



## Clinical trial results:

**Karisma II: A randomized, double blinded, six-armed placebo controlled study to investigate optimal dose of tamoxifen with the most favourable side effect spectra and with mammographic density reduction non-inferior to that of 20 mg tamoxifen.**

### Summary

EudraCT number	2016-000882-22
Trial protocol	SE
Global end of trial date	25 October 2019

### Results information

Result version number	v1 (current)
This version publication date	18 July 2021
First version publication date	18 July 2021

### Trial information

#### Trial identification

Sponsor protocol code	KARISMAII
-----------------------	-----------

#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03346200
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Karolinska Institutet
Sponsor organisation address	Fatburs Brunnsgata 7, Stockholm, Sweden, SE-118 28
Public contact	Karma Study Center at Södersjukhuset Breast Center, Karolinska Institutet at Södersjukhuset Breast Center, 0046 70750 2110, per.hall@ki.se
Scientific contact	Karma Study Center at Södersjukhuset Breast Center, Karolinska Institutet at Södersjukhuset Breast Center, 0046 70750 2110, per.hall@ki.se

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	20 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2019
Global end of trial reached?	Yes
Global end of trial date	25 October 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Identify the minimal dose of tamoxifen non-inferior in its ability to reduce mammographic density and with less side effects compared to 20 mg of tamoxifen.

Protection of trial subjects:

The study was performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects that were adopted in 1964 by the 18th World Medical Assembly, in Helsinki, Finland, with later revisions and the International Conference on Harmonisation (ICH) Guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 2016
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	Sweden: 1440
Worldwide total number of subjects	1440
EEA total number of subjects	1440

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)	1096
From 65 to 84 years	344
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Study invitations were sent to women invited for mammography in the Swedish mammography screening program. Of 159 027 women invited, 2 314 showed interest of participating and were assessed for eligibility. At study screening 874 did not meet the inclusion/exclusion criteria and eventually 1 440 women were randomized.

### Pre-assignment

Screening details:

Exclusion criteria were made to not allowing women with previous cancer or with elevated risk for cardiovascular disorders.

### Period 1

Period 1 title	6 months on IMP (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

0 mg of IMP (tamoxifen)

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

Dosage and administration details:

Once daily for 6 months.

<b>Arm title</b>	1 mg of IMP
------------------	-------------

Arm description:

1 mg of IMP (tamoxifen)

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

Dosage and administration details:

Once daily for 6 months.

<b>Arm title</b>	2,5 mg of IMP
------------------	---------------

Arm description:

2,5 mg of IMP (tamoxifen)

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Tamoxifen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Once daily for 6 months.	
<b>Arm title</b>	5 mg of IMP
Arm description:	
5 mg of IMP (tamoxifen)	
Arm type	Experimental
Investigational medicinal product name	Tamoxifen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Once daily for 6 months.	
<b>Arm title</b>	10 mg of IMP
Arm description:	
10 mg of IMP (tamoxifen)	
Arm type	Experimental
Investigational medicinal product name	Tamoxifen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Once daily for 6 months.	
<b>Arm title</b>	20 mg of IMP
Arm description:	
20 mg of IMP (tamoxifen)	
Arm type	Active comparator
Investigational medicinal product name	Tamoxifen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Once daily for 6 months.	

<b>Number of subjects in period 1</b>	Placebo	1 mg of IMP	2,5 mg of IMP
Started	242	239	235
Completed	211	205	200
Not completed	31	34	35
Consent withdrawn by subject	22	22	20

Adverse event, non-fatal	9	12	15
--------------------------	---	----	----

<b>Number of subjects in period 1</b>	5 mg of IMP	10 mg of IMP	20 mg of IMP
Started	240	243	241
Completed	201	210	203
Not completed	39	33	38
Consent withdrawn by subject	22	19	17
Adverse event, non-fatal	17	14	21

## Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: 0 mg of IMP (tamoxifen)	
Reporting group title	1 mg of IMP
Reporting group description: 1 mg of IMP (tamoxifen)	
Reporting group title	2,5 mg of IMP
Reporting group description: 2,5 mg of IMP (tamoxifen)	
Reporting group title	5 mg of IMP
Reporting group description: 5 mg of IMP (tamoxifen)	
Reporting group title	10 mg of IMP
Reporting group description: 10 mg of IMP (tamoxifen)	
Reporting group title	20 mg of IMP
Reporting group description: 20 mg of IMP (tamoxifen)	

Reporting group values	Placebo	1 mg of IMP	2,5 mg of IMP
Number of subjects	242	239	235
Age categorical			
Age categories, all 1 440 randomized, stratified per dose arm.			
Units: Subjects			
Adults (18-64 years)	177	193	181
From 65-84 years	65	46	54
Gender categorical			
Units: Subjects			
Female	242	239	235
Male	0	0	0

Reporting group values	5 mg of IMP	10 mg of IMP	20 mg of IMP
Number of subjects	240	243	241
Age categorical			
Age categories, all 1 440 randomized, stratified per dose arm.			
Units: Subjects			
Adults (18-64 years)	185	179	181
From 65-84 years	55	64	60
Gender categorical			
Units: Subjects			
Female	240	243	241
Male	0	0	0

Reporting group values	Total		
Number of subjects	1440		

Age categorical			
Age categories, all 1 440 randomized, stratified per dose arm.			
Units: Subjects			
Adults (18-64 years)	1096		
From 65-84 years	344		
Gender categorical			
Units: Subjects			
Female	1440		
Male	0		

---

### Subject analysis sets

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

Subject analysis set description:

Mean relative dense area change (%) and difference in mean change at six-months in the primary intention to treat population

---

<b>Reporting group values</b>	Efficacy		
Number of subjects	1230		
Age categorical			
Age categories, all 1 440 randomized, stratified per dose arm.			
Units: Subjects			
Adults (18-64 years)	982		
From 65-84 years	248		
Gender categorical			
Units: Subjects			
Female	1230		
Male	0		

---

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: 0 mg of IMP (tamoxifen)	
Reporting group title	1 mg of IMP
Reporting group description: 1 mg of IMP (tamoxifen)	
Reporting group title	2,5 mg of IMP
Reporting group description: 2,5 mg of IMP (tamoxifen)	
Reporting group title	5 mg of IMP
Reporting group description: 5 mg of IMP (tamoxifen)	
Reporting group title	10 mg of IMP
Reporting group description: 10 mg of IMP (tamoxifen)	
Reporting group title	20 mg of IMP
Reporting group description: 20 mg of IMP (tamoxifen)	
Subject analysis set title	Efficacy
Subject analysis set type	Intention-to-treat
Subject analysis set description: Mean relative dense area change (%) and difference in mean change at six-months in the primary intention to treat population	

### Primary: Efficacy

End point title	Efficacy
End point description: Mean relative dense area change (%) and difference in mean change at six-months in the primary intention to treat population	
End point type	Primary
End point timeframe: Evaluated after 6 months on IMP.	

End point values	Placebo	1 mg of IMP	2,5 mg of IMP	5 mg of IMP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	211 <sup>[1]</sup>	205	200	201
Units: Absolute numbers	211	205	200	201

Notes:

[1] - Absolute difference in mammographic density

End point values	10 mg of IMP	20 mg of IMP	Efficacy	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	210	203	1230	
Units: Absolute numbers	210	203	1230	

<b>Attachments (see zip file)</b>	Efficacy figure/Efficacy KARISMA 2.pdf
-----------------------------------	--

## Statistical analyses

<b>Statistical analysis title</b>	Intention to treat
-----------------------------------	--------------------

Statistical analysis description:

For primary efficacy endpoint, evaluating the primary intention to treat population (N=1,230) the difference in mean change (compared with the 20 mg treatment group) at six-months, stratified by menopausal status and tamoxifen dose.

Comparison groups	Placebo v 1 mg of IMP v 2,5 mg of IMP v 5 mg of IMP v 10 mg of IMP v 20 mg of IMP v Efficacy
Number of subjects included in analysis	2460
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[2]</sup>
P-value	< 0.025 <sup>[3]</sup>
Method	Wald tests
Parameter estimate	Mean difference (net)
Confidence interval	
level	Other: 97.5 %
sides	1-sided
Variability estimate	Standard error of the mean

Notes:

[2] - Non-inferiority was declared if the corrected p-values were less than 0.025. We reported one-sided 97.5% normal-based confidence intervals.

[3] - For the primary endpoint, we calculated one-sided p-values for non-inferiority using Wald tests.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During the 6 months of participation.

Adverse event reporting additional description:

Safety and adverse events were assessed by study personnel available through study center phone, a phone app for spontaneous reports, and through scheduled questionnaires at month 1, 3, and 6.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	23.1
--------------------	------

### Reporting groups

Reporting group title	All participants
-----------------------	------------------

Reporting group description: -

Serious adverse events	All participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 1440 (0.76%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	3 / 1440 (0.21%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Monoclonal gammopathy			
subjects affected / exposed	1 / 1440 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of head and neck			
subjects affected / exposed	1 / 1440 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Varicophlebitis			

subjects affected / exposed	1 / 1440 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Meningioma benign			
subjects affected / exposed	1 / 1440 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 1440 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Peptic ulcer haemorrhage			
subjects affected / exposed	1 / 1440 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pyelonephritis acute			
subjects affected / exposed	2 / 1440 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	All participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	342 / 1440 (23.75%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	140 / 1440 (9.72%)		
occurrences (all)	193		
Night sweats			
subjects affected / exposed	109 / 1440 (7.57%)		
occurrences (all)	189		

Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	93 / 1440 (6.46%)		
occurrences (all)	121		

## 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/33734864>