Clinical trial results:
Combined Suppression Of Cholesterol Bioavailability And Androgen Deprivation Therapy To Treat Castration Resistant Prostate Cancer

Summary

EudraCT number	2015-003720-32
Trial protocol	GB
Global end of trial date	31 July 2019

Results information

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

Trial information

Trial identification

Sponsor protocol code	SPECTRE2015

Additional study identifiers

ISRCTN number	ISRCTN16951765
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor reference: GN14ON621, Protocol Name: SPECTRE2015

Notes:

Sponsors

Sponsor organisation name	NHS Greater Glasgow and Clyde and University of Glasgow
Sponsor organisation address	NHS Greater Glasgow and Clyde Research & Innovation Ward 11 Dykebar Hospital Grahamston Road, Paisley , United Kingdom, PA2 7DE
Public contact	Joanne McGarry, NHS Greater Glasgow and Clyde, 44 01413144001, joanne.mcgarry@ggc.scot.nhs.uk
Scientific contact	Joanne McGarry, NHS Greater Glasgow and Clyde, 44 01413144001, joanne.mcgarry@ggc.scot.nhs.uk

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 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore the impact of atorvastatin on androgen receptor signalling in castration-resistant prostate cancer.

Protection of trial subjects:

The SPTECTRE trial was performed according to the Research Governance Framework for Health and Community Care (Second edition; 2006) and the Medicines for Human Use (Clinical Trials) Regulations, 2004 SI 2004:1031 (as amended) and World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended). All patients were consented only after being provided with full explanation of the trial and time for consideration, and were free to withdraw at any time, without giving any reason, without medical care being affected.

Background therapy:

Not applicable

Evidence for comparator:

not applicable - single arm trial design

Actual start date of recruitment	20 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: 14
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	1
From 65 to 84 years	12
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study opened to recruitment in January 2017, with the first patient recruited in March 2017. This study was opened to recruitment at a single UK centre only.

Pre-assignment

Screening details:

The screening period for the trial was up to 28 days prior to registration. Prior to screening investigations commencing patient must have provided informed consent to participate in the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable.

Arms

Arm title	Atorvastatin

Arm description:

Atorvastatin 40mg orally once daily continuously for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	Atorvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Atorvastatin 40mg orally once daily continuously for 6 weeks.

Number of subjects in period 1	Atorvastatin
Started	14
Completed	12
Not completed	2
Consent withdrawn by subject	1
Unevaluable (insufficient treatment taken)	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1	1	
From 65-84 years	12	12	
85 years and over	1	1	
Age continuous Units: years			
median	73		
inter-quartile range (Q1-Q3)	70 to 77	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	14	14	
Baseline PSA Units: ng/ml			
median	4.4		
inter-quartile range (Q1-Q3)	3.7 to 10.6	-	

End points

End points reporting groups

Reporting group title	Atorvastatin
Reporting group description:	
Atorvastatin 40mg orally once daily continuously for 6 weeks.	
Subject analysis set title	ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients registered on to the study	
Subject analysis set title	Evaluable Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All eligible patients who do not meet any of the following criteria for non-evaluability: • They do not complete 80% of 6 weeks of atorvastatin medication and neither have a drop of >=50% in PSA levels from baseline nor PSA progression • Only 3 PSA measurements are available post start of atorvastatin medication and none of these correspond to a >=50% drop from baseline or PSA progression	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who took at least one dose of study medication	
Subject analysis set title	Eligible Study Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All registered patients excluding those with gross eligibility deviations	

Primary: PSA Response Rate

End point title	PSA Response Rate
End point description:	
PSA response is the achievement of ≥50% drop from baseline in PSA levels at any time over the 6-week period of statins medication	
End point type	Primary
End point timeframe:	
Over 6 weeks of study treatment	

End point values	Atorvastatin	Evaluable Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	12		
Units: Patients				
Responders	1	1		
Non-responders	11	11		
Unevaluable	2	0		

Statistical analyses

Statistical analysis title	PSA Response Rate

Statistical analysis description:

Single arm proportion and 80% Clopper-Pearson confidence interval.

The intended methods of exact inference described in Koyama and Chen[Koyama T, Chen H. Proper inference from Simon's two-stage designs. Stat Med. 2008;27(16):3145–54. doi: 10.1002/sim.3123. View ArticlePubMedGoogle Scholar] were not required since the study did not proceed to stage 2. A standard Clopper-Pearson confidence interval was presented instead.

Comparison groups	Atorvastatin v Evaluable Population
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Proportion
Point estimate	8.3
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	2.5
upper limit	24.2

Notes:

[1] - NOTE: 12 patients are included in this analysis, not 26 as the system shows

This is a single arm study using a Simon two-stage optimal design (90% power, 10% 1-sided significance level) to distinguish an "ineffective" PSA response rate of <=10% from an "effective" PSA response rate of >=30%. This required 12 patients at stage 1. If <=1 of these 12 patients responded, recruitment would end with the conclusion that the use of statins is ineffective in this setting. Only 1 response was observed

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs (including SAEs) must be followed until resolution or for at least 28 days after discontinuation of trial medication until toxicity has resolved to baseline or ≤ grade 1, or until the toxicity is considered to be irreversible.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Cardiac disorders - Other, specify	Additional description: TRIFASCICULAR BLOCK AND INTERMITTENT 2:1 AV BLOCK		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Transient ischaemic attack			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vestibular disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorder			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders - Other specify			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Arthritis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorder - Other specify			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infections and infestations			
Lip infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Lung infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2017	Substantial Changes to Protocol: 1. Within the inclusion criteria, the washout period for prior statin use at trial entry was amended from 2 months to 28 days. The purpose of this update was to provide more flexibility for low risk patients already receiving statin treatment who wish to enter the study. This was discussed by the study Investigators/Co-Investigators and is deemed to be clinically appropriate. 2. Within the inclusion criteria, the fasting glucose level requirement of ≤ 5.6mmol/L was removed. This was discussed by the study Investigators/Co-Investigators and was deemed to be clinically appropriate. The requirement for fasting glucose was removed as it was agreed it would unnecessarily exclude patients. The NICE guidelines for the use of stains in individuals with diabetes were consulted as part of these discussions, and it was agreed that the benefit of statins use outweighed the small risk of developing Diabetes Mellitus 2 over a 10yr period. In the SPECTRE cohort of Castration Resistant Prostate Cancer patients with life expectancy of <2years the risk of causing Diabetes Mellitus 2 with 6 weeks of statin is negligible. The protocol was also updated to include guidance that the study patient's GPs should be contacted in the event of fasting glucose > 7mmol/L, to ensure it is monitored/treated as per normal practice. 3. The timing of the first tumour biopsy was updated from being prior to atorvastatin start to being +/- 7 days of atorvastatin start. The purpose of this change wass to provide more flexibility for scheduling the biopsies around the patient's clinic attendance without compromising the validity of the samples/data. Non-substantial Changes: 1. The contact details of several study team members were updated.
13 March 2018	Protcol Updates: 1. Update to the inclusion requirements for proven prostate cancer, to bring SPECTRE in line with many other clinical studies in progressing prostate cancer with the use of histologic, cytologic or biochemical parameters as confirmation of the presence of prostate cancer. 2. Protocol inclusion criteria updated to include patients who have been treated with abiraterone acetate or enzalutamide. 3. Protocol inclusion criteria updated to allow ongoing castration with abiraterone or enzalutamide. 4. Corection made to typographical error at inclusion level of haemoglobin and platelets 5. Clarification added that the tumour biopsies are an optional component of the study. 6. Exclusion criteria updated to allow prior chemotherapy and prior second-line androgen deprivation therapy 7. Guidance added to the Safety Reporting section regarding the reporting of pregnancies. 8. The Patient Information sheet/consent form was updated with guidance on possible side effects for patients continuing on abiraterone during SPECTRE study treatment.

31 July 2019	Protcol Updates: This amendment was submitted 06-Feb-2020 1. Update to study team contact details 2. The study objective 'Change in adrenal steroid DHEA (dehydroepiandrosterone) levels' was amended from being a secondary objective to an exploratory objective 3. Typographical corrections made to the Safety Reporting section

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported