



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 publication (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 patients 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 | - | |
| weighth | | | |
| weighth | | | |
| 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 (\pm 20) | 5460 (\pm 24) | 5171 (\pm 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 (\pm 27) | 198 (\pm 28) | 187 (\pm 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 (\pm 60) | 23 (\pm 53) | 21 (\pm 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 (\pm 16) | 324 (\pm 21) | 313 (\pm 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 (\pm 56) | 28 (\pm 50) | 27 (\pm 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>