Clinical trial results:
A randomized phase II trial evaluating the endocrine activity and efficacy of neoadjuvant degarelix versus triptorelin in premenopausal patients receiving letrozole for locally advanced endocrine responsive breast cancer.

Summary

EudraCT number	2012-005326-29
Trial protocol	IT
Global end of trial date	25 August 2017

Results information

Result version number	v1 (current)
This version publication date	01 April 2020
First version publication date	01 April 2020

Trial information

Trial identification

Sponsor protocol code	IBCSG 41-13 TREND

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02005887
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 31389 93 91, regulatoryoffice@ibscg.org
Scientific contact	IBCSG Coordinating Center, International Breast Cancer Study Group (IBCSG), +41 31389 93 91, regulatoryoffice@ibscg.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	Final
Date of interim/final analysis	05 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 August 2017
Global end of trial reached?	Yes
Global end of trial date	25 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This trial evaluated neoadjuvant endocrine therapy (degarelix [GnRH antagonist] versus triptorelin [GnRH agonist]) in combination with letrozole as treatment for premenopausal women diagnosed with endocrine responsive breast cancer.

Protection of trial subjects:

- In compliance with GDPR.
- Adverse events were reported and in case of adverse events and treatment-related toxicities management guidance was provided in the study protocol to treat trial subjects in adequately manner.
- The safety of the trial treatment was regularly reviewed by the IBCSG Data Safety Monitoring Committee (DSMC).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2013
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	Italy: 51
Worldwide total number of subjects	51
EEA total number of subjects	51

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)	51
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was activated on 28 March 2013 and the first patient was enrolled on 24 February 2014. The trial was activated in seven participating centers in Italy. Three centers enrolled patients. Final enrollment was 51 patients. The study completed accrual on 10 January 2017 and closed on 12 January 2017.

Pre-assignment

Screening details:

Premenopausal patients with histologically confirmed primary breast cancer and with primary tumor which is ER+ and PgR+ (>50%) and HER2-negative or not amplified

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	triptorelin + letrozole

Arm description:

Triptorelin 3.75 mg i.m. on day 1 every 28 days for 6 cycles + letrozole 2.5 mg/day orally for 6 cycles

Arm type	Experimental
Investigational medicinal product name	Triptorelin
Investigational medicinal product code	
Other name	decapeptyl
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Triptorelin 3.75 mg injected into the muscle on day 1 every 28 days for 6 cycles (1 cycle= 28 days)

Arm title	degarelix + letrozole

Arm description:

Degarelix 240 mg s.c. on day 1 of cycle 1, followed by 80 mg s.c. on day 1 of cycles 2 to 6 + letrozole 2.5 mg every day orally for 6 cycles

Arm type	Experimental
Investigational medicinal product name	Degarelix
Investigational medicinal product code	
Other name	firmagon
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Degarelix 240 mg injected under the skin given as two injections of 120 mg on the first day of treatment, followed by injection of 80 mg on day 1 of cycles 2 to 6 (1 cycle=28 days)

Number of subjects in period 1	triptorelin + letrozole	degarelix + letrozole
Started	26	25
Completed	26	23
Not completed	0	2
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	triptorelin + letrozole
Reporting group description:	
Triptorelin 3.75 mg i.m. on day 1 every 28 days for 6 cycles + letrozole 2.5 mg/day orally for 6 cycles	
Reporting group title	degarelix + letrozole
Reporting group description:	
Degarelix 240 mg s.c. on day 1 of cycle 1, followed by 80 mg s.c. on day 1 of cycles 2 to 6 + letrozole 2.5 mg every day orally for 6 cycles	

Reporting group values	triptorelin + letrozole	degarelix + letrozole	Total
Number of subjects	26	25	51
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 Units: years			
median	44.0	45	
inter-quartile range (Q1-Q3)	42.2 to 47.5	42 to 50	-
Gender categorical Units: Subjects			
Female	26	25	51
Male	0	0	0
Region of Enrollment Units: Subjects			
Italy	26	25	51

End points

End points reporting groups

Reporting group title	triptorelin + letrozole
Reporting group description:	
Triptorelin 3.75 mg i.m. on day 1 every 28 days for 6 cycles + letrozole 2.5 mg/day orally for 6 cycles	
Reporting group title	degarelix + letrozole
Reporting group description:	
Degarelix 240 mg s.c. on day 1 of cycle 1, followed by 80 mg s.c. on day 1 of cycles 2 to 6 + letrozole 2.5 mg every day orally for 6 cycles	

Primary: Time to Optimal Ovarian Function Suppression

End point title	Time to Optimal Ovarian Function Suppression
End point description:	
Time from the first injection of degarelix or triptorelin to the first assessment of centrally assessed 17-β-estradiol (E2) level in the range of optimal ovarian function suppression (≤2.72 pg/mL or ≤10 pmol/L) during the 6 cycles of neoadjuvant treatments.	
End point type	Primary
End point timeframe:	
up to 24 weeks	

End point values	triptorelin + letrozole	degarelix + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: days				
median (confidence interval 95%)	14 (8 to 14)	3 (3 to 3)		

Statistical analyses

Statistical analysis title	Statistical analysis primary endpoint
Statistical analysis description:	
The primary endpoint will be compared between the two treatment arms using a stratified two-sample log-rank test, with age as stratification factor. The distribution of the primary endpoint will be summarized using the method of Kaplan-Meier and the two-sided 95% confidence interval (CI) for the difference in proportion of patients who achieve optimal ovarian function suppression between the two treatment arms at the end of the 1st, 2nd and 4th cycle will also be provided.	
Comparison groups	degarelix + letrozole v triptorelin + letrozole
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	3.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.65
upper limit	5.65

Secondary: Ki67 Proliferation Marker Changes

End point title	Ki67 Proliferation Marker Changes

End point description:

The percent change in Ki67 expression from pre-treatment diagnostic (baseline) biopsy to surgery, calculated as (surgery-baseline)/baseline*100

End point type	Secondary

End point timeframe:

Before day 1 of cycle 1 and surgery

End point values	triptorelin + letrozole	degarelix + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[1]	22[2]		
Units: Percentage change				
median (inter-quartile range (Q1-Q3))	-10.0 (-15.0 to -5.0)	-8.0 (-15.8 to -4.2)		

Notes:

[1] - Four patients are not evaluable

[2] - Four patients are not evaluable

Statistical analyses

No statistical analyses for this end point

Secondary: Preoperative Endocrine Prognostic Index (PEPI) Score

End point title	Preoperative Endocrine Prognostic Index (PEPI) Score

End point description:

Preoperative Endocrine Prognostic Index (PEPI) is the sum of the risk points (tumor size, nodal status, Ki67 level, ER status) with a 0-12 score representing the best prognostic feature (0 being the best score; 12 being the worst score), as previously determined to be associated with recurrence-free survival.

End point type	Secondary

End point timeframe:

After 24 weeks or the time of surgery

End point values	triptorelin + letrozole	degarelix + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23[3]		
Units: Scores on a scale				
median (inter-quartile range (Q1-Q3))	6.5 (4.0 to 7.0)	6.0 (4.0 to 7.0)		

Notes:

[3] - Two patients who did not have surgery were not evaluated

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall (Disease) Response

End point title	Best Overall (Disease) Response

End point description:

Based on WHO tumor measurement and response criteria [1], measured from the start of treatment across all time points until disease progression or the end of 6 cycles of neoadjuvant therapies, whichever comes first. Response was determined by the IBCSG Head of Medical Affairs. An internal review (IR) form was created to record the final determination on best overall response. Confirmation of partial or complete response by an additional scan was not required in this trial. Best overall response was assessed based on changes in tumor size from baseline to the assessments after 3 and after 6 cycles (denoted as day 1 of cycle 4 and prior to surgery respectively) as measured physically by caliper or ruler and as measured by breast tumor imaging (i.e., bilateral mammography and breast ultrasound).

End point type	Secondary

End point timeframe:

From day 1 of cycle 1 across all time points until disease progression

End point values	triptorelin + letrozole	degarelix + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: Percentage of patients				
number (confidence interval 90%)	46.2 (30.1 to 62.2)	44.0 (27.7 to 60.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With Node-negative Disease at Surgery

End point title	Percentage of Patients With Node-negative Disease at Surgery

End point description:

The number of lymph nodes assessed at surgery minus the number of positives nodes identified, equal to zero.

End point type	Secondary

End point timeframe:

During surgery, an average of 2 hours

End point values	triptorelin + letrozole	degarelix + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: Percentage of patients				
number (confidence interval 90%)	34.6 (19.3 to 50.0)	43.5 (26.5 to 60.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Who Underwent Breast-Conserving Surgery (BCS)

End point title	Percentage of Patients Who Underwent Breast-Conserving Surgery (BCS)

End point description:

Whether or not patient undergoes BCS (per Surgery form).

End point type	Secondary

End point timeframe:

During surgery, an average of 2 hours

End point values	triptorelin + letrozole	degarelix + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23[4]		
Units: Percentage of patients				
number (confidence interval 90%)	42.3 (26.4 to 58.2)	52.2 (35.0 to 69.3)		

Notes:

[4] - Two patients who did not have surgery were not evaluated

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-reported Symptoms (PRS) Outcomes

End point title	Patient-reported Symptoms (PRS) Outcomes

End point description:

The patient-reported symptoms (PRS) will be assessed using the Functional Assessment of Cancer Therapy Endocrine Subscale (FACT-ES) comprising 18 items (each has score range from 0 to 4) with a possible minimum total score of 0 and maximum total score of 72 (72 is best). Functional Assessment of Chronic Illness Therapy (FACIT) guidelines will be used for scoring and interpretation of the FACT-ES total score.

End point type	Secondary

End point timeframe:

At baseline, day 1 of cycle 2 and cycle 4 and prior to surgery; cycle 4 reported

End point values	triptorelin + letrozole	degarelix + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: Units on a scale				
number (confidence interval 90%)	64 (62 to 67)	62 (59 to 64)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) forms were submitted at the end of every cycle (28 days) and 30 days after surgery. All patients submitted AE data during 6 cycles of treatment period when available.

Adverse event reporting additional description:

Adverse events were collected using CTCAE v4.0. Each targeted AE will be classified according to the maximum grade of the event while on trial treatment (grade 0,1,2,3,4,5; where 0=no report). Other grade 3-5 AEs will be classified according to the maximum grade of any reported other AE.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	triptorelin + letrozole
Reporting group description: -	
Reporting group title	degarelix + letrozole

Reporting group description: -

Serious adverse events	triptorelin + letrozole	degarelix + letrozole	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	triptorelin + letrozole	degarelix + letrozole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 26 (88.46%)	23 / 25 (92.00%)	
Investigations			
Alanine aminotransferase			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hot flashes/flushes			
subjects affected / exposed	18 / 26 (69.23%)	20 / 25 (80.00%)	
occurrences (all)	18	23	
Hypertension			

subjects affected / exposed	1 / 26 (3.85%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 26 (11.54%)	1 / 25 (4.00%)	
occurrences (all)	3	1	
Injection site reaction			
subjects affected / exposed	0 / 26 (0.00%)	6 / 25 (24.00%)	
occurrences (all)	0	7	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 26 (3.85%)	4 / 25 (16.00%)	
occurrences (all)	1	4	
Reproductive system and breast disorders			
Vaginal dryness			
subjects affected / exposed	1 / 26 (3.85%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 26 (7.69%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Depression			
subjects affected / exposed	1 / 26 (3.85%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Insomnia			
subjects affected / exposed	3 / 26 (11.54%)	6 / 25 (24.00%)	
occurrences (all)	4	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 26 (53.85%)	8 / 25 (32.00%)	
occurrences (all)	16	9	
Myalgia			

subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 25 (4.00%) 1	

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/30589600