Clinical trial results:
A randomized phase II pilot study to evaluate safety and efficacy of the addition of vismodegib to standard neoadjuvant chemotherapy in triple negative breast cancer patients.

Summary

EudraCT number	2014-001287-35
Trial protocol	ES
Global end of trial date	13 November 2018

Results information

Result version number	v1 (current)
This version publication date	24 September 2021
First version publication date	24 September 2021
Summary attachment (see zip file)	SPANISH REPORT (20210409_Informe_Final_SHH-CM.pdf)

Trial information

Trial identification

Sponsor protocol code	SHH-CM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02694224
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Clínica Universidad de Navarra
Sponsor organisation address	Avda. Pío XII,36, Pamplona, Spain, 31008
Public contact	UCICEC, Clinica Universidad de Navarra, 34 948 25 54 00 1144, ucicec@unav.es
Scientific contact	UCICEC, Clinica Universidad de Navarra, 34 948 25 54 00 1144, ucicec@unav.es

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	09 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 November 2018
Global end of trial reached?	Yes
Global end of trial date	13 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety and efficacy of vismodegib with standard neoadjuvant chemotherapy in breast cancer patients based on the CTCAE v4 2010 scale.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2015
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	Spain: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	25
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Woman between 18 and 75 years.

Pre-assignment

Screening details:

Patients diagnosed with breast cancer (stages I-III) with triple negative subtype, who have not previously received chemotherapy or systemic therapy. In these patients, treatment with neoadjuvant chemotherapy established in the protocol is indicated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental group

Arm description:

19 patients were randomized, of whom 18 completed the treatment phase. These patients were administered the usual neoadjuvant treatment of Paclitaxel, sequenced to epirubicin and cyclophosphamide in combination with Vismodegib.

Arm type	Experimental
Investigational medicinal product name	Vismodegib
Investigational medicinal product code	
Other name	Erivedge
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

150 mg/day orally during the paclitaxel stage.
Vismodegib will be administered daily for 12 weeks (84 days), coinciding with the duration of paclitaxel treatment (21-day cycles, with administration on days 1, 8 and 15 of the cycle, 12 administrations).

Arm title	Control group

Arm description:

10 patients were randomized, of whom 9 completed the treatment. These patients are given neoadjuvant treatment of paclitaxel sequenced to epirubicin plus cyclophosphamide. Two to three weeks would pass between the last cycle of paclitaxel and the start of anthracyclines.

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Weekly administration at a dose of 80 mg/m2 intravenously on days 1, 8 and 15 of each 21-day cycle (for 12 weeks).

Investigational medicinal product name	Epirubicina
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Injection

Dosage and administration details:

Intravenous route at a dose of 90 mg/m2. A total of 4 doses will be received every 2 weeks with granulocyte and monocyte factor support. Administered in combination with cyclophosphamide to all randomized patients.

Investigational medicinal product name	Ciclofosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Injection

Dosage and administration details:

Intravenous route at a dose of 600 mg/m2. A total of 4 doses will be received every 2 weeks with granulocyte and monocyte factor support. It is administered in combination with epirubicin to all randomized patients.

Number of subjects in period 1	Experimental group	Control group
Started	19	9
Completed	18	9
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Experimental group
Reporting group description:	
19 patients were randomized, of whom 18 completed the treatment phase. These patients were administered the usual neoadjuvant treatment of Paclitaxel, sequenced to epirubicin and cyclophosphamide in combination with Vismodegib.	
Reporting group title	Control group
Reporting group description:	
10 patients were randomized, of whom 9 completed the treatment. These patients are given neoadjuvant treatment of paclitaxel sequenced to epirubicin plus cyclophosphamide. Two to three weeks would pass between the last cycle of paclitaxel and the start of anthracyclines.	

Reporting group values	Experimental group	Control group	Total
Number of subjects	19	9	28
Age categorical Units: Subjects			
Adults (18-64 years)			0
From 65-84 years			0
Age continuous Units: years			
arithmetic mean	53.6	49.1	
standard deviation	± 9.3	± 9.7	-
Gender categorical Units: Subjects			
Female	19	9	28
Male	0	0	0

End points

End points reporting groups

Reporting group title	Experimental group

Reporting group description:

19 patients were randomized, of whom 18 completed the treatment phase. These patients were administered the usual neoadjuvant treatment of Paclitaxel, sequenced to epirubicin and cyclophosphamide in combination with Vismodegib.

Reporting group title	Control group

Reporting group description:

10 patients were randomized, of whom 9 completed the treatment. These patients are given neoadjuvant treatment of paclitaxel sequenced to epirubicin plus cyclophosphamide. Two to three weeks would pass between the last cycle of paclitaxel and the start of anthracyclines.

Primary: Safety and efficacy

End point title	Safety and efficacy

End point description:

Efficacy is analyzed by pathological complete response (pCR), which is determined by Miller & Paine calssification evaluated after surgery. In the control group 67% of patients were found to have a pCR, while in the experimental group 56% of patients obtained pCR. Fisher's exact test was used to determine a possible relationship between the group and having pCR or not. A p-value = 0.69 was obtained, which is not significant, so there is no statistical evidence to affirm that there are differences between the two variables.

End point type	Primary

End point timeframe:

Markers of safety ans efficacy will be collected whith each systemic therapy. Toxicity will be evaluated based on CTCAE v4 2010 scale.

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	9		
Units: patients				
number (confidence interval 95%)				
Pathological complete response (pCR)	0.53 (0.36 to 0.84)	0.67 (0.31 to 0.91)		

Statistical analyses

Statistical analysis title	Relationship between groups
Comparison groups	Experimental group v Control group

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The description of AEs was coded using the PT and SOC level of the MedDRA medical dictionary version 22.0.

Adverse event reporting additional description:

The CRF records the description, start date, end date, intensity, relationship with treatment, expected, evolution, action taken and whether the adverse events are serious or not.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Experimental group

Reporting group description: -

Reporting group title	Control group

Reporting group description: -

Serious adverse events	Experimental group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 19 (26.32%)	0 / 9 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	2 / 19 (10.53%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gatrointestinal disorders			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Infections and infestations			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (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: 1 %

Non-serious adverse events	Experimental group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)	9 / 9 (100.00%)	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	4 / 19 (21.05%)	1 / 9 (11.11%)	
occurrences (all)	4	1	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	17 / 19 (89.47%)	8 / 9 (88.89%)	
occurrences (all)	17	8	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	7 / 19 (36.84%)	4 / 9 (44.44%)	
occurrences (all)	7	4	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	4 / 19 (21.05%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			

subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	15 / 19 (78.95%)	6 / 9 (66.67%)	
occurrences (all)	15	6	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	5 / 19 (26.32%)	6 / 9 (66.67%)	
occurrences (all)	5	6	
Eye disorders			
Eye disorders			
subjects affected / exposed	1 / 19 (5.26%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	14 / 19 (73.68%)	8 / 9 (88.89%)	
occurrences (all)	14	8	
Skin and subcutaneous tissue disorders			
Skin and subcutaneus tissue disorders			
subjects affected / exposed	16 / 19 (84.21%)	8 / 9 (88.89%)	
occurrences (all)	16	8	
Hyperpigmentation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	1 / 19 (5.26%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	12 / 19 (63.16%)	2 / 9 (22.22%)	
occurrences (all)	12	2	
Infections and infestations			
Infections and infestations			

subjects affected / exposed occurrences (all)	4 / 19 (21.05%) 4	1 / 9 (11.11%) 1	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	 5 / 19 (26.32%) 5	 3 / 9 (33.33%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2016	new protocol version, Version 3
21 September 2016	new protocol version. Version 4

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported