & as an antipyretic. These drugs inhibit the enzyme cyclo-oxygenase which is involved in the metabolism of prostaglandins & thromboxanes, which in turn are involved in many physiological pathways including inflammation & platelet function. Aspirin is a reversible inhibitor of cyclo-oxygenase 1 (COX-1). Data suggests that in contrast to other NSAIDs, it may have anti-carcinogenic properties for many cancer types, including prostate cancer. Kashiwaqi demonstrated that aspirin down-regulated the androgen receptor which drives prostate cancer metabolism, & down-regulates prostate specific antigen (PSA) levels within prostate cancer cells. Kashiwaqi demonstrated that aspirin up-regulates prostaglandin receptor subtype EP3, which again influences androgen receptor expression & cell proliferation, thought to be important in prostate carcinogenesis. Epidemiological studies have also provided data on the benefit of aspirin on prostate cancer incidence & progression.

Vitamin D is a fat-soluble secosteroid responsible for intestinal absorption of calcium & phosphate. Data suggest Vitamin D may influence the incidence of cancer. The mechanism for action may be due to calcitriol's influence on cellular proliferation, differentiation and apoptosis. The Vitamin D receptor is

known to be highly expressed in epithelial cells at risk of carcinogenesis, such as prostate. Mondul identified that genetic variants related to lower 25(OH)D levels were associated with a decreased risk of aggressive prostate cancer. It has been suggested that Vitamin D deficiency over time may contribute to the progression of insignificant prostate cancer to clinically significant disease. Marshall & colleagues evaluated Vitamin D supplementation in men with low to intermediate risk prostate cancer, reporting that those receiving Vitamin D had a lower number of positive cancer cores on repeat biopsy at 1 year.

Actual start date of recruitment	16 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 104
Worldwide total number of subjects	104
EEA total number of subjects	104

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	64
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment will take place in prostate clinics at 6 participating centres, based within the UK only. The aim will be to recruit 102 participants over a 12 month period, starting Dec 2016.

Recruitment tools = study invitation letter, trial poster & a trial website.

Pre-assignment

Screening details:

Potentially eligible patient given a Patient Info Sheet & added to local Pre-screening log, (initials & DOB only). Informed consent taken from interested patients & pre-randomisation Eligibility Assessment conducted.

Participants must have a corrected serum calcium level $\leq 2.65\text{mmol/l}$ & a negative H Pylori test result prior to starting IMP.

Period 1

Period 1 title	Overall Trial Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Randomisation will be by bespoke web-based application. All relevant research staff will be trained in its use. Eligible participants will be randomised in a 6-arm 1:1:1:1:1:1 design. Randomised blocks will be used to maintain balance amongst these 6 arms, & the aspirin placebo groups will be block randomised to either small or large aspirin placebo tablets.

The allocated unique study number will correspond to a particular arm of the trial, & used to label & identify all trial samples.

Arms

Are arms mutually exclusive?	Yes
Arm title	Large Aspirin (Active) & Vitamin D (Active)

Arm description:

Aspirin 300mg & Vitamin D

Arm type	Active comparator
Investigational medicinal product name	Aspirin 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Take 1 Aspirin tablet, whole, with water at the same time of every day, ideally in the morning. The tablets must be taken daily for 18 months.

If you miss a tablet, you may take it later, as long as it is at least 6 hours before your next dose is due - do not take more than one study tablet at the same time, and no more than two per 24 hours. Otherwise, missed doses should be recorded on the diary card, plus any comments or reasons for the missed dose.

If you vomit after taking a dose of your study medication, do not take a further dose that day, but record this on your diary card. If this happens again and you think it may be related to the medication, then please contact your local research team. Please store your medicines in a cool, dry place, away from heat or sunlight.

Investigational medicinal product name	Vitamin D Oil
Investigational medicinal product code	
Other name	Vigantol® Oil

Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Take 8 drops of Vitamin D solution with food at the same time of day, ideally in the morning. The drops will be taken daily for 18 months.

The solution may be dropped onto bread, or taken on a spoon, mixed with a small quantity of fruit juice if preferred, but NOT added to a full glass of beverage.

If you miss the drops, you may take them later or with the next dose. Do not take more than two days doses together.

Otherwise, missed doses should be recorded on the diary card, plus any comments or reasons for the missed dose.

If you vomit after taking a dose of your study medication, do not take a further dose that day, but record this on your diary card. If this happens again and you think it may be related to the medication, then please contact your local research team. Please store your medicines in a cool, dry place, away from heat & sunlight.

Arm title	Large Aspirin (Active) & Vitamin D (Placebo)
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Arm description:

Aspirin 300mg + Vitamin D3 placebo

Arm type	Active comparator & placebo
Investigational medicinal product name	Vitamin D Placebo
Investigational medicinal product code	
Other name	Miglyol@812 Oil
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Take 8 drops of Vitamin D solution with food at the same time of day, ideally in the morning. The drops will be taken daily for 18 months.

The solution may be dropped onto bread, or taken on a spoon, mixed with a small quantity of fruit juice if preferred, but NOT added to a full glass of beverage.

If you miss the drops, you may take them later or with the next dose. Do not take more than two days doses together.

Otherwise, missed doses should be recorded on the diary card, plus any comments or reasons for the missed dose.

If you vomit after taking a dose of your study medication, do not take a further dose that day, but record this on your diary card. If this happens again and you think it may be related to the medication, then please contact your local research team. Please store your medicines in a cool, dry place, away from heat & sunlight.

Investigational medicinal product name	Aspirin 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Take 1 Aspirin tablet, whole, with water at the same time of every day, ideally in the morning. The tablets must be taken daily for 18 months.

If you miss a tablet, you may take it later, as long as it is at least 6 hours before your next dose is due - do not take more than one study tablet at the same time, and no more than two per 24 hours.

Otherwise, missed doses should be recorded on the diary card, plus any comments or reasons for the missed dose.

If you vomit after taking a dose of your study medication, do not take a further dose that day, but record this on your diary card. If this happens again and you think it may be related to the medication, then please contact your local research team. Please store your medicines in a cool, dry place, away from heat or sunlight.

Arm title	Small Aspirin (Active) & Vitamin D (Active)
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Arm description:

Aspirin 100mg + Vitamin D3

Arm type	Active comparator
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Investigational medicinal product name	Aspirin 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Take 1 Aspirin tablet, whole, with water at the same time of every day, ideally in the morning. The tablets must be taken daily for 18 months.

If you miss a tablet, you may take it later, as long as it is at least 6 hours before your next dose is due - do not take more than one study tablet at the same time, and no more than two per 24 hours.

Otherwise, missed doses should be recorded on the diary card, plus any comments or reasons for the missed dose.

If you vomit after taking a dose of your study medication, do not take a further dose that day, but record this on your diary card. If this happens again and you think it may be related to the medication, then please contact your local research team. Please store your medicines in a cool, dry place, away from heat or sunlight.

Investigational medicinal product name	Vitamin D Oil
Investigational medicinal product code	
Other name	Vigantol® Oil
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Take 8 drops of Vitamin D solution with food at the same time of day, ideally in the morning. The drops will be taken daily for 18 months.

The solution may be dropped onto bread, or taken on a spoon, mixed with a small quantity of fruit juice if preferred, but NOT added to a full glass of beverage.

If you miss the drops, you may take them later or with the next dose. Do not take more than two days doses together.

Otherwise, missed doses should be recorded on the diary card, plus any comments or reasons for the missed dose.

If you vomit after taking a dose of your study medication, do not take a further dose that day, but record this on your diary card. If this happens again and you think it may be related to the medication, then please contact your local research team. Please store your medicines in a cool, dry place, away from heat & sunlight.

Arm title	Small Aspirin (Active) & Vitamin D (Placebo)
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Arm description:

Aspirin 100mg + Vitamin D3 placebo

Arm type	Active comparator & placebo
Investigational medicinal product name	Vitamin D Oil placebo
Investigational medicinal product code	
Other name	Miglyol®812 Oil
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Take 8 drops of Vitamin D solution with food at the same time of day, ideally in the morning. The drops will be taken daily for 18 months.

The solution may be dropped onto bread, or taken on a spoon, mixed with a small quantity of fruit juice if preferred, but NOT added to a full glass of beverage.

If you miss the drops, you may take them later or with the next dose. Do not take more than two days doses together.

Otherwise, missed doses should be recorded on the diary card, plus any comments or reasons for the missed dose.

If you vomit after taking a dose of your study medication, do not take a further dose that day, but record this on your diary card. If this happens again and you think it may be related to the medication, then please contact your local research team. Please store your medicines in a cool, dry place, away from heat & sunlight.

Investigational medicinal product name	Aspirin 100 mg
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Take 1 Aspirin tablet, whole, with water at the same time of every day, ideally in the morning. The tablets must be taken daily for 18 months.

If you miss a tablet, you may take it later, as long as it is at least 6 hours before your next dose is due - do not take more than one study tablet at the same time, and no more than two per 24 hours. Otherwise, missed doses should be recorded on the diary card, plus any comments or reasons for the missed dose.

If you vomit after taking a dose of your study medication, do not take a further dose that day, but record this on your diary card. If this happens again and you think it may be related to the medication, then please contact your local research team. Please store your medicines in a cool, dry place, away from heat or sunlight.

Arm title	Aspirin (placebo) + Vitamin D3 (active)
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Arm description:

Aspirin placebo + Vitamin D3

Arm type	Active comparator & placebo
Investigational medicinal product name	Aspirin placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Take 1 Aspirin tablet, whole, with water at the same time of every day, ideally in the morning. The tablets must be taken daily for 18 months.

If you miss a tablet, you may take it later, as long as it is at least 6 hours before your next dose is due - do not take more than one study tablet at the same time, and no more than two per 24 hours. Otherwise, missed doses should be recorded on the diary card, plus any comments or reasons for the missed dose.

If you vomit after taking a dose of your study medication, do not take a further dose that day, but record this on your diary card. If this happens again and you think it may be related to the medication, then please contact your local research team. Please store your medicines in a cool, dry place, away from heat or sunlight.

Investigational medicinal product name	Vitamin D Oil
Investigational medicinal product code	
Other name	Vigantol® Oil
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Take 8 drops of Vitamin D solution with food at the same time of day, ideally in the morning. The drops will be taken daily for 18 months.

The solution may be dropped onto bread, or taken on a spoon, mixed with a small quantity of fruit juice if preferred, but NOT added to a full glass of beverage.

If you miss the drops, you may take them later or with the next dose. Do not take more than two days doses together.

Otherwise, missed doses should be recorded on the diary card, plus any comments or reasons for the missed dose.

If you vomit after taking a dose of your study medication, do not take a further dose that day, but record this on your diary card. If this happens again and you think it may be related to the medication, then please contact your local research team. Please store your medicines in a cool, dry place, away from heat & sunlight.

Arm title	Aspirin (placebo) + Vitamin D3 (placebo)
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Arm description:

Aspirin placebo + Vitamin D3 placebo

Arm type	Placebo
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Investigational medicinal product name	Aspirin placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Take 1 Aspirin tablet, whole, with water at the same time of every day, ideally in the morning. The tablets must be taken daily for 18 months.

If you miss a tablet, you may take it later, as long as it is at least 6 hours before your next dose is due - do not take more than one study tablet at the same time, and no more than two per 24 hours.

Otherwise, missed doses should be recorded on the diary card, plus any comments or reasons for the missed dose.

If you vomit after taking a dose of your study medication, do not take a further dose that day, but record this on your diary card. If this happens again and you think it may be related to the medication, then please contact your local research team. Please store your medicines in a cool, dry place, away from heat or sunlight.

Investigational medicinal product name	Vitamin D Placebo
Investigational medicinal product code	
Other name	Miglyol@812 Oil
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Take 8 drops of Vitamin D solution with food at the same time of day, ideally in the morning. The drops will be taken daily for 18 months.

The solution may be dropped onto bread, or taken on a spoon, mixed with a small quantity of fruit juice if preferred, but NOT added to a full glass of beverage.

If you miss the drops, you may take them later or with the next dose. Do not take more than two days doses together.

Otherwise, missed doses should be recorded on the diary card, plus any comments or reasons for the missed dose.

If you vomit after taking a dose of your study medication, do not take a further dose that day, but record this on your diary card. If this happens again and you think it may be related to the medication, then please contact your local research team. Please store your medicines in a cool, dry place, away from heat & sunlight.

Number of subjects in period 1	Large Aspirin (Active) & Vitamin D (Active)	Large Aspirin (Active) & Vitamin D (Placebo)	Small Aspirin (Active) & Vitamin D (Active)
Started	17	16	19
Completed	7	10	8
Not completed	10	6	11
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	1	-	1
Physician decision	5	2	6
Inter-current illness	-	-	1
Testicular pain	-	-	-
Adverse event, non-fatal	-	-	1
Patient excluded	2	2	1
Patient unhappy to continue	-	-	-
Lost to follow-up	-	1	-

Patient wishes to come off Active Surveillance	2	-	1
Unacceptable toxicity/intolerable side effects	-	-	-

Number of subjects in period 1	Small Aspirin (Active) & Vitamin D (Placebo)	Aspirin (placebo) + Vitamin D3 (active)	Aspirin (placebo) + Vitamin D3 (placebo)
	Started	18	16
Completed	9	10	9
Not completed	9	6	9
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	1	1	-
Physician decision	3	3	1
Inter-current illness	-	-	-
Testicular pain	1	-	-
Adverse event, non-fatal	-	-	1
Patient excluded	2	1	1
Patient unhappy to continue	-	-	1
Lost to follow-up	1	-	1
Patient wishes to come off Active Surveillance	1	1	3
Unacceptable toxicity/intolerable side effects	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial Period
Reporting group description: All randomised patients.	

Reporting group values	Overall Trial Period	Total	
Number of subjects	104	104	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	61		
inter-quartile range (Q1-Q3)	56 to 66	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	104	104	

Subject analysis sets

Subject analysis set title	All patients
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients randomised into the PROVENT trial.	
Subject analysis set title	Active Vitamin D patients
Subject analysis set type	Intention-to-treat
Subject analysis set description: Those patients receiving active vitamin D3 treatment	
Subject analysis set title	Placebo Vitamin D Patients
Subject analysis set type	Intention-to-treat
Subject analysis set description: Those patients receiving placebo vitamin D3 treatment	
Subject analysis set title	Active Aspirin Patients
Subject analysis set type	Intention-to-treat
Subject analysis set description: Those patients receiving active aspirin treatment (either 100mg OR 300mg)	

Subject analysis set title	Placebo Aspirin Patients
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients receiving placebo aspirin treatment	
Subject analysis set title	100mg Aspirin Patients
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients receiving 100mg of aspirin	
Subject analysis set title	300mg Aspirin Patients
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients receiving 300mg of aspirin	
Subject analysis set title	Pathology review baseline subjects
Subject analysis set type	Sub-group analysis
Subject analysis set description: Eighty-two patients whose biopsy tissue was centrally-reviewed after baseline biopsy	
Subject analysis set title	Pathology review month-12 subjects
Subject analysis set type	Sub-group analysis
Subject analysis set description: Twenty-five patients whose biopsy tissue was centrally-reviewed at 12 months	
Subject analysis set title	Paired MRI patients
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients that had MRI lesion detected at baseline and 12 months for volume comparison	

Reporting group values	All patients	Active Vitamin D patients	Placebo Vitamin D Patients
Number of subjects	104	52	52
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	61	62	61
inter-quartile range (Q1-Q3)	56 to 66	56 to 67	56 to 67
Gender categorical Units: Subjects			
Female	0		
Male	104		

Reporting group values	Active Aspirin Patients	Placebo Aspirin Patients	100mg Aspirin Patients
Number of subjects	70	34	37

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	61	65	62
inter-quartile range (Q1-Q3)	56 to 66	56 to 67	59 to 66
Gender categorical Units: Subjects			
Female			
Male			

Reporting group values	300mg Aspirin Patients	Pathology review baseline subjects	Pathology review month-12 subjects
Number of subjects	33	82	25
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	60		
inter-quartile range (Q1-Q3)	55 to 64		
Gender categorical Units: Subjects			
Female			
Male			

Reporting group values	Paired MRI patients		
Number of subjects	11		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks)			

Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Large Aspirin (Active) & Vitamin D (Active)
Reporting group description:	Aspirin 300mg & Vitamin D
Reporting group title	Large Aspirin (Active) & Vitamin D (Placebo)
Reporting group description:	Aspirin 300mg + Vitamin D3 placebo
Reporting group title	Small Aspirin (Active) & Vitamin D (Active)
Reporting group description:	Aspirin 100mg + Vitamin D3
Reporting group title	Small Aspirin (Active) & Vitamin D (Placebo)
Reporting group description:	Aspirin 100mg + Vitamin D3 placebo
Reporting group title	Aspirin (placebo) + Vitamin D3 (active)
Reporting group description:	Aspirin placebo + Vitamin D3
Reporting group title	Aspirin (placebo) + Vitamin D3 (placebo)
Reporting group description:	Aspirin placebo + Vitamin D3 placebo
Subject analysis set title	All patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	All patients randomised into the PROVENT trial.
Subject analysis set title	Active Vitamin D patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	Those patients receiving active vitamin D3 treatment
Subject analysis set title	Placebo Vitamin D Patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	Those patients receiving placebo vitamin D3 treatment
Subject analysis set title	Active Aspirin Patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	Those patients receiving active aspirin treatment (either 100mg OR 300mg)
Subject analysis set title	Placebo Aspirin Patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	Patients receiving placebo aspirin treatment
Subject analysis set title	100mg Aspirin Patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	Patients receiving 100mg of aspirin
Subject analysis set title	300mg Aspirin Patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	Patients receiving 300mg of aspirin
Subject analysis set title	Pathology review baseline subjects

Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Eighty-two patients whose biopsy tissue was centrally-reviewed after baseline biopsy	
Subject analysis set title	Pathology review month-12 subjects
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Twenty-five patients whose biopsy tissue was centrally-reviewed at 12 months	
Subject analysis set title	Paired MRI patients
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients that had MRI lesion detected at baseline and 12 months for volume comparison	

Primary: Patient recruitment

End point title	Patient recruitment ^[1]
End point description:	
There is no formal analysis for patient recruitment. A target of 102 patients (approximately 17 per arm) was set and met.	
End point type	Primary
End point timeframe:	
December 2016 to December 2017	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There was no formal statistical analysis of the primary endpoint. There was an aim to recruit 102 patients based on an estimated 30% recruitment rate. The number of patients actually recruited was 104 and so the primary endpoint was met.

End point values	All patients			
Subject group type	Subject analysis set			
Number of subjects analysed	104 ^[2]			
Units: Patients recruited	104			

Notes:

[2] - No formal analysis for patient recruitment. A target of 102 patients (approximately 17 per arm) was

Statistical analyses

No statistical analyses for this end point

Secondary: Disease progression by MRI

End point title	Disease progression by MRI
End point description:	
Disease progression is defined as increase in lesion volume of >33% or an upgrading of MRI stage of disease to T3 or above.	
In the case where no lesion was identified by MRI screening, disease progression is defined as the development of a lesion of 0.2cc or greater and being assigned a PIRADS score of 4 or 5	
Disease regression is defined as a decrease in lesion volume of > 33% or the absence of a lesion at 12 months where one was detected at baseline	
End point type	Secondary
End point timeframe:	
Baseline to 12 months	

End point values	Large Aspirin (Active) & Vitamin D (Active)	Large Aspirin (Active) & Vitamin D (Placebo)	Small Aspirin (Active) & Vitamin D (Active)	Small Aspirin (Active) & Vitamin D (Placebo)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	8	8	5
Units: Patients				
Disease regression	1	5	5	0
Stable disease	4	3	2	4
Disease progression	4	0	1	1

End point values	Aspirin (placebo) + Vitamin D3 (active)	Aspirin (placebo) + Vitamin D3 (placebo)	Active Vitamin D patients	Placebo Vitamin D Patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	9	8	26	21
Units: Patients				
Disease regression	3	2	9	7
Stable disease	6	6	12	13
Disease progression	0	0	5	1

End point values	Active Aspirin Patients	Placebo Aspirin Patients	100mg Aspirin Patients	300mg Aspirin Patients
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	17	13	33
Units: Patients				
Disease regression	11	5	5	6
Stable disease	13	12	6	7
Disease progression	6	0	2	4

Statistical analyses

No statistical analyses for this end point

Secondary: Biochemical disease progression (PSA)

End point title Biochemical disease progression (PSA)

End point description:

Biochemical disease progression was defined as observing an increase in PSA levels of at least 50% over 12 months.

Biochemical disease regression was defined as observing a decrease in PSA levels of at least 50% over 12 months.

End point type	Secondary
End point timeframe:	
Baseline to 12 months	

End point values	Large Aspirin (Active) & Vitamin D (Active)	Large Aspirin (Active) & Vitamin D (Placebo)	Small Aspirin (Active) & Vitamin D (Active)	Small Aspirin (Active) & Vitamin D (Placebo)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	11	10
Units: Patients				
Disease Regression	1	2	0	0
Stable Disease	9	10	10	10
Disease Progression	2	1	11	0

End point values	Aspirin (placebo) + Vitamin D3 (active)	Aspirin (placebo) + Vitamin D3 (placebo)	Active Vitamin D patients	Placebo Vitamin D Patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	12	15	35	38
Units: Patients				
Disease Regression	0	1	1	3
Stable Disease	10	13	29	33
Disease Progression	2	1	5	2

End point values	Active Aspirin Patients	Placebo Aspirin Patients	100mg Aspirin Patients	300mg Aspirin Patients
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	46	27	21	25
Units: Patients				
Disease Regression	3	1	0	3
Stable Disease	39	23	20	19
Disease Progression	4	3	1	3

Statistical analyses

No statistical analyses for this end point

Secondary: Histological disease progression by Gleason scoring

End point title	Histological disease progression by Gleason scoring
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End point description:

Histological disease progression is defined as an increase in Gleason score or primary grade upon repeat

biopsy at 12 months

Histological disease regression is defined as a decrease in Gleason score or primary grade upon repeat biopsy at 12 months

End point type	Secondary
End point timeframe:	
Baseline to 12 months	

End point values	Large Aspirin (Active) & Vitamin D (Active)	Large Aspirin (Active) & Vitamin D (Placebo)	Small Aspirin (Active) & Vitamin D (Active)	Small Aspirin (Active) & Vitamin D (Placebo)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	8	8	5
Units: Patients				
Disease Regression	0	0	1	0
Stable Disease	4	4	4	3
Disease Progression	1	4	3	2

End point values	Aspirin (placebo) + Vitamin D3 (active)	Aspirin (placebo) + Vitamin D3 (placebo)	Active Vitamin D patients	Placebo Vitamin D Patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	8	9	21	22
Units: Patients				
Disease Regression	0	0	1	0
Stable Disease	5	8	13	15
Disease Progression	3	1	7	7

End point values	Active Aspirin Patients	Placebo Aspirin Patients	100mg Aspirin Patients	300mg Aspirin Patients
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	17	13	13
Units: Patients				
Disease Regression	1	0	1	0
Stable Disease	15	13	7	8
Disease Progression	10	4	5	5

Statistical analyses

No statistical analyses for this end point

Secondary: Histological disease progression by Maximum Cancer Core Length

End point title	Histological disease progression by Maximum Cancer Core Length
End point description:	Disease progression will be defined as a 50% increase in maximum cancer core length as determined by repeat biopsy at 12 months
	Disease regression will be defined as a 50% decrease in maximum cancer core length as determined by repeat biopsy at 12 months
End point type	Secondary
End point timeframe:	Baseline to 12 months

End point values	Large Aspirin (Active) & Vitamin D (Active)	Large Aspirin (Active) & Vitamin D (Placebo)	Small Aspirin (Active) & Vitamin D (Active)	Small Aspirin (Active) & Vitamin D (Placebo)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	8	8	5
Units: Patients				
Disease Regression	1	0	1	0
Stable Disease	3	2	5	3
Disease Progression	1	6	2	2

End point values	Aspirin (placebo) + Vitamin D3 (active)	Aspirin (placebo) + Vitamin D3 (placebo)	Active Vitamin D patients	Placebo Vitamin D Patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	8	9	21	22
Units: Patients				
Disease Regression	2	0	4	0
Stable Disease	3	3	11	8
Disease Progression	3	6	6	14

End point values	Active Aspirin Patients	Placebo Aspirin Patients	100mg Aspirin Patients	300mg Aspirin Patients
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	17	13	13
Units: Patients				
Disease Regression	2	2	1	1
Stable Disease	13	6	8	5
Disease Progression	11	9	4	7

Statistical analyses

No statistical analyses for this end point

Secondary: Pathology review (baseline)

End point title Pathology review (baseline)

End point description:

Central review of biopsy tissue for 82 patients at baseline

End point type Secondary

End point timeframe:

Baseline

End point values	Pathology review baseline subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: Concordant pathology reports				
Concordant reviews	77			
Discordant Gleason score	3			
Discordant Other	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Pathology review at 12 months

End point title Pathology review at 12 months

End point description:

Central review of biopsy tissue at 12 months

End point type Secondary

End point timeframe:

Month 12

End point values	Pathology review month-12 subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: Concordant pathology reports				
Concordant report	22			
Discordant Gleason score	0			
Discordant other	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs should be reported from the date of first randomisation until the end of trial, defined as the date of the Last Patient Last Visit (LPLV) & 30 days.

Adverse event reporting additional description:

3 monthly fup. Adverse event CRF completed & patient diary checked by the research nurse at each appointment.

Patient stops treatment early or does not attend their 'End of Study' appointment? The LCO is responsible for checking their AE status via a telephone at least 30 days after the date the participant has stated they stopped their IMP.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20
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Reporting groups

Reporting group title	A: Aspirin 300mg & Vitamin D
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Reporting group description: -	
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Reporting group title	B: Aspirin 300mg & Vitamin D placebo
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Reporting group description: -	
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Reporting group title	C: Aspirin 100mg & Vitamin D
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Reporting group description: -	
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Reporting group title	D: Aspirin 100mg & Vitamin D placebo
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Reporting group description: -	
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Reporting group title	E: Aspirin placebo & Vitamin D
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Reporting group description: -	
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Reporting group title	F: Aspirin placebo & Vitamin D placebo
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Reporting group description: -	
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Serious adverse events	A: Aspirin 300mg & Vitamin D	B: Aspirin 300mg & Vitamin D placebo	C: Aspirin 100mg & Vitamin D
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 17 (11.76%)	2 / 16 (12.50%)	2 / 19 (10.53%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
Mass in brain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Rectal bleeding			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention postoperative			
subjects affected / exposed	1 / 17 (5.88%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Febrile infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serious adverse events			
Serious adverse events	D: Aspirin 100mg & Vitamin D placebo	E: Aspirin placebo & Vitamin D	F: Aspirin placebo & Vitamin D placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	0 / 18 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Vascular disorders Hypotension subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders Cardiac arrest subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions Mass in brain subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders Rectal bleeding subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders Testicular pain subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders Urinary retention postoperative subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations Febrile infection subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	A: Aspirin 300mg & Vitamin D	B: Aspirin 300mg & Vitamin D placebo	C: Aspirin 100mg & Vitamin D
Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 17 (29.41%)	9 / 16 (56.25%)	6 / 19 (31.58%)
Vascular disorders			
Transient ischaemic attack subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Abdominal aortic aneurysm subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Abdominal crampy pains subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Acid reflux subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Acute back pain subjects affected / exposed	1 / 17 (5.88%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Arm pain subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Back ache subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Bacterial infection due to helicobacter pylori (H. pylori) subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Bleeding postoperative			

subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Bloating			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood in urine			
subjects affected / exposed	1 / 17 (5.88%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood stool			
subjects affected / exposed	1 / 17 (5.88%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Chest infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Coccyx pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Cold			
subjects affected / exposed	0 / 17 (0.00%)	2 / 16 (12.50%)	1 / 19 (5.26%)
occurrences (all)	0	3	1
Constipation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Dark circles under eyes			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Fast Heart Beat			
subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Fever			

subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Flu-like symptoms			
subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Flu prophylaxis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Foot pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Fractured ribs			
subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Haemospermia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hay fever			
subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Head cold			
subjects affected / exposed	1 / 17 (5.88%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Hematuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Indigestion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Left hip pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Left knee meniscal tear			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Leg pain			

subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Lichen simplex			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Nose bleed			
subjects affected / exposed	0 / 17 (0.00%)	3 / 16 (18.75%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Pain in hips, knees and shoulders			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Pain stomach			
subjects affected / exposed	1 / 17 (5.88%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Pins and needles			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Polymyalgia rheumatica			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Postoperative pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Prolapsing haemorrhoid			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rash, headache, insomnia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Rectal bleeding			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Removal of basal cell			

subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Sore throat			
subjects affected / exposed	0 / 17 (0.00%)	2 / 16 (12.50%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Stomach ache			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Stomach acid			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Swelling (r) testicle			
subjects affected / exposed	1 / 17 (5.88%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Swollen toes			
subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 17 (0.00%)	1 / 16 (6.25%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Upset stomach			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Urinary urgency			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Urine volume increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Haematuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	1 / 19 (5.26%) 1
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Post procedural constipation subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0 0 / 17 (0.00%) 0	1 / 16 (6.25%) 1 0 / 16 (0.00%) 0	0 / 19 (0.00%) 0 0 / 19 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 3 2 / 17 (11.76%) 4	1 / 16 (6.25%) 1 3 / 16 (18.75%) 6	0 / 19 (0.00%) 0 0 / 19 (0.00%) 0
Ear and labyrinth disorders Ear infection subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	0 / 19 (0.00%) 0
Eye disorders Teary eyes subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	0 / 19 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0	0 / 16 (0.00%) 0 2 / 16 (12.50%) 2 0 / 16 (0.00%) 0	1 / 19 (5.26%) 1 1 / 19 (5.26%) 2 1 / 19 (5.26%) 2
Gastrooesophageal reflux disease	Additional description: 1		

subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	0 / 19 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1	0 / 19 (0.00%) 0
Skin and subcutaneous tissue disorders			
Dermatitis subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	0 / 19 (0.00%) 0
Lichen planus subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	0 / 19 (0.00%) 0
Renal and urinary disorders			
Lower urinary tract symptoms subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2	0 / 16 (0.00%) 0	0 / 19 (0.00%) 0
Nocturia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1	0 / 19 (0.00%) 0
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	0 / 19 (0.00%) 0
Urinary retention subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 16 (0.00%) 0	0 / 19 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0	1 / 19 (5.26%) 1
Gout subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	0 / 19 (0.00%) 0
Infections and infestations			
Fever/Virus subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	0 / 19 (0.00%) 0

Non-serious adverse events	D: Aspirin 100mg & Vitamin D placebo	E: Aspirin placebo & Vitamin D	F: Aspirin placebo & Vitamin D placebo
Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 18 (22.22%)	7 / 16 (43.75%)	11 / 18 (61.11%)
Vascular disorders			
Transient ischaemic attack subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Abdominal aortic aneurysm subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Abdominal crampy pains subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Acid reflux subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Acute back pain subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Arm pain subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Back ache subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Bacterial infection due to helicobacter pylori (H. pylori) subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Bleeding postoperative subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Bloating subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Blood in urine			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood stool			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Chest infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Coccyx pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Cold			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	3 / 18 (16.67%)
occurrences (all)	0	2	3
Constipation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Dark circles under eyes			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Fast Heart Beat			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Fever			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Flu-like symptoms			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

Flu prophylaxis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Foot pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Fractured ribs			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Haemospermia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hay fever			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Head cold			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hematuria			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Indigestion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Left hip pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Left knee meniscal tear			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Leg pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Lichen simplex			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

Mouth ulceration			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nose bleed			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Pain in hips, knees and shoulders			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pain stomach			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pins and needles			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Polymyalgia rheumatica			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Postoperative pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Prolapsing haemorrhoid			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Rash, headache, insomnia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rectal bleeding			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Removal of basal cell			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Sore throat			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Stomach ache			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Stomach acid			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Swelling (r) testicle			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Swollen toes			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Upset stomach			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Urinary urgency			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Urine volume increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Haematuria			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	1 / 18 (5.56%) 1
Post procedural constipation subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	0 / 18 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	0 / 18 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 2	1 / 18 (5.56%) 2
Ear and labyrinth disorders			
Ear infection subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	1 / 18 (5.56%) 1
Eye disorders			
Tearful eyes subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	1 / 18 (5.56%) 1
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	0 / 18 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	2 / 18 (11.11%) 2
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	0 / 18 (0.00%) 0
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	1 / 18 (5.56%) 1
Nausea subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	0 / 18 (0.00%) 0
Skin and subcutaneous tissue disorders			

Dermatitis subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	1 / 18 (5.56%) 1
Lichen planus subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1	0 / 18 (0.00%) 0
Renal and urinary disorders Lower urinary tract symptoms subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	0 / 18 (0.00%) 0
Nocturia subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	1 / 18 (5.56%) 1
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	1 / 18 (5.56%) 1
Urinary retention subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	0 / 18 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	1 / 18 (5.56%) 1
Gout subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 16 (6.25%) 2	0 / 18 (0.00%) 0
Infections and infestations Fever/Virus subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0	1 / 18 (5.56%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2016	<p>Substantial Amendment #1 Changes to the protocol</p> <ul style="list-style-type: none">• New Chief Investigator.• Change in Co-investigator, additions of new Collaborators, Trial Statistician.• Updated contact details of the Project Manager.• A new Representative of the Sponsor• Removal of the MRI review process & Trial Radiologist• One additional progression event – an upgrading of MRI Disease stage to ≥ 3• An increased number of Vitamin D3 drops to be ingested from 6, to 8 drops per day. This is due to a change in the bottle dropper size. The dosage remains unchanged.• Removal of the use of email/SMS to send participants appointment reminders & compliance prompts.• Non-Compliance changed to Non-Conformance with a definition.• Additional safeguards around dispensation of the study drugs.• An update on SAE reporting from the trials unit to the sponsor.• SAE reporting from the trials unit to the sponsor updated and 'Service Level Agreement 'replaced by the' Conditions of Sponsorship'• Removal of the requirement for CIOMs form completion as it's not a requirement for CTIMPS within the UK.• Clarification about PIs ability to sign SAEs and SUSARs electronically within study app.• More explicit instructions for unblinding participants in the event of a SUSAR.• Clearer definition of the reference safety information.• Administrative changes and clarified definition of source data.• Provision of urine for translational research to Myriad Genetics. Inc. This is not an additional sample. The company are receiving 15ml of the 35ml sample we are already collecting.• More information on storage of biopsy samples and storage & testing of urine samples.• Treatment holiday more explicitly defined, and a definition for lost to follow-up added.• Patients may be withdrawn from trial medication, and/or the study in the event of interruption of study drug intake for greater than 60 days.

24 August 2016

Substantial Amendment #1 continued.

- Patients who interrupt study drug intake for a cumulative total of greater than 90 60 days, in a 3 month period between follow-up appointments will be considered as non-compliant and will be discontinued from the study.
- Various administration changes, e.g. the 'Withdrawal from Treatment' CRF is now called the 'End of Study' CRF, unblinding patients.
- Clearer 'long-term follow-up' & 'End of Study' definitions.
- The 'End of Study' has been redefined in the protocol. Long-term follow-up has been excluded and a post treatment pharmacovigilance period has been accommodated.
- Plans for dissemination of study results to the public added.
- Collection of tissue in the event of a participant undergoing a radical prostatectomy clarified.
- More explicit instructions for unblinding participants in the event of a SUSAR.
- Adding more precautions to safeguard patient's safety in regards to biopsy procedure.
- Information on dose interruptions.
- Addition of post treatment pharmacovigilance period. End of Study Visit will take place at 18 months plus \geq to 30 days.
- Adding a new suggestion for ingesting Vitamin D3: added to a small quantity of fruit juice.
- Addition of a link to the study website and addition of IRAS ID number.
- Addition of new references.
- Clear documentation to site staff that pregnancies do not have to be reported.
- Administrative changes to treatment discontinuation.
- Pre-screening log. Data not entered into trial application. Informed Consent, Eligibility Assessed & Blood Samples for PSA & Serum taken. Participants must fulfil the inclusion and exclusion criteria. All patients who meet the eligibility criteria and are randomised will be included in the intention to treat (ITT) analysis.
- PID would not be used to send appointment reminders.
- Purpose for collecting contact details updated.

24 August 2016

Substantial amendment #1 continued (2)

Changes to sites

- Number of sites increased from 'Up to 5', to 'Up to 7' to accommodate Guy's & Coventry Hospitals.

Changes to study documents

- PROVENT Consent Form V1.0
 - Removal of consent to receive appointment reminders
 - Clearer documentation around the use of samples and personal details for the collection of long-term follow-up data.
 - Administrative changes.
 - Not necessary to have the study number on the consent form.
 - Addition of IRAS ID number.
 - More information on completing the consent form.
- PROVENT Patient Information Sheet V2.0
 - Update re: exclusive storage & testing of urine samples by QMUL
 - More explicit instructions for taking the Vitamin D3 oil.
 - Addition of information regarding the reimbursement of travel expenses.
 - Update re: collection & storage of participant contact details and their use to collect long-term follow-up data as part of a separate, ethically approved research study
 - Administrative amendments.
- PROVENT Patient Diary V2.0
 - Advice re: back up reference for contact details.
 - More explicit instructions for taking the Vitamin D3 oil.
 - Increase in number of drops to be taken, from 6 to 8.
 - New diary card & dosage instructions given out more frequently.
- PROVENT IMP Labels;
 - PROVENT Label Aspirin 100 – Update V1.0: Change of CI and change in dispensing instructions to 'Take as directed in patient diary'.
 - PROVENT Label Aspirin 300 – Update V1.0: Change of CI and change in dispensing instructions to 'Take as directed in patient diary'.
 - PROVENT Vitamin D – Update V1.0: Change of CI and increase in number of drops from 6 to 8 and change in dispensing instructions to 'Take as directed in patient diary'.
 - PROVENT Outer Pack Label Aspirin 100 & Vitamin D – Update V1.0: Change of CI.
 - PROVENT Outer Pack Label Aspirin 100 & Vitamin D – Update V1.0: Change of CI.
 - PROVENT labels for replacement IMP dropped.

05 June 2017	<p>Substantial Amendment #2. Changes to Protocol, V3.0, 5th May 2016</p> <ul style="list-style-type: none"> • Change of Chief Investigator from Professor Thomas Powles to Mr Greg Shaw, effective from the 1st June 2017. • Reduction of the randomisation period from 18 to 12 months, to accommodate the shorter expiry date on one of the IMPs, whilst still being able to offer participants the full 18 months treatment. • Removal of TMPRESS-2 ERG testing by Hologic Gen Probe as a result of financial constraints experienced by the company. • Replacement of PCA3 testing with 'exploratory research' due to Hologic Gen Probe no longer being able to provide the required collection tubes and reagents for the duration of the trial. • Revised timings of the recruitment rate review to 3, 6, 9, & 12 month, to reflect the new randomisation period. • More accurate definition of the inclusion criterion relating to Gleason grading. Some patients with Gleason Grade 3+4 prostate cancer would be eligible for active surveillance, patients with 4+3 would not by NICE and European Association of Urology guidance. • More accurate definition of the exclusion criterion relating to participation in other trials. All active surveillance patients at one of our sites are encouraged to participate in an observational/questionnaire study. The amendment will allow these patients to join PROVENT also. Addition of resources to assist sites with recruitment; a patient invitation letter, a trial poster & a study website. • Justification for the absence of an IMPD for the Aspirin placebo. • Correction to the composition details of the Vitamin D3 active product; 40 drops/ml = 20,000 IU/0.5mg cholecalciferol. Currently documented as 30 drops. • Revised timings for the baseline serum calcium blood test result. An existing serum result will be acceptable if taken within 2 months prior to the Eligibility Assessment date.
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05 June 2017	<p>Substantial Amendment #2 (continued)</p> <p>More explicit instructions regarding a participant's right to request that their treatment is unblinded. Removal of instructions for sending samples by ambient temperature. Sites agreed to freeze samples locally, for bulk shipment at a later date.</p> <ul style="list-style-type: none"> • Addition of the Project Manager's name. • Correction to Mr Paul Cathcart's title. • Removal of CR-UK's endorsement due to the delayed start of the trial • Minor administrative amendments, e.g. , correction to the protocol version & date. <p>Changes to sites</p> <ul style="list-style-type: none"> • Removal of Bedford Hospital • The addition of 4 sites: Churchill Hospital, Oxford, Southampton General Hospital, Western General Hospital, Edinburgh and Darent Valley Hospital, Kent. <p>Changes to study documents</p> <ul style="list-style-type: none"> • PROVENT Consent Form V2.0, 22nd March 2016: <ul style="list-style-type: none"> - Screening/Pre-randomisation ID: One additional box added to accommodate the full PROVENT pre-randomisation ID number. - Updated with the details of the new version of the Patient Information Sheet. • PROVENT Patient Information Sheet V3.0, 5th May 2016: <ul style="list-style-type: none"> - Reduction of the randomisation period from 18 to 12 months, to accommodate the shorter expiry date on one of the IMPs, whilst still being able to offer participants the full 18 months treatment. - Removal of CR-UK's endorsement due to the delayed start of the trial. - Revised timings for the baseline serum calcium blood test result. An existing serum result will be acceptable if taken within 2 months prior to the Eligibility Assessment date. • PROVENT Label Aspirin 100 -Update V2.0 & PROVENT Label Aspirin 300 Update V2.0: Combined to produce one label for both drugs, i.e. ASPIRIN 300mg OR Aspirin 100mg OR PLACEBO, for the following reasons; (a)The change to the label means all packs are fully blinded from the outer packs (b) Having single Master labels for the tablet pots & outer cartons makes the trial more secure. • PROVENT Wallet Cards: <ul style="list-style-type: none"> - Contact details updated
04 September 2017	<p>Substantial amendment #3. NB: The amendment date is the date it was approved by the MREC. There was no requirement to submit to the Regulatory Authority. The purpose of the amendment was to add the Royal Free Hospital London as a Patient Identification Site for University College Hospital London. No trial documents were changed as a consequence.</p>

03 October 2018	<p>Substantial Amendment #4 Changes to Protocol, V4.0, 16th February 2017</p> <ul style="list-style-type: none"> • Change of sponsor representative details • Change of Project Manager from Roseann Kealy to Adedayo Oke • Change of Trial Statistician from Amar Ahmed to Jacqueline Murphy • Clarification on where study prostate tissue samples will be stored • The addition of 'Occurrence of any other malignancy' as a reason for early study withdrawal • The dietary supplements/medication composition description changed from "Vitamin D3" to the less specific "Vitamin D" on page 10 of the protocol. • The addition of Sarcoidosis and Tuberculosis to the protocol exclusion criteria list. • The IMP bottle /container labels were corrected in the protocol to reflect those approved & used for the study. • Clarification on the frequency of Digital Rectal Examination (DRE), and the timing of repeat MRI Scans and Prostate Biopsies which should be conducted in line with routine care. DRE and post-DRE urine sample collected at the 12 and 18 month visits only. • Removal of the communication plan between the CI/PI and members of the study team document, from the list of study documents to be filed in the Investigator Files (IF) and Pharmacy Site Files (PSF). • The reference to the study type in the protocol is corrected from Type B to Type A based on the MHRA Guidelines. • Administrative changes to the Schedule of Assessment table making it consistent with the wording within the protocol and associated SOPs/manuals which accurately reflects the study procedures & time points. • The secondary objective "50% increase in serum PSA at 12 months from baseline" revised to "Change in serum PSA at 6 and 12 months from baseline" • SAE definition updated to include "Is otherwise considered medically significant by the investigator" • Removal of "Interruption of study drug intake for greater than 60 days from the criteria for early study/IMP withdrawal. <p>Addition to the study website:</p> <ul style="list-style-type: none"> • Information added to the study
17 December 2019	<p>Substantial Amendment #5 Changes to Protocol, V5.0, 18th August 2018</p> <ul style="list-style-type: none"> • Updated protocol number, version and date • Project Manager name and contact details updated. • A new Trial Statistician • A change to the end of trial definition to allow for the receipt of the Cell Cycle Progression (CCP (ii)) analyses results. Our principal site, with the highest number of participants has experienced some difficulty obtaining the 12 month pathology samples required for CCP analysis. The CCP scores relate to the secondary endpoint 'To evaluate markers of disease progression'. The amendment will afford us more time for this activity. <p>The change to the end of trial definition does not involve an extension to participants' treatment or follow-up.</p> <ul style="list-style-type: none"> • A revision of the study duration to accommodate the change in end of trial definition.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

