Clinical trial results:
Phase III trial of LHRH analog administration during chemotherapy to reduce ovarian failure following chemotherapy in early stage, hormone-receptor negative breast cancer.

Summary

EudraCT number	2006-002600-33
Trial protocol	BE IT HU
Global end of trial date	20 January 2017

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	IBCSG 34-05/SWOG 0230/ POEMS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00068601
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IBCSG
Sponsor organisation address	Effingerstrasse 40, Bern, Switzerland, 3008
Public contact	IBCSG Coordinating Center, International Breast Cancer Study Group (IBCSG), +41 31 511 94 00, regulatoryoffice@ibcsg.org
Scientific contact	IBCSG Coordinating Center, International Breast Cancer Study Group (IBCSG), +41 31 511 94 00, regulatoryoffice@ibcsg.org

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	Interim
Date of interim/final analysis	22 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 January 2014
Global end of trial reached?	Yes
Global end of trial date	20 January 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the rate of premature ovarian failure at two years following standard adjuvant chemotherapy or neoadjuvant chemotherapy with or without the addition of ovarian suppression with a LHRH analog during chemotherapy in premenopausal women with early stage, hormone-receptor negative breast cancer

Protection of trial subjects:

Participating institutions' ethics committees or Institutional Review Boards approved the trial according to local laws and regulations. All patients gave written informed consent, and the trial was performed in compliance with the Helsinki Declaration. The Data Safety and Monitoring Board reviewed the data from this research throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 February 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 31
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Australia: 37
Country: Number of subjects enrolled	New Zealand: 21
Country: Number of subjects enrolled	United States: 152
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Switzerland: 7
Worldwide total number of subjects	257
EEA total number of subjects	39

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	257
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 257 patients were randomized between February 2004 and May 2011.

Pre-assignment

Screening details:

The trial used a web-based randomization system.

Period 1

Period 1 title	Overall Study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Arm 1

Arm description:

Patients receive cyclophosphamide-containing chemotherapy alone.

cyclophosphamide: Part of planned chemotherapy regimen

Arm type	Active comparator
Investigational medicinal product name	cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patient's planned treatment must include 3 to 8 months or cycles of an alkylating agent containing post-operative or pre-operative chemotherapy regimen that can be anthracycline-based or non-anthracycline-based. Examples of anthracycline-based regimens include:
AC (3 months or 4 cycles), CAF (6 months/cycles), TAC (6 months/cycles), CEF (6 months/cycles), and AC followed by a taxane (6 to 8 months or cycles). An example of non-anthracycline-based regimen is CMF (6 months).

Arm title	Arm 2

Arm description:

Patients receive goserelin subcutaneously once every 4 weeks beginning 1 week before start of cyclophosphamide-containing chemotherapy. Treatment continues until completion of chemotherapy in the absence of disease progression or unacceptable toxicity.

cyclophosphamide: Part of planned chemotherapy regimen

goserelin acetate: Given subcutaneously

Arm type	Experimental
Investigational medicinal product name	goserelin acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Subcutaneous use

Dosage and administration details:

Goserelin acetate, 3.6 mg implant.
Goserelin is administered once every 4 weeks for duration of chemotherapy

Number of subjects in period 1	Arm 1	Arm 2
Started	131	126
Completed	69	66
Not completed	62	60
Ineligible	11	13
Consent withdrawn by subject	5	4
Missing primary outcome data	30	34
Death	11	3
Lost to Follow-up	3	2
Not evaluable: hysterectomy/oophorectomy	2	4

Period 2

Period 2 title	ITT analysis
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1

Arm description:

Patients receive cyclophosphamide-containing chemotherapy alone.

cyclophosphamide: Part of planned chemotherapy regimen

Arm type	Active comparator
Investigational medicinal product name	cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patient's planned treatment must include 3 to 8 months or cycles of an alkylating agent containing post-operative or pre-operative chemotherapy regimen that can be anthracycline-based or non-anthracycline-based. Examples of anthracycline-based regimens include:
AC (3 months or 4 cycles), CAF (6 months/cycles), TAC (6 months/cycles), CEF (6 months/cycles), and AC followed by a taxane (6 to 8 months or cycles). An example of non-anthracycline-based regimen is CMF (6 months).

Arm title	Arm 2

Arm description:

Patients receive goserelin subcutaneously once every 4 weeks beginning 1 week before start of cyclophosphamide-containing chemotherapy. Treatment continues until completion of chemotherapy in the absence of disease progression or unacceptable toxicity.

cyclophosphamide: Part of planned chemotherapy regimen

goserelin acetate: Given subcutaneously

Arm type	Experimental
Investigational medicinal product name	goserelin acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Subcutaneous use

Dosage and administration details:

Goserelin acetate, 3.6 mg implant.
Goserelin is administered once every 4 weeks for duration of chemotherapy

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics were only reported for Intention-to-treat population

Number of subjects in period 2[2]	Arm 1	Arm 2
Started	113	105
Completed	113	105

Notes:

[2] - 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: Intention-to-treat population excludes 24 pts that were ineligible, 9 pts that withdrew consent and 6 pts that were not evaluable due to hysterectomy/oophorectomy

Baseline characteristics

Reporting groups

Reporting group title	Arm 1

Reporting group description:

Patients receive cyclophosphamide-containing chemotherapy alone.

cyclophosphamide: Part of planned chemotherapy regimen

Reporting group title	Arm 2

Reporting group description:

Patients receive goserelin subcutaneously once every 4 weeks beginning 1 week before start of cyclophosphamide-containing chemotherapy. Treatment continues until completion of chemotherapy in the absence of disease progression or unacceptable toxicity.

cyclophosphamide: Part of planned chemotherapy regimen

goserelin acetate: Given subcutaneously

Reporting group values	Arm 1	Arm 2	Total
Number of subjects	113	105	218
Age categorical 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)	0	0	0
From 65-84 years	113	105	218
85 years and over	0	0	0
Years	0	0	0
Age continuous			
Number analyzed			
Units: years			
median	38.7	37.6	
full range (min-max)	25.1 to 49.9	26.1 to 48.6	-
Gender categorical Units: Subjects			
Female	113	105	218
Male	0	0	0

Subject analysis sets

Subject analysis set title	Overall Number of Baseline Participants
Subject analysis set type	Full analysis

Subject analysis set description:

Patients who are both eligible and evaluable

Reporting group values	Overall Number of Baseline Participants		
Number of subjects	218		
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	218		
85 years and over	0		
Years	0		
Age continuous			
Number analyzed			
Units: years			
median	37.7		
full range (min-max)	25.1 to 49.9		
Gender categorical Units: Subjects			
Female	218		
Male	0		

End points

End points reporting groups

Reporting group title	Arm 1

Reporting group description:

Patients receive cyclophosphamide-containing chemotherapy alone.

cyclophosphamide: Part of planned chemotherapy regimen

Reporting group title	Arm 2

Reporting group description:

Patients receive goserelin subcutaneously once every 4 weeks beginning 1 week before start of cyclophosphamide-containing chemotherapy. Treatment continues until completion of chemotherapy in the absence of disease progression or unacceptable toxicity.

cyclophosphamide: Part of planned chemotherapy regimen

goserelin acetate: Given subcutaneously

Reporting group title	Arm 1

Reporting group description:

Patients receive cyclophosphamide-containing chemotherapy alone.

cyclophosphamide: Part of planned chemotherapy regimen

Reporting group title	Arm 2

Reporting group description:

Patients receive goserelin subcutaneously once every 4 weeks beginning 1 week before start of cyclophosphamide-containing chemotherapy. Treatment continues until completion of chemotherapy in the absence of disease progression or unacceptable toxicity.

cyclophosphamide: Part of planned chemotherapy regimen

goserelin acetate: Given subcutaneously

Subject analysis set title	Overall Number of Baseline Participants
Subject analysis set type	Full analysis

Subject analysis set description:

Patients who are both eligible and evaluable

Primary: Rate of Premature Ovarian Failure at 2 Years

End point title	Rate of Premature Ovarian Failure at 2 Years

End point description:

Ovarian failure at two years is defined as amenorrhea (absence of menstrual bleeding) for the preceding six months AND the presence of follicle-stimulating hormone (FSH) in the post-menopausal range.

End point type	Primary

End point timeframe:

2 years

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	66		
Units: Participants	15	5		

Statistical analyses

Statistical analysis title	stratified logistic-regression analysis
Comparison groups	Arm 2 v Arm 1
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.04
Method	t-test, 2-sided
Parameter estimate	Odds ratio (OR)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.97

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Only adverse events related to hormonal effects and serious adverse events that occurred during chemotherapy with or without
goserelin were routinely assessed, with assessment according to the Common Terminology Criteria for Adverse Events, version 3

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Arm 1

Reporting group description:

Patients receive cyclophosphamide-containing chemotherapy alone.

cyclophosphamide: Part of planned chemotherapy regimen

Reporting group title	Arm 2

Reporting group description:

Patients receive goserelin subcutaneously once every 4 weeks beginning 1 week before start of cyclophosphamide-containing chemotherapy. Treatment continues until completion of chemotherapy in the absence of disease progression or unacceptable toxicity.

cyclophosphamide: Part of planned chemotherapy regimen

goserelin acetate: Given subcutaneously

Serious adverse events	Arm 1	Arm 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 111 (8.11%)	4 / 103 (3.88%)	
number of deaths (all causes)	17	8	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Diarrhea G3			
subjects affected / exposed	0 / 111 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain and fever			
subjects affected / exposed	1 / 111 (0.90%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile neutropenia			

subjects affected / exposed	5 / 111 (4.50%)	3 / 103 (2.91%)	
occurrences causally related to treatment / all	7 / 7	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 111 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC			
subjects affected / exposed	1 / 111 (0.90%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with Grade 3 or 4 neutrophils - catheter related			
subjects affected / exposed	1 / 111 (0.90%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection prothesis site R breast			
subjects affected / exposed	1 / 111 (0.90%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Arm 1	Arm 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 111 (24.32%)	50 / 103 (48.54%)	
Vascular disorders			
Hot flashes			
subjects affected / exposed	17 / 111 (15.32%)	33 / 103 (32.04%)	
occurrences (all)	17	33	
Thromboembolism			
subjects affected / exposed	0 / 111 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 111 (1.80%)	12 / 103 (11.65%)	
occurrences (all)	2	12	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 111 (0.90%)	2 / 103 (1.94%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	2 / 111 (1.80%)	0 / 103 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Irregular menses			
subjects affected / exposed	2 / 111 (1.80%)	7 / 103 (6.80%)	
occurrences (all)	2	7	
Vaginal dryness			
subjects affected / exposed	9 / 111 (8.11%)	12 / 103 (11.65%)	
occurrences (all)	9	12	
Skin and subcutaneous tissue disorders			
Sweating			
subjects affected / exposed	7 / 111 (6.31%)	10 / 103 (9.71%)	
occurrences (all)	7	10	
Psychiatric disorders			
Decrease in libido			
subjects affected / exposed	6 / 111 (5.41%)	9 / 103 (8.74%)	
occurrences (all)	6	9	
Agitation			
subjects affected / exposed	5 / 111 (4.50%)	6 / 103 (5.83%)	
occurrences (all)	5	6	
Anxiety			
subjects affected / exposed	4 / 111 (3.60%)	9 / 103 (8.74%)	
occurrences (all)	4	9	
Depression			
subjects affected / exposed	3 / 111 (2.70%)	9 / 103 (8.74%)	
occurrences (all)	3	9	
Musculoskeletal and connective tissue disorders			

Joint pain			
subjects affected / exposed	2 / 111 (1.80%)	0 / 103 (0.00%)	
occurrences (all)	2	0	
Muscle pain			
subjects affected / exposed	2 / 111 (1.80%)	1 / 103 (0.97%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2010	Inclusion of eligibility data on the Prestudy Form

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25738668