



Clinical trial results:

A Phase 1b/2 Study of GS-5829 in Combination with Fulvestrant or Exemestane in Subjects with Advanced Estrogen Receptor Positive, HER2 Negative Breast Cancer

Summary

EudraCT number	2016-002365-63
Trial protocol	ES BE GB FR
Global end of trial date	19 July 2018

Results information

Result version number	v1 (current)
This version publication date	31 July 2019
First version publication date	31 July 2019

Trial information

Trial identification

Sponsor protocol code	GS-US-350-1937
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02983604
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the Phase 1b Dose Escalation part of this study were to characterize the safety and tolerability of GS-5829 in combination with exemestane or fulvestrant and to determine the maximum tolerated dose (MTD) or the recommended Phase 2 dose of GS-5829 in combination with fulvestrant in women with advanced estrogen receptor positive, HER2-negative (ER+/HER2-) breast cancer.

The primary objective of the Randomized Phase 2 Dose Expansion portion of this study was to evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in women with advanced ER+/HER2- breast cancer.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 January 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	United States: 14
Worldwide total number of subjects	14
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	14
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States. The first participant was screened on 10 January 2017. The last study visit occurred on 19 July 2018.

Pre-assignment

Screening details:

17 participants were screened.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	GS-5829 4 mg + Exemestane

Arm description:

GS-5829 4 mg tablets once daily + exemestane 25 mg tablet once daily

Arm type	Experimental
Investigational medicinal product name	GS-5829
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

4 mg once daily

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	Aromasin®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg once daily

Arm title	GS-5829 4 mg + Fulvestrant
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Arm description:

GS-5829 4 mg tablets once daily + fulvestrant 500 mg administered intramuscularly on Days 1, 15, and 29, and then every 28 days (or in accordance with locally approved labeling)

Arm type	Experimental
Investigational medicinal product name	GS-5829
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

4 mg once daily

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	Faslodex®

Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
500 mg every 28 days (\pm 3 days)	

Arm title	GS-5829 6 mg + Fulvestrant
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Arm description:

GS-5829 6 mg tablets once daily + fulvestrant 500 mg administered intramuscularly on Days 1, 15, and 29, and then every 28 days (or in accordance with locally approved labeling)

Arm type	Experimental
Investigational medicinal product name	GS-5829
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

6 mg once daily

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	Faslodex®
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg every 28 days (\pm 3 days)

Arm title	GS-5829 9 mg + Fulvestrant
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Arm description:

GS-5829 9 mg tablets once daily + fulvestrant 500 mg administered intramuscularly on Days 1, 15, and 29, and then every 28 days (or in accordance with locally approved labeling)

Arm type	Experimental
Investigational medicinal product name	GS-5829
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

9 mg once daily

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	Faslodex®
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg every 28 days (\pm 3 days)

Number of subjects in period 1^[1]	GS-5829 4 mg + Exemestane	GS-5829 4 mg + Fulvestrant	GS-5829 6 mg + Fulvestrant
Started	4	3	3
Completed	4	3	3

Number of subjects in period 1^[1]	GS-5829 9 mg + Fulvestrant
Started	3
Completed	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1 participant who was enrolled but not treated is not included in the subject disposition table.

Baseline characteristics

Reporting groups

Reporting group title	GS-5829 4 mg + Exemestane
Reporting group description:	GS-5829 4 mg tablets once daily + exemestane 25 mg tablet once daily
Reporting group title	GS-5829 4 mg + Fulvestrant
Reporting group description:	GS-5829 4 mg tablets once daily + fulvestrant 500 mg administered intramuscularly on Days 1, 15, and 29, and then every 28 days (or in accordance with locally approved labeling)
Reporting group title	GS-5829 6 mg + Fulvestrant
Reporting group description:	GS-5829 6 mg tablets once daily + fulvestrant 500 mg administered intramuscularly on Days 1, 15, and 29, and then every 28 days (or in accordance with locally approved labeling)
Reporting group title	GS-5829 9 mg + Fulvestrant
Reporting group description:	GS-5829 9 mg tablets once daily + fulvestrant 500 mg administered intramuscularly on Days 1, 15, and 29, and then every 28 days (or in accordance with locally approved labeling)

Reporting group values	GS-5829 4 mg + Exemestane	GS-5829 4 mg + Fulvestrant	GS-5829 6 mg + Fulvestrant
Number of subjects	4	3	3
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	59.3	61.3	63.0
standard deviation	± 4.50	± 7.51	± 9.54
Gender categorical			
Units: Subjects			
Female	4	3	3
Male	0	0	0
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	4	3	3
Race			
Units: Subjects			
White	3	3	3
Other	1	0	0

Reporting group values	GS-5829 9 mg + Fulvestrant	Total	
Number of subjects	3	13	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	65.0		
standard deviation	± 12.29	-	

Gender categorical Units: Subjects			
Female	3	13	
Male	0	0	
Ethnicity Units: Subjects			
Not Hispanic or Latino	3	13	
Race Units: Subjects			
White	3	12	
Other	0	1	

End points

End points reporting groups

Reporting group title	GS-5829 4 mg + Exemestane
Reporting group description: GS-5829 4 mg tablets once daily + exemestane 25 mg tablet once daily	
Reporting group title	GS-5829 4 mg + Fulvestrant
Reporting group description: GS-5829 4 mg tablets once daily + fulvestrant 500 mg administered intramuscularly on Days 1, 15, and 29, and then every 28 days (or in accordance with locally approved labeling)	
Reporting group title	GS-5829 6 mg + Fulvestrant
Reporting group description: GS-5829 6 mg tablets once daily + fulvestrant 500 mg administered intramuscularly on Days 1, 15, and 29, and then every 28 days (or in accordance with locally approved labeling)	
Reporting group title	GS-5829 9 mg + Fulvestrant
Reporting group description: GS-5829 9 mg tablets once daily + fulvestrant 500 mg administered intramuscularly on Days 1, 15, and 29, and then every 28 days (or in accordance with locally approved labeling)	

Primary: Phase 1b Dose Escalation: Number of Participants Experiencing Dose Limiting Toxicities (DLTs) Through Day 28 at Each Dose Level of GS-5829

End point title	Phase 1b Dose Escalation: Number of Participants Experiencing Dose Limiting Toxicities (DLTs) Through Day 28 at Each Dose Level of GS-5829 ^[1]
End point description: A DLT was a toxicity defined as: • Grade ≥ 4 neutropenia, • Grade ≥ 3 neutropenia with fever, • Grade ≥ 3 thrombocytopenia, • Grade ≥ 2 bleeding, • Grade ≥ 3 or higher non-hematologic toxicity, except: 1) Grade 3 nausea or emesis with maximum duration of 48 hrs on adequate medical therapy, 2) Grade 3 diarrhea which persists for < 72 hrs in the absence of adequate medical therapy, • Grade ≥ 2 non-hematologic TEAE that in the opinion of the investigator is of potential clinical significance such that further dose escalation would expose participants to unacceptable risk, • Treatment interruption of ≥ 7 days due to unresolved toxicity, or • Grade 3 or Grade 4 elevation in aspartate transaminase or alanine transaminase associated with a Grade 2 elevation in bilirubin that is at least possibly related to study drug. DLT Analysis Set included participants who completed all treatment & safety procedures through Day 28, inclusive, or experienced a DLT prior to Day 28, exclusive.	
End point type	Primary
End point timeframe: Baseline up to 28 days	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical comparison was planned or performed.

End point values	GS-5829 4 mg + Exemestane	GS-5829 4 mg + Fulvestrant	GS-5829 6 mg + Fulvestrant	GS-5829 9 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: participants	1	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Randomized Phase 2 Dose Expansion: Progression-Free Survival

End point title	Randomized Phase 2 Dose Expansion: Progression-Free Survival ^[2]
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End point description:

Progression-Free Survival (PFS) was defined as the interval from date of randomization to the earlier of the first documented confirmed disease progression or death from any cause. As the study was terminated prior to the Phase 2 portion of the study, no participants were enrolled in the Phase 2 portion of the study and data was not collected for this endpoint.

End point type	Primary
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End point timeframe:

Baseline up to 2 years

Notes:

[2] - 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: As the study was terminated prior to the Phase 2 portion of the study, no participants were enrolled in the Phase 2 portion of the study and data was not collected for this endpoint.

End point values	GS-5829 4 mg + Exemestane	GS-5829 4 mg + Fulvestrant	GS-5829 6 mg + Fulvestrant	GS-5829 9 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[3]	0 ^[4]	0 ^[5]	0 ^[6]
Units: Not applicable				

Notes:

[3] - No participants were enrolled in the Phase 2 portion of the study.

[4] - No participants were enrolled in the Phase 2 portion of the study.

[5] - No participants were enrolled in the Phase 2 portion of the study.

[6] - No participants were enrolled in the Phase 2 portion of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b Dose Escalation: Pharmacokinetic (PK) Parameter: Cmax of GS-5829

End point title	Phase 1b Dose Escalation: Pharmacokinetic (PK) Parameter: Cmax of GS-5829
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End point description:

Cmax is defined as the maximum observed concentration of drug. The PK Analysis Set included all enrolled participants who received at least 1 dose of study drug and have at least 1 nonmissing postdose concentration value reported by the PK laboratory, excluding participants who received concomitant medications prohibited in this study. Only participants with available data were analyzed.

End point type	Secondary
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End point timeframe:

Predose, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours postdose on Days 1 and 15

End point values	GS-5829 4 mg + Exemestane	GS-5829 4 mg + Fulvestrant	GS-5829 6 mg + Fulvestrant	GS-5829 9 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	2
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (N = 4, 3, 3, 2)	318.25 (± 107.844)	247.00 (± 3.464)	244.00 (± 9.000)	518.00 (± 60.811)
Day 15 (N = 3, 3, 3, 2)	389.666 (± 105.6424)	370.333 (± 52.5483)	375.666 (± 67.0919)	634.000 (± 46.6690)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b Dose Escalation: PK Parameter: AUCtau of GS-5829

End point title	Phase 1b Dose Escalation: PK Parameter: AUCtau of GS-5829
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End point description:

AUCtau is defined as concentration of drug over time (the area under the concentration verses time curve over the dosing interval). Participants in the PK Analysis Set with available data were analyzed.

End point type	Secondary
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End point timeframe:

Predose, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours postdose on Day 15

End point values	GS-5829 4 mg + Exemestane	GS-5829 4 mg + Fulvestrant	GS-5829 6 mg + Fulvestrant	GS-5829 9 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	2
Units: h*ng/mL				
arithmetic mean (standard deviation)	4989.809 (± 1655.8737)	5218.820 (± 1326.2407)	3937.709 (± 667.4396)	7638.847 (± 938.3444)

Statistical analyses

No statistical analyses for this end point

Secondary: Randomized Phase 2 Dose Expansion: Overall Safety Profile as Assessed by the Percentage of Participants Experiencing Any Adverse Events (AEs), Grade 3 or 4 AEs, Treatment-Related AEs, or Abnormalities in Laboratory Tests or Electrocardiograms

End point title	Randomized Phase 2 Dose Expansion: Overall Safety Profile as Assessed by the Percentage of Participants Experiencing Any Adverse Events (AEs), Grade 3 or 4 AEs, Treatment-Related AEs, or Abnormalities in Laboratory Tests or Electrocardiograms
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End point description:

As the study was terminated prior to the Phase 2 portion of the study, no participants were enrolled in the Phase 2 portion of the study and data was not collected for this endpoint.

End point type	Secondary
End point timeframe:	
Baseline up to 2 years	

End point values	GS-5829 4 mg + Exemestane	GS-5829 4 mg + Fulvestrant	GS-5829 6 mg + Fulvestrant	GS-5829 9 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[7]	0 ^[8]	0 ^[9]	0 ^[10]
Units: Not applicable				

Notes:

[7] - No participants were enrolled in the Phase 2 portion of the study.

[8] - No participants were enrolled in the Phase 2 portion of the study.

[9] - No participants were enrolled in the Phase 2 portion of the study.

[10] - No participants were enrolled in the Phase 2 portion of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Randomized Phase 2 Dose Expansion: Overall Response Rate

End point title	Randomized Phase 2 Dose Expansion: Overall Response Rate
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End point description:

Overall response rate (ORR) was defined as the proportion of participants who achieve complete response (CR) or partial response (PR), based on Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 study progression criteria. As the study was terminated prior to the Phase 2 portion of the study, no participants were enrolled in the Phase 2 portion of the study and data was not collected for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline up to 2 years

End point values	GS-5829 4 mg + Exemestane	GS-5829 4 mg + Fulvestrant	GS-5829 6 mg + Fulvestrant	GS-5829 9 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[11]	0 ^[12]	0 ^[13]	0 ^[14]
Units: Not applicable				

Notes:

[11] - No participants were enrolled in the Phase 2 portion of the study.

[12] - No participants were enrolled in the Phase 2 portion of the study.

[13] - No participants were enrolled in the Phase 2 portion of the study.

[14] - No participants were enrolled in the Phase 2 portion of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Randomized Phase 2 Dose Expansion: Clinical Benefit Rate

End point title	Randomized Phase 2 Dose Expansion: Clinical Benefit Rate
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End point description:

Clinical benefit rate (CBR) was defined as the proportion of participants who achieve CR, PR, or stable disease that lasts for > 24 weeks based on RECIST v. 1.1 study progression criteria. As the study was terminated prior to the Phase 2 portion of the study, no participants were enrolled in the Phase 2 portion of the study and data was not collected for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline up to 2 years

End point values	GS-5829 4 mg + Exemestane	GS-5829 4 mg + Fulvestrant	GS-5829 6 mg + Fulvestrant	GS-5829 9 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[15]	0 ^[16]	0 ^[17]	0 ^[18]
Units: Not applicable				

Notes:

[15] - No participants were enrolled in the Phase 2 portion of the study.

[16] - No participants were enrolled in the Phase 2 portion of the study.

[17] - No participants were enrolled in the Phase 2 portion of the study.

[18] - No participants were enrolled in the Phase 2 portion of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Randomized Phase 2 Dose Expansion: Overall Survival

End point title	Randomized Phase 2 Dose Expansion: Overall Survival
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End point description:

Overall survival was defined as the interval from date of randomization to date of death from any cause. As the study was terminated prior to the Phase 2 portion of the study, no participants were enrolled in the Phase 2 portion of the study and data was not collected for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline up to 2 years

End point values	GS-5829 4 mg + Exemestane	GS-5829 4 mg + Fulvestrant	GS-5829 6 mg + Fulvestrant	GS-5829 9 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[19]	0 ^[20]	0 ^[21]	0 ^[22]
Units: Not applicable				

Notes:

[19] - No participants were enrolled in the Phase 2 portion of the study.

[20] - No participants were enrolled in the Phase 2 portion of the study.

[21] - No participants were enrolled in the Phase 2 portion of the study.

[22] - No participants were enrolled in the Phase 2 portion of the study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose date to last dose date (average: 14.5 weeks; maximum: 53 weeks) plus 30 days

Adverse event reporting additional description:

Safety Analysis Set included all participants who were enrolled and received at least 1 dose of any study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	GS-5829 4 mg + Exemestane
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Reporting group description:

GS-5829 4 mg tablets once daily + exemestane 25 mg tablet once daily

Reporting group title	GS-5829 4 mg + Fulvestrant
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Reporting group description:

GS-5829 4 mg tablets once daily + fulvestrant 500 mg administered intramuscularly every 28 days (\pm 3 days)

Reporting group title	GS-5829 6 mg + Fulvestrant
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Reporting group description:

GS-5829 6 mg tablets once daily + fulvestrant 500 mg administered intramuscularly every 28 days (\pm 3 days)

Reporting group title	GS-5829 9 mg + Fulvestrant
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Reporting group description:

GS-5829 9 mg tablets once daily + fulvestrant 500 mg administered intramuscularly every 28 days (\pm 3 days)

Serious adverse events	GS-5829 4 mg + Exemestane	GS-5829 4 mg + Fulvestrant	GS-5829 6 mg + Fulvestrant
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 3 (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
Hypercalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	GS-5829 9 mg + Fulvestrant		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	GS-5829 4 mg + Exemestane	GS-5829 4 mg + Fulvestrant	GS-5829 6 mg + Fulvestrant
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 4 (50.00%)	2 / 3 (66.67%)	1 / 3 (33.33%)
occurrences (all)	2	2	1
Asthenia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site bruising			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Breast haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 4 (50.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Dyspnoea			
subjects affected / exposed	2 / 4 (50.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Dysphonia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Investigations			
Weight decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 3	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Nervous system disorders			
Dysgeusia subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Balance disorder subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 3
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Sciatica subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Blood and lymphatic system disorders			
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Anaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Neutropenia			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 4 (75.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	4	1	1
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)	2 / 3 (66.67%)	2 / 3 (66.67%)
occurrences (all)	1	2	2
Vomiting			
subjects affected / exposed	2 / 4 (50.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	3	0	1
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Abdominal tenderness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Irritable bowel syndrome			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Salivary hypersecretion subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0
Alopecia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Dermatitis acneiform subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 3 (33.33%) 1	1 / 3 (33.33%) 1
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 3 (33.33%) 1	1 / 3 (33.33%) 1
Arthralgia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Flank pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0

Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Musculoskeletal discomfort subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Infections and infestations			
Cellulitis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Fungal skin infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0
Gastroenteritis viral subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Herpes zoster subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Oral candidiasis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Oral infection subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Pharyngitis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Urinary tract infection			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 4 (50.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Dehydration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	GS-5829 9 mg + Fulvestrant		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Gait disturbance			

subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Injection site bruising			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Breast haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Vaginal haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Investigations			

Weight decreased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Balance disorder subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Sciatica subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 3		
Anaemia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Neutropenia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	3 / 3 (100.00%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Abdominal tenderness			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Irritable bowel syndrome			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Oral pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Salivary hypersecretion			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		

Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Dermatitis acneiform			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Rash maculo-papular			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Flank pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		

Musculoskeletal discomfort subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Pain in extremity subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Infections and infestations			
Cellulitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Fungal skin infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Gastroenteritis viral subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Herpes zoster subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Oral infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Pharyngitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Viral infection			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Dehydration			
subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2016	<ul style="list-style-type: none">• Updated inclusion/exclusion criteria• Clarified contraception methods• Clarified prior therapies• Updated clinical experience with GS-5829• Updated statistical modeling of probability of DLT occurrence rate based on emerging safety data from Studies GS-US-350-1604 and GS-US-350-1599• Clarified pregnancy testing timing
05 May 2017	<ul style="list-style-type: none">• Updated study design: 1) Phase 1b Dose Escalation: Group A (GS-5829 + exemestane) no longer enrolled past the 4-mg safety assessment, 2) Phase 2 Dose Expansion: Removal of Group 1 (GS-5829+ exemestane and exemestane alone)• Added stratification to the Phase 2 Dose Expansion. Participants were to be stratified by prior CDK4/6 inhibitor plus AI status (naive vs. progressed). The target number of participants in each of the 2 strata was approximately 60 (40 subjects for GS-5829 + fulvestrant and 20 participants for fulvestrant alone).• Reduced the Phase 1b target number of participants from 60 to 30• Revised the inclusion/exclusion criteria for clarity and due to changing study design• Defined study drug initiation as Cycle 1 Day 1 throughout the inclusion/exclusion criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 July 2018	Enrollment in Group A (GS-5829 + exemestane) was stopped following safety assessments of the 4-mg GS-5829 dose. Enrollment in Group B (GS-5829 + fulvestrant) was stopped following safety assessments of the 9-mg GS-5829 dose. The study was terminated prior to the initiation of the Phase 2 portion of the study.	-

Notes:

Limitations and caveats

None reported