Clinical trial results:
Phase III study evaluating palbociclib (PD-0332991), a cyclin-dependent kinase (CDK) 4/6 inhibitor, in patients with hormone-receptor positive, HER2 normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy (PENELOPE-B trial).

Summary

EudraCT number	2013-001040-62
Trial protocol	DE ES AT IE FR GB
Global end of trial date	21 December 2020

Results information

Result version number	v1 (current)
This version publication date	27 October 2021
First version publication date	27 October 2021
Summary attachment (see zip file)	Penelope CSR Synopsis (GBG78_PENELOPE-B_CSR_V3.0 28Apr2021_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	GBG78/BIG1-13

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01864746
WHO universal trial number (UTN)	-
Other trial identifiers	IND FDA: 123239

Notes:

Sponsors

Sponsor organisation name	GBG Forschungs GmbH
Sponsor organisation address	Martin Behaim Str. 12, Neu-Isenburg, Germany,
Public contact	Medicine and Research, GBG Forschungs GmbH, +49 610274800, Publications@GBG.de
Scientific contact	Medicine and Research, GBG Forschungs GmbH, +49 610274800, Publications@GBG.de

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	30 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 August 2020
Global end of trial reached?	Yes
Global end of trial date	21 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare invasive disease free survival (iDFS) for palbociclib vs. placebo in patients with residual invasive breast cancer and high CPS-EG score after neoadjuvant chemotherapy receiving standard adjuvant endocrine therapy for hormone-receptor positive, HER2 normal primary breast cancer.

Protection of trial subjects:

The trial protocol including amendments, the patient information and the informed consent were reviewed and approved from a properly constituted IRB/IEC for each site prior to the study start. The study was conducted in accordance with the Declaration of Helsinki and its revisions, the International Conference on Harmonization (ICH) - Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), and in accordance with applicable laws of the pertinent regulatory authorities in all aspects of preparation, monitoring, reporting, auditing, and archiving. IDMC was to ensure the ethical conduct of the trial and to protect patients' safety interests in this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 October 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 171
Country: Number of subjects enrolled	Korea, Republic of: 50
Country: Number of subjects enrolled	Japan: 45
Country: Number of subjects enrolled	Australia: 90
Country: Number of subjects enrolled	Spain: 263
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Austria: 25
Country: Number of subjects enrolled	France: 121
Country: Number of subjects enrolled	Germany: 434
Country: Number of subjects enrolled	Ireland: 47
Worldwide total number of subjects	1250
EEA total number of subjects	890

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)	1126
From 65 to 84 years	124
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 4 years (Q-I 2014 –Q-IV 2017) in 221 sites worldwide (11 countries). 1708 patients were screened, 1250 patients were
randomized (Palbociclib 631; Placebo 619).

Pre-assignment

Screening details:

Female patients >=18 years with residual invasive disease after NACT (in breast or lymph nodes), centrally assessed ER+ and/or PgR+ and HER2- tumors
and centrally assessed Ki-67 status and a CPS-EG score of >=3 or 2 with ypN1 (after amendment 3, February 9, 2015) were eligible. >=16weeks NACT (incl. 6 weeks taxane), surgery and radiation received.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Palbociclib

Arm description:

palbociclib at a dose of 125 mg once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for 13 cycles

Arm type	Experimental
Investigational medicinal product name	Palbociclib
Investigational medicinal product code	PD-0332991
Other name	Ibrance®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

palbociclib at a dose of 125 mg once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for 13 cycles

Arm title	Placebo

Arm description:

Placebo of palbociclib once daily Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for 13 cycles.

Arm type	Placebo
Investigational medicinal product name	Placebo of palbociclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The placebo of palbociclib matched the various palbociclib formulations in size and Color. Placebo of palbociclib once daily Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for thirteen cycles.

Number of subjects in period 1	Palbociclib	Placebo
Started	631	619
Completed	508	523
Not completed	123	96
Adverse event, serious fatal	2	1
Consent withdrawn by subject	56	41
Physician decision	5	6
Disease recurrence	25	40
Adverse event, non-fatal	33	5
Second primary invasive nonbreast cancer	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Palbociclib
Reporting group description:	
palbociclib at a dose of 125 mg once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for 13 cycles	

Reporting group title	Placebo
Reporting group description:	
Placebo of palbociclib once daily Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for 13 cycles.	

Reporting group values	Palbociclib	Placebo	Total
Number of subjects	631	619	1250
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	49	48	
full range (min-max)	22 to 76	19 to 79	-
Gender categorical			
Units: Subjects			
Female	631	619	1250
Male	0	0	0

End points

End points reporting groups

Reporting group title	Palbociclib

Reporting group description:

palbociclib at a dose of 125 mg once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for 13 cycles

Reporting group title	Placebo

Reporting group description:

Placebo of palbociclib once daily Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for 13 cycles.

Primary: invasive disease-free survival, estimated 3-year iDFS rate

End point title	invasive disease-free survival, estimated 3-year iDFS rate

End point description:

The following events were considered as first events:
- Ipsi- or contralateral invasive in-breast or loco-regional recurrence
- Distant recurrence
- Death from breast cancer
- Death from non-breast cancer cause
- Death from unknown cause
- Invasive contralateral breast cancer
- Second primary invasive cancer (non-breast)

End point type	Primary

End point timeframe:

time in months between randomization and first event

End point values	Palbociclib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	631[1]	619[2]		
Units: percent				
number (not applicable)	81.2	77.7		

Notes:

[1] - At median FU of 42.8 months, 152 patients had an event

[2] - At median FU of 42.8 months, 156 patients had an event

Statistical analyses

Statistical analysis title	Stratified log-rank (CHW)

Statistical analysis description:

To address the concern of possible inflation of the type I error because of the sample size increase, statistical significance was determined using a weighted statistic of the stratified log-rank test (stratified by risk status, nodal involvement after surgery, Ki-67, age, but not global region of participating site, as prespecified in the Protocol) based on the method of CHW (Cui L, Hung HM, Wamg SJ. Biometrics 1999) with CHW interim monitoring implemented in EAST version 6.5 (Cytel Inc).

Comparison groups	Palbociclib v Placebo

Number of subjects included in analysis	1250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.525 [3]
Method	Logrank

Notes:

[3] - Stratified log-rank (CHW) P = 0.525
HR: Palbociclib to Placebo 0.93, 95% RCI (CHW) (0.74, 1.17); RCI=Repeated CI taking into account the adaptive sample size re-estimation and group-sequential nature of the design

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring during the study treatment period were reported.

Adverse event reporting additional description:

Non-serious AEs are reported per pt; any grade (1-4) predefined AEs during the complete treatment duration for the overall safety population.
Other AEs (non-predefined) are listed if occurring in >20%
Note, overall number of single AE occurrences per term was not assessed, only per pt.
Preferred term of SAEs are listed if they occurred >1

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Palbociclib
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Palbociclib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	59 / 633 (9.32%)	54 / 611 (8.84%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign and malignant (including cysts and polyps)			
subjects affected / exposed	1 / 633 (0.16%)	4 / 611 (0.65%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 633 (0.32%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures			

subjects affected / exposed	0 / 633 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	1 / 633 (0.16%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	2 / 633 (0.32%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	2 / 633 (0.32%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	1 / 633 (0.16%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	7 / 633 (1.11%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	4 / 7	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	2 / 633 (0.32%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Seroma			
subjects affected / exposed	2 / 633 (0.32%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 633 (0.00%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	2 / 633 (0.32%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 633 (0.16%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 633 (0.32%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 633 (0.32%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	1 / 633 (0.16%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorders			

subjects affected / exposed	1 / 633 (0.16%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	3 / 633 (0.47%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepato-biliary disorders			
subjects affected / exposed	0 / 633 (0.00%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	3 / 633 (0.47%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal, connective tissue and bone disorders			
subjects affected / exposed	3 / 633 (0.47%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	4 / 633 (0.63%)	5 / 611 (0.82%)	
occurrences causally related to treatment / all	1 / 4	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	3 / 633 (0.47%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	3 / 633 (0.47%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 633 (0.00%)	3 / 611 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 633 (0.16%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 633 (0.16%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 633 (0.32%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	2 / 633 (0.32%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Palbociclib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	632 / 633 (99.84%)	610 / 611 (99.84%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	277 / 633 (43.76%)	311 / 611 (50.90%)	
occurrences (all)	277	311	
Hypertension			

subjects affected / exposed	54 / 633 (8.53%)	60 / 611 (9.82%)	
occurrences (all)	54	60	
Embolism			
subjects affected / exposed	13 / 633 (2.05%)	7 / 611 (1.15%)	
occurrences (all)	13	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	420 / 633 (66.35%)	312 / 611 (51.06%)	
occurrences (all)	420	312	
Peripheral oedema			
subjects affected / exposed	126 / 633 (19.91%)	99 / 611 (16.20%)	
occurrences (all)	126	99	
Pyrexia			
subjects affected / exposed	71 / 633 (11.22%)	49 / 611 (8.02%)	
occurrences (all)	71	49	
Other general disorders and administration site conditions	Additional description: other (non-predefined) AE		
subjects affected / exposed	150 / 633 (23.70%)	148 / 611 (24.22%)	
occurrences (all)	150	148	
Reproductive system and breast disorders			
Vaginal dryness			
subjects affected / exposed	52 / 633 (8.21%)	55 / 611 (9.00%)	
occurrences (all)	52	55	
Vaginal hemorrhage			
subjects affected / exposed	12 / 633 (1.90%)	15 / 611 (2.45%)	
occurrences (all)	12	15	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	132 / 633 (20.85%)	99 / 611 (16.20%)	
occurrences (all)	132	99	
Dyspnoea			
subjects affected / exposed	73 / 633 (11.53%)	43 / 611 (7.04%)	
occurrences (all)	73	43	
Epistaxis			

subjects affected / exposed	38 / 633 (6.00%)	8 / 611 (1.31%)	
occurrences (all)	38	8	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	138 / 633 (21.80%)	141 / 611 (23.08%)	
occurrences (all)	138	141	
Aspartate aminotransferase increased			
subjects affected / exposed	131 / 633 (20.70%)	102 / 611 (16.69%)	
occurrences (all)	131	102	
Blood alkaline phosphatase increased			
subjects affected / exposed	106 / 633 (16.75%)	120 / 611 (19.64%)	
occurrences (all)	106	120	
Blood creatinine increased			
subjects affected / exposed	78 / 633 (12.32%)	67 / 611 (10.97%)	
occurrences (all)	78	67	
Blood albumin decreased			
subjects affected / exposed	63 / 633 (9.95%)	46 / 611 (7.53%)	
occurrences (all)	63	46	
Blood bilirubin increased			
subjects affected / exposed	42 / 633 (6.64%)	44 / 611 (7.20%)	
occurrences (all)	42	44	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	41 / 633 (6.48%)	32 / 611 (5.24%)	
occurrences (all)	41	32	
Headache	Additional description: other (non-predefined) AE		
subjects affected / exposed	147 / 633 (23.22%)	141 / 611 (23.08%)	
occurrences (all)	147	141	
Other nervous system disorders	Additional description: other (non-predefined) AE		
subjects affected / exposed	133 / 633 (21.01%)	138 / 611 (22.59%)	
occurrences (all)	133	138	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	628 / 633 (99.21%)	427 / 611 (69.89%)	
occurrences (all)	628	427	
Neutropenia			

subjects affected / exposed	606 / 633 (95.73%)	143 / 611 (23.40%)	
occurrences (all)	606	143	
Anaemia			
subjects affected / exposed	468 / 633 (73.93%)	185 / 611 (30.28%)	
occurrences (all)	468	185	
Thrombopenia			
subjects affected / exposed	358 / 633 (56.56%)	99 / 611 (16.20%)	
occurrences (all)	358	99	
Febrile neutropenia			
subjects affected / exposed	16 / 633 (2.53%)	1 / 611 (0.16%)	
occurrences (all)	16	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	46 / 633 (7.27%)	43 / 611 (7.04%)	
occurrences (all)	46	43	
Eye disorders			
Cataract			
subjects affected / exposed	6 / 633 (0.95%)	7 / 611 (1.15%)	
occurrences (all)	6	7	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	150 / 633 (23.70%)	126 / 611 (20.62%)	
occurrences (all)	150	126	
Stomatitis			
subjects affected / exposed	174 / 633 (27.49%)	53 / 611 (8.67%)	
occurrences (all)	174	53	
Constipation			
subjects affected / exposed	140 / 633 (22.12%)	84 / 611 (13.75%)	
occurrences (all)	140	84	
Diarrhoea			
subjects affected / exposed	116 / 633 (18.33%)	96 / 611 (15.71%)	
occurrences (all)	116	96	
Vomiting			
subjects affected / exposed	66 / 633 (10.43%)	57 / 611 (9.33%)	
occurrences (all)	66	57	
Abdominal distension			

subjects affected / exposed	17 / 633 (2.69%)	21 / 611 (3.44%)	
occurrences (all)	17	21	
Other gastrointestinal disorders	Additional description: other (non-predefined) AE		
subjects affected / exposed	147 / 633 (23.22%)	107 / 611 (17.51%)	
occurrences (all)	147	107	
Skin and subcutaneous tissue disorders			
Other skin and subcutaeneous tissue disorders	Additional description: other (non-predefined) AE		
subjects affected / exposed	175 / 633 (27.65%)	145 / 611 (23.73%)	
occurrences (all)	175	145	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	261 / 633 (41.23%)	286 / 611 (46.81%)	
occurrences (all)	261	286	
Myalgia			
subjects affected / exposed	128 / 633 (20.22%)	113 / 611 (18.49%)	
occurrences (all)	128	113	
Bone pain			
subjects affected / exposed	109 / 633 (17.22%)	117 / 611 (19.15%)	
occurrences (all)	109	117	
Other musculoskeletal, connective tissue and bone disorders	Additional description: other (non-predefined) AE		
subjects affected / exposed	122 / 633 (19.27%)	133 / 611 (21.77%)	
occurrences (all)	122	133	
Infections and infestations			
Infection			
subjects affected / exposed	379 / 633 (59.87%)	312 / 611 (51.06%)	
occurrences (all)	379	312	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	223 / 633 (35.23%)	149 / 611 (24.39%)	
occurrences (all)	223	149	
Hypomagnesemia			
subjects affected / exposed	186 / 633 (29.38%)	173 / 611 (28.31%)	
occurrences (all)	186	173	
Hyperkalemia			

subjects affected / exposed	67 / 633 (10.58%)	80 / 611 (13.09%)	
occurrences (all)	67	80	
Hypernatraemia			
subjects affected / exposed	57 / 633 (9.00%)	52 / 611 (8.51%)	
occurrences (all)	57	52	
Hyponatraemia			
subjects affected / exposed	47 / 633 (7.42%)	41 / 611 (6.71%)	
occurrences (all)	47	41	
Hypokalaemia			
subjects affected / exposed	52 / 633 (8.21%)	30 / 611 (4.91%)	
occurrences (all)	52	30	
Decreased appetite			
subjects affected / exposed	51 / 633 (8.06%)	29 / 611 (4.75%)	
occurrences (all)	51	29	
Hypercalcaemia			
subjects affected / exposed	20 / 633 (3.16%)	27 / 611 (4.42%)	
occurrences (all)	20	27	
Glucose tolerance impaired			
subjects affected / exposed	14 / 633 (2.21%)	14 / 611 (2.29%)	
occurrences (all)	14	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2014	Protocol B (Version 7, 12-Jun-2014) Editorial Amendment to update the protocol version B, with the administrative letters 1-4 (DIL) into the protocol, update of Appendix 10 (Declaration of Helsinki).
06 August 2014	Protocol C (Version 8, 06-Aug-2014) Prognostic Marker Inclusion Criterion #12 with score CPS-EG, allowed now the use of surgical biopsy: … using local estrogen receptor status and grade assessed on core biopsies taken before start of neoadjuvant treatment either / or surgical biopsy. Predictive Marker Inclusion Criterion #5, had to be PR positive in residual tissue or with the core biopsy: … (>=1% ER and/or PR positive stained cells). Retreatment and dose reduction section: Increased clarifications to guidance was provided based on gained experience in the palbociclib program. Exclusion criterion #14 now allowed prior neoadjuvant treatment to allow the entry of patients from ADAPT and similar trials: Prior neoadjuvant treatment was acceptable. Section 6.3.3 "Human Pharmacokinetik Data", Section 6.3.4 "QTc Evaluation Data, Chapter 6.3.7 "Combination with other endocrine agents", and Section 6.3.8 "Long Term Toxicity Data" were updated with the most recent nonclinical and clinical information. The blood sample for ctDNA was increased from 10 ml to 20 ml. Editorial amendment to update protocol version C with administrative letter 5 (DIL), FDA-IND number amended.
09 February 2015	Protocol D (Version 9, 09-Feb-2015) Inclusion criterion #5: Clarification for testing in case of bilateral breast cancer; inclusion criterion #6: Centrally testing possibility was extended to core biopsy; inclusion criterion #12: Now allowed patients with a CPS-EG Score of 2, if ypN+, to participate; exclusion criterion #15: Proton Pump Inhibitors were no longer unallowed. Addition of additional stratification criteria: CPS EG score 3 vs. 2 and ypN+. Update of Section 6.3.3 "Human Pharmacokinetic (PK) Data; update of Section 12.5.1 "Prohibited Medication", proton pump inhibitors removed; update of section 15.5 ff: Statistical Analysis due to change of inclusion criterion.

12 April 2016	Protocol E (Version 10, 12-Apr-2016) Inclusion criterion #2: Specification for bilaterial breast cancer was added; inclusion criterion #5: Specification which tissue could be used for central testing was added; inclusion criterion #6: Specification for bilaterial breast cancer was added; inclusion criterion #10: Radiotherapy requirements were adjusted to standard guidelines; exclusion criterion #5: Specified to electrolyte disorders in general, exclusion criterion #13: Removal of endocrine treatment timing which was a description but not an exclusion criterion (was replaced with definition of radiotherapy window); exclusion criterion #16: Study entry time was specified as date of randomization. Endocrine treatment options were updated. Patients could now receive either tamoxifen or AI (letrozole, anastrozole, or exemestane). For premenopausal patients, concurrent LHRH agonist use was allowed. Patients could now concurrently receive bisphosphonates or rank ligand inhibitors, if necessary for treatment or prevention of osteopenia or osteoporosis. Safety monitoring frequency was adjusted to IDMC recommendation. Ophthamologic assessment was removed due to new information in palbociclib IB versions. Optional samples for circulating tumor cells (CTC), RNAlater and fresh frozen tissue was removed. An optional ctDNA sample collection time-point at detection of progressive disease was added. Specification of relevant overdose definition and removal of notification requirement for non-relevant overdose.
04 May 2017	Protocol G (Version 11, 04-May-2017) Specification of potential outcomes of the EIA (futility, sample size re-estimation up to a new total number of 1250 patients, efficacy) were added to the statistical sections. Rationale: The adaptive design of the study allowed adjustment of the patient number based on outcome of the 1st EIA. New information on human PK data based on the IB (2017) was added.
09 April 2019	Administrative Amendment Protocol G (Version 11 –- 9th April 2019) Summary of changes Update of GBG Subboard Neoadjuvant, and International Steering Committee members, resp. (chapter 1). Change of International Principal Investigator / Coordinating Investigator (chapter 1). Adding of new position “Unblinded independent statistician” (chapter 1).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33793299