Clinical trial results:
The effect of curcumin and piperine on the pharmacokinetics of tamoxifen in patients with estrogen receptor positive breast cancer 'the ELDORADO study'

Summary

EudraCT number	2016-004008-71
Trial protocol	NL
Global end of trial date	01 May 2018

Results information

Result version number	v1 (current)
This version publication date	01 December 2021
First version publication date	01 December 2021
Summary attachment (see zip file)	Cancers pubilcation (cancers-11-00403.pdf)

Trial information

Trial identification

Sponsor protocol code	ELDORADO

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Erasmus MC
Sponsor organisation address	Doctor Molewaterplein 40, Rotterdam, Netherlands,
Public contact	Ron Mathijssen, Erasmus MC, a.mathijssen@erasmusmc.nl
Scientific contact	Ron Mathijssen, Erasmus MC, a.mathijssen@erasmusmc.nl

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	01 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 May 2018
Global end of trial reached?	Yes
Global end of trial date	01 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the influence of curcumin with or without piperine, in patients with estrogen receptor positive breast cancer, on tamoxifen/endoxifen plasma pharmacokinetics (AUC).

Protection of trial subjects:

Patients were seen by a doctor on regular visits to the outpatient clinic and also during hospital admissions

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 17
Worldwide total number of subjects	17
EEA total number of subjects	17

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)	17
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were included from january 2017 until may 2018

Pre-assignment

Screening details:

Seventeen patients were screened and included in the study. One patient was excluded because of voluntary
withdrawal, resulting in 16 evaluable patients.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	arm ABC

Arm description:

Patients started with tamoxifen monotherapy followed by tamoxifen + curcumin and followed by tamoxifen+curcumin+piperin

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

Dosage and administration details:

1200 mg three times daily

Investigational medicinal product name	Piperin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10 mg three times daily

Arm title	Randomisation CBA

Arm description:

Reversed order so patients started with curcumin+piperin+tamoxifen followed by tamoxifen+curcumin and ultimately followed by tamoxifen monotherapy

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

Dosage and administration details:

1200 mg three times daily

Investigational medicinal product name	Piperin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10 mg three times daily

Number of subjects in period 1[1]	arm ABC	Randomisation CBA
Started	9	7
Completed	9	7

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: There were 17 patienst enrolled but there were 16 patients analyzed.

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	16	16	
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			
Age median			
Units: years			
median	45		
inter-quartile range (Q1-Q3)	42 to 58	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	1	1	
Race			
Race			
Units: Subjects			
caucasian	15	15	
arabic	1	1	
WHO performance status Units: Subjects			
One	3	3	
zero	13	13	
Previous chemotherapy Units: Subjects			
yes	12	12	
no	4	4	
Previous radiotherapy Units: Subjects			
yes	10	10	
no	6	6	
Genotype			
Genotype of 2D6			

Units: Subjects			
EM	7	7	
IM	7	7	
PM	1	1	
UM	1	1	
Genotype 3A4			
Genotype of 3A4			
Units: Subjects			
EM	16	16	
tamoxifen dose			
Units: Subjects			
20 mg	15	15	
30 mg	1	1	
height			
Height of patients			
Units: centimeter			
median	171		
inter-quartile range (Q1-Q3)	167 to 176	-	
weigth			
weigth			
Units: kilogram(s)			
median	73		
inter-quartile range (Q1-Q3)	65 to 91	-	

End points

End points reporting groups

Reporting group title	arm ABC
Reporting group description:	
Patients started with tamoxifen monotherapy followed by tamoxifen + curcumin and followed by tamoxifen+curcumin+piperin	
Reporting group title	Randomisation CBA
Reporting group description:	
Reversed order so patients started with curcumin+piperin+tamoxifen followed by tamoxifen+curcumin and ultimately followed by tamoxifen monotherapy	
Subject analysis set title	Phase A
Subject analysis set type	Full analysis
Subject analysis set description:	
Phase A	
Subject analysis set title	Phase B
Subject analysis set type	Full analysis
Subject analysis set description:	
phase B	
Subject analysis set title	Phase C
Subject analysis set type	Full analysis
Subject analysis set description:	
phase C	

Primary: Area under the curve tamoxifen

End point title	Area under the curve tamoxifen
End point description:	
End point type	Primary
End point timeframe:	
Assessment period was from january 2017 to may 2018	

End point values	Phase A	Phase B	Phase C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	16	16	16	
Units: nanomole(s)/millilitre				
geometric mean (geometric coefficient of variation)	5951 (± 20)	5460 (± 24)	5171 (± 23)	

Statistical analyses

Statistical analysis title	Relative difference
Comparison groups	Phase A v Phase C

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.02
Method	t-test, 2-sided
Parameter estimate	relative difference
Point estimate	-12.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	-6

Primary: AUC endoxifen	
End point title	AUC endoxifen
End point description:	

End point type	Primary
End point timeframe:	
From january 2017 to may 2018	

End point values	Phase A	Phase B	Phase C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	16	16	16	
Units: nanomole(s)/millilitre				
geometric mean (geometric coefficient of variation)	597 (± 59)	556 (± 52)	518 (± 54)	

Statistical analyses

Statistical analysis title	Relative difference A vsC
Comparison groups	Phase C v Phase A
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.02
Method	t-test, 2-sided
Parameter estimate	Relative difference
Point estimate	-12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22
upper limit	-2

Notes:
[1] - Relative difference

Secondary: Ctrough tamoxifen

End point title	Ctrough tamoxifen
End point description: Same statistical evaluation as AUC	
End point type	Secondary
End point timeframe: january 2017 to may 2018	

End point values	Phase A	Phase B	Phase C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed				
Units: nanomole(s)/millilitre				
geometric mean (geometric coefficient of variation)	213 (± 27)	198 (± 28)	187 (± 24)	

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough endoxifen

End point title	Ctrough endoxifen
End point description: Same statistical evaluation as AUC	
End point type	Secondary
End point timeframe: january 2017 to may 2018	

End point values	Phase A	Phase B	Phase C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed				
Units: nanomole(s)/millilitre				
geometric mean (geometric coefficient of variation)	25 (± 60)	23 (± 53)	21 (± 55)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax tamoxifen	
End point title	Cmax tamoxifen
End point description: Same statistical evaluation as AUC	
End point type	Secondary
End point timeframe: january 2017 to may 2018	

End point values	Phase A	Phase B	Phase C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed				
Units: nanomole(s)/millilitre				
geometric mean (geometric coefficient of variation)	356 (± 16)	324 (± 21)	313 (± 22)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax endoxifen	
End point title	Cmax endoxifen
End point description: Same statistical evaluation as AUC	
End point type	Secondary
End point timeframe: january 2017 to may 2018	

End point values	Phase A	Phase B	Phase C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed				
Units: nanomole(s)/millilitre				
geometric mean (geometric coefficient of variation)	31 (± 56)	28 (± 50)	27 (± 51)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax tamoxifen	
End point title	Tmax tamoxifen

End point description:

End point type	Secondary

End point timeframe:
january 2017 to may 2018

End point values	Phase A	Phase B	Phase C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed				
Units: hour				
median (inter-quartile range (Q1-Q3))	2.4 (1.9 to 3.1)	2.4 (1.9 to 3.0)	2.7 (1.9 to 3.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: tmax

End point title	tmax

End point description:

End point type	Secondary

End point timeframe:
january 2017 to may 2018

End point values	Phase A	Phase B	Phase C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed				
Units: hour				
median (inter-quartile range (Q1-Q3))	2.0 (1.3 to 3.0)	1.7 (1.2 to 2.6)	1.8 (1.1 to 3.1)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events were graded up to 2 weeks after the last visit of the last patient in may 2018

Assessment type	Systematic

Dictionary used

Dictionary name	Openclinica
Dictionary version	3

Reporting groups

Reporting group title	ABC group

Reporting group description:

Patients started with tamoxifen monotherapy followed by tamoxifen + curcumin and followed by tamoxifen+curcumin+piperin

Reporting group title	CBA group

Reporting group description:

Reversed order so patients started with curcumin+piperin+tamoxifen followed by tamoxifen+curcumin and ultimately followed by tamoxifen monotherapy

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: We had some adverse events in our group as posted in the article, but there were no serious or unexpected adverse events. Therefore we mentioned zero non-serious adverse events in these results, since they were expected regular clinical side-effects

Serious adverse events	ABC group	CBA group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
collaps	Additional description: Patient experienced a collapse during study, probably not related to the study treatment		
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	ABC group	CBA group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	

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/30909366