Clinical trial results:
A Multicentre Phase 2 Study of SFX-01 Treatment and Evaluation in Patients with Estrogen Receptor (ER) Positive and Human Epidermal Growth Factor Receptor 2 (HER2) Negative Metastatic Breast Cancer Progressing on either an Aromatase Inhibitor (AI) or Tamoxifen or Fulvestrant

Summary

EudraCT number	2015-004851-28
Trial protocol	GB ES FR
Global end of trial date	10 January 2019

Results information

Result version number	v1 (current)
This version publication date	29 February 2020
First version publication date	29 February 2020

Trial information

Trial identification

Sponsor protocol code	EVG001BC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02970682
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Evgen Pharma PLC
Sponsor organisation address	Liverpool Science Park, Innovation Centre 2, 146 Brownlow Hill, Liverpool, United Kingdom, L3 5RF
Public contact	Clinical Development Officer, Evgen Pharma PLC, 44 1625466591, enquiries@evgen.com
Scientific contact	Clinical Development Officer, Evgen Pharma PLC, 44 1625466591, enquiries@evgen.com

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	08 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2019
Global end of trial reached?	Yes
Global end of trial date	10 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To determine the safety and tolerability of SFX-01 in combination with AI, tamoxifen and fulvestrant
2. To determine clinical benefit rate (CBR) (complete response [CR] + partial response [PR] + stable disease [SD]) at 24 weeks using Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1)

Protection of trial subjects:

Trial subjects were only eligible if they met all 17 inclusion criteria and were excluded for any one of 12 reasons. All patients had to sign an informed consent document, indicating that they understood the purpose of, and procedures required for the study and were willing to participate in the study. A patient could withdraw from the study at any time, and the physician responsible for the patient's wellbeing could also withdraw the patient at any time for an appropriate medical reason. Withdrawn patients were followed up for safety by the site staff. If a patient prematurely discontinued treatment, the reason for discontinuation was recorded.

Safety was assessed by means of clinical examination, vital signs (weight, heart rate, temperature, blood pressure and respiratory rate), performance status, laboratory evaluations (clinical chemistry and haematology), electrocardiograms (ECGs), recording of concurrent illness/therapy and documenting AEs.

Background therapy:

This study was a multi-centre study conducted over a 2-year period. Patients needed to have histologically confirmed ER-positive, HER2-negative, metastatic or locally advanced breast cancer (MBC) with at least 1 site of measurable disease. They previously were to be on either a third generation AI, tamoxifen or fulvestrant and had to have documented evidence of PD immediately prior to entry into this study, but were suitable for continuing the endocrine therapy (ET) they had progressed on according to the treating clinician. Patients continued to receive the same endocrine treatment with the addition of SFX-01.

Evidence for comparator:

Not applicable

Actual start date of recruitment	22 December 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	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	France: 7

Worldwide total number of subjects	46
EEA total number of subjects	46

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)	27
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was a multi-centre study conducted over a 2-year period. Patients were recruited from those attending sites in the UK, France, Belgium and Spain for treatment of MBC.

Pre-assignment

Screening details:

The Screening Phase was up to 28 days prior to enrolment. Patients previously were to be on either a third generation AI, tamoxifen or fulvestrant and had to have documented evidence of PD, but were suitable for continuing ET according to the treating clinician. Patients continued to receive the same treatment with the addition of SFX-01

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Aromatase inhibitor plus SFX-01

Arm type	Experimental
Investigational medicinal product name	Sulforadex
Investigational medicinal product code	SFX-01
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

300mg SFX-01, one capsule taken twice daily, 12 hours apart after food, preferably within 2 hours of eating.
Aromatase inhibitor continued at the same dose prior to entry into the study.

Arm title	Arm B

Arm description:

Tamoxifen plus SFX-01

Arm type	Experimental
Investigational medicinal product name	Sulforadex
Investigational medicinal product code	SFX-01
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

300mg SFX-01, one capsule taken twice daily, 12 hours apart after food, preferably within 2 hours of eating.
Tamoxifen continued at the same dose prior to entry into the study.

Arm title	Arm C

Arm description:

Fulvestrant plus SFX 01

Arm type	Experimental

Investigational medicinal product name	Sulforadex
Investigational medicinal product code	SFX-01
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

300mg SFX-01, one capsule taken twice daily, 12 hours apart after food, preferably within 2 hours of eating.
Fulvestrant continued at 500mg injected intramuscularly every 28 days.

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	31	8	7
Completed	7	4	1
Not completed	24	4	6
Consent withdrawn by subject	1	-	-
Patient choice: progressive disease & AEs	2	-	-
Adverse event, non-fatal	1	-	-
progressive disease	19	4	6
noncompliance/protocol violation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Aromatase inhibitor plus SFX-01	
Reporting group title	Arm B
Reporting group description:	
Tamoxifen plus SFX-01	
Reporting group title	Arm C
Reporting group description:	
Fulvestrant plus SFX 01	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	31	8	7
Age categorical			
Age category at study entry			
Units: Subjects			
Adults (18-64 years)	16	6	5
From 65-84 years	15	2	2
Age continuous			
Age at study entry			
Units: years			
median	64	55	62
full range (min-max)	43 to 82	45 to 81	55 to 77
Gender categorical			
Female only			
Units: Subjects			
Female	31	8	7
Male	0	0	0

Reporting group values	Total		
Number of subjects	46		
Age categorical			
Age category at study entry			
Units: Subjects			
Adults (18-64 years)	27		
From 65-84 years	19		
Age continuous			
Age at study entry			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Female only			
Units: Subjects			
Female	46		
Male	0		

Subject analysis sets	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) included all patients who received any amount of the IP (SFX 01 or ET).	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all patients who received at least 1 dose of study treatment (SFX-01).	

Reporting group values	FAS	Safety	
Number of subjects	46	46	
Age categorical			
Age category at study entry			
Units: Subjects			
Adults (18-64 years)	27	27	
From 65-84 years	19	19	
Age continuous			
Age at study entry			
Units: years			
median	63	63	
full range (min-max)	43 to 82	43 to 82	
Gender categorical			
Female only			
Units: Subjects			
Female	46	46	
Male	0	0	

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: Aromatase inhibitor plus SFX-01	
Reporting group title	Arm B
Reporting group description: Tamoxifen plus SFX-01	
Reporting group title	Arm C
Reporting group description: Fulvestrant plus SFX 01	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set (FAS) included all patients who received any amount of the IP (SFX 01 or ET).	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population included all patients who received at least 1 dose of study treatment (SFX-01).	

Primary: CBR (Clinical Benefit Rate)

End point title	CBR (Clinical Benefit Rate)[1]
End point description: Primary efficacy endpoint was CBR i.e. the percentage of patients who had a best overall response of confirmed CR or confirmed PR in the first 25 weeks, or who had SD for a minimum of 23 weeks according to RECIST v1.1, based on the investigator's assessments of radiological data.	
End point type	Primary
End point timeframe: CBR at Week 24 (FAS)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal stats analysis was pre-specified in the protocol / SAP

End point values	Arm A	Arm B	Arm C	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	31	8	7	46
Units: number of patients	7	4	0	11

Statistical analyses

No statistical analyses for this end point

Secondary: ORR (Objective Response Rate)

End point title	ORR (Objective Response Rate)
End point description: Objective response rate (ORR) at 24 weeks using RECIST v1.1	

End point type	Secondary

End point timeframe:

ORR at 24 weeks

End point values	Arm A	Arm B	Arm C	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	31	8	7	46
Units: Number of patients	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: CR (Complete Response)

End point title	CR (Complete Response)

End point description:

Complete response (CR) at 24 weeks using RECIST v1.1

End point type	Secondary

End point timeframe:

CR (complete response) at 24 weeks

End point values	Arm A	Arm B	Arm C	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	31	8	7	46
Units: Number of patients	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed PR (Partial Response)

End point title	Confirmed PR (Partial Response)

End point description:

Confirmed partial response (PR) at 24 weeks using RECIST v1.1

End point type	Secondary

End point timeframe:

Confirmed partial response (PR) at 24 weeks

End point values	Arm A	Arm B	Arm C	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	31	8	7	46
Units: Number of patients	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Unconfirmed PR (Partial Response)

End point title	Unconfirmed PR (Partial Response)

End point description:

Unconfirmed partial response (PR) at 24 weeks using RECIST v1.1

End point type	Secondary

End point timeframe:

Unconfirmed PR (partial response) at 24 weeks

End point values	Arm A	Arm B	Arm C	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	31	8	7	46
Units: Number of patients	0	1	1	2

Statistical analyses

No statistical analyses for this end point

Secondary: SD (Stable Disease)

End point title	SD (Stable Disease)

End point description:

Stable disease (SD) at 24 weeks using RECIST v1.1

End point type	Secondary

End point timeframe:

SD (stable disease) at 24 weeks

End point values	Arm A	Arm B	Arm C	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	31	8	7	46
Units: Number of patients	17	5	1	23

Statistical analyses

No statistical analyses for this end point

Secondary: PD (Progressive Disease)

End point title	PD (Progressive Disease)

End point description:

Progressive Disease (PD) at 24 weeks using RECIST v1.1

End point type	Secondary

End point timeframe:

PD (progressive disease) at 24 weeks

End point values	Arm A	Arm B	Arm C	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	31	8	7	46
Units: Number of patients	13	2	4	19

Statistical analyses

No statistical analyses for this end point

Secondary: Missing

End point title	Missing

End point description:

Missing RECIST v 1.1 tumor assessment response data at 24 weeks.

End point type	Secondary

End point timeframe:

Missing at 24 weeks

End point values	Arm A	Arm B	Arm C	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	31	8	7	46
Units: Number of Patients	1	0	1	2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 week study period plus 30 days after last dose of SFX-01 + ET

Adverse event reporting additional description:

All AEs were recorded, with details of the duration and the severity of each episode, the action taken with respect to IP, investigator's evaluation of its relationship to IP and the patient outcome. The intensity (severity of the AE) was assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Safety

Reporting group description: -

Serious adverse events	Safety		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 46 (21.74%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Fibrin D dimer increased			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ligament sprain			

subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract stoma complication				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Spinal cord compression				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Condition aggravated				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal distension				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				

subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pleuritic pain				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 46 (97.83%)		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 46 (13.04%)		
occurrences (all)	7		
Alanine aminotransferase increased			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	5		
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	6		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Platelet count decreased			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Weight decreased			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Dysgeusia			

subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 46 (19.57%)		
occurrences (all)	13		
Asthenia			
subjects affected / exposed	8 / 46 (17.39%)		
occurrences (all)	9		
Pain			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	7		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	25 / 46 (54.35%)		
occurrences (all)	28		
Dyspepsia			
subjects affected / exposed	15 / 46 (32.61%)		
occurrences (all)	17		
Diarrhoea			
subjects affected / exposed	12 / 46 (26.09%)		
occurrences (all)	12		
Vomiting			
subjects affected / exposed	10 / 46 (21.74%)		
occurrences (all)	11		
Abdominal pain			
subjects affected / exposed	7 / 46 (15.22%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	4		
Gastrooesophageal reflux disease			

subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all)	4 / 46 (8.70%) 4 3 / 46 (6.52%) 4 3 / 46 (6.52%) 3		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 4 / 46 (8.70%) 4		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 4 / 46 (8.70%) 4		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 10 / 46 (21.74%) 10 5 / 46 (10.87%) 7 5 / 46 (10.87%) 5 3 / 46 (6.52%) 4		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 6 / 46 (13.04%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2016	Amendment 01, Version 2.0 Inclusion criterion no. 12 revised to state that no more than 3 prior lines of ET for the MBC
30 August 2016	Amendment 02, Version 3.0 Added a pregnancy test as study Baseline Visit to the current pregnancy tests at Visit 2 and Visit 11 Amended schedule of events to include the Visit 11 pregnancy test and updated the description of Visit 11 assessments
07 October 2016	Amendement 03, Version 4.0 Removed tumour biopsy at week 16 Three exploratory objectives (based on: pharmacogenomics, tumour tissue or whole blood samples; liquid biopsy; proteomics) were deleted Made provision for historical paraffin embedded tissue block (or slides derived from this) if available from a previous tumour biopsy to be collected at screening from consented patients Made provision for patients who are receiving clinical benefit to continue to receive SFX-01 after week 24

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.

The reported results only present the data from the 24-week main study period. Data from patients who continued SFX-01 + endocrine therapy beyond 24 weeks in the extended use phase of the study are not presented.

Notes: