



## Clinical trial results:

### An Open-label Phase 2 Study of MLN0128 (A TORC1/2 Inhibitor) in Combination With Fulvestrant in Women With ER-Positive/HER2-Negative Advanced or Metastatic Breast Cancer That Has Progressed During or After Aromatase Inhibitor Therapy

#### Summary

EudraCT number	2015-003612-20
Trial protocol	ES
Global end of trial date	25 November 2019

#### Results information

Result version number	v1 (current)
This version publication date	06 December 2020
First version publication date	06 December 2020

#### Trial information

##### Trial identification

Sponsor protocol code	C31006
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02756364
WHO universal trial number (UTN)	U1111-1174-2165

Notes:

##### Sponsors

Sponsor organisation name	Millennium Pharmaceuticals, Inc.
Sponsor organisation address	40 Lansdowne Street, Cambridge, MA, United States, 02139
Public contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.com
Scientific contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	25 November 2019
Is this the analysis of the primary completion data?	No

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Global end of trial reached?	Yes
Global end of trial date	25 November 2019
Was the trial ended prematurely?	No

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Notes:

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**General information about the trial**

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Main objective of the trial:

The main objective of this study is to compare the progression free survival (PFS) of participants treated with the combination of fulvestrant plus daily sapanisertib and fulvestrant plus weekly sapanisertib versus participants treated with single-agent fulvestrant.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Spain: 90
Country: Number of subjects enrolled	United States: 51
Worldwide total number of subjects	141
EEA total number of subjects	90

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Notes:

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**Subjects enrolled per age group**

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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)	96
From 65 to 84 years	45
85 years and over	0

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## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 50 investigative sites in Spain and the United States from 28 July 2016 to 25 November 2019. After all data was collected and participants were transitioned to post-trial access, the Sponsor stopped the study site, defined as 'Site terminated by the Sponsor'.

### Pre-assignment

Screening details:

Female participants with a diagnosis of estrogen receptor (ER)-positive/human epidermal growth factor receptor-2 (HER2)-negative advanced or metastatic breast cancer that has progressed during or after aromatase inhibitor therapy were enrolled in 1:1:1 ratio to receive fulvestrant, fulvestrant + sapanisertib QD and fulvestrant + sapanisertib QW.

### 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
<b>Arm title</b>	Arm A: Fulvestrant 500 mg

Arm description:

Fulvestrant 500 mg, intramuscularly (IM), once on Days 1 and 15 in Cycle 1, and then on Day 1 of each subsequent 28-day cycle until progressive disease, unacceptable toxicity, or withdrawal of consent (Median duration of treatment was 16.0 weeks).

Arm type	Active comparator
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Fulvestrant IM injection.

<b>Arm title</b>	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD
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Arm description:

Fulvestrant 500 mg, IM, once on Days 1 and 15 in Cycle 1, and then on Day 1 of each subsequent 28-day cycle along with the sapanisertib 4 mg, capsules, orally, once daily in each 28-day treatment cycle until progressive disease, unacceptable toxicity, or withdrawal of consent (Median duration of treatment was 20.1 and 20.3 weeks for fulvestrant and sapanisertib respectively).

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

Dosage and administration details:

Fulvestrant IM injection.

Investigational medicinal product name	Sapanisertib 4 mg QD
Investigational medicinal product code	
Other name	MLN0128
Pharmaceutical forms	Capsule

Routes of administration	Oral use
Dosage and administration details: Sapanisertib capsule.	

<b>Arm title</b>	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW
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Arm description:

Fulvestrant 500 mg, IM, once on Days 1 and 15 in Cycle 1, and then on Day 1 of each subsequent 28-day cycle along with sapanisertib 30 mg, capsule, orally, once weekly in each 28-day treatment cycle until progressive disease, unacceptable toxicity, or withdrawal of consent (Median duration of treatment was 17.0 weeks for fulvestrant and sapanisertib, each).

Arm type	Experimental
Investigational medicinal product name	Fulvestrant 500 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Fulvestrant IM injection.

Investigational medicinal product name	Sapanisertib 30 mg QW
Investigational medicinal product code	
Other name	MLN0128
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Sapanisertib capsule.

Number of subjects in period 1	Arm A: Fulvestrant 500 mg	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW
Started	46	47	48
Completed	0	0	0
Not completed	46	47	48
Adverse event, serious fatal	20	15	18
Site Terminated by Sponsor	24	30	21
Withdrawal by Patient	2	1	8
Lost to follow-up	-	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	Arm A: Fulvestrant 500 mg
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Reporting group description:

Fulvestrant 500 mg, intramuscularly (IM), once on Days 1 and 15 in Cycle 1, and then on Day 1 of each subsequent 28-day cycle until progressive disease, unacceptable toxicity, or withdrawal of consent (Median duration of treatment was 16.0 weeks).

Reporting group title	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD
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Reporting group description:

Fulvestrant 500 mg, IM, once on Days 1 and 15 in Cycle 1, and then on Day 1 of each subsequent 28-day cycle along with the sapanisertib 4 mg, capsules, orally, once daily in each 28-day treatment cycle until progressive disease, unacceptable toxicity, or withdrawal of consent (Median duration of treatment was 20.1 and 20.3 weeks for fulvestrant and sapanisertib respectively).

Reporting group title	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW
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Reporting group description:

Fulvestrant 500 mg, IM, once on Days 1 and 15 in Cycle 1, and then on Day 1 of each subsequent 28-day cycle along with sapanisertib 30 mg, capsule, orally, once weekly in each 28-day treatment cycle until progressive disease, unacceptable toxicity, or withdrawal of consent (Median duration of treatment was 17.0 weeks for fulvestrant and sapanisertib, each).

Reporting group values	Arm A: Fulvestrant 500 mg	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW
Number of subjects	46	47	48
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)	30	32	34
From 65-84 years	16	15	14
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	60.3	60.3	57.9
standard deviation	± 10.10	± 10.92	± 12.04
Sex: Female, Male Units: participants			
Female	46	47	48
Male	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	4	7
Not Hispanic or Latino	37	41	40
Unknown or Not Reported	4	2	1
Race (NIH/OMB)			

Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	44	45	44
More than one race	0	0	0
Unknown or Not Reported	1	2	3
Region of Enrollment			
Units: Subjects			
Spain	23	34	33
United States	23	13	15

<b>Reporting group values</b>	Total		
Number of subjects	141		
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)	96		
From 65-84 years	45		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: participants			
Female	141		
Male	0		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	16		
Not Hispanic or Latino	118		
Unknown or Not Reported	7		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	2		
White	133		
More than one race	0		
Unknown or Not Reported	6		
Region of Enrollment			

Units: Subjects			
Spain	90		
United States	51		

## End points

### End points reporting groups

Reporting group title	Arm A: Fulvestrant 500 mg
Reporting group description: Fulvestrant 500 mg, intramuscularly (IM), once on Days 1 and 15 in Cycle 1, and then on Day 1 of each subsequent 28-day cycle until progressive disease, unacceptable toxicity, or withdrawal of consent (Median duration of treatment was 16.0 weeks).	
Reporting group title	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD
Reporting group description: Fulvestrant 500 mg, IM, once on Days 1 and 15 in Cycle 1, and then on Day 1 of each subsequent 28-day cycle along with the sapanisertib 4 mg, capsules, orally, once daily in each 28-day treatment cycle until progressive disease, unacceptable toxicity, or withdrawal of consent (Median duration of treatment was 20.1 and 20.3 weeks for fulvestrant and sapanisertib respectively).	
Reporting group title	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW
Reporting group description: Fulvestrant 500 mg, IM, once on Days 1 and 15 in Cycle 1, and then on Day 1 of each subsequent 28-day cycle along with sapanisertib 30 mg, capsule, orally, once weekly in each 28-day treatment cycle until progressive disease, unacceptable toxicity, or withdrawal of consent (Median duration of treatment was 17.0 weeks for fulvestrant and sapanisertib, each).	

### Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description: PFS was defined as the time from the date of randomization to the date of first documentation of progressive disease (PD) or death due to any cause, whichever occurred first. Per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, PD was defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Full Analysis Set included all randomized participants.	
End point type	Primary
End point timeframe: Up to 40 months	

End point values	Arm A: Fulvestrant 500 mg	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	47	48	
Units: months				
median (confidence interval 95%)	3.5 (1.9 to 5.6)	7.2 (3.9 to 10.6)	5.6 (4.1 to 9.0)	

### Statistical analyses



<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Arm A: Fulvestrant 500 mg v Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.537
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.26

Notes:

[1] - HR obtained by stratified Cox proportional hazard model with treatment arm, original interactive response technology (IRT) stratification factors as covariates. A hazard ratio of <1 was considered statistically significant.

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Arm A: Fulvestrant 500 mg v Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority <sup>[2]</sup>
P-value	= 0.849
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.45

Notes:

[2] - HR obtained by stratified Cox proportional hazard model with treatment arm, original IRT stratification factors as covariates. A hazard ratio of <1 was considered statistically significant.

## Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS was defined as the time from the date of randomization to the date of death. 9999 indicates the median and upper limit of CI was not estimable due to fewer number of participants with event. 99999 indicates the upper limit of confidence interval (CI) was not estimable due to fewer number of participants with event. Full Analysis Set included all randomized participants.	
End point type	Secondary
End point timeframe:	
Up to 164 weeks	

<b>End point values</b>	Arm A: Fulvestrant 500 mg	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	47	48	
Units: months				
median (confidence interval 95%)	30.5 (21.5 to 99999)	9999 (29.9 to 9999)	34.2 (20.0 to 99999)	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Arm A: Fulvestrant 500 mg v Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
P-value	= 0.276
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.4

Notes:

[3] - HR obtained by stratified Cox proportional hazard model with treatment arm, original IRT stratification factors as covariates. A hazard ratio of <1 was considered statistically significant.

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Arm A: Fulvestrant 500 mg v Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority <sup>[4]</sup>
P-value	= 0.47
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.68

Notes:

[4] - HR obtained by stratified Cox proportional hazard model with treatment arm, original IRT stratification factors as covariates. A hazard ratio of <1 was considered statistically significant.

## Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)
End point description:	
TTP was defined as the time from the date of randomization to the date of first documentation of progression. Per RECIST v1.1, PD was defined as at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Full Analysis Set included all randomized participants.	
End point type	Secondary
End point timeframe:	
Up to 40 months	

End point values	Arm A: Fulvestrant 500 mg	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	47	48	
Units: months				
median (confidence interval 95%)	3.5 (1.9 to 5.6)	7.2 (5.5 to 10.6)	5.6 (4.1 to 9.0)	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Arm A: Fulvestrant 500 mg v Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority <sup>[5]</sup>
P-value	= 0.495
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.25

Notes:

[5] - HR obtained by stratified Cox proportional hazard model with treatment arm, original IRT stratification factors as covariates. A hazard ratio of <1 was considered statistically significant.

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Arm A: Fulvestrant 500 mg v Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority <sup>[6]</sup>
P-value	= 0.646
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.38

Notes:

[6] - HR obtained by stratified Cox proportional hazard model with treatment arm, original IRT stratification factors as covariates. A hazard ratio of <1 was considered statistically significant.

## Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)
End point description:	
ORR was defined as the percentage of participants who achieve a best response of complete response (CR) or partial response (PR) according to RECIST v1.1 criteria. CR was defined as disappearance of all target lesions, non-target lesions, no new lesions, and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, no progression in non-target lesion, and no new lesions. Safety Analysis Set included all participants who received at least 1 dose of study drug.	
End point type	Secondary
End point timeframe:	
Up to 40 months	

End point values	Arm A: Fulvestrant 500 mg	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	47	47	
Units: percentage of participants				
number (not applicable)	10.9	21.3	12.8	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm A: Fulvestrant 500 mg v Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD

Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority <sup>[7]</sup>
Parameter estimate	Odds ratio (OR)
Point estimate	2.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	7.29

Notes:

[7] - The odds ratio and 95% CIs were obtained using a stratified Cochran-Mantel-Haenszel model with the original IRT stratification factors (visceral metastases, previous sensitivity to hormonal therapy, and previous exposure to CDK4/6 inhibitors).

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Arm A: Fulvestrant 500 mg v Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	4.39

## Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)
End point description:	
CBR was defined as the percentage of participants who achieved a best response of CR, PR, or stable disease (SD) of any duration. CR was defined as disappearance of all target lesions, non-target lesions, no new lesions, and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, no progression in non-target lesion, and no new lesions. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Safety Analysis Set included all participants who received at least 1 dose of study drug.	
End point type	Secondary
End point timeframe:	
Up to 40 months	

<b>End point values</b>	Arm A: Fulvestrant 500 mg	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	47	47	
Units: percentage of participants				

number (not applicable)	60.9	74.5	66.0	
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## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW v Arm A: Fulvestrant 500 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	4.44

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Arm A: Fulvestrant 500 mg v Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	2.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	6.94

## Secondary: Percentage of Participants who Experienced at Least One Treatment-emergent Adverse Event (TEAE)

End point title	Percentage of Participants who Experienced at Least One Treatment-emergent Adverse Event (TEAE)
End point description:	
An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. Safety Analysis Set included all participants who received at least 1 dose of study drug.	
End point type	Secondary
End point timeframe:	
Up to 164 weeks	

<b>End point values</b>	Arm A: Fulvestrant 500 mg	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	47	47	
Units: percentage of participants				
number (not applicable)	89.1	100.0	100.0	

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 164 weeks

Adverse event reporting additional description:

At each visit investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by participant or observed by investigator was recorded, irrespective of relation to study treatment. All-cause Mortality (deaths) were collected in FAS population. AEs were collected in Safety Analysis Set.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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### Reporting groups

Reporting group title	Arm A: Fulvestrant 500 mg
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Reporting group description:

Fulvestrant 500 mg, intramuscularly (IM), once on Days 1 and 15 in Cycle 1, and then on Day 1 of each subsequent 28-days cycle until progressive disease, unacceptable toxicity, or withdrawal of consent (Median duration of treatment was 16.0 weeks).

Reporting group title	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW
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Reporting group description:

Fulvestrant 500 mg, IM, once on Days 1 and 15 in Cycle 1, and then on Day 1 of each subsequent 28-days cycle along with sapanisertib 30 mg, capsule, orally, once weekly in each 28-days treatment cycle until progressive disease, unacceptable toxicity, or withdrawal of consent (Median duration of treatment was 17.0 weeks for fulvestrant and sapanisertib, each).

Reporting group title	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD
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Reporting group description:

Fulvestrant 500 mg, IM, once on Days 1 and 15 in Cycle 1, and then on Day 1 of each subsequent 28-day cycle along with the sapanisertib 4 mg, capsules, orally, once daily in each 28-days treatment cycle until progressive disease, unacceptable toxicity, or withdrawal of consent (Median duration of treatment was 20.1 and 20.3 weeks for fulvestrant and sapanisertib respectively).

Serious adverse events	Arm A: Fulvestrant 500 mg	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 46 (17.39%)	8 / 47 (17.02%)	13 / 47 (27.66%)
number of deaths (all causes)	20	18	15
number of deaths resulting from adverse events			
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			



Pyrexia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 46 (4.35%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 46 (4.35%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Disorientation			
subjects affected / exposed	1 / 46 (2.17%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 46 (0.00%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 46 (2.17%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 46 (2.17%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	1 / 46 (2.17%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 46 (0.00%)	1 / 47 (2.13%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nausea			
subjects affected / exposed	0 / 46 (0.00%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 46 (2.17%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 46 (2.17%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 46 (0.00%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 46 (2.17%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 46 (2.17%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pyelonephritis acute			
subjects affected / exposed	0 / 46 (0.00%)	2 / 47 (4.26%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 46 (0.00%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			

subjects affected / exposed	1 / 46 (2.17%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	Arm A: Fulvestrant 500 mg	Arm C: Fulvestrant 500 mg + Sapanisertib 30 mg QW	Arm B: Fulvestrant 500 mg + Sapanisertib 4 mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 46 (82.61%)	47 / 47 (100.00%)	47 / 47 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 46 (15.22%)	5 / 47 (10.64%)	4 / 47 (8.51%)
occurrences (all)	26	16	8
Hot flush			
subjects affected / exposed	5 / 46 (10.87%)	1 / 47 (2.13%)	1 / 47 (2.13%)
occurrences (all)	5	1	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 46 (23.91%)	21 / 47 (44.68%)	13 / 47 (27.66%)
occurrences (all)	14	99	30
Pyrexia			
subjects affected / exposed	3 / 46 (6.52%)	4 / 47 (8.51%)	4 / 47 (8.51%)
occurrences (all)	3	7	5
Fatigue			
subjects affected / exposed	10 / 46 (21.74%)	11 / 47 (23.40%)	17 / 47 (36.17%)
occurrences (all)	11	29	27
Injection site pain			
subjects affected / exposed	5 / 46 (10.87%)	2 / 47 (4.26%)	2 / 47 (4.26%)
occurrences (all)	6	2	2
Pain			
subjects affected / exposed	1 / 46 (2.17%)	1 / 47 (2.13%)	3 / 47 (6.38%)
occurrences (all)	1	2	3
Malaise			

subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0	4 / 47 (8.51%) 25	1 / 47 (2.13%) 1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	7 / 46 (15.22%)	2 / 47 (4.26%)	5 / 47 (10.64%)
occurrences (all)	10	2	6
Cough			
subjects affected / exposed	5 / 46 (10.87%)	1 / 47 (2.13%)	7 / 47 (14.89%)
occurrences (all)	6	1	9
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 46 (10.87%)	2 / 47 (4.26%)	5 / 47 (10.64%)
occurrences (all)	5	2	5
Depression			
subjects affected / exposed	3 / 46 (6.52%)	3 / 47 (6.38%)	4 / 47 (8.51%)
occurrences (all)	3	3	5
Insomnia			
subjects affected / exposed	0 / 46 (0.00%)	4 / 47 (8.51%)	3 / 47 (6.38%)
occurrences (all)	0	4	3
Investigations			
Weight decreased			
subjects affected / exposed	1 / 46 (2.17%)	6 / 47 (12.77%)	11 / 47 (23.40%)
occurrences (all)	1	17	22
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 46 (4.35%)	6 / 47 (12.77%)	6 / 47 (12.77%)
occurrences (all)	2	8	8
Alanine aminotransferase increased			
subjects affected / exposed	2 / 46 (4.35%)	4 / 47 (8.51%)	6 / 47 (12.77%)
occurrences (all)	3	7	10
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 46 (2.17%)	3 / 47 (6.38%)	5 / 47 (10.64%)
occurrences (all)	1	8	7
Blood cholesterol increased			
subjects affected / exposed	0 / 46 (0.00%)	1 / 47 (2.13%)	5 / 47 (10.64%)
occurrences (all)	0	2	6

Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1	1 / 47 (2.13%) 1	3 / 47 (6.38%) 4
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0	2 / 47 (4.26%) 8	3 / 47 (6.38%) 8
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	9 / 46 (19.57%) 10	10 / 47 (21.28%) 20	4 / 47 (8.51%) 4
Dizziness subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1	5 / 47 (10.64%) 5	4 / 47 (8.51%) 10
Dysgeusia subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0	7 / 47 (14.89%) 7	8 / 47 (17.02%) 8
Somnolence subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0	0 / 47 (0.00%) 0	4 / 47 (8.51%) 4
Tremor subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0	1 / 47 (2.13%) 1	3 / 47 (6.38%) 7
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	3 / 46 (6.52%) 3	2 / 47 (4.26%) 4	3 / 47 (6.38%) 7
Ear and labyrinth disorders			
Tinnitus subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0	0 / 47 (0.00%) 0	3 / 47 (6.38%) 3
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	9 / 46 (19.57%) 10	41 / 47 (87.23%) 118	23 / 47 (48.94%) 40
Vomiting subjects affected / exposed occurrences (all)	4 / 46 (8.70%) 5	33 / 47 (70.21%) 152	14 / 47 (29.79%) 26

Diarrhoea			
subjects affected / exposed	1 / 46 (2.17%)	13 / 47 (27.66%)	24 / 47 (51.06%)
occurrences (all)	2	28	71
Stomatitis			
subjects affected / exposed	3 / 46 (6.52%)	15 / 47 (31.91%)	16 / 47 (34.04%)
occurrences (all)	3	26	25
Constipation			
subjects affected / exposed	8 / 46 (17.39%)	6 / 47 (12.77%)	4 / 47 (8.51%)
occurrences (all)	8	6	5
Dry mouth			
subjects affected / exposed	1 / 46 (2.17%)	3 / 47 (6.38%)	12 / 47 (25.53%)
occurrences (all)	1	3	13
Abdominal pain upper			
subjects affected / exposed	1 / 46 (2.17%)	9 / 47 (19.15%)	5 / 47 (10.64%)
occurrences (all)	1	10	18
Abdominal pain			
subjects affected / exposed	3 / 46 (6.52%)	4 / 47 (8.51%)	4 / 47 (8.51%)
occurrences (all)	3	4	6
Dyspepsia			
subjects affected / exposed	0 / 46 (0.00%)	3 / 47 (6.38%)	4 / 47 (8.51%)
occurrences (all)	0	4	4
Gastritis			
subjects affected / exposed	0 / 46 (0.00%)	2 / 47 (4.26%)	3 / 47 (6.38%)
occurrences (all)	0	2	5
Odynophagia			
subjects affected / exposed	0 / 46 (0.00%)	3 / 47 (6.38%)	1 / 47 (2.13%)
occurrences (all)	0	3	2
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 46 (0.00%)	7 / 47 (14.89%)	14 / 47 (29.79%)
occurrences (all)	0	13	34
Pruritus			
subjects affected / exposed	0 / 46 (0.00%)	8 / 47 (17.02%)	15 / 47 (31.91%)
occurrences (all)	0	13	24
Dry skin			



subjects affected / exposed	2 / 46 (4.35%)	3 / 47 (6.38%)	3 / 47 (6.38%)
occurrences (all)	2	3	5
Alopecia			
subjects affected / exposed	2 / 46 (4.35%)	3 / 47 (6.38%)	2 / 47 (4.26%)
occurrences (all)	2	3	2
Erythema			
subjects affected / exposed	0 / 46 (0.00%)	2 / 47 (4.26%)	3 / 47 (6.38%)
occurrences (all)	0	6	3
Rash maculo-papular			
subjects affected / exposed	0 / 46 (0.00%)	1 / 47 (2.13%)	3 / 47 (6.38%)
occurrences (all)	0	1	5
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 46 (0.00%)	3 / 47 (6.38%)	2 / 47 (4.26%)
occurrences (all)	0	3	3
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 46 (15.22%)	2 / 47 (4.26%)	6 / 47 (12.77%)
occurrences (all)	10	3	7
Pain in extremity			
subjects affected / exposed	6 / 46 (13.04%)	4 / 47 (8.51%)	3 / 47 (6.38%)
occurrences (all)	7	4	5
Arthralgia			
subjects affected / exposed	5 / 46 (10.87%)	3 / 47 (6.38%)	4 / 47 (8.51%)
occurrences (all)	6	5	4
Bone pain			
subjects affected / exposed	4 / 46 (8.70%)	4 / 47 (8.51%)	2 / 47 (4.26%)
occurrences (all)	4	4	2
Myalgia			
subjects affected / exposed	0 / 46 (0.00%)	4 / 47 (8.51%)	2 / 47 (4.26%)
occurrences (all)	0	9	3
Musculoskeletal pain			
subjects affected / exposed	4 / 46 (8.70%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences (all)	4	1	0
Musculoskeletal chest pain			

subjects affected / exposed	3 / 46 (6.52%)	1 / 47 (2.13%)	1 / 47 (2.13%)
occurrences (all)	3	1	1
Flank pain			
subjects affected / exposed	0 / 46 (0.00%)	3 / 47 (6.38%)	0 / 47 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 46 (4.35%)	7 / 47 (14.89%)	7 / 47 (14.89%)
occurrences (all)	2	9	7
Upper respiratory tract infection			
subjects affected / exposed	2 / 46 (4.35%)	1 / 47 (2.13%)	5 / 47 (10.64%)
occurrences (all)	2	1	5
Nasopharyngitis			
subjects affected / exposed	4 / 46 (8.70%)	3 / 47 (6.38%)	5 / 47 (10.64%)
occurrences (all)	4	4	5
Respiratory tract infection			
subjects affected / exposed	3 / 46 (6.52%)	1 / 47 (2.13%)	2 / 47 (4.26%)
occurrences (all)	3	1	2
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	10 / 46 (21.74%)	26 / 47 (55.32%)	27 / 47 (57.45%)
occurrences (all)	15	115	185
Decreased appetite			
subjects affected / exposed	5 / 46 (10.87%)	19 / 47 (40.43%)	15 / 47 (31.91%)
occurrences (all)	5	30	21
Dehydration			
subjects affected / exposed	0 / 46 (0.00%)	3 / 47 (6.38%)	1 / 47 (2.13%)
occurrences (all)	0	4	1

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2016	The primary purpose of this amendment was to make typographical changes.
07 March 2017	The primary purposes of this amendment were to update the dosing conditions for participants receiving QW sapanisertib in Arm C, to update the PK sampling schedule to reflect the dosing change in Arm C, to update the window for baseline disease assessment, to clarify procedures and/or timing for imaging collection and clinical laboratory evaluations, to update the inclusion and exclusion criteria, to update the safety reporting contact information, to clarify the guidance relating to dose modifications, to update the list of investigator responsibilities, to update references to study manuals throughout the protocol, and to update the participant enrollment plan.
02 October 2017	The primary purposes of this amendment were to update those sections affected by new nonclinical data for sapanisertib metabolism by specific cytochrome P-450 (CYP) isoforms. The study's exclusion criteria, list of prohibited concomitant medications, list of relevant CYP inhibitors and inducers, and dietary restrictions related to CYP inhibitors and inducers were updated accordingly. The number of study sites, recommendations for initiation of crossover treatment, and guidance for fasting serum glucose post-dose collection were also updated.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported