Clinical trial results:
A Phase Ib/III Study of Ipatasertib Plus Palbociclib and Fulvestrant Versus Placebo Plus Palbociclib and Fulvestrant in Hormone Receptor Positive and HER2 Negative Locally Advanced Unresectable or Metastatic Breast Cancer

Summary

EudraCT number	2019-001072-11
Trial protocol	ES
Global end of trial date	29 August 2023

Results information

Result version number	v1 (current)
This version publication date	12 September 2024
First version publication date	12 September 2024

Trial information

Trial identification

Sponsor protocol code	CO41012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04060862
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.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	29 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 August 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the Phase Ib portion of the trial was to evaluate the safety and pharmacokinetics of ipatasertib in combination with palbociclib and fulvestrant to identify a dose of ipatasertib that can be combined with palbociclib and fulvestrant in the Phase III portion. The Phase III portion of this trial was never initiated.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 2019
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: 3
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 1
Worldwide total number of subjects	20
EEA total number of subjects	6

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)	18
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in this study at 12 investigative centers in 7 countries from 15 November 2019 to 29 August 2023.

Pre-assignment

Screening details:

This study was planned to include two phases- Phase Ib and Phase III. No participant was enrolled in Phase III as the study was terminated early.

Period 1

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

Arms

Arm title	Phase Ib: Ipatasertib + Palbociclib +Fulvestrant

Arm description:

Participants received ipatasertib 300 mg orally (PO) once daily (QD) during an initial 5-7 day during run-in and thereafter on Days 1-21 of each cycle (Cycle length= 28 days) along with palbociclib, 125 mg PO QD on Days 1-21 of each cycle and fulvestrant, 500 mg, intramuscularly (IM) on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent cycle for a maximum of 35 months. Only the first 10 participants received single agent ipatasertib during the initial 5-7 day safety run-in. After safety assessment of the run-in participants, further participants were enrolled in this arm to start receiving study treatments on Cycle 1 Day 1.

Arm type	Experimental
Investigational medicinal product name	Ipatasertib
Investigational medicinal product code	RO5532961, GDC-0068
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ipatasertib 300 mg, PO QD during an initial 5-7 day run-in period, then continued on Days 1-21 of Cycle 1 and each subsequent cycle (Cycle length= 28 days) thereafter.

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

Dosage and administration details:

Fulvestrant 500 mg, IM on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle.

Investigational medicinal product name	Palbociclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Palbociclib 125 mg, PO QD on Days 1-21 of each 28-day cycle.

Number of subjects in period 1	Phase Ib: Ipatasertib + Palbociclib +Fulvestrant
Started	20
Completed	0
Not completed	20
Physician decision	1
Un-specified	6
Symptomatic Deterioration	1
Progressive disease	12

Baseline characteristics

Reporting groups	
Reporting group title	Phase Ib: Ipatasertib + Palbociclib +Fulvestrant

Reporting group description:

Participants received ipatasertib 300 mg orally (PO) once daily (QD) during an initial 5-7 day during run-in and thereafter on Days 1-21 of each cycle (Cycle length= 28 days) along with palbociclib, 125 mg PO QD on Days 1-21 of each cycle and fulvestrant, 500 mg, intramuscularly (IM) on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent cycle for a maximum of 35 months. Only the first 10 participants received single agent ipatasertib during the initial 5-7 day safety run-in. After safety assessment of the run-in participants, further participants were enrolled in this arm to start receiving study treatments on Cycle 1 Day 1.

Reporting group values	Phase Ib: Ipatasertib + Palbociclib +Fulvestrant	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	54.6		
standard deviation	± 8.6	-	
Sex: Female, Male Units: participants			
Female	20	20	
Male	0	0	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	4	4	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	15	15	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity Units: Subjects			
Hispanic or Latino	4	4	
Not Hispanic or Latino	14	14	
Unknown or Not Reported	2	2	

End points

End points reporting groups

Reporting group title	Phase Ib: Ipatasertib + Palbociclib +Fulvestrant

Reporting group description:

Participants received ipatasertib 300 mg orally (PO) once daily (QD) during an initial 5-7 day during run-in and thereafter on Days 1-21 of each cycle (Cycle length= 28 days) along with palbociclib, 125 mg PO QD on Days 1-21 of each cycle and fulvestrant, 500 mg, intramuscularly (IM) on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent cycle for a maximum of 35 months. Only the first 10 participants received single agent ipatasertib during the initial 5-7 day safety run-in. After safety assessment of the run-in participants, further participants were enrolled in this arm to start receiving study treatments on Cycle 1 Day 1.

Subject analysis set title	Phase III: Ipatasertib + Palbociclib +Fulvestrant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Ipatasertib, 300 mg PO QD along with palbociclib, 125 mg PO QD on Days 1-21 of each 28-day cycle and fulvestrant, 500 mg, IM injections on Days 1 and 15 of Cycle 1, then on Day 1 of each subsequent 28-day cycle until progressive disease (PD) or unacceptable toxicity, whichever occurs first.

Subject analysis set title	Phase III: Placebo + Palbociclib + Fulvestrant
Subject analysis set type	Safety analysis

Subject analysis set description:

Placebo PO QD along with palbociclib, 125 mg PO QD on Days 1-21 of each 28-day and fulvestrant, 500 mg IM injection on Days 1 and 15 of Cycle 1, then on Day 1 of each subsequent 28-day cycle until PD or unacceptable toxicity, whichever occurs first.

Primary: Phase III: Progression-Free Survival (PFS), as Determined by the Investigator According to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

End point title	Phase III: Progression-Free Survival (PFS), as Determined by the Investigator According to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)[1]

End point description:

PFS was defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurred first. Progressive disease (PD) is at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥5 millimeters (mm). The study was terminated before the initiation of Phase III, as per the sponsor's decision. Hence, no participants were enrolled, and no data were collected, assessed, or analyzed for this endpoint.

End point type	Primary

End point timeframe:

From randomization in Phase III until the first occurrence of disease progression or death from any cause, whichever occurs first, up to approximately 36 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: Statistical analyses is not relevant for this endpoint.

End point values	Phase III: Ipatasertib + Palbociclib +Fulvestrant	Phase III: Placebo + Palbociclib + Fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[2]	0[3]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[2] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

[3] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Number of Participants with Adverse Events and Adverse Events with Severity Determined According to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)

End point title	Phase Ib: Number of Participants with Adverse Events and Adverse Events with Severity Determined According to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. Severity of AEs were rated per NCI CTCAE v5 where, Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL); Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL; Grade 4 Life-threatening consequences; urgent intervention indicated; Grade 5 Death related to AE. Safety evaluable population included all randomized participants who received any amount of study drug (i.e., ipatasertib + palbociclib + fulvestrant).

End point type	Secondary

End point timeframe:

Up to 36 Months

End point values	Phase Ib: Ipatasertib + Palbociclib +Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants				
Any AE: Any Grade	20			
Grade 1	3			
Grade 2	3			
Grade 3	12			
Grade 4	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Plasma Concentration of Ipatasertib and its Metabolite G-037720

End point title	Phase Ib: Plasma Concentration of Ipatasertib and its Metabolite G-037720

End point description:

Plasma concentrations of Ipatasertib and its metabolite G-037720 are reported. Pharmacokinetic (PK)-evaluable population included all participants who received study treatment. Number analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Cycle 1, Day 1 and 15: 0.25 hours pre-dose, 0.5, 1, 2, 3, 4 and 6 hours post- dose ; Cycle 2, Day 15: 0.25 hours pre-dose; Cycle 3, Day 15: 0.15 hours pre-dose, 2 hours post-dose (each cycle = 28 days)

End point values	Phase Ib: Ipatasertib + Palbociclib +Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Ipatasertib: Cycle 1 Day 15 0.25-hr pre-dose	46.6 (± 56.0)			
Ipatasertib: Cycle 1 Day 15 0.5-hr postdose	150 (± 112.3)			
Ipatasertib: Cycle 1 Day 15 1-hr postdose	236 (± 83.4)			
Ipatasertib: Cycle 1 Day 15 2-hr postdose	299 (± 68.0)			
Ipatasertib: Cycle 1 Day 15 3-hr postdose	290 (± 34.2)			
Ipatasertib: Cycle 1 Day 15 4-hr postdose	244 (± 30.2)			
Ipatasertib: Cycle 1 Day 15 6-hr postdose	192 (± 40.1)			
Ipatasertib: Cycle 2 Day 15 0.25-hr predose	42.8 (± 46.4)			
Ipatasertib: Cycle 3 Day 15 0.15-hr predose	37.6 (± 58.3)			
Ipatasertib: Cycle 3 Day 15 2-hr postdose	258 (± 40.8)			
G-037720: Cycle 1 Day 15 0.25-hr predose	22.9 (± 69.3)			
G-037720: Cycle 1 Day 15 0.5-hr postdose	38.2 (± 82.5)			
G-037720: Cycle 1 Day 15 1-hr postdose	74.1 (± 96.3)			
G-037720: Cycle 1 Day 15 2-hr postdose	110 (± 74.0)			
G-037720: Cycle 1 Day 15 3-hr postdose	116 (± 47.6)			
G-037720: Cycle 1 Day 15 4-hr postdose	99.9 (± 47.9)			
G-037720: Cycle 1 Day 15 6-hr postdose	81.2 (± 52.7)			
G-037720: Cycle 2 Day 15 0.25-hr predose	17.5 (± 45.6)			
G-037720: Cycle 3 Day 15 0.15-hr predose	16.4 (± 45.2)			

G-037720: Cycle 3 Day 15 2-hr postdose	92.5 (± 40.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Maximum Concentration (Cmax) of Ipatasertib and its Metabolite G-037720 in Plasma

End point title	Phase Ib: Maximum Concentration (Cmax) of Ipatasertib and its Metabolite G-037720 in Plasma

End point description:

Cmax of ipatasertib and its metabolite G-037720 in plasma are reported. PK-evaluable population included all participants who received study treatment. Number analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Cycle 1: Day 1 and Day 15

End point values	Phase Ib: Ipatasertib + Palbociclib +Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Ipatasertib: Cycle 1 Day 1	294 (± 52.6)			
Ipatasertib: Cycle 1 Day 15	437 (± 41.1)			
G-037720: Cycle 1 Day 1	120 (± 84.2)			
G-037720: Cycle 1 Day 15	137 (± 53.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Time to Maximum Concentration (Tmax) of Ipatasertib and its Metabolite G-037720

End point title	Phase Ib: Time to Maximum Concentration (Tmax) of Ipatasertib and its Metabolite G-037720

End point description:

Tmax of ipatasertib and its metabolite G-037720 are reported. PK-evaluable population included all participants who received study treatment. Number analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Cycle 1: Day 1 and Day 15

End point values	Phase Ib: Ipatasertib + Palbociclib +Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: hours				
median (full range (min-max))				
Ipatasertib: Cycle 1 Day 1	1.00 (0.50 to 4.00)			
Ipatasertib: Cycle 1 Day 15	1.92 (0.50 to 4.00)			
G-037720: Cycle 1 Day 1	2.00 (0.97 to 4.00)			
G-037720: Cycle 1 Day 15	2.00 (1.00 to 3.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Area Under the Plasma Concentration Time-curve From Zero to 24 Hours (AUC0-24) of Ipatasertib and its Metabolite G-037720

End point title	Phase Ib: Area Under the Plasma Concentration Time-curve From Zero to 24 Hours (AUC0-24) of Ipatasertib and its Metabolite G-037720

End point description:

AUC0-24 of Ipatasertib and its metabolite G-037720 is reported. PK-evaluable population included all participants who received study treatment. Number analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Cycle 1: Day 1 and Day 15

End point values	Phase Ib: Ipatasertib + Palbociclib +Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: hour*nanograms/milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
Ipatasertib: Cycle 1 Day 1	2169.88 (± 43.6)			

Ipatasertib: Cycle 1 Day 15	3636.97 (± 33.7)			
G-037720: Cycle 1 Day 1	1157.02 (± 76.6)			
G-037720: Cycle 1 Day 15	1391.60 (± 44.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase III: Objective Response Rate (ORR) as Determined by the Investigator According to RECIST v1.1

End point title	Phase III: Objective Response Rate (ORR) as Determined by the Investigator According to RECIST v1.1

End point description:

ORR was defined as the percentage of participants with a complete response (CR) or partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1. CR is defined as the disappearance of all target lesions. Any pathological lymph nodes must have a reduction in the short axis to <10 mm. PR is defined as at least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. The study was terminated before the initiation of Phase III, as per the sponsor's decision. Hence, no participants were enrolled, and no data were collected, assessed, or analyzed for this endpoint.

End point type	Secondary

End point timeframe:

From randomization in Phase III up to approximately 36 months

End point values	Phase III: Ipatasertib + Palbociclib +Fulvestrant	Phase III: Placebo + Palbociclib + Fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[4]	0[5]		
Units: percentage of participants				
number (not applicable)				

Notes:

[4] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

[5] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase III: Duration of Objective Response (DOR) as Determined by the Investigator According to RECIST v1.1

End point title	Phase III: Duration of Objective Response (DOR) as Determined by the Investigator According to RECIST v1.1

End point description:

DOR=time from first occurrence of documented objective response to first occurrence of disease progression per the investigator per RECIST v1.1, or death from any cause, whichever occurs first. Objective response per RECIST v1.1 criteria: CR=disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm. PR=at least 30% decrease in sum of

diameters (SOD) of all target lesions, taking as reference the baseline SOD, in absence of CR. PD=at least 20% increase in the SOD of target lesions, taking as reference the smallest SOD at prior timepoints (including baseline). In addition to relative increase of 20%, SOD must also demonstrate absolute increase of ≥5 mm. Stable disease (SD)=neither sufficient shrinkage to qualify for CR/PR nor sufficient increase to qualify for PD. The study was terminated before initiation of Phase III, per sponsor's decision. Hence, no participants were enrolled, & no data were collected or analyzed for this

End point type	Secondary

End point timeframe:

From randomization in Phase III until the first occurrence of disease progression or death from any cause, whichever occurs first, up to approximately 36 months

End point values	Phase III: Ipatasertib + Palbociclib +Fulvestrant	Phase III: Placebo + Palbociclib + Fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[6]	0[7]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[6] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

[7] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase III: Clinical Benefit Rate (CBR) as Determined by the Investigator According to RECIST v1.1

End point title	Phase III: Clinical Benefit Rate (CBR) as Determined by the Investigator According to RECIST v1.1

End point description:

CBR = percentage of participants with CR/PR, or SD for at least 24 weeks, as determined by investigator per RECIST v1.1. CR = disappearance of all target lesions. Any pathological lymph nodes must have a reduction in the short axis to <10 mm. PR = at least a 30% decrease in sum of diameters of all target lesions, taking as reference baseline sum of diameters, in absence of CR. SD = neither sufficient shrinkage to qualify for CR/PR nor sufficient increase to qualify for PD. PD = at least a 20% increase in sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline). In addition to the relative increase of 20%, sum of diameters must also demonstrate an absolute increase of ≥ 5 mm. The study was terminated before the initiation of Phase III, as per the sponsor's decision. Hence, no participants were enrolled, and no data were collected, assessed, or analyzed for this endpoint.

End point type	Secondary

End point timeframe:

From randomization in Phase III until the first occurrence of disease progression or death from any cause, whichever occurs first, up to approximately 36 months

End point values	Phase III: Ipatasertib + Palbociclib +Fulvestrant	Phase III: Placebo + Palbociclib + Fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[8]	0[9]		
Units: percentage of participants				
number (not applicable)				

Notes:

[8] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

[9] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase III: Overall Survival (OS) as Determined by the Investigator According to RECIST v1.1

End point title	Phase III: Overall Survival (OS) as Determined by the Investigator According to RECIST v1.1

End point description:

OS was defined as the time from randomization to death from any cause. The study was terminated before the initiation of Phase III, as per the sponsor's decision. Hence, no participants were enrolled, and no data were collected, assessed, or analyzed for this endpoint.

End point type	Secondary

End point timeframe:

From randomization in Phase III until the first occurrence of disease progression or death from any cause, whichever occurs first, up to approximately 36 months

End point values	Phase III: Ipatasertib + Palbociclib +Fulvestrant	Phase III: Placebo + Palbociclib + Fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[10]	0[11]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[10] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

[11] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase III: Time to Deterioration (TTD) in Severity of Pain, According to the Brief Pain Inventory-Short Form (BPI-SF)

End point title	Phase III: Time to Deterioration (TTD) in Severity of Pain, According to the Brief Pain Inventory-Short Form (BPI-SF)

End point description:

TTD in severity of pain is defined as the time from randomization to the first documentation of a 2-point or more increase from baseline on the "worst pain" item from the BPI-SF. A 2-point change is defined as

clinically meaningful. The BPI-SF is a widely used patient-reported outcome (PRO) for assessing pain, and the "worst pain" item, frequently used for evaluating increases in the severity of pain. The BPI-SF asks participants to rate their pain at its worst in the last week on a scale from 0 (No pain) to 10 (Pain as bad as one can imagine). Higher score indicates more pain. The study was terminated before the initiation of Phase III, as per the sponsor's decision. Hence, no participants were enrolled, and no data were collected, assessed, or analyzed for this endpoint.

End point type	Secondary

End point timeframe:

From randomization in Phase III to the first documentation of a ≥2-point increase in pain scale, (up to approximately 36 months)

End point values	Phase III: Ipatasertib + Palbociclib +Fulvestrant	Phase III: Placebo + Palbociclib + Fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[12]	0[13]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[12] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.
[13] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase III: TTD in Presence and Interference of Pain According to the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30) Pain Scale

End point title	Phase III: TTD in Presence and Interference of Pain According to the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30) Pain Scale

End point description:

TTD in presence & interference of pain=time from randomization to first documentation of ≥10-point increase from baseline in EORTC QLQ-C30 pain scale (items 9 & 19). EORTC QLQ-C30=validated 30-item measure assessing 5 aspects of participant functioning (physical, emotional, role, cognitive &social), 8 symptom scales (fatigue, nausea &vomiting, pain, dyspnea, insomnia, appetite loss, constipation, & diarrhea), financial difficulties &global health status/QoL. Functioning &symptoms items, scored on 4-point scale (1=not at all to 4=very much). Pain scale, scored on 4-point scale (1=Not at All to 4=Very Much) including Item 9: have you had pain? & Item 19: did pain interfere with your daily activity? both range from 1=not at All to 4=very much. Sub-scores are linearly transformed to a range of 0-100. High scores=worse pain symptoms. Study was terminated before initiation of Phase III, per sponsor's decision. Hence, no participants were enrolled & no data was collected for this endpoint.

End point type	Secondary

End point timeframe:

From randomization in Phase III to the first documentation of a ≥10-point increase (up to approximately 36 months)

End point values	Phase III: Ipatasertib + Palbociclib +Fulvestrant	Phase III: Placebo + Palbociclib + Fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[14]	0[15]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[14] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

[15] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase III: TTD in Physical Functioning (PF), Role Functioning (RF), and GHS/QoL According to EORTC QLQ-C30

End point title	Phase III: TTD in Physical Functioning (PF), Role Functioning (RF), and GHS/QoL According to EORTC QLQ-C30

End point description:

TTD in PF, RF & GHS/QoL = time to first documented ≥10-point decrease from baseline in following scales of EORTC QLQ-C30: PF, RF & GHS/QoL. EORTC QLQ-C30 is validated 30-item self-report measure assessing 5 aspects of participant functioning (physical, emotional, role, cognitive, & social), eight symptom scales (fatigue, nausea & vomiting, pain, dyspnea, insomnia, appetite loss, constipation, & diarrhea), financial difficulties, & GHS/QoL with recall period of previous week. The PF scale has 5 questions about participants' physical functioning. PF & RF scales are scored on 4-point scale (1=Not at All to 4=Very Much). The GHS/QoL scale has 7 possible scores of responses (1=Very poor to 7=Excellent). Scores are linearly transformed to score range of 0-100, higher score indicate higher response level. The study was terminated before initiation of Phase III as per sponsor’s decision; hence this outcome measure was not assessed & no data collected.

End point type	Secondary

End point timeframe:

From randomization in Phase III to the first documentation of a ≥10-point decrease in the PF, RF and GHS/QoL function of EORTC QLQ-C30, (up to approximately 36 months)

End point values	Phase III: Ipatasertib + Palbociclib +Fulvestrant	Phase III: Placebo + Palbociclib + Fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[16]	0[17]		
Units: weeks				
median (confidence interval 95%)	(to)	(to)		

Notes:

[16] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

[17] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase III: Number of Participants with Adverse Events

End point title	Phase III: Number of Participants with Adverse Events

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any unfavorable and unintended sign symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product; any new disease or exacerbation of an existing disease; recurrence of an intermittent medical condition; any deterioration in a laboratory value or other clinical test; AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment. The study was terminated before the initiation of Phase III, as per the sponsor's decision. Hence, no participants were enrolled, and no data were collected, assessed, or analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Up to approximately 36 months

End point values	Phase III: Ipatasertib + Palbociclib +Fulvestrant	Phase III: Placebo + Palbociclib + Fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[18]	0[19]		
Units: participants				

Notes:

[18] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.
[19] - No participants were enrolled in Phase III as the study was terminated early per sponsors decision.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Upto 36 months

Adverse event reporting additional description:

Safety evaluable population included all randomized participants who received any amount of study drug (i.e., ipatasertib + palbociclib + fulvestrant).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Phase 1b: Ipatasertib + Palbociclib +Fulvestrant

Reporting group description:

Participants received ipatasertib 300 mg PO QD during an initial 5-7 day run-in, and thereafter on Days 1-21 of each cycle (Cycle length= 28 days) along with palbociclib, 125 mg PO QD on Days 1-21 of each cycle and fulvestrant, 500 mg, IM on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent cycle for a maximum of 35 months. Only the first 10 participants received single agent ipatasertib during the initial 5-7 day safety run-in. After safety assessment of the run-in participants, further participants were enrolled in this arm to start receiving study treatments on Cycle 1 Day 1.

Serious adverse events	Phase 1b: Ipatasertib + Palbociclib +Fulvestrant		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 20 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Soft tissue infection			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudomembranous colitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase 1b: Ipatasertib + Palbociclib +Fulvestrant		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	5		
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Thrombosis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Asthenia			

subjects affected / exposed	8 / 20 (40.00%)			
occurrences (all)	8			
Application site pain				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Chills				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Fatigue				
subjects affected / exposed	5 / 20 (25.00%)			
occurrences (all)	5			
Oedema peripheral				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Mucosal inflammation				
subjects affected / exposed	4 / 20 (20.00%)			
occurrences (all)	5			
Malaise				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Injection site reaction				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Injection site pain				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Influenza like illness				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Pyrexia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Peripheral swelling				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Pain				

subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Wheezing subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	 3 / 20 (15.00%) 3 3 / 20 (15.00%) 3 5 / 20 (25.00%) 6 1 / 20 (5.00%) 1 3 / 20 (15.00%) 3		
Psychiatric disorders Hallucination subjects affected / exposed occurrences (all) Confusional state subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 3 / 20 (15.00%) 3 2 / 20 (10.00%) 2		
Investigations			

Aspartate aminotransferase increased			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	5		
Alanine aminotransferase increased			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	3		
Lymphocyte count decreased			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Neutrophil count decreased			
subjects affected / exposed	8 / 20 (40.00%)		
occurrences (all)	20		
Platelet count decreased			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	22		
Weight decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Accidental overdose			

subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	6		
Contusion			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin abrasion			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Radiation pneumonitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Muscle injury			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Overdose			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Dysgeusia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Paresis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Paraesthesia			

subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Neuropathy peripheral subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Hypoaesthesia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Headache subjects affected / exposed occurrences (all)	6 / 20 (30.00%) 10		
Spinal cord compression subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	9 / 20 (45.00%) 30		
Anaemia subjects affected / exposed occurrences (all)	8 / 20 (40.00%) 13		
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 2		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Eye disorders Dry eye subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Dacryostenosis acquired subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Gastrointestinal disorders			

Abdominal distension				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Abdominal pain				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	2			
Abdominal pain lower				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Abdominal pain upper				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	4			
Abdominal tenderness				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Constipation				
subjects affected / exposed	10 / 20 (50.00%)			
occurrences (all)	11			
Dysphagia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	5 / 20 (25.00%)			
occurrences (all)	7			
Diarrhoea				
subjects affected / exposed	17 / 20 (85.00%)			
occurrences (all)	70			
Flatulence				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Gingival pain				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	16 / 20 (80.00%)			
occurrences (all)	25			

Vomiting			
subjects affected / exposed	10 / 20 (50.00%)		
occurrences (all)	13		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cellulite			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Night sweats			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Urticaria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pruritus			

subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	8 / 20 (40.00%)		
occurrences (all)	11		
Rash maculo-papular			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Rash pruritic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	7		
Arthralgia			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Bone pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Sacral pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Musculoskeletal chest pain			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Muscle spasms			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Flank pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Neck pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Subcutaneous abscess			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Injection site infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Varicella zoster virus infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	6		
Dehydration			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hypercholesterolaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Hypertriglyceridaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2019	- Risks Associated with Palbociclib: The new risk, interstitial lung disease (ILD)/pneumonitis was added. - Section on Pneumonitis was updated to reflect this new risk and to state the specific guidance required for palbociclib. Additional safety measures were added to the Adverse Event Management Guidance. - Inclusion Criteria and Exclusion Criteria, the timing of the contraception requirement and the corresponding intent to become pregnant after permanent discontinuation of study treatment given the differential requirements for fulvestrant based on different local prescribing information was clarified.
12 February 2020	- Restriction of relapse specifically during the initial 5 years was removed throughout the protocol. - Pneumonitis was added to the list of potentially overlapping toxicities that may be exacerbated when combining ipatasertib and palbociclib. - Addition of "worst pain" item from the Brief Pain Inventory-Short Form (BPI-SF) and European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Breast Cancer Module 23 (EORTC QLQ-BR23). - Eligibility criteria for the phase III portion were updated to no longer allow prior CDK4/6 inhibitor for locally advanced unresectable or metastatic breast cancer. - The sampling window for post-dose PK samples for Phase III patients on Cycle 1, Day 1 and Cycle 1, Day 15 were updated and aligned with that on Cycle 2, Day 15 so that PK can be compared between cycles more easily - A clarification was added that after the end of the adverse event reporting period, only participants in the Phase III portion of the study will be followed for long-term survival. - An additional exclusion criterion of no more than 1 prior line of endocrine-based therapy for Phase III participants was added. - Guidance for resuming palbociclib for Grade 1 interstitial lung disease/pneumonitis was provided. - The screening windows for participants in Phase Ib were updated for consistency with the remainder of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
29 August 2023	The study was terminated before initiation of Phase III as per sponsor's decision; hence no primary efficacy and secondary efficacy, safety and pharmacokinetic outcome measures were assessed or analyzed, and no data was collected for Phase III.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the early termination Phase III portion of the trial was not evaluated.

Notes: