



## Clinical trial results:

### SONATINA: A Phase II Multi-Centre Randomised Controlled Study of Nelfinavir Addition to Radiotherapy Treatment in Neo-Adjuvant Therapy for Rectal Cancer

#### Summary

EudraCT number	2010-020621-40
Trial protocol	GB
Global end of trial date	20 January 2014

#### Results information

Result version number	v1 (current)
This version publication date	21 July 2016
First version publication date	05 August 2015

#### Trial information

##### Trial identification

Sponsor protocol code	OCTO_021
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##### Additional study identifiers

ISRCTN number	ISRCTN29580179
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Clinical Trials and Research Governance, Joint Research Office, Block 60, Churchill Hosp, Old Road , Headington, Oxford, United Kingdom, OX3 7LE
Public contact	University of Oxford, University of Oxford, 44 1865 572224, ctrg@admin.ox.ac.uk
Scientific contact	University of Oxford, University of Oxford, 44 1865 572224, ctrg@admin.ox.ac.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	10 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2014
Global end of trial reached?	Yes
Global end of trial date	20 January 2014
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To investigate the activity of the drug, Nelfinavir, when it is used to sensitise rectal cancer to radiotherapy treatment to try to make the radiotherapy more effective.

Protection of trial subjects:

The trial received ethical and regulatory approval, and was run in compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004, and amendments thereafter, the guidelines for Good Clinical Practice, and the applicable policies of the Sponsor, the University of Oxford. Together, these regulations implement the ethical principles of the Declaration of Helsinki (2008) and the regulatory requirements for clinical trials of an investigational medicinal product as set out in the European Union (EU) Directives 2001/20/EC (Clinical Trials) and 2005/28/EC (GCP). Patients also were seen for study assessments every 4 weeks from their last day of radiotherapy for 5 months as consistent with standard NHS therapy.

Background therapy:

No other background therapies/treatments used.

Evidence for comparator:

No comparator used - single arm study.

Actual start date of recruitment	05 April 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	5
From 65 to 84 years	5
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment was open from April 2011 until January 2014. 8 patients were recruited from a single centre to assess safety prior to extending to the multi-centre randomised trial, and this was then extended to 16 patients. However, because recruitment targets were not met, the study was terminated early with only 10 patients recruited.

### Pre-assignment

Screening details:

19 patients were screened, of which 9 were ineligible. 2 patients had a performance status of 3 (eligibility criteria required 0-2), 3 patients were suitable for alternative trials, one patient's primary tumour was not symptomatic, one patient had impaired memory, one patient declined & for one patient the MDT did not feel SCRT was appropriate.

### Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Arm title	Baseline
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Nelfinavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Nelfinavir was administered orally 1250mg bd from day-7 (7 days before RT commences on day 1) to day 7 (the last day of RT). Radiotherapy was delivered in fractions of 5 Gy daily from day 1 to day 7. Total dose of radiotherapy is 25 Gy prescribed to the ICRU reference point. Radiotherapy technique could be 3D-conformal or IMRT.

Number of subjects in period 1	Baseline
Started	10
Completed	10

**Period 2**

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

**Arms**

<b>Arm title</b>	Nelfinavir + radiotherapy
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## Arm description:

When the trial had been halted for an interim analysis, the decision to extend the initial safety cohort from 8 patients to 16 patients was made, before the decision was made to close the trial early due to slow recruitment. Therefore all the patients in this arm (the safety cohort) received the Nelfinavir + short course radiotherapy (SCRT).

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

## Dosage and administration details:

Nelfinavir was administered orally 1250mg bd from day-7 (7 days before RT commences on day 1) to day 7 (the last day of RT). Radiotherapy was delivered in fractions of 5 Gy daily from day 1 to day 7. Total dose of radiotherapy is 25 Gy prescribed to the ICRU reference point. Radiotherapy technique could be 3D-conformal or IMRT.

<b>Number of subjects in period 2</b>	Nelfinavir + radiotherapy
Started	10
Completed	8
Not completed	2
Adverse event, non-fatal	2

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	10	10	
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)	5	5	
From 65-84 years	5	5	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	5	5	
Male	5	5	
ECOG performance status			
Units: Subjects			
PS 0	4	4	
PS 1	6	6	
Rectal sub-site of target lesion			
Units: Subjects			
Low	7	7	
Low to Mid	1	1	
Mid	1	1	
Mid to Upper	1	1	
Extramural vascular invasion (EMVI)			
Units: Subjects			
Yes	5	5	
No	5	5	

## End points

### End points reporting groups

Reporting group title	Baseline
Reporting group description: -	
Reporting group title	Nelfinavir + radiotherapy
Reporting group description: When the trial had been halted for an interim analysis, the decision to extend the initial safety cohort from 8 patients to 16 patients was made, before the decision was made to close the trial early due to slow recruitment. Therefore all the patients in this arm (the safety cohort) received the Nelfinavir + short course radiotherapy (SCRT).	

### Primary: Incidence of any CTCAE grade 3 or higher toxicities

End point title	Incidence of any CTCAE grade 3 or higher toxicities <sup>[1]</sup>
End point description: The primary outcome for the SONATINA safety cohort analysis is safety measured by incidence of any grade 3 or higher non-haematological or haematological toxicity (according to CTCAE v 4.0) up to 28 days post-SCRT. Toxicities that occurred up to 28 days post-SCRT have been summarised by Adverse Event Term. No formal comparison has been made as there is only one treatment arm.	
End point type	Primary
End point timeframe: Up to 28 days post the last day of radiotherapy treatment	
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: The primary outcome for the SONATINA safety cohort analysis was safety measured by incidence of any grade 3 or higher non-haematological or haematological toxicity (according to CTCAE v 4.0) up to 28 days post-SCRT. Toxicities that occurred up to 28 days post-SCRT have been summarised. No formal comparison has been made as there is only one treatment arm.	

End point values	Nelfinavir + radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: CTCAE grade 3 or higher toxicity				
Grade 3 Drug Reaction	1			
Grade 3 Diarrhoea	2			
Grade 3 Peri-Anal Pain	1			
Grade 3 Lymphopenia	2			
Grade 3 Hyponatremia	1			
Grade 3 Vomiting	1			

### Statistical analyses

No statistical analyses for this end point

### Primary: TCD in biopsy taken 7 days from last fraction of protocol radiotherapy.

End point title	TCD in biopsy taken 7 days from last fraction of protocol radiotherapy. <sup>[2]</sup>
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End point description:

The primary aim of the main SONATINA trial was to investigate the effect of Nelfinavir (the study drug) added to short-course radiotherapy in improving response rate in patients with rectal cancer patients, whilst testing the feasibility of using Tumour Cell Density (TCD) in the primary tumour to measure response rate. The primary tumour TCD of each patient was measured before and after their Nelfinavir and SCRT treatment.

End point type	Primary
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End point timeframe:

Before and after the Nelfinavir and SCRT treatment

Notes:

[2] - 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: The primary outcome for the SONATINA trial (before it was closed due to slow recruitment) was Tumour Cell Density (TCD) in primary tumour biopsy taken 7 days from last fraction of SCRT. No formal comparison has been made as there is only one treatment arm, and only a very small number of patients.

End point values	Nelfinavir + radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	9 <sup>[3]</sup>			
Units: Tumour Cell Density (% Tumour)				
median (inter-quartile range (Q1-Q3))				
Pre-treatment TCD (% Tumour)	24.3 (13.4 to 44.5)			
Post-treatment TCD (% Tumour)	9.2 (3.3 to 16.3)			
Difference pre to post treat (% Tumour)	15.1 (10.1 to 28.2)			

Notes:

[3] - One patient had no tumour in their post treatment biopsy

<b>Attachments (see zip file)</b>	TCD comparison: Pre to Post
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## Statistical analyses

No statistical analyses for this end point

## Secondary: Radiological response of primary tumour at 8 weeks post SCRT evaluated by RECIST

End point title	Radiological response of primary tumour at 8 weeks post SCRT evaluated by RECIST
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End point description:

Radiological response evaluated by RECIST (version 1.1) assessment of primary tumour on MRI at 8 weeks post-SCRT. 8 out of 10 patients (80%) can be classed as responders, as they had Complete Response, Partial Response or Stable Disease at 8 weeks. Patient ST1002 had Progressive Disease at 8 weeks, and ST1010 is Not Evaluable as they had died before the 8 week assessment, so these two patients are classed as non-responders.

End point type	Secondary
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End point timeframe:

8 weeks post short course radiotherapy (SCRT) treatment



<b>End point values</b>	Nelfinavir + radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	9 <sup>[4]</sup>			
Units: Patients				
Complete Response	3			
Partial Response	4			
Stable Disease	1			
Progressive Disease	1			

Notes:

[4] - One patient died before their 8 week scan

### Statistical analyses

No statistical analyses for this end point

### Secondary: Radiological response of primary tumour at 8 weeks post SCRT evaluated by mrTRG assessment

End point title	Radiological response of primary tumour at 8 weeks post SCRT evaluated by mrTRG assessment
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End point description:

Radiological response evaluated by mrTRG assessment of primary tumour on MRI at 8 weeks post-SCRT. As well as being assessed with RECIST criteria, the patients' primary tumours were also assessed using mrTRG scores by two radiologists. If the two radiologists did not agree in their assessment, there was a third radiologist's opinion. The overall mrTRG score that was assigned to each patient is presented. 5/9 (56%) of the mrTRG assessed SONATINA patients' primary tumours were classed as good overall by the radiologists.

End point type	Secondary
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End point timeframe:

8 weeks post short course radiotherapy (SCRT) treatment.

<b>End point values</b>	Nelfinavir + radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	9 <sup>[5]</sup>			
Units: Patients				
Good mrTRG assessment	5			
Poor mrTRG assessment	4			

Notes:

[5] - One patient died before their 8 week scan

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of patients proceeding to resectional pelvic surgery

End point title	Proportion of patients proceeding to resectional pelvic surgery
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End point description:

The proportion of SONATINA patients proceeding to pelvic surgery within 6 months from last fraction of radiotherapy. No SONATINA patients proceeded to have pelvic surgery within 6 months of their radiotherapy treatment.

End point type	Secondary
End point timeframe:	
Within 6 months from last fraction of short course radiotherapy (SCRT)	

<b>End point values</b>	Nelfinavir + radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Patients				
Proceeded to pelvic surgery	0			
Did not proceed to pelvic surgery	10			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 6 months post-SCRT

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.0
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### Reporting groups

Reporting group title	Nelfinivir + radiotherapy
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Reporting group description:

Nelfinavir + radiotherapy

Serious adverse events	Nelfinivir + radiotherapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Nelfinivir + radiotherapy		
Total subjects affected by non-serious adverse events subjects affected / exposed	9 / 10 (90.00%)		
Nervous system disorders			
Peripheral neuropathy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Sensory peripheral neuropathy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Bilateral Paresthesia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Lymphopenia subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 6		
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	7 / 10 (70.00%) 9		
Pyrexia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Extravasation of CT contrast subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Dizzy and confused after scan subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Drug reaction subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		

Bleeding during biopsy subjects affected / exposed occurrences (all)	Additional description: Minor bleeding during biopsy		
	1 / 10 (10.00%) 1		
Ear and labyrinth disorders Labyrinthitis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Eye disorders Burst blood vessel subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Gastrointestinal disorders Anal pain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Bloating subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Constipation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	6 / 10 (60.00%) 15		
Flatulence subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Nausea subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 7		
Per rectal bleeding subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Perianal discomfort subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Perianal pain			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Proctitis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Stomach cramps			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	6		
Reproductive system and breast disorders			
Vaginal pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dry macular skin rash			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Radiation skin injury	Additional description: Radiation skin reaction		
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Erythema	Additional description: Skin erythema - natal cleft		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Urinary incontinence	Additional description: Urinary symptoms; frequency, urgency and incontinence		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	3		

Dysuria			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Tenesmus			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Prostatism	Additional description: Prostatism (cystitis noninfective)		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Trismus			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Left flank pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Anorexia and bulimia syndrome			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Low appetite			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2012	The main purpose of this amendment was to clarify the definition of the safety cohort and to amend the definition of end of trial.
17 September 2012	The main purpose of this amendment was to expand the safety cohort from 8 to 16 patients since the levels of grade 3/4 toxicity experienced were slightly, but not significantly, higher than one would expect from radiotherapy alone. So we needed to study more patients in order to be able to tell whether there is any significant toxicity from the combination of radiotherapy and Nelfinavir being tested in this trial.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 January 2014	Early trial termination submitted 20 January 2014. The justification for premature end of the trial was: due to insufficient recruitment (SONATINA protocol section 11.1 states 'Recruitment rate should average 1-2 patients per month per site in order to accrue to the projected accrual target within 24 months'), whereas In the last 12 month period, the recruitment rate has been 0.16 patients recruited per month, it is therefore not feasible to continue the trial	-

Notes:

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Early termination due to slow recruitment leading to a very small number of subjects analysed

Notes: