



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 |
|-----------------------|--------|

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) |
|------------------|---|

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 |
|----------|--------------|

| | |
|--|-----------|
| 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) |
|------------------|--|

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 |
|------------------|--|

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) |
|------------------|--|

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) |
|------------------|--|

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] |
|-----------------|---|

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 |
|----------------|---------|

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] |
|-----------------|---|

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

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 |
|-------------------------|----|---|----|---|

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] |
|-----------------|--|

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 |
|----------------|---------|

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] |
|-----------------|--|

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 |
|----------------|---------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 | | |
|------------------|-------------------------------------|--|--|--|

| | 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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|---------------------|

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- | | |
|------------------|----------|----------|--|--|

| | 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) | | |
|------------------|---|---|--|--|
|------------------|---|---|--|--|

| | | | | |
|-----------------------------|--------------------|--------------------|--|--|
| 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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Phase I-GSK525762 60mg+FUL 500mg(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 60mg+FUL 500mg (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 80mg+FUL 500mg (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 60+FUL500mg CDK4/6+AI Fail>=12M Bone Disease |
|-----------------------|--|

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) |
|-----------------------|--|

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) |
|-----------------------|--|

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) Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Taste disorder subjects affected / exposed occurrences (all) | 4 / 7 (57.14%) 4 1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 | 7 / 11 (63.64%) 8 3 / 11 (27.27%) 5 1 / 11 (9.09%) 1 2 / 11 (18.18%) 2 | 25 / 42 (59.52%) 30 10 / 42 (23.81%) 11 8 / 42 (19.05%) 11 0 / 42 (0.00%) 0 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) | 3 / 7 (42.86%) 4 4 / 7 (57.14%) 8 1 / 7 (14.29%) 1 | 2 / 11 (18.18%) 2 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 | 15 / 42 (35.71%) 19 8 / 42 (19.05%) 14 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. |

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|-------------------|---|
| 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. |

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| 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