Clinical trial results:
A Phase 2, Multicenter Study of the Effect of the Addition of SNDX-275 to Continued Aromatase Inhibitor (AI) Therapy in Postmenopausal Women with ER+ Breast Cancer Whose Disease is Progressing

Summary

EudraCT number	2007-006415-23
Trial protocol	GB IE
Global end of trial date	24 November 2009

Results information

Result version number	v1
This version publication date	25 June 2022
First version publication date	25 June 2022

Trial information

Trial identification

Sponsor protocol code	SNDX-275-0303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00828854
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Syndax Pharmaceuticals, Inc.
Sponsor organisation address	35 Gatehouse Drive, Building D, Floor 3, Waltham, MA, United States, 02451
Public contact	Main Telephone Number, Syndax Pharmaceuticals, Inc., +1 781-419-1400, clinicaltrials@syndax.com
Scientific contact	Main Telephone Number, Syndax Pharmaceuticals, Inc., +1 781-419-1400, clinicaltrials@syndax.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	24 November 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 November 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the tumor responses to SNDX-275 in combination with continued AI therapy as measured by clinical benefit rate (CBR) during the first 6 cycles of study treatment, that is, complete response (CR), partial response (PR), or stable disease (SD) for at least 6 months.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2008
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	United Kingdom: 18
Country: Number of subjects enrolled	Ireland: 9
Worldwide total number of subjects	27
EEA total number of subjects	9

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)	7
From 65 to 84 years	20

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 8 investigative sites in the United Kingdom (UK) and Ireland from 1 October 2008 to 24 November 2009.

Pre-assignment

Screening details:

Participants with a diagnosis of estrogen receptor-positive (ER+) breast cancer whose disease was progressing were enrolled to receive entinostat 5 milligrams (mg) in combination with continued AI therapy.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study.

Arms

Arm title	Entinostat 5 mg + AI

Arm description:

Entinostat 5 mg tablet orally every week on Days 1, 8, 15 and 22 of each 28-day treatment cycle in combination with continued treatment with AI therapy at labeled dose and schedule until disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Entinostat
Investigational medicinal product code	
Other name	SNDX-275
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Entinostat 5 mg per oral (PO) every week

Investigational medicinal product name	Aromatase Inhibitor Therapy
Investigational medicinal product code	
Other name	AI Therapy
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AI therapy at labeled dose and schedule as prescribed in clinical practice. AI therapies included: Arimidex (anastrozole) 1 mg/day PO, Fermara (letrozole) 2.5 mg/day PO, Aromasin (exemestane) 25 mg/day PO.

Number of subjects in period 1	Entinostat 5 mg + AI
Started	27
Completed	0
Not completed	27
Adverse event, non-fatal	9
Reason Not Specified	1
Disease Progression	17

Baseline characteristics

Reporting groups	
Reporting group title	Entinostat 5 mg + AI
Reporting group description:	
Entinostat 5 mg tablet orally every week on Days 1, 8, 15 and 22 of each 28-day treatment cycle in combination with continued treatment with AI therapy at labeled dose and schedule until disease progression or unacceptable toxicity.	

Reporting group values	Entinostat 5 mg + AI	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	7	7	
From 65-84 years	20	20	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	68		
standard deviation	± 7.0	-	
Gender categorical Units: Subjects			
Female	27	27	
Male	0	0	
Eastern Cooperative Oncology Group (ECOG) Status			
ECOG performance status is an assessment of a participant's general well-being and activities of daily of life. Scores range from 0=perfect health (asymptomatic; able to carry out activities without restriction) to 5=death.			
Units: Subjects			
Score=0	9	9	
Score=1	18	18	
Age, Customized Units: Subjects			
45 to 64 years	7	7	
65 to 74 years	15	15	
75 years and older	5	5	
Race (National Institutes of Health/Office of Management and Budget) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	

Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	26	26	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Entinostat 5 mg + AI
Reporting group description:	
Entinostat 5 mg tablet orally every week on Days 1, 8, 15 and 22 of each 28-day treatment cycle in combination with continued treatment with AI therapy at labeled dose and schedule until disease progression or unacceptable toxicity.	
Subject analysis set title	Per-protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants from the full analysis who met eligibility criteria, completed at least 2 cycles and who had baseline and post-baseline tumor assessments.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All eligible participants who signed informed consent.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All participants who received at least 1 dose of study drug.	

Primary: Clinical Benefit Rate

End point title	Clinical Benefit Rate[1]
End point description:	
CBR is defined as the percentage of participants who achieved CR or PR or SD for 6 months as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. CR is defined as the disappearance of all target lesions. PR is defined as at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum LD since the treatment started.	
End point type	Primary
End point timeframe:	
6 months	

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: Only the 95% confidence interval is reported for this end point.

End point values	Per-protocol Set			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: Percentage of Participants				
number (confidence interval 95%)	15.4 (4.4 to 34.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS is defined as the number of months from the date of randomization to the earlier of PD or death due to any cause.

End point type	Secondary

End point timeframe:

From date of randomization to discontinuation due to disease progression or death up to primary completion date (Median follow-up 7.4 months)

End point values	Per-protocol Set			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: Months				
median (confidence interval 95%)	3.9 (1.9 to 5.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) During the First 6 Cycles of Study Treatment

End point title	Objective Response Rate (ORR) During the First 6 Cycles of Study Treatment

End point description:

ORR is defined as the percentage of participants with response during treatment classified as CR or PR, as assessed by the investigator based on RECIST, version 1.0. CR is defined as the disappearance of all target lesions. PR is defined as at least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.

End point type	Secondary

End point timeframe:

From date of randomization to discontinuation due to disease progression or intolerable adverse event (AE) up to primary completion date (Median follow-up 7.4 months)

End point values	Per-protocol Set			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: Percentage of Participants				
number (confidence interval 95%)	3.9 (0.1 to 19.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With AEs

End point title	Number of Participants With AEs

End point description:

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. Worsening of a pre-existing medical condition was considered an AE if there was either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes. Abnormal clinical laboratory findings determined by the investigator to be clinically significant were recorded as AEs.

End point type	Secondary

End point timeframe:

Up to 8, 28-day cycles + 30 days (approximately 254 days)

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: Participants	27			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 8, 28-day cycles + 30 days (Approximately 254 days)

Adverse event reporting additional description:

Safety Set included all participants who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	Entinostat 5 mg + AI

Reporting group description:

Entinostat 5 mg tablet orally every week on Days 1, 8, 15 and 22 of each 28-day treatment cycle in combination with continued treatment with AI therapy at labeled dose and schedule until disease progression or unacceptable toxicity.

Serious adverse events	Entinostat 5 mg + AI		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 27 (55.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 27 (3.70%)		
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 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Hypotension				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure congestive				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Convulsion				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
VIth nerve paralysis				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				

subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalemia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Entinostat 5 mg + AI		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Blood albumin decreased			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Blood potassium increased			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Blood urea increased			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3		
Haemoglobin decreased subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 6		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Neutrophil count decreased subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 5		
Platelet count decreased subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 8		
Weight decreased subjects affected / exposed occurrences (all)	11 / 27 (40.74%) 15		
White blood cell count decreased subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 8		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Nervous system disorders Lethargy subjects affected / exposed occurrences (all)	8 / 27 (29.63%) 11		
Dizziness subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3		
Paraesthesia subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	10		
Thrombocytopenia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	15 / 27 (55.56%)		
occurrences (all)	33		
Pain			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	8		
Oedema peripheral			
subjects affected / exposed	10 / 27 (37.04%)		
occurrences (all)	11		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	13 / 27 (48.15%)		
occurrences (all)	22		
Dyspepsia			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	9		
Eructation			

subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	6		
Lip dry			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	15 / 27 (55.56%)		
occurrences (all)	26		
Vomiting			
subjects affected / exposed	7 / 27 (25.93%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	7 / 27 (25.93%)		
occurrences (all)	7		
Cough			
subjects affected / exposed	7 / 27 (25.93%)		
occurrences (all)	8		
Pleural effusion			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Purpura			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Psychiatric disorders			

Depressed mood subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 3 3 / 27 (11.11%) 5		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 4 / 27 (14.81%) 4 5 / 27 (18.52%) 6 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2		
Infections and infestations Cellulitis subjects affected / exposed occurrences (all) Lower respiratory tract infection subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2 4 / 27 (14.81%) 4		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	 4 / 27 (14.81%) 5		

Decreased appetite subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4		
Hypokalaemia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2008	• The number of participating sites was increased from 6 in the UK to between 10 and 13 in the UK and Ireland. • Physical examination was added to the Day 1 visit assessments. • Compliance assessments were added to the schedule of observations.
08 October 2008	• Ancillary study of markers of bone turnover was restricted to participants who had never received a bisphosphonate. • Inclusion criterion relating to a measurable lesion was amended as follows: if the only measurable lesion was located in a previously irradiated area, the lesion must have demonstrated progression according to RECIST criteria. • Exclusion criterion addressing concurrent medical conditions was expanded to include myocardial infarction or thromboembolic events and specificity relating to prior malignancies. • The maximum treatment duration of 6 cycles was removed. • Overall survival was added as an exploratory endpoint. • 12-lead electrocardiogram was added at each cycle and end-of-treatment. • Sampling times for serum marker of bone turnover, urine marker of bone turnover, and tumor markers were expanded. • Independent Data Monitoring Board provision was added to monitor safety and efficacy on an ongoing basis. • Provision for a planned interim analysis of efficacy was added (but with no early stopping contingency).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported