



Clinical trial results:

A phase I/II dose escalation and expansion study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK525762 in combination with fulvestrant in subjects with hormone receptor-positive/HER2-negative (HR+/HER2-) advanced or metastatic breast cancer

Summary

EudraCT number	2016-003074-40
Trial protocol	GB ES FR
Global end of trial date	19 July 2021

Results information

Result version number	v4 (current)
This version publication date	14 September 2022
First version publication date	13 October 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	201973
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom, TW8 9GS
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.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	Interim
Date of interim/final analysis	05 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2020
Global end of trial reached?	Yes
Global end of trial date	19 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main obj:Ph1-To determine recommended Ph2 dose of GSK525762,when given in combination with fulvestrant in women with advanced/metastatic hormone receptor positive human epidermal receptor 2 negative breast cancer (HR+/HER2-BC).Ph2-Evaluate effect of treatment with GSK525762&fulvestrant,when given in combination,on PFS in women with advanced/metastatic

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2017
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	Australia: 7
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	Canada: 30
Country: Number of subjects enrolled	Spain: 16
Worldwide total number of subjects	123
EEA total number of subjects	20

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)	96
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This is Phase I/II study of GSK525762 in combination with fulvestrant in participants with hormone receptor-positive/HER2-negative (HR+/HER2-) advanced/metastatic breast cancer.

Pre-assignment

Screening details:

Per protocol, an interim analysis was conducted during ph 1, and following assessment of data, ph 2 was not initiated. But, all existing participants receiving treatment in ph 1, deriving benefit were continued on study (at investigators decision), until progression or death/withdrawal. 124 participants were enrolled and 1 of them was not treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I-GSK525762 60 mg+FUL 500 mg (AI Failure)

Arm description:

Participants with aromatase inhibitor (AI) failure received GSK525762 60 milligrams (mg) tablet orally once daily and Fulvestrant (FUL) 500 mg was administered intramuscularly (IM) on days 1, 15, 29, and once monthly thereafter.

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 was available as clear, colorless to yellow, viscous liquid. Participants received fulvestrant intramuscularly on days 1, 15, 29 and once a month thereafter.

Investigational medicinal product name	GSK525762
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GSK525762 was available as white to slightly colored, round, biconvex tablet. Participants received GSK525762 orally once daily.

Arm title	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)
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Arm description:

Participants with Cyclin-Dependent Kinase (CDK4/6)/AI failure within 12 months received GSK525762 60 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.

Arm type	Experimental
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Investigational medicinal product name	GSK525762
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GSK525762 was available as white to slightly colored, round, biconvex tablet. Participants received GSK525762 orally once daily.

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

Dosage and administration details:

Fulvestrant was available as clear, colorless to yellow, viscous liquid. Participants received fulvestrant intramuscularly on days 1, 15, 29 and once a month thereafter.

Arm title	Phase I-GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure >= 12M)
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Arm description:

Participants with CDK4/6/AI failure >=12 months received GSK525762 60 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.

Arm type	Experimental
Investigational medicinal product name	GSK525762
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GSK525762 was available as white to slightly colored, round, biconvex tablet. Participants received GSK525762 orally once daily.

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

Dosage and administration details:

Fulvestrant was available as clear, colorless to yellow, viscous liquid. Participants received fulvestrant intramuscularly on days 1, 15, 29 and once a month thereafter.

Arm title	PhaseI-GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis
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Arm description:

Participants with CDK4/6/AI failure >=12 months with bone only disease received GSK525762 60 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.

Arm type	Experimental
Investigational medicinal product name	GSK525762
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GSK525762 was available as white to slightly colored, round, biconvex tablet. Participants received GSK525762 orally once daily.

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

Dosage and administration details:

Fulvestrant was available as clear, colorless to yellow, viscous liquid. Participants received fulvestrant intramuscularly on days 1, 15, 29 and once a month thereafter.

Arm title	Phase I-GSK525762 80mg + FUL 500 mg (AI Failure)
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Arm description:

Participants with AI failure received GSK525762 80 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.

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 was available as clear, colorless to yellow, viscous liquid. Participants received fulvestrant intramuscularly on days 1, 15, 29 and once a month thereafter.

Investigational medicinal product name	GSK525762
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GSK525762 was available as white to slightly colored, round, biconvex tablet. Participants received GSK525762 orally once daily.

Arm title	Phase I-GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)
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Arm description:

Participants with CDK4/6/AI failure received GSK525762 80 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.

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 was available as clear, colorless to yellow, viscous liquid. Participants received fulvestrant intramuscularly on days 1, 15, 29 and once a month thereafter.

Investigational medicinal product name	GSK525762
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GSK525762 was available as white to slightly colored, round, biconvex tablet. Participants received GSK525762 orally once daily.

Number of subjects in period 1	Phase I-GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I-GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure ≥ 12M)
Started	33	12	42
Completed	7	1	17
Not completed	26	11	25
Adverse event, serious fatal	11	9	12
Consent withdrawn by subject	1	-	1
Physician decision	2	-	3
Study terminated by Sponsor	9	1	9
Protocol specified Withdrawal criteria met	-	1	-
Unknown	3	-	-

Number of subjects in period 1	PhaseI-GSK525762 60+FUL500mg CDK4/6+AI Fail≥12M Bone only dis	Phase I-GSK525762 80mg + FUL 500 mg (AI Failure)	Phase I-GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)
Started	7	18	11
Completed	1	2	3
Not completed	6	16	8
Adverse event, serious fatal	2	10	5
Consent withdrawn by subject	1	-	1
Physician decision	-	1	-
Study terminated by Sponsor	3	3	2
Protocol specified Withdrawal criteria met	-	1	-
Unknown	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Phase I-GSK525762 60 mg+FUL 500 mg (AI Failure)
Reporting group description: Participants with aromatase inhibitor (AI) failure received GSK525762 60 milligrams (mg) tablet orally once daily and Fulvestrant (FUL) 500 mg was administered intramuscularly (IM) on days 1, 15, 29, and once monthly thereafter.	
Reporting group title	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)
Reporting group description: Participants with Cyclin-Dependent Kinase (CDK4/6)/AI failure within 12 months received GSK525762 60 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.	
Reporting group title	Phase I-GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure >= 12M)
Reporting group description: Participants with CDK4/6/AI failure >=12 months received GSK525762 60 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.	
Reporting group title	PhaseI-GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis
Reporting group description: Participants with CDK4/6/AI failure >=12 months with bone only disease received GSK525762 60 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.	
Reporting group title	Phase I-GSK525762 80mg + FUL 500 mg (AI Failure)
Reporting group description: Participants with AI failure received GSK525762 80 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.	
Reporting group title	Phase I-GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)
Reporting group description: Participants with CDK4/6/AI failure received GSK525762 80 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.	

Reporting group values	Phase I-GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I-GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure >= 12M)
Number of subjects	33	12	42
Age categorical			
The interim analysis failed to demonstrate clinically meaningful activity, hence Phase II was not initiated.			
Units: Participants			
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)	19	12	34
From 65-84 years	14	0	8
85 years and over	0	0	0

Age Continuous			
The interim analysis failed to demonstrate clinically meaningful activity, hence Phase II was not initiated.			
Units: years			
arithmetic mean	60.6	53.3	55.7
standard deviation	± 9.40	± 8.48	± 9.82
Sex: Female, Male			
The interim analysis failed to demonstrate clinically meaningful activity, hence Phase II was not initiated.			
Units: Participants			
Female	33	12	42
Male	0	0	0
Race/Ethnicity, Customized			
The interim analysis failed to demonstrate clinically meaningful activity, hence Phase II was not initiated.			
Units: Subjects			
Central south Asian Heritage	0	0	1
East Asian Heritage	7	2	8
Japanese Heritage	1	0	0
South East Asian Heritage	1	0	0
Black or African American	2	1	2
Arabic/North African Heritage	1	0	2
White/Caucasian/European Heritage	19	8	28
Multiple	1	1	0
Missing	1	0	1

Reporting group values	PhaseI-GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis	Phase I-GSK525762 80mg + FUL 500 mg (AI Failure)	Phase I-GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)
Number of subjects	7	18	11
Age categorical			
The interim analysis failed to demonstrate clinically meaningful activity, hence Phase II was not initiated.			
Units: Participants			
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)	5	15	11
From 65-84 years	2	3	0
85 years and over	0	0	0
Age Continuous			
The interim analysis failed to demonstrate clinically meaningful activity, hence Phase II was not initiated.			
Units: years			
arithmetic mean	58.7	54.4	51.5
standard deviation	± 7.97	± 8.45	± 12.04

Sex: Female, Male			
The interim analysis failed to demonstrate clinically meaningful activity, hence Phase II was not initiated.			
Units: Participants			
Female	7	18	11
Male	0	0	0
Race/Ethnicity, Customized			
The interim analysis failed to demonstrate clinically meaningful activity, hence Phase II was not initiated.			
Units: Subjects			
Central south Asian Heritage	0	0	0
East Asian Heritage	1	6	2
Japanese Heritage	0	0	0
South East Asian Heritage	0	0	1
Black or African American	1	1	1
Arabic/North African Heritage	0	0	0
White/Caucasian/European Heritage	5	11	7
Multiple	0	0	0
Missing	0	0	0

Reporting group values	Total		
Number of subjects	123		
Age categorical			
The interim analysis failed to demonstrate clinically meaningful activity, hence Phase II was not initiated.			
Units: Participants			
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	27		
85 years and over	0		
Age Continuous			
The interim analysis failed to demonstrate clinically meaningful activity, hence Phase II was not initiated.			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
The interim analysis failed to demonstrate clinically meaningful activity, hence Phase II was not initiated.			
Units: Participants			
Female	123		
Male	0		
Race/Ethnicity, Customized			
The interim analysis failed to demonstrate clinically meaningful activity, hence Phase II was not initiated.			
Units: Subjects			
Central south Asian Heritage	1		

East Asian Heritage	26		
Japanese Heritage	1		
South East Asian Heritage	2		
Black or African American	8		
Arabic/North African Heritage	3		
White/Caucasian/European Heritage	78		
Multiple	2		
Missing	2		

End points

End points reporting groups

Reporting group title	Phase I-GSK525762 60 mg+FUL 500 mg (AI Failure)
Reporting group description: Participants with aromatase inhibitor (AI) failure received GSK525762 60 milligrams (mg) tablet orally once daily and Fulvestrant (FUL) 500 mg was administered intramuscularly (IM) on days 1, 15, 29, and once monthly thereafter.	
Reporting group title	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)
Reporting group description: Participants with Cyclin-Dependent Kinase (CDK4/6)/AI failure within 12 months received GSK525762 60 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.	
Reporting group title	Phase I-GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure >= 12M)
Reporting group description: Participants with CDK4/6/AI failure >=12 months received GSK525762 60 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.	
Reporting group title	PhaseI-GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis
Reporting group description: Participants with CDK4/6/AI failure >=12 months with bone only disease received GSK525762 60 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.	
Reporting group title	Phase I-GSK525762 80mg + FUL 500 mg (AI Failure)
Reporting group description: Participants with AI failure received GSK525762 80 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.	
Reporting group title	Phase I-GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)
Reporting group description: Participants with CDK4/6/AI failure received GSK525762 80 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.	

Primary: Phase I: Number of participants with adverse events (AEs) and serious adverse events (SAEs)

End point title	Phase I: Number of participants with adverse events (AEs) and serious adverse events (SAEs) ^[1]
End point description: An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A SAE is defined as any untoward medical occurrence that, at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, any other situation such as important medical events according to medical or scientific judgement or is associated with liver injury and impaired liver function. Any other adverse event apart from SAE is considered as non-SAE. All Treated Population consisted of participants who received at least one dose of study treatment (GSK525762 or fulvestrant).	
End point type	Primary
End point timeframe: Up to 3 year and 8 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: There are no statistical data to report

End point values	Phase I- GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure >= 12M)	PhaseI- GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[2]	12 ^[3]	42 ^[4]	7 ^[5]
Units: Participants				
Non-serious AEs	33	12	42	7
SAEs	5	1	10	3

Notes:

[2] - All Treated Population

[3] - All Treated Population

[4] - All Treated Population

[5] - All Treated Population

End point values	Phase I- GSK525762 80mg + FUL 500 mg (AI Failure)	Phase I- GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[6]	11 ^[7]		
Units: Participants				
Non-serious AEs	18	11		
SAEs	6	2		

Notes:

[6] - All Treated Population

[7] - All Treated Population

Statistical analyses

No statistical analyses for this end point

Primary: Phase I: Number of participants with dose limiting toxicities (DLTs)

End point title	Phase I: Number of participants with dose limiting toxicities (DLTs) ^[8]
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End point description:

An event was considered DLT if it occurred within first 28 days of treatment and met one of following DLT criteria: Grade3 or greater neutropenia for ≥ 5 days, febrile neutropenia, Grade4 anemia of any duration, Grade4 thrombocytopenia of any duration or Grade3 thrombocytopenia with bleeding, alanine aminotransferase (ALT) > 3 times (x) upper limit of normal (ULN)+bilirubin $\geq 2 \times \text{ULN}$ ($> 35\%$ direct) or ALT between $3-5 \times \text{ULN}$ with bilirubin $< 2 \times \text{ULN}$ but with hepatitis symptoms or rash, Grade3 nausea,vomiting or diarrhea that did not improve within 72hour despite appropriate supportive treatment(s), Grade4 nausea,vomiting,or diarrhea, Grade3 hypertension (uncontrolled despite addition of upto 2 antihypertensive medications), Grade4 hypertension, other Grade3 or greater clinically significant non-hematologic toxicity (including QT duration corrected for heart rate by Fridericia's formula (QTcF), ejection fraction $<$ lower limit of normal (LLN) with an absolute decrease of $> 10\%$ from

End point type	Primary
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End point timeframe:

Up to 28 days

Notes:

[8] - 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: There are no statistical data to report

End point values	Phase I- GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure >= 12M)	PhaseI- GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[9]	12 ^[10]	42 ^[11]	7 ^[12]
Units: Participants	2	0	1	1

Notes:

[9] - All Treated Population

[10] - All Treated Population

[11] - All Treated Population

[12] - All Treated Population

End point values	Phase I- GSK525762 80mg + FUL 500 mg (AI Failure)	Phase I- GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[13]	11 ^[14]		
Units: Participants	0	2		

Notes:

[13] - All Treated Population

[14] - All Treated Population

Statistical analyses

No statistical analyses for this end point

Primary: Phase I: Number of participants with dose reductions and dose interruption/delays

End point title	Phase I: Number of participants with dose reductions and dose interruption/delays ^[15]
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End point description:

Number of participants with dose reductions and dose interruption or delay due to any reason is presented.

End point type	Primary
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End point timeframe:

Up to 3 year and 8 months

Notes:

[15] - 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: There are no statistical data to report

End point values	Phase I- GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure >= 12M)	PhaseI- GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[16]	12 ^[17]	42 ^[18]	7 ^[19]
Units: Participants				
Dose reduction	9	3	14	3

Dose interruption/delay	23	9	23	4
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Notes:

[16] - All Treated Population

[17] - All Treated Population

[18] - All Treated Population

[19] - All Treated Population

End point values	Phase I- GSK525762 80mg + FUL 500 mg (AI Failure)	Phase I- GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[20]	11 ^[21]		
Units: Participants				
Dose reduction	7	8		
Dose interruption/delay	15	9		

Notes:

[20] - All Treated Population

[21] - All Treated Population

Statistical analyses

No statistical analyses for this end point

Primary: Phase I: Objective response rate-Investigator assessment

End point title	Phase I: Objective response rate-Investigator assessment ^[22]
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End point description:

Objective Response Rate is defined as the percentage of participants who demonstrate a Best Response of confirmed complete response (CR) or partial response (PR), as assessed by the investigator per response evaluation criteria in solid tumors (RECIST) version (v) 1.1 criteria. Modified All Treated Population consisted of all participants who received at least one dose of GSK525762 and fulvestrant.

End point type	Primary
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End point timeframe:

Up to 3 year and 8 months

Notes:

[22] - 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: There are no statistical data to report

End point values	Phase I- GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure >= 12M)	PhaseI- GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[23]	12 ^[24]	42 ^[25]	7 ^[26]
Units: Percentage of participants				
number (confidence interval 95%)	21 (9.0 to 38.9)	0 (0.0 to 26.5)	12 (4.0 to 25.6)	0 (0.0 to 41.0)

Notes:

[23] - Modified All Treated Population

[24] - Modified All Treated Population

[25] - Modified All Treated Population

[26] - Modified All Treated Population

End point values	Phase I- GSK525762 80mg + FUL 500 mg (AI Failure)	Phase I- GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[27]	11 ^[28]		
Units: Percentage of participants				
number (confidence interval 95%)	17 (3.6 to 41.4)	9 (0.2 to 41.3)		

Notes:

[27] - Modified All Treated Population

[28] - Modified All Treated Population

Statistical analyses

No statistical analyses for this end point

Primary: Phase I: Plasma concentration of GSK525762

End point title	Phase I: Plasma concentration of GSK525762 ^[29]
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End point description:

Blood samples were collected at indicated time points for pharmacokinetic (PK) analysis of GSK525762. PK Population comprised of participants from the All Treated Population for whom a PK sample was obtained and analyzed. Only those participants with data available at the indicated time points were analyzed (indicated by n=X in category titles). 99999 indicates no concentration values were detected for pre-dose. 88888 indicates standard deviation could not be calculated due to single participant. 77777 indicates standard deviation could not be calculated due to high proportion of non-quantifiable (NQ) values (more than [>] 30 percent [%] of values were imputed. 66666 indicates data is not available.

End point type	Primary
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End point timeframe:

Day 1: Pre-dose, 0.5, 1, 3 hours on Weeks 1 and 3; Day 1: Pre-dose, 0.5-1, 4-8 hours on Week 5; Day 1: Pre-dose, 0.5-1 hour on Weeks 9, 17, 25

Notes:

[29] - 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: There are no statistical data to report

End point values	Phase I- GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure >= 12M)	PhaseI- GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31 ^[30]	12 ^[31]	41 ^[32]	7 ^[33]
Units: Nanograms per milliliter				
arithmetic mean (standard deviation)				
Week 1 Day 1, Pre-dose, n=30,11,41,7,17,11	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Week 1 Day 1, 0.5 hour, n=31,11,40,7,17,10	895.466 (± 520.7900)	814.364 (± 465.7197)	824.081 (± 605.1745)	646.251 (± 537.3585)
Week 1 Day 1, 1 hour, n=31,10,40,7,18,10	855.734 (± 374.3789)	828.800 (± 216.0544)	947.343 (± 443.7234)	634.300 (± 331.3116)

Week 1 Day 1, 3 hours, n=31,10,39,6,17,10	637.097 (± 220.5013)	526.400 (± 106.3591)	717.769 (± 293.5412)	732.833 (± 394.3660)
Week 3 Day 1, Pre-dose, n=29,12,31,5,16,8	7.046 (± 8.2049)	15.797 (± 20.7736)	8.598 (± 13.2639)	150.410 (± 295.0514)
Week 3 Day 1, 0.5 hour, n=28,11,29,4,13,7	766.179 (± 330.0370)	680.936 (± 435.2668)	504.516 (± 342.6658)	730.250 (± 410.6356)
Week 3 Day 1, 1 hour, n=28,11,30,5,13,7	737.536 (± 310.4540)	576.427 (± 298.5082)	581.073 (± 273.6803)	596.800 (± 134.6540)
Week 3 Day 1, 3 hours, n=28,10,29,5,13,7	423.500 (± 190.6163)	447.700 (± 179.1889)	369.179 (± 171.4981)	422.800 (± 120.6512)
Week 5 Day 1, Pre-dose, n=26,9,34,5,14,10	5.804 (± 7.7777)	15.251 (± 18.1145)	66.527 (± 198.8847)	15.814 (± 21.5282)
Week 5 Day 1, 0.5-1 hour, n=24,7,26,3,11,7	640.700 (± 380.5152)	463.854 (± 476.0195)	555.237 (± 336.1938)	705.667 (± 208.2218)
Week 5 Day 1, 4-8 hours, n=6,1,9,1,5,0	306.900 (± 153.8008)	145.000 (± 88888)	303.000 (± 177.1489)	431.000 (± 88888)
Week 9 Day 1, Pre-dose, n=17,2,23,2,10,4	7.257 (± 11.2876)	5.055 (± 0.7142)	9.000 (± 13.3106)	3.265 (± 77777)
Week 9 Day 1, 0.5-1 hour, n=13,1,17,2,6,3	607.408 (± 528.6891)	69.400 (± 88888)	445.291 (± 388.9562)	817.000 (± 287.0854)
Week 17 Day 1, Pre-dose, n=11,2,8,2,6,3	9.401 (± 13.0880)	1.365 (± 77777)	3.591 (± 77777)	16.850 (± 2.0506)
Week 17 Day 1, 0.5-1 hour, n=9,2,9,2,4,1	372.778 (± 214.7812)	32.100 (± 30.2642)	521.241 (± 404.3103)	270.000 (± 354.9676)
Week 25 Day 1, Pre-dose, n=9,1,5,2,4,1	34.847 (± 92.3723)	99999 (± 99999)	10.198 (± 10.4909)	10.740 (± 9.1358)
Week 25 Day 1, 0.5-1 hour, n=5,0,6,2,2,1	418.000 (± 173.5439)	66666 (± 66666)	380.483 (± 338.1430)	251.350 (± 225.7792)

Notes:

[30] - PK Population

[31] - PK Population

[32] - PK Population

[33] - PK Population

End point values	Phase I- GSK525762 80mg + FUL 500 mg (AI Failure)	Phase I- GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[34]	11 ^[35]		
Units: Nanograms per milliliter				
arithmetic mean (standard deviation)				
Week 1 Day 1, Pre-dose, n=30,11,41,7,17,11	99999 (± 99999)	99999 (± 99999)		
Week 1 Day 1, 0.5 hour, n=31,11,40,7,17,10	969.265 (± 659.5862)	1155.300 (± 329.8983)		
Week 1 Day 1, 1 hour, n=31,10,40,7,18,10	1061.722 (± 397.9207)	1069.400 (± 269.4864)		
Week 1 Day 1, 3 hours, n=31,10,39,6,17,10	831.176 (± 293.0363)	782.600 (± 191.9283)		
Week 3 Day 1, Pre-dose, n=29,12,31,5,16,8	11.371 (± 17.8450)	6.799 (± 5.7108)		
Week 3 Day 1, 0.5 hour, n=28,11,29,4,13,7	808.846 (± 548.7639)	917.714 (± 498.7183)		
Week 3 Day 1, 1 hour, n=28,11,30,5,13,7	875.077 (± 343.5570)	895.286 (± 358.3172)		
Week 3 Day 1, 3 hours, n=28,10,29,5,13,7	471.154 (± 160.2908)	523.714 (± 207.9308)		

Week 5 Day 1, Pre-dose, n=26,9,34,5,14,10	14.603 (± 17.0653)	77.465 (± 217.4469)		
Week 5 Day 1, 0.5-1 hour, n=24,7,26,3,11,7	685.773 (± 446.6621)	457.229 (± 301.9096)		
Week 5 Day 1, 4-8 hours, n=6,1,9,1,5,0	352.400 (± 98.5890)	66666 (± 66666)		
Week 9 Day 1, Pre-dose, n=17,2,23,2,10,4	16.469 (± 23.7102)	6.640 (± 7.0298)		
Week 9 Day 1, 0.5-1 hour, n=13,1,17,2,6,3	621.867 (± 440.4829)	309.627 (± 375.4223)		
Week 17 Day 1, Pre-dose, n=11,2,8,2,6,3	7.217 (± 10.1456)	7.270 (± 77777)		
Week 17 Day 1, 0.5-1 hour, n=9,2,9,2,4,1	640.000 (± 273.7846)	214.000 (± 88888)		
Week 25 Day 1, Pre-dose, n=9,1,5,2,4,1	1.560 (± 77777)	99999 (± 99999)		
Week 25 Day 1, 0.5-1 hour, n=5,0,6,2,2,1	314.000 (± 90.5097)	186.000 (± 88888)		

Notes:

[34] - PK Population

[35] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Number of participants who withdrew due to toxicity and changes in Safety Assessment

End point title	Phase I: Number of participants who withdrew due to toxicity and changes in Safety Assessment
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End point description:

Number of participants who withdrew due to toxicity and changes in safety assessment including laboratory parameters and vital signs have been presented.

End point type	Secondary
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End point timeframe:

Up to 4 year and 4 months

End point values	Phase I- GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure >= 12M)	PhaseI- GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[36]	12 ^[37]	42 ^[38]	7 ^[39]
Units: Participants	6	0	6	2

Notes:

[36] - All Treated Population

[37] - All Treated Population

[38] - All Treated Population

[39] - All Treated Population

End point values	Phase I- GSK525762 80mg + FUL	Phase I- GSK525762 80 mg + FUL 500		
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	500 mg (AI Failure)	mg (CDK4/6+AI Failure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[40]	11 ^[41]		
Units: Participants	1	2		

Notes:

[40] - All Treated Population

[41] - All Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Disease control rate (DCR)

End point title	Phase I: Disease control rate (DCR)
End point description:	
DCR is defined as the percentage of participants in the population with a confirmed complete response (CR), confirmed partial response (PR), or stable disease (SD) lasting ≥ 6 months, as assessed by the investigator per RECIST v1.1 criteria.	
End point type	Secondary
End point timeframe:	
Up to 3 year and 8 months	

End point values	Phase I- GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure $\geq 12M$)	PhaseI- GSK525762 60+FUL500mg CDK4/6+AI Fail $\geq 12M$ Bone only dis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[42]	12 ^[43]	42 ^[44]	7 ^[45]
Units: Percentage of participants				
number (confidence interval 95%)	36 (20.4 to 54.9)	0 (0.0 to 26.5)	17 (7.0 to 31.4)	14 (0.4 to 57.9)

Notes:

[42] - Modified All Treated Population.

[43] - Modified All Treated Population.

[44] - Modified All Treated Population.

[45] - Modified All Treated Population.

End point values	Phase I- GSK525762 80mg + FUL 500 mg (AI Failure)	Phase I- GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[46]	11 ^[47]		
Units: Percentage of participants				
number (confidence interval 95%)	28 (9.7 to 53.5)	9 (0.2 to 41.3)		

Notes:

[46] - Modified All Treated Population.

[47] - Modified All Treated Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Duration of response (DoR)

End point title	Phase I: Duration of response (DoR)
End point description:	
DoR is defined as the time (in months) from date of first documented evidence of confirmed CR or PR to the date of first documented PD, as assessed by the investigator per RECIST v1.1 criteria, or to the date of death due to any cause among participants with a Best overall response (BOR) of confirmed CR or PR. Only those participants with a BOR of confirmed CR or PR based on RECIST v1.1 were analyzed hence N=0 for Phase I-GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M) and Phase I-GSK525762 60+FUL500mg CDK4/6+AI Failure>=12M Bone Only Disease arms. 55555 indicates <75% of participants experienced the event within the treatment arm. Hence, third-quartile could not be derived. 99999 indicates that Inter-quartile range is not applicable due to single participant, and the median value presented here is the actual DOR for this single participant.	
End point type	Secondary
End point timeframe:	
Up to 3 year and 8 months	

End point values	Phase I- GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure >= 12M)	PhaseI- GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7 ^[48]	0 ^[49]	5 ^[50]	0 ^[51]
Units: Months				
median (inter-quartile range (Q1-Q3))	13.1 (6.5 to 26.3)	(to)	5.8 (5.7 to 55555)	(to)

Notes:

[48] - Modified All Treated Population.

[49] - Modified All Treated Population.

[50] - Modified All Treated Population.

[51] - Modified All Treated Population.

End point values	Phase I- GSK525762 80mg + FUL 500 mg (AI Failure)	Phase I- GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3 ^[52]	1 ^[53]		
Units: Months				
median (inter-quartile range (Q1-Q3))	14.0 (5.4 to 16.4)	4.3 (-99999 to 99999)		

Notes:

[52] - Modified All Treated Population.

[53] - Modified All Treated Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Progression-free survival (PFS)

End point title	Phase I: Progression-free survival (PFS)
End point description:	
PFS is defined as the time (in months) from the date of first dose until the date of first documented PD, as assessed by the investigator per RECIST v1.1 criteria, or date of death due to any cause, whichever occurs first. PD is defined as at least a 20% increase in the sum of the diameters of target lesions. 55555 indicates <75% of participants experienced the event within the treatment arm. Hence, third-quartile could not be derived.	
End point type	Secondary
End point timeframe:	
Up to 3 year and 8 months	

End point values	Phase I- GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure >= 12M)	PhaseI- GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[54]	12 ^[55]	42 ^[56]	7 ^[57]
Units: Months				
median (inter-quartile range (Q1-Q3))	5.6 (3.5 to 14.1)	1.7 (1.6 to 2.1)	2.1 (1.7 to 7.1)	7.2 (3.7 to 55555)

Notes:

[54] - Modified All Treated Population

[55] - Modified All Treated Population

[56] - Modified All Treated Population

[57] - Modified All Treated Population

End point values	Phase I- GSK525762 80mg + FUL 500 mg (AI Failure)	Phase I- GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[58]	11 ^[59]		
Units: Months				
median (inter-quartile range (Q1-Q3))	4.0 (1.8 to 9.4)	1.8 (1.7 to 3.6)		

Notes:

[58] - Modified All Treated Population

[59] - Modified All Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Plasma concentration of GSK3529246

End point title	Phase I: Plasma concentration of GSK3529246
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End point description:

Blood samples were collected at indicated time points for PK analysis of GSK3529246. GSK3529246 is an active metabolite of GSK525762. Only those participants with data available at the indicated time points were analyzed (indicated by n=X in category titles). 99999 indicates no concentration values were detected for pre-dose. 88888 indicates standard deviation could not be calculated due to single participant. 77777 indicates standard deviation could not be calculated due to high proportion of non-quantifiable (NQ) values (more than [$>$] 30 percent [%] of values were imputed. 66666 indicates data is not available.

End point type	Secondary
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End point timeframe:

Day 1: Pre-dose, 0.5, 1, 3 hours on Weeks 1 and 3; Day 1: Pre-dose, 0.5-1, 4-8 hours on Week 5, Day 1: pre-dose, 0.5-1 hour on Weeks 9, 17, 25

End point values	Phase I- GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure \geq 12M)	PhaseI- GSK525762 60+FUL500mg CDK4/6+AI Fail \geq 12M Bone only dis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31 ^[60]	12 ^[61]	41 ^[62]	7 ^[63]
Units: Nanograms per milliliter				
arithmetic mean (standard deviation)				
Week 1 Day 1, Pre-dose, n=30,11,41,7,17,11	99999 (\pm 99999)	99999 (\pm 99999)	99999 (\pm 99999)	99999 (\pm 99999)
Week 1 Day 1, 0.5 hour, n=31,11,39, 7,17,10	174.474 (\pm 143.3693)	126.818 (\pm 84.5894)	135.012 (\pm 128.9738)	115.419 (\pm 108.8723)
Week 1 Day 1, 1 hour, n=31,11,41,7,18,10	249.793 (\pm 128.5670)	205.364 (\pm 70.6856)	228.597 (\pm 118.1550)	175.197 (\pm 154.0632)
Week 1 Day 1, 3 hours, n=31,11,39,6,17,10	276.516 (\pm 67.1798)	216.364 (\pm 50.0685)	262.044 (\pm 91.2467)	243.517 (\pm 136.5840)
Week 3 Day 1, Pre-dose, n=29,12,31,5,16,8	37.972 (\pm 31.9814)	58.708 (\pm 64.1009)	42.213 (\pm 30.7403)	121.820 (\pm 190.5127)
Week 3 Day 1, 0.5 hour, n=28,11,30,4,13,7	290.482 (\pm 155.8106)	243.736 (\pm 130.5650)	195.037 (\pm 147.9176)	192.275 (\pm 149.9568)
Week 3 Day 1, 1 hour, n=28,11,30,5,13,7	414.143 (\pm 118.8203)	294.573 (\pm 102.1516)	323.767 (\pm 169.5878)	271.200 (\pm 145.3227)
Week 3 Day 1, 3 hours, n=28,10,29,5,13,7	369.821 (\pm 85.0124)	341.500 (\pm 95.5118)	321.404 (\pm 131.8554)	252.000 (\pm 96.1587)
Week 5 Day 1, Pre-dose, n=26,9,34,5,14,10	37.480 (\pm 32.2441)	41.600 (\pm 24.1873)	56.659 (\pm 70.2933)	36.620 (\pm 26.8511)
Week 5 Day 1, 0.5-1 hour, n=24,7,26,3,11,7	270.979 (\pm 153.7445)	237.614 (\pm 211.1272)	211.846 (\pm 171.4081)	170.800 (\pm 66.2851)
Week 5 Day 1, 4-8 hours, n=6,1,9,1,5,0	263.833 (\pm 52.9619)	208.000 (\pm 88888)	322.778 (\pm 166.2354)	292.000 (\pm 88888)
Week 9 Day 1, Pre-dose, n=17,2,23,2,10,4	31.041 (\pm 28.3504)	33.850 (\pm 19.4454)	39.323 (\pm 40.8779)	22.700 (\pm 77777)
Week 9 Day 1, 0.5-1 hour, n=13,1,17,2,6,3	244.162 (\pm 189.0153)	36.000 (\pm 88888)	178.914 (\pm 148.8777)	228.000 (\pm 140.0071)
Week 17 Day 1, Pre-dose, n=11,2,8,2,6,3	41.445 (\pm 35.8541)	21.450 (\pm 5.4447)	21.214 (\pm 27.8382)	72.450 (\pm 55.9321)

Week 17 Day 1, 0.5-1 hour, n=9,2,9,2,4,1	189.422 (± 146.0021)	71.800 (± 66.7509)	183.671 (± 149.1568)	129.050 (± 135.6938)
Week 25 Day 1, Pre-dose, n=9,1,5,2,4,1	65.756 (± 125.0011)	30.100 (± 88888)	49.700 (± 26.2679)	64.500 (± 60.1041)
Week 25 Day 1, 0.5-1 hour, n=5,0,6,2,2,1	203.160 (± 192.2849)	66666 (± 66666)	220.367 (± 195.6110)	204.950 (± 164.1195)

Notes:

[60] - PK Population

[61] - PK Population

[62] - PK Population

[63] - PK Population

End point values	Phase I- GSK525762 80mg + FUL 500 mg (AI Failure)	Phase I- GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[64]	11 ^[65]		
Units: Nanograms per milliliter				
arithmetic mean (standard deviation)				
Week 1 Day 1, Pre-dose, n=30,11,41,7,17,11	99999 (± 99999)	99999 (± 99999)		
Week 1 Day 1, 0.5 hour, n=31,11,39, 7,17,10	202.224 (± 225.2895)	186.970 (± 108.3133)		
Week 1 Day 1, 1 hour, n=31,11,41,7,18,10	327.072 (± 186.8822)	299.100 (± 92.9043)		
Week 1 Day 1, 3 hours, n=31,11,39,6,17,10	365.059 (± 130.8231)	300.000 (± 95.1595)		
Week 3 Day 1, Pre-dose, n=29,12,31,5,16,8	48.013 (± 39.6626)	49.230 (± 40.3798)		
Week 3 Day 1, 0.5 hour, n=28,11,30,4,13,7	256.669 (± 173.4439)	288.671 (± 166.5404)		
Week 3 Day 1, 1 hour, n=28,11,30,5,13,7	511.692 (± 196.3468)	441.571 (± 140.2353)		
Week 3 Day 1, 3 hours, n=28,10,29,5,13,7	438.692 (± 91.5946)	403.571 (± 96.7348)		
Week 5 Day 1, Pre-dose, n=26,9,34,5,14,10	52.243 (± 44.0710)	54.231 (± 57.2752)		
Week 5 Day 1, 0.5-1 hour, n=24,7,26,3,11,7	295.518 (± 235.4897)	203.486 (± 111.2642)		
Week 5 Day 1, 4-8 hours, n=6,1,9,1,5,0	382.400 (± 98.2588)	66666 (± 66666)		
Week 9 Day 1, Pre-dose, n=17,2,23,2,10,4	58.890 (± 62.2330)	69.625 (± 53.3875)		
Week 9 Day 1, 0.5-1 hour, n=13,1,17,2,6,3	283.667 (± 177.1211)	161.367 (± 113.1437)		
Week 17 Day 1, Pre-dose, n=11,2,8,2,6,3	44.483 (± 48.7589)	84.600 (± 74.6129)		
Week 17 Day 1, 0.5-1 hour, n=9,2,9,2,4,1	322.500 (± 237.0787)	301.000 (± 88888)		
Week 25 Day 1, Pre-dose, n=9,1,5,2,4,1	20.508 (± 29.5669)	99999 (± 99999)		
Week 25 Day 1, 0.5-1 hour, n=5,0,6,2,2,1	121.300 (± 90.0854)	76.300 (± 88888)		

Notes:

[64] - PK Population

[65] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Plasma concentration of Fulvestrant

End point title	Phase I: Plasma concentration of Fulvestrant
End point description:	
Blood samples were collected at indicated time points for PK analysis of Fulvestrant. Only those participants with data available at the indicated time points were analyzed (indicated by n=X in category titles). 99999 indicates no concentration values were detected for pre-dose. 88888 indicates standard deviation could not be calculated due to single participant.	
End point type	Secondary
End point timeframe:	
Day 1: Pre-dose on Weeks 1, 3, 5, 9, 17, 25	

End point values	Phase I- GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure >= 12M)	Phase I- GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30 ^[66]	11 ^[67]	40 ^[68]	7 ^[69]
Units: Nanograms per milliliter				
arithmetic mean (standard deviation)				
Week 1 Day 1, Pre-dose, n=30,11,40,6,17,11	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Week 3 Day 1, Pre-dose, n=30,11,32,7,16,10	13.32481 (± 6.603131)	9.42742 (± 3.584881)	12.44415 (± 5.669148)	11.34839 (± 2.085675)
Week 5 Day 1, Pre-dose, n=25,9,31,5,16,10	19.82642 (± 6.917439)	14.72467 (± 3.338039)	16.51574 (± 5.957079)	15.35394 (± 5.395372)
Week 9 Day 1, Pre-dose, n=19,3,19,1,10,5	16.33764 (± 5.719390)	13.05750 (± 4.266495)	13.98242 (± 4.138764)	20.43840 (± 88888)
Week 17 Day 1, Pre-dose, n=15,2,6,1,6,3	16.70103 (± 5.826390)	20.63475 (± 7.753497)	13.62853 (± 1.536930)	12.59940 (± 88888)
Week 25 Day 1, Pre-dose, n=10,1,4,1,4,1	18.07473 (± 5.933472)	14.21220 (± 88888)	18.60548 (± 5.300211)	19.05100 (± 88888)

Notes:

[66] - PK Population

[67] - PK Population

[68] - PK Population

[69] - PK Population

End point values	Phase I- GSK525762 80mg + FUL 500 mg (AI Failure)	Phase I- GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17 ^[70]	11 ^[71]		
Units: Nanograms per milliliter				
arithmetic mean (standard deviation)				
Week 1 Day 1, Pre-dose, n=30,11,40,6,17,11	99999 (± 99999)	99999 (± 99999)		

Week 3 Day 1, Pre-dose, n=30,11,32,7,16,10	12.41568 (± 4.873113)	10.25047 (± 3.121508)		
Week 5 Day 1, Pre-dose, n=25,9,31,5,16,10	16.87293 (± 8.018589)	13.83940 (± 4.449118)		
Week 9 Day 1, Pre-dose, n=19,3,19,1,10,5	11.10370 (± 2.864192)	11.84244 (± 4.615995)		
Week 17 Day 1, Pre-dose, n=15,2,6,1,6,3	12.81337 (± 3.550671)	16.33830 (± 4.410823)		
Week 25 Day 1, Pre-dose, n=10,1,4,1,4,1	16.05110 (± 2.384935)	12.24970 (± 88888)		

Notes:

[70] - PK Population

[71] - PK Population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Phase I: Number of participants with non-serious adverse events (AEs) and serious adverse events (SAEs) until End of the study

End point title	Phase I: Number of participants with non-serious adverse events (AEs) and serious adverse events (SAEs) until End of the study
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End point description:

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A SAE is defined as any untoward medical occurrence that, at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, any other situation such as important medical events according to medical or scientific judgement or is associated with liver injury and impaired liver function. Any other adverse event apart from SAE is considered as non-SAE. Number of participants with non-serious AEs and SAEs collected from start of the treatment until end of the study were reported.

End point type	Other pre-specified
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End point timeframe:

Up to 4 year and 4 months

End point values	Phase I- GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+ AI Failure ≥ 12M)	PhaseI- GSK525762 60+FUL500mg CDK4/6+AI Fail≥12M Bone only dis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[72]	12 ^[73]	42 ^[74]	7 ^[75]
Units: Participants				
Non-serious AEs	33	12	42	7
SAEs	5	1	10	3

Notes:

[72] - All Treated Population

[73] - All Treated Population

[74] - All Treated Population

[75] - All Treated Population

End point values	Phase I-	Phase I-		
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	GSK525762 80mg + FUL 500 mg (AI Failure)	GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[76]	11 ^[77]		
Units: Participants				
Non-serious AEs	18	11		
SAEs	6	2		

Notes:

[76] - All Treated Population

[77] - All Treated Population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Phase I: Number of participants with dose reductions and dose interruption/delays until End of the study

End point title	Phase I: Number of participants with dose reductions and dose interruption/delays until End of the study
End point description:	Number of participants with dose reductions and dose interruption or delay due to any reason is presented. Number of participants with dose reductions and dose interruption or delay due to any reason from start of the treatment until end of the study were reported.
End point type	Other pre-specified
End point timeframe:	Up to 4 year and 4 months

End point values	Phase I- GSK525762 60 mg+FUL 500 mg (AI Failure)	Phase-I GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure <12M)	Phase I- GSK525762 60 mg+FUL 500 mg (CDK4/6+AI Failure >= 12M)	PhaseI- GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone only dis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[78]	12 ^[79]	42 ^[80]	7 ^[81]
Units: Participants				
Dose reduction	9	3	14	3
Dose interruption/delay	23	9	23	4

Notes:

[78] - All Treated Population

[79] - All Treated Population

[80] - All Treated Population

[81] - All Treated Population

End point values	Phase I- GSK525762 80mg + FUL 500 mg (AI Failure)	Phase I- GSK525762 80 mg + FUL 500 mg (CDK4/6+AI Failure)		
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Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[82]	11 ^[83]		
Units: Participants				
Dose reduction	7	8		
Dose interruption/delay	15	9		

Notes:

[82] - All Treated Population

[83] - All Treated Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality, serious and non-serious adverse events were collected up to 4 year and 4 months

Adverse event reporting additional description:

All Treated Population. Results presented are approximately up to 4years & 4months. Interim analysis failed to demonstrate clinically meaningful activity hence Phase II was not initiated. Data is presented only for Phase I.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Phase I-GSK525762 60mg+FUL 500mg(AI Failure)
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Reporting group description:

Participants with aromatase inhibitor (AI) failure received GSK525762 60 milligrams (mg) tablet orally once daily and Fulvestrant (FUL) 500 mg was administered intramuscularly (IM) on days 1, 15, 29, and once monthly thereafter.

Reporting group title	Phase I-GSK525762 60mg+FUL 500mg (CDK4/6+AI Failure < 12M)
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Reporting group description:

Participants with Cyclin-Dependent Kinase (CDK4/6)/AI failure within 12 months received GSK525762 60 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.

Reporting group title	Phase I-GSK525762 80mg+FUL 500mg (AI Failure)
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Reporting group description:

Participants with AI failure received GSK525762 80 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.

Reporting group title	Phase I-GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone Disease
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Reporting group description:

Participants with CDK4/6/AI failure >=12 months with bone only disease received GSK525762 60 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.

Reporting group title	Phase I-GSK525762 80mg+FUL 500mg (CDK4/6+AI Failure)
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Reporting group description:

Participants with CDK4/6/AI failure received GSK525762 80 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.

Reporting group title	Phase I-GSK525762 60mg+FUL 500mg (CDK4/6+AI Failure >=12M)
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Reporting group description:

Participants with CDK4/6/AI failure >=12 months received GSK525762 60 mg tablet orally once daily and FUL 500 mg was administered IM on days 1, 15, 29, and once monthly thereafter.

Serious adverse events	Phase I-GSK525762 60mg+FUL 500mg(AI Failure)	Phase I-GSK525762 60mg+FUL 500mg (CDK4/6+AI Failure < 12M)	Phase I-GSK525762 80mg+FUL 500mg (AI Failure)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 33 (15.15%)	1 / 12 (8.33%)	6 / 18 (33.33%)
number of deaths (all causes)	11	9	10

number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extramammary Paget's disease			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter site haematoma			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 33 (3.03%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Electrocardiogram QT prolonged subjects affected / exposed	1 / 33 (3.03%)	0 / 12 (0.00%)	0 / 18 (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
Troponin increased subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Diaphragmatic injury subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	1 / 18 (5.56%)
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			
Acute coronary syndrome subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Microangiopathic haemolytic anaemia			

subjects affected / exposed	0 / 33 (0.00%)	1 / 12 (8.33%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	1 / 18 (5.56%)
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			
Hepatic function abnormal			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	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	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	1 / 33 (3.03%)	0 / 12 (0.00%)	0 / 18 (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			
Appendicitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 12 (0.00%)	0 / 18 (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
Diverticulitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

	Phase I-GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone Disease	Phase I-GSK525762 80mg+FUL 500mg (CDK4/6+AI Failure)	Phase I-GSK525762 60mg+FUL 500mg (CDK4/6+AI Failure >=12M)
Serious adverse events			
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	2 / 11 (18.18%)	10 / 42 (23.81%)
number of deaths (all causes)	2	5	12
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extramammary Paget's disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 42 (2.38%)
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			

Catheter site haematoma			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 42 (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
General physical health deterioration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Diaphragmatic injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 42 (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
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Microangiopathic haemolytic anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 42 (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
Intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nausea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	3 / 42 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Streptococcal sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Viral infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 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 %

Non-serious adverse events	Phase I-GSK525762 60mg+FUL 500mg(AI Failure)	Phase I-GSK525762 60mg+FUL 500mg (CDK4/6+AI Failure < 12M)	Phase I-GSK525762 80mg+FUL 500mg (AI Failure)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)	12 / 12 (100.00%)	18 / 18 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 33 (0.00%)	1 / 12 (8.33%)	3 / 18 (16.67%)
occurrences (all)	0	1	4
Hypertension			
subjects affected / exposed	4 / 33 (12.12%)	1 / 12 (8.33%)	1 / 18 (5.56%)
occurrences (all)	4	1	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 33 (57.58%)	4 / 12 (33.33%)	9 / 18 (50.00%)
occurrences (all)	24	6	12
Asthenia			
subjects affected / exposed	4 / 33 (12.12%)	0 / 12 (0.00%)	3 / 18 (16.67%)
occurrences (all)	5	0	6
Chest pain			
subjects affected / exposed	2 / 33 (6.06%)	0 / 12 (0.00%)	3 / 18 (16.67%)
occurrences (all)	2	0	3
Chills			
subjects affected / exposed	2 / 33 (6.06%)	0 / 12 (0.00%)	2 / 18 (11.11%)
occurrences (all)	3	0	2
Injection site pain			
subjects affected / exposed	2 / 33 (6.06%)	2 / 12 (16.67%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Pyrexia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 12 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 7	2 / 12 (16.67%) 4	3 / 18 (16.67%) 4
Cough subjects affected / exposed occurrences (all)	9 / 33 (27.27%) 9	2 / 12 (16.67%) 2	1 / 18 (5.56%) 2
Epistaxis subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	1 / 12 (8.33%) 1	0 / 18 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	1 / 12 (8.33%) 1	0 / 18 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	1 / 12 (8.33%) 1	3 / 18 (16.67%) 3
Investigations Platelet count decreased subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 25	2 / 12 (16.67%) 3	6 / 18 (33.33%) 12
Blood bilirubin increased subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 6	2 / 12 (16.67%) 2	10 / 18 (55.56%) 20
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 7	2 / 12 (16.67%) 2	5 / 18 (27.78%) 10
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 7	3 / 12 (25.00%) 3	4 / 18 (22.22%) 5
Amylase increased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 3	2 / 12 (16.67%) 3	4 / 18 (22.22%) 5
Weight decreased subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 6	1 / 12 (8.33%) 1	3 / 18 (16.67%) 3
International normalised ratio increased			

subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 12 (0.00%) 0	4 / 18 (22.22%) 8
Lipase increased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 12 (0.00%) 0	2 / 18 (11.11%) 3
Troponin T increased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 3	1 / 12 (8.33%) 2	1 / 18 (5.56%) 5
Lymphocyte count decreased subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 12 (0.00%) 0	0 / 18 (0.00%) 0
Neutrophil count decreased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 7	0 / 12 (0.00%) 0	0 / 18 (0.00%) 0
N-terminal prohormone brain natriuretic peptide increased subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 2	1 / 12 (8.33%) 3	2 / 18 (11.11%) 2
White blood cell count decreased subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 3	0 / 12 (0.00%) 0	0 / 18 (0.00%) 0
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 3	1 / 12 (8.33%) 1	3 / 18 (16.67%) 4
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 12 (0.00%) 0	1 / 18 (5.56%) 2
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	14 / 33 (42.42%) 16	2 / 12 (16.67%) 3	10 / 18 (55.56%) 14
Headache subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 6	3 / 12 (25.00%) 4	7 / 18 (38.89%) 10
Dizziness			

subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	1 / 12 (8.33%) 1	2 / 18 (11.11%) 5
Taste disorder subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 6	1 / 12 (8.33%) 1	1 / 18 (5.56%) 2
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	1 / 12 (8.33%) 1	6 / 18 (33.33%) 9
Thrombocytopenia subjects affected / exposed occurrences (all)	8 / 33 (24.24%) 15	4 / 12 (33.33%) 4	3 / 18 (16.67%) 9
Neutropenia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 12 (0.00%) 0	3 / 18 (16.67%) 3
Eye disorders			
Dry eye subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 12 (0.00%) 0	3 / 18 (16.67%) 4
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	12 / 33 (36.36%) 17	7 / 12 (58.33%) 10	11 / 18 (61.11%) 21
Diarrhoea subjects affected / exposed occurrences (all)	13 / 33 (39.39%) 19	4 / 12 (33.33%) 4	10 / 18 (55.56%) 24
Vomiting subjects affected / exposed occurrences (all)	7 / 33 (21.21%) 8	2 / 12 (16.67%) 3	7 / 18 (38.89%) 9
Dry mouth subjects affected / exposed occurrences (all)	8 / 33 (24.24%) 8	2 / 12 (16.67%) 2	3 / 18 (16.67%) 4
Constipation subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 5	1 / 12 (8.33%) 1	3 / 18 (16.67%) 4
Abdominal pain			

subjects affected / exposed	2 / 33 (6.06%)	1 / 12 (8.33%)	3 / 18 (16.67%)
occurrences (all)	3	1	6
Dyspepsia			
subjects affected / exposed	7 / 33 (21.21%)	0 / 12 (0.00%)	4 / 18 (22.22%)
occurrences (all)	8	0	5
Abdominal pain upper			
subjects affected / exposed	3 / 33 (9.09%)	1 / 12 (8.33%)	1 / 18 (5.56%)
occurrences (all)	4	1	2
Stomatitis			
subjects affected / exposed	2 / 33 (6.06%)	1 / 12 (8.33%)	4 / 18 (22.22%)
occurrences (all)	2	1	7
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 33 (6.06%)	0 / 12 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	8 / 33 (24.24%)	4 / 12 (33.33%)	4 / 18 (22.22%)
occurrences (all)	10	4	7
Pruritus			
subjects affected / exposed	6 / 33 (18.18%)	2 / 12 (16.67%)	5 / 18 (27.78%)
occurrences (all)	7	2	5
Dry skin			
subjects affected / exposed	1 / 33 (3.03%)	1 / 12 (8.33%)	2 / 18 (11.11%)
occurrences (all)	1	1	2
Rash maculo-papular			
subjects affected / exposed	1 / 33 (3.03%)	1 / 12 (8.33%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Dermatitis acneiform			
subjects affected / exposed	0 / 33 (0.00%)	1 / 12 (8.33%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 33 (12.12%)	1 / 12 (8.33%)	3 / 18 (16.67%)
occurrences (all)	5	1	3
Musculoskeletal pain			

subjects affected / exposed	4 / 33 (12.12%)	0 / 12 (0.00%)	3 / 18 (16.67%)
occurrences (all)	4	0	3
Muscle spasms			
subjects affected / exposed	6 / 33 (18.18%)	2 / 12 (16.67%)	3 / 18 (16.67%)
occurrences (all)	7	2	6
Arthralgia			
subjects affected / exposed	4 / 33 (12.12%)	0 / 12 (0.00%)	2 / 18 (11.11%)
occurrences (all)	7	0	2
Pain in extremity			
subjects affected / exposed	3 / 33 (9.09%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Myalgia			
subjects affected / exposed	3 / 33 (9.09%)	0 / 12 (0.00%)	3 / 18 (16.67%)
occurrences (all)	5	0	4
Bone pain			
subjects affected / exposed	1 / 33 (3.03%)	0 / 12 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Flank pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 33 (12.12%)	3 / 12 (25.00%)	2 / 18 (11.11%)
occurrences (all)	7	4	2
Herpes zoster			
subjects affected / exposed	5 / 33 (15.15%)	0 / 12 (0.00%)	2 / 18 (11.11%)
occurrences (all)	5	0	2
Upper respiratory tract infection			
subjects affected / exposed	2 / 33 (6.06%)	0 / 12 (0.00%)	4 / 18 (22.22%)
occurrences (all)	2	0	4
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	14 / 33 (42.42%)	2 / 12 (16.67%)	9 / 18 (50.00%)
occurrences (all)	18	3	15
Hyperglycaemia			
subjects affected / exposed	13 / 33 (39.39%)	3 / 12 (25.00%)	6 / 18 (33.33%)
occurrences (all)	21	3	11
Hypertriglyceridaemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 12 (8.33%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 12 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Hyponatraemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 12 (8.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Phase I-GSK525762 60+FUL500mg CDK4/6+AI Fail>=12M Bone Disease	Phase I-GSK525762 80mg+FUL 500mg (CDK4/6+AI Failure)	Phase I-GSK525762 60mg+FUL 500mg (CDK4/6+AI Failure >=12M)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	11 / 11 (100.00%)	42 / 42 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	9 / 42 (21.43%)
occurrences (all)	0	2	9
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	3 / 11 (27.27%)	3 / 42 (7.14%)
occurrences (all)	0	3	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	7 / 11 (63.64%)	25 / 42 (59.52%)
occurrences (all)	1	10	38
Asthenia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 11 (9.09%)	7 / 42 (16.67%)
occurrences (all)	5	1	8
Chest pain			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 11 (9.09%) 1	1 / 42 (2.38%) 1
Chills subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 11 (0.00%) 0	1 / 42 (2.38%) 1
Injection site pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 11 (0.00%) 0	2 / 42 (4.76%) 2
Pyrexia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 11 (0.00%) 0	3 / 42 (7.14%) 4
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	4 / 11 (36.36%) 5	13 / 42 (30.95%) 17
Cough subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	3 / 11 (27.27%) 5	13 / 42 (30.95%) 15
Epistaxis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 11 (0.00%) 0	8 / 42 (19.05%) 9
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 11 (0.00%) 0	4 / 42 (9.52%) 4
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	5 / 42 (11.90%) 6
Investigations Platelet count decreased subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 5	4 / 11 (36.36%) 6	12 / 42 (28.57%) 21
Blood bilirubin increased subjects affected / exposed occurrences (all)	4 / 7 (57.14%) 7	2 / 11 (18.18%) 3	8 / 42 (19.05%) 9
Alanine aminotransferase increased			

subjects affected / exposed	3 / 7 (42.86%)	2 / 11 (18.18%)	11 / 42 (26.19%)
occurrences (all)	5	2	15
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 7 (42.86%)	2 / 11 (18.18%)	10 / 42 (23.81%)
occurrences (all)	8	2	12
Amylase increased			
subjects affected / exposed	2 / 7 (28.57%)	0 / 11 (0.00%)	4 / 42 (9.52%)
occurrences (all)	3	0	5
Weight decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	4 / 42 (9.52%)
occurrences (all)	1	1	5
International normalised ratio increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	5 / 42 (11.90%)
occurrences (all)	1	0	7
Lipase increased			
subjects affected / exposed	2 / 7 (28.57%)	0 / 11 (0.00%)	6 / 42 (14.29%)
occurrences (all)	3	0	10
Troponin T increased			
subjects affected / exposed	1 / 7 (14.29%)	2 / 11 (18.18%)	3 / 42 (7.14%)
occurrences (all)	1	6	3
Lymphocyte count decreased			
subjects affected / exposed	2 / 7 (28.57%)	0 / 11 (0.00%)	5 / 42 (11.90%)
occurrences (all)	5	0	7
Neutrophil count decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	4 / 42 (9.52%)
occurrences (all)	3	1	6
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
White blood cell count decreased			
subjects affected / exposed	2 / 7 (28.57%)	0 / 11 (0.00%)	3 / 42 (7.14%)
occurrences (all)	3	0	4
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 11 (0.00%) 0	4 / 42 (9.52%) 4
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 11 (0.00%) 0	3 / 42 (7.14%) 4
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	4 / 7 (57.14%) 4	7 / 11 (63.64%) 8	25 / 42 (59.52%) 30
Headache subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	3 / 11 (27.27%) 5	10 / 42 (23.81%) 11
Dizziness subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	8 / 42 (19.05%) 11
Taste disorder subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 11 (18.18%) 2	0 / 42 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	3 / 7 (42.86%) 4	2 / 11 (18.18%) 2	15 / 42 (35.71%) 19
Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 7 (57.14%) 8	1 / 11 (9.09%) 1	8 / 42 (19.05%) 14
Neutropenia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 11 (0.00%) 0	4 / 42 (9.52%) 5
Eye disorders Dry eye subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 11 (0.00%) 0	4 / 42 (9.52%) 4
Gastrointestinal disorders Nausea			

subjects affected / exposed	5 / 7 (71.43%)	9 / 11 (81.82%)	30 / 42 (71.43%)
occurrences (all)	9	9	38
Diarrhoea			
subjects affected / exposed	6 / 7 (85.71%)	4 / 11 (36.36%)	20 / 42 (47.62%)
occurrences (all)	10	4	28
Vomiting			
subjects affected / exposed	2 / 7 (28.57%)	2 / 11 (18.18%)	8 / 42 (19.05%)
occurrences (all)	2	2	9
Dry mouth			
subjects affected / exposed	2 / 7 (28.57%)	3 / 11 (27.27%)	4 / 42 (9.52%)
occurrences (all)	2	3	4
Constipation			
subjects affected / exposed	4 / 7 (57.14%)	4 / 11 (36.36%)	6 / 42 (14.29%)
occurrences (all)	4	4	6
Abdominal pain			
subjects affected / exposed	2 / 7 (28.57%)	3 / 11 (27.27%)	4 / 42 (9.52%)
occurrences (all)	2	3	4
Dyspepsia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	2 / 42 (4.76%)
occurrences (all)	1	0	2
Abdominal pain upper			
subjects affected / exposed	2 / 7 (28.57%)	1 / 11 (9.09%)	5 / 42 (11.90%)
occurrences (all)	2	1	7
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	4 / 42 (9.52%)
occurrences (all)	0	2	4
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	4 / 42 (9.52%)
occurrences (all)	2	1	4
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 7 (14.29%)	2 / 11 (18.18%)	10 / 42 (23.81%)
occurrences (all)	1	2	11
Pruritus			
subjects affected / exposed	2 / 7 (28.57%)	1 / 11 (9.09%)	6 / 42 (14.29%)
occurrences (all)	2	1	6

Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	3 / 11 (27.27%)	8 / 42 (19.05%)
occurrences (all)	0	3	8
Rash maculo-papular			
subjects affected / exposed	0 / 7 (0.00%)	3 / 11 (27.27%)	4 / 42 (9.52%)
occurrences (all)	0	3	4
Dermatitis acneiform			
subjects affected / exposed	0 / 7 (0.00%)	3 / 11 (27.27%)	2 / 42 (4.76%)
occurrences (all)	0	3	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 7 (42.86%)	1 / 11 (9.09%)	8 / 42 (19.05%)
occurrences (all)	4	1	9
Musculoskeletal pain			
subjects affected / exposed	3 / 7 (42.86%)	2 / 11 (18.18%)	3 / 42 (7.14%)
occurrences (all)	3	2	3
Muscle spasms			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	2 / 42 (4.76%)
occurrences (all)	2	0	3
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	4 / 42 (9.52%)
occurrences (all)	1	1	4
Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	5 / 42 (11.90%)
occurrences (all)	1	1	6
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	4
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	4
Flank pain			
subjects affected / exposed	0 / 7 (0.00%)	3 / 11 (27.27%)	2 / 42 (4.76%)
occurrences (all)	0	3	2
Musculoskeletal chest pain			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	5 / 42 (11.90%) 5
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	2 / 11 (18.18%)	1 / 42 (2.38%)
occurrences (all)	1	2	2
Herpes zoster			
subjects affected / exposed	2 / 7 (28.57%)	1 / 11 (9.09%)	2 / 42 (4.76%)
occurrences (all)	2	1	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 7 (42.86%)	6 / 11 (54.55%)	18 / 42 (42.86%)
occurrences (all)	5	7	19
Hyperglycaemia			
subjects affected / exposed	3 / 7 (42.86%)	2 / 11 (18.18%)	16 / 42 (38.10%)
occurrences (all)	5	5	22
Hypertriglyceridaemia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 11 (0.00%)	3 / 42 (7.14%)
occurrences (all)	2	0	6
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	2 / 42 (4.76%)
occurrences (all)	1	0	3
Hyponatraemia			
subjects affected / exposed	3 / 7 (42.86%)	0 / 11 (0.00%)	2 / 42 (4.76%)
occurrences (all)	5	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2016	Amend1:Clarification of permitted prophylactic anticoagulation therapies in Excl Crit4;Correction of spelling of goserelin,Change to toxicity management guidelines for below:Update to dose interruption/reduction/discontinuation guidelines for Grade(G)4 thrombocytopenia;Dose reduction for participant if QTcF>=60 msec change from Baseline occurs/QTcF>=500;Permanent discontinuation of study medication for participant with troponin levels approaching threshold for MI;Clarification on length of followup for participant with LVEF increase;Monitoring of blood sugar&dose reduction guidelines for participant with moderate to severe hypoglycemia;Dose reduction&event management for participant with G3-4 diarrhea;Dose interruption&reduction for participant with G3-4 mucositis;Dose interruption/reduction/discontinuation&event management for all G of pneumonitis;Dose interruption&/reduction for participant with G3-4 other non-hematologic events.Clarification of timing for sites to report pregnancies to GSK(24h vs 2wks,based on reproductive toxicity seen in preclinical GSK525762 studies); Addition of clarifying language around survival follow up after EoT visit;Addition of clarifying language around fresh biopsies around timing of CBC draws in Wk1;& incl crit6&excl crit1-3 around prior treatment history;Clarified wording for disease assessment schedule after Wk52;Removal of Sect:Valvular Toxicity Stopping Criteria &there are no preclinical/clinical valvular toxicity findings for GSK525762.Update to option of scan(now ECHO/MUGA);Removal of Disease Related Events,this section is only to be included if there are predefined disease related events.Update to G3&4 thrombocytopenia management guideline to make it more stringent,based upon emerging data that will be provided in INDSR.Removal of fever management guideline as part of ongoing safety review for GSK525762,there is no apparent clinical correlation to preclinical in vitro findings suggesting a potential for fever.
31 January 2017	Amendment 02-Based upon review and comment on the protocol by the Medicines and Healthcare products Regulatory Agency (MHRA), the following changes are being implemented as a standalone amendment for the United Kingdom (UK): Clarification of the length of time, post treatment completion, that the approved list of contraceptives must be used by female participants of childbearing potential; clarification in Section 5.4 that pregnancy is a reason for participant discontinuation from the study. A forthcoming amendment (03) will include these revisions as part of a global protocol amendment.
07 March 2017	Amendment 03-Clarification to the prior treatment participants may have received; update to the timelines of the study, based upon new enrollment projections; clarification of inclusion criteria #6 regarding prior treatment participants may have received; clarification of exclusion criteria #1 and #3 regarding number of prior lines of therapy; addition of two new exclusion criteria regarding use of NSAIDS and history of bleeding events; clarification in Section 5.4 that pregnancy for participants of childbearing potential is a cause for study discontinuation; clarification regarding the liquid that participants are permitted to use when taking GSK525762; clarification around the dosing window for fulvestrant; addition of Table 3 which clarifies dose reductions; clarification around use of Aspirin; update to the prohibited meds table in Section 6.11.2.1 and the cautionary meds table in Section 6.11.2.3; clarification around use of medication containing acetaminophen; update to the schedule of assessments in the Time and Events tables for both Phase I and II of the study; update to the schedule of laboratory assessments in both Phase I and II of the study; update to the +- visit windows for Weeks 2, 3, 4, 5, and 9; added logistical and medical guidance around when on treatment fresh biopsies and planned surgical procedure can take place; updated the thrombocytopenia management guidelines in Table 13 to be in line with regulatory feedback; clarification of baseline imaging windows; clarification of approved contraception and length of time said contraception needs to be used post study treatment.

18 October 2017	Amendment 04-Based upon review and comment on the protocol by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), the following changes are being implemented: language added to Section 6.11.2.3 around concomitant medications that are substrates of CYP3A4; update to the toxicity management guidelines for QTcF monitoring in Appendix 2, Table 13; Times and Events tables in Section 7.1, updated to clarify the schedule of assessments post week 49. Additional changes to the protocol include: update to protocol authors; update to the primary GlaxoSmithKline (GSK) medical monitor, update to Sponsor signatory; ERS1 mutational status in the objectives and endpoints has been updated to exploratory, and Section 7.7 has been updated to reflect the translational analysis changes; removal of the time to progression (TTP) endpoints; update to description of Phase I enrolment during the dose escalation phase and the definition of study completion in Phase II; update to statistical analysis descriptions throughout the protocol; addition of information around the dose escalation meetings; Section 6.6 on the handling of GSK525762; clarification in Section 5.1, Table 2, regarding acceptability of both Troponin I or T; Times and Events tables in Section 7.1, updated to clarify Echocardiogram (ECHO)/ Multigated Acquisition Scan (MUGA) scan requirements for screening and W1D1, timing of on treatment biopsy collection in Phase I, lab assessment requirements, and length of screening window (also updated throughout the document); update to the toxicity management guidelines for QT duration corrected for heart rate by Fridericia's formula (QTcF) re-challenge in Appendix 2, Table 13; removal of predefined events of interest.
11 September 2018	Amend 05:Updating protocol title to HR+/HER2-Breast cancer (BC) to align with incl crit.which requires both ER+ & PR+BC participants. Update to clarify-dose level (DL)2 (80mg) has been discontinued. New sections added to address & update to PhaseI-include DL2 80mg discontinuation,update DL1(60mg) cohort2 population to include participants must have received >=12months of prior (CDK4/6+ AI) for metastatic disease&progressed while on treatment&allow bone only disease.encl/excl criteria:Provision of fresh tumor biopsy sample at screening;letrozole has been expanded to include all AI agents;prior treatment allowed in CDK4/6 participant population;participant must have received >=12month of prior CDK4/6+AI for metastatic disease&progressed while on treatment;bone only disease is allowed(screening biopsy not required after discussion with MM);update to criteria for severe/uncontrolled systemic diseases;Baseline QTcF.Update to QTc stopping criteria;removal of former Guidelines for Events of Special Interest;include granulocyte colony-stimulating factor as permitted medication;update to wording in Prohibited Medication&removal of former Table4;Cautionary Medication&removal of former T5;Clarification regarding both prescription&non-prescription herbal preparation/medication;Time&Event Table5&8:Update regarding ECG,requirement of fresh biopsies at screening&collection window,clarification of requirement around fresh tumor biopsies sample;Pregnancy Test-X is removed from Column for Q12wks(Wk49 &after).This was an error & Q4wks is correct.Clarification regarding PK sample collection for participants with interrupted dosing;update to guidelines for ECG assessment;Clinical Labs regarding collection of troponin; guidance on screening&on treatment biopsy;&toxicity management for QTcF events&explanation for reconsent;Collection of pregnancy information regarding elective termination is clarified that only those performed due to medical reasons are required to be reported.

06 May 2020	<p>Amendment 06 applies to all global study sites. These changes are based on the decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed participant population. The totality of Phase I data assessed at the interim analysis does not support continuing investigation of GSK525762 (molibresib) in combination with fulvestrant for the treatment of hormone receptor-positive/HER2-negative (HR+/HER2-) advanced or metastatic breast cancer patients. Enrolment into the study is now closed. The study will conclude when the last participant has completed/discontinued study treatment and completed the end of treatment visit. Changes to the protocol include: Enrolment into the study is now closed, Removes the requirement for specific protocol assessments and survival followup (Section 7.1 – Time and Events Tables) Updates to contraceptive measures required for study participants, based upon January 2020 updates to the fulvestrant Summary of Product Characteristics Update to the GSK signatory and GSK medical monitor, Provides updated guidance for participants who have discontinued combination treatment & are on fulvestrant monotherapy, Provides clarification on clinical supply dosages available for the study, Administrative changes including minor clarifications, formatting and typographical errors.</p>
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported