Clinical trial results:
PHASE III RANDOMIZED CHEMOPREVENTION STUDY OF SELENIUM ON THE RECURRENCE OF NON-INVASIVE BLADDER CANCER

Summary

EudraCT number	2008-005431-15
Trial protocol	BE
Global end of trial date	31 December 2015

Results information

Result version number	v1 (current)
This version publication date	07 February 2023
First version publication date	07 February 2023
Summary attachment (see zip file)	Publication1 (Designing the selenium and bladder cancer trial (SELEBLAT), a phase lll randomized chemoprevention study with selenium on recurrence of bladder cancer in Belgium-2.pdf) Publication 2 (Phase III randomised chemoprevention study with selenium on the recurrence of non-invasive urothelial carcinoma. The SELEnium and BLAdder cancer Trial.pdf)

Trial information

Trial identification

Sponsor protocol code	ML 5220

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00729287
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	KU Leuven, Department of General Practice
Sponsor organisation address	Kapucijnenvoer 33, blok J bus 7001, Leuven, Belgium, 3000
Public contact	Dr Frank Buntinx, KU Leuven, Department of General Practice, 32 0475/ 41 90 53, Maria.Goossens@sciensano.be
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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 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 May 2015
Global end of trial reached?	Yes
Global end of trial date	31 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to determine the effect of selenium, in addition to standard care, on the recurrence of bladder cancer.

Protection of trial subjects:

Adverse events and adverse reactions will be monitored during each follow-up visit and will be noted on the case report forms. The obligation starts from the moment the informed consent is signed until 30 days after the administration of the last dose. The principal Investigator will decide whether the serious adverse event is related or unrelated to the trial treatment. It is anticipated that the risk and side effects of the additional supplement of 200µg selenium will be minor. Nevertheless, harm-related data will be collected and reported according the recommendation made by the CONSORT statement.

Background therapy:

In Belgium, bladder cancer (BC) is the fifth most common cancer in men. The per-patient lifetime cost is high. Previous epidemiological studies have consistently reported that selenium concentrations were inversely associated with the risk of BC. We therefore hypothesised that selenium may be suitable for chemoprevention of recurrence of BC.

Evidence for comparator: -

Actual start date of recruitment	18 September 2009
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	Belgium: 292
Worldwide total number of subjects	292
EEA total number of subjects	292

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)	65
From 65 to 84 years	195
85 years and over	32

Subject disposition

Recruitment

Recruitment details:

Eligible patients were recruited through the urology department of 14 Belgian hospitals. Eligible patients provided their written informed consent. Patients were randomly assigned by a computer program to oral selenium yeast 200 µg once a day or placebo for three years, in addition to standard care.

Pre-assignment

Screening details:

All randomised patients were included in the intention to treat and safety analyses. Per protocol analyses included all patients in the study three months after start date. Between September 18, 2009 and April 18, 2013, 151 and 141 patients were randomised in the selenium and placebo group. Patients were followed until December 31, 2015.

Pre-assignment period milestones

Number of subjects started	694[1]
Intermediate milestone: Number of subjects	Assessed for eligibility: 694
Intermediate milestone: Number of subjects	Randomised: 292
Number of subjects completed	292

Pre-assignment subject non-completion reasons

Reason: Number of subjects	not meeting inclusion criteria: 243
Reason: Number of subjects	No malignity: 57
Reason: Number of subjects	Not available: 50
Reason: Number of subjects	Declined to participate: 39
Reason: Number of subjects	cystectomy: 8
Reason: Number of subjects	Adverse event, serious fatal: 5

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 694 pts were assessed for eligibility. Out of this number, 402 pts were exluded, leaving 292 pts that could be randomised. In the Intention to treat analysis (292 pts in total) 151 pts were allocated to the Selenium 200mcg group and 141 pts were allocated to placebo.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Selenium

Arm description: -

Arm type	Experimental

Investigational medicinal product name	selenium (200µg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One tablet (selenium/placebo) once daily at breakfast for a period of three years.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	selenium (200µg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One tablet (selenium/placebo) once daily at breakfast for a period of three years.

Number of subjects in period 1	Selenium	Placebo
Started	151	141
Completed	151	141

Period 2

Period 2 title	Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Selenium

Arm description:

Arm I: Patients receive oral placebo daily additionally to standard care.
Arm II: Patients receive oral selenium (200µg) daily additionally to standard care.

Arm type	Experimental
Investigational medicinal product name	selenium (200µg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
One tablet (selenium/placebo) once daily at breakfast for a period of three years.

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	selenium (200µg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
One tablet (selenium/placebo) once daily at breakfast for a period of three years.

Number of subjects in period 2	Selenium	Placebo
Started	151	141
Follow-up 3 Months	136	123
Follow-up 36 Months	110	106
Completed	110	106
Not completed	41	35
Adverse event, serious fatal	1	-
Consent withdrawn by subject	32	19
cystectomy	-	3
Adverse event, non-fatal	2	2
Recurrence	-	1
not meeting inclusion criteria	6	10

Baseline characteristics

Reporting groups	
Reporting group title	Selenium
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Selenium	Placebo	Total
Number of subjects	151	141	292
Age categorical			
Median age was 68 years ranging from 46 to 90 and 91 years for the selenium and the placebo group. Specific numbers per group are not specified in the results.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	57	41	98
From 65-84 years	82	80	162
85 years and over	12	20	32
Age continuous			
Median age was 68 years ranging from 46 to 90 and 91 years for the selenium and the placebo group. No further details regarding age were mentioned in the resulst.			
Units: years			
median	68	68	
full range (min-max)	46 to 90	46 to 91	-
Gender categorical			
Units: Subjects			
Female	20	30	50
Male	131	111	242
Number of tumours			
Units: Subjects			
solitary tumour	81	80	161
2-7	54	44	98
>=8	2	2	4
unknown	14	15	29
Primary tumour			
Units: Subjects			
Primary tumour	102	88	190
Recurrent	35	41	76
Unknown	14	12	26

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT analysis showed recurrence in 43 (28%; 95% CI, 0.21e0.35) and 45 (32%; 95% CI, 0.24e0.40) patients in the selenium and placebo group. HR (hazard ratio) was 0.85 (95% CI, 0.56e1.29). The log-rank test was not significant (p Z 0.44). Adjustment for age, gender, smoking status, staging, baseline serum selenium level and hospital did not alter the results. There was no interaction between treatment and gender, age or smoking status. Excluding those patients who discontinued the intervention did not alter HR of ITT analysis (p Z 0.39).

Subject analysis set title	PPA
Subject analysis set type	Per protocol

Subject analysis set description:

PPA, performed for all patients still participating at T3, showed an overall recurrence for 42 and 39 (28%; 95% CI, 0.20e0.35) patients in the selenium and placebo group (HR Z 0.96 [95% CI, 0.62e1.48]). The log-rank test was not significant (p Z 0.85) (Fig. 2). Excluding those patients who discontinued the intervention resulted in an HR of 0.94 (95% CI, 0.61e1.45). The log-rank test was not significant (p Z 0.78).

Reporting group values	ITT	PPA	
Number of subjects	292	259	
Age categorical			
Median age was 68 years ranging from 46 to 90 and 91 years for the selenium and the placebo group. Specific numbers per group are not specified in the results.			
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)	72	67	
From 65-84 years	195	173	
85 years and over	25	19	
Age continuous			
Median age was 68 years ranging from 46 to 90 and 91 years for the selenium and the placebo group. No further details regarding age were mentioned in the resulst.			
Units: years			
median	68	68	
full range (min-max)	46 to 90	46 to 91	
Gender categorical			
Units: Subjects			
Female	39	55	
Male	253	204	
Number of tumours			
Units: Subjects			
solitary tumour	161	142	
2-7	98	87	
>=8	4	3	
unknown	29	27	
Primary tumour			
Units: Subjects			
Primary tumour	190	162	

Recurrent	76	75	
Unknown	26	22	

End points

End points reporting groups

Reporting group title	Selenium
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Selenium

Reporting group description:

Arm I: Patients receive oral placebo daily additionally to standard care.
Arm II: Patients receive oral selenium (200µg) daily additionally to standard care.

Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT analysis showed recurrence in 43 (28%; 95% CI, 0.21e0.35) and 45 (32%; 95% CI, 0.24e0.40) patients in the selenium and placebo group. HR (hazard ratio) was 0.85 (95% CI, 0.56e1.29). The log-rank test was not significant (p Z 0.44). Adjustment for age, gender, smoking status, staging, baseline serum selenium level and hospital did not alter the results. There was no interaction between treatment and gender, age or smoking status. Excluding those patients who discontinued the intervention did not alter HR of ITT analysis (p Z 0.39).

Subject analysis set title	PPA
Subject analysis set type	Per protocol

Subject analysis set description:

PPA, performed for all patients still participating at T3, showed an overall recurrence for 42 and 39 (28%; 95% CI, 0.20e0.35) patients in the selenium and placebo group (HR Z 0.96 [95% CI, 0.62e1.48]). The log-rank test was not significant (p Z 0.85) (Fig. 2). Excluding those patients who discontinued the intervention resulted in an HR of 0.94 (95% CI, 0.61e1.45). The log-rank test was not significant (p Z 0.78).

Primary: Primary outcome: recurrence

End point title	Primary outcome: recurrence

End point description:

Adjustment for age, gender, smoking status, staging, baseline serum selenium level and hospital did not alter the results. There was no interaction between treatment and gender, age or smoking status. Excluding those patients who discontinued the intervention did not alter HR of ITT analysis (p Z 0.39).

End point type	Primary

End point timeframe:

The ITT analysis showed recurrence in 43 (28%; 95% CI, 0.21e0.35) and 45 (32%; 95% CI, 0.24e0.40) patients in the selenium and placebo group. HR was 0.85 (95% CI, 0.56e1.29). The log-rank test was not significant (p Z 0.44).

End point values	ITT	PPA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151	141		
Units: patients				
number (confidence interval 95%)				
recurrence	0.28 (0.21 to 0.35)	0.28 (0.20 to 0.35)		

Attachments (see zip file)	Table 1/Phase III randomised chemoprevention study with

Statistical analyses

Statistical analysis title	Difference in percent of BC recurrence after 3Y

Statistical analysis description:

All randomised patients were included in the intention to treat (ITT) and safety analyses. KaplaneMeier estimates of a recurrence-free interval were used to compare treatment groups descriptively, while log-rank tests were used to test the hypothesis of no difference between treatments. Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) comparing patients randomised to selenium or placebo. T0 was when ICF was signed.

Comparison groups	ITT v PPA
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.05 [2]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.29
Variability estimate	Standard deviation
Dispersion value	21.5

Notes:

[1] - The end date for each pt was the day of recurrence, cystectomy or death, or the day the pt withdrew from the trial, or 3 Y after T0, or the end date of the trial (31Dec15). PPA included all patients in the study 3 months after the starting date (T3). Pts who withdrew as well as pts with cystectomy within the first 3 months were excluded from PPA. Two sensitivity analyses were performed excluding all pts that ended the trial prematurely, the first based on ITT analysis, the second based on PPA.
[2] - KM estimates of a recurrence-free interval to compare trtmnt groups descriptively, log-rank tests to test the hypothesis of no difference between trtmnts. Cox proportional hazards regression models to estimate HR and 95%CI comparing pts rand to Se/Pl

Secondary: Secondary outcome: progression

End point title	Secondary outcome: progression

End point description:

Twenty-nine patients showed progression of whom 15 occurred in the selenium group and 14 in the placebo group. Performing the ITT analysis resulted in an HR of 0.97 (95% CI, 0.47e2.00; p Z 0.93). Patients taking selenium had 48% more chance of progression than those in the placebo group, although not statistically significant (HR Z 1.48 [95% CI, 0.65e3.38]; p Z 0.35). Excluding those patients from the analysis who discontinued their treatment resulted in a similar HR.

End point type	Secondary

End point timeframe:

After three months (T3), progression was seen in 24 patients. The mean progression time was 22 months for both groups.

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	292			
Units: patients				
number (confidence interval 95%)				
Progression	0.97 (0.47 to 2.00)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and adverse reactions were monitored during each follow-up visit and were noted on the case report forms. The obligation started from the moment the informed consent was signed until 30 days after the administration of the last dose.

Adverse event reporting additional description:

The principal Investigator will decide whether the serious adverse event is related or unrelated to the trial treatment. The decision will be recorded on the serious adverse event form. The principal Investigator will sign the form.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	Selenium
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Selenium	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 151 (0.00%)	0 / 141 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1.3 %

Non-serious adverse events	Selenium	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 151 (5.30%)	9 / 141 (6.38%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 151 (0.66%)	2 / 141 (1.42%)	
occurrences (all)	1	2	
Pain			
subjects affected / exposed	1 / 151 (0.66%)	0 / 141 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 151 (0.66%)	0 / 141 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 151 (0.66%)	0 / 141 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 151 (0.66%)	1 / 141 (0.71%)	
occurrences (all)	1	1	
stomach/intestinal			
subjects affected / exposed	1 / 151 (0.66%)	4 / 141 (2.84%)	
occurrences (all)	1	4	
Constipation			
subjects affected / exposed	1 / 151 (0.66%)	1 / 141 (0.71%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Nail injury			
subjects affected / exposed	0 / 151 (0.00%)	1 / 141 (0.71%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	1 / 151 (0.66%)	0 / 141 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27814472

http://www.ncbi.nlm.nih.gov/pubmed/22436453