Clinical trial results:
AIPAC (Active Immunotherapy PAClitaxel): A multicentre, Phase IIb, randomised, double blind, placebo-controlled study in hormone receptor-positive metastatic breast carcinoma patients receiving IMP321 (LAG-3Ig fusion protein) or placebo as adjunctive to a standard chemotherapy treatment regimen of paclitaxel.

Summary

EudraCT number	2015-002541-63
Trial protocol	NL BE HU FR DE PL GB
Global end of trial date	14 May 2021

Results information

Result version number	v1 (current)
This version publication date	09 July 2022
First version publication date	09 July 2022

Trial information

Trial identification

Sponsor protocol code	IMP321-P011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02614833
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Immutep S.A.S
Sponsor organisation address	21 rue Jean Rostand, Orsay Cedex, France, 91893
Public contact	Clinical Trial Disclosure Enquiries, Immutep S.A.S, +33 146835822, enquiries@immutep.com
Scientific contact	Clinical Trial Disclosure Enquiries, Immutep S.A.S, +33 146835822, enquiries@immutep.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	28 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2020
Global end of trial reached?	Yes
Global end of trial date	14 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of efti combined with weekly paclitaxel compared to weekly paclitaxel plus placebo in hormone receptor-positive metastatic breast cancer subjects.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.
Throughout the Randomisation stage of the study, an Independent Data Monitoring Committee (IDMC) monitored subject safety, survival rates and demographics at regular intervals and had the possibility to convene ad hoc upon the request of the PI, Medical Monitor or Sponsor and in accordance with the IDMC charter. During the randomised, placebo-controlled stage of this study, the IDMC received tables, listings and figures per treatment arm. The IDMC received reports of all adverse events (AEs) by system organ class. The IDMC had the authority to recommend any dose de-escalation steps, if needed or stopping the study if at any time during the study unacceptable AEs or safety concerns related to the study treatment occurred.

Background therapy:

Paclitaxel was given in both treatment arms.
The Randomisation Stage (Stage 2) was a randomised, placebo-controlled and double-blind stage. The study design and conduct followed the 'Note for Guidance on evaluation of anti-cancer medicinal products in man' (EMA/CHMP/205/95/rev.4). All subjects received standard-of-care weekly paclitaxel to be ethically treated for the disease. Subjects received weekly paclitaxel instead of every three weeks because this has been observed to result in higher efficacy and less toxicity. Weekly Paclitaxel has become a standard of care administration schedule since more than 15 years ago.

Evidence for comparator:

In this study the use of a placebo associated with double blinding greatly improve the quality of the data and its interpretation. It therefore alleviates many of the statistical biases observed in open label phase II studies. It hence also requires that one of the study arms receives placebo rather than just simply prohibiting the use of endocrine therapy subsequently to termination of the chemoimmunotherapy stage in this arm.

Actual start date of recruitment	12 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 35
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	United Kingdom: 28

Country: Number of subjects enrolled	Belgium: 88
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Hungary: 12
Worldwide total number of subjects	226
EEA total number of subjects	198

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)	147
From 65 to 84 years	78
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The 1st ICF for the randomisation stage was signed on 06Jan2017.
32 sites in 7 countries.
Number of sites per country: 9 BE, 3 FR, 5 DE, 2 HU, 8 NL, 2 PL, 3 UK

Pre-assignment

Screening details:

Subjects with hormone receptor positive (HR+), HER2 negative metastatic breast cancer eligible to weekly paclitaxel.
Randomisation Stage: 277 subjects screened, 50 subjects screen failures. 1 subject randomised, but subject did not receive drug

Period 1

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

Blinding implementation details:

The Randomisation stage used a double-blind design with regard to the subjects and the Investigators, research staff at the site and sponsor staff, in order to eliminate systematic observer or performance bias. Unblinding of the Investigator was only allowed in case of emergency. To avoid unblinding, staff of the Immutep S.A.S. lab did not have access to the eCRF nor attended any meeting where subject data were discussed until unblinding for primary analysis occured.

Arms

Are arms mutually exclusive?	Yes
Arm title	Paclitaxel + Placebo

Arm description:

Placebo Arm:
Paclitaxel (80 mg/m2 Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + placebo in a double-blinded fashion

Arm type	Placebo
Investigational medicinal product name	Placebo to IMP321
Investigational medicinal product code	Placebo to IMP321
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo drug product matched the appearance and injection characteristics of efti drug product and comprised efti formulation buffer. The placebo drug product is a single-use, preservative-free, sterile solution for subcutaneous injections. Preparation of study drug was done according to the Investigational Medicinal Product (IMP) Handling Manual. The placebo was administered via subcutaneous injection (single anatomical site) on the anterior face of the thigh.
Repeated s.c. doses of the placebo were administered on Day 2 and Day 16 of each 4-week cycle during the 6 cycles of weekly paclitaxel chemotherapy (chemo-immunotherapy phase). After completion of this chemo-immunotherapy phase, responding or stable subjects received study agent (i.e. without paclitaxel) every 4 weeks during the maintenance phase for an additional 12 injections.

Arm title	Paclitaxel + 30 mg efti

Arm description:

30 mg Efti Arm:
Paclitaxel (80 mg/m2 Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + 30 mg Efti

Arm type	Experimental

Investigational medicinal product name	IMP321
Investigational medicinal product code	IMP321
Other name	eftilagimod alfa
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Efti drug product is a single-use, preservative-free, sterile solution of efti for subcutaneous injections. Preparation of study drug was done according to the Investigational Medicinal Product (IMP) Handling Manual. The 30 mg dose of efti was administered via subcutaneous injection (single anatomical site) on the anterior face of the thigh.
Repeated s.c. doses of efti were administered on Day 2 and Day 16 of each 4-week cycle during the 6 cycles of weekly paclitaxel chemotherapy (chemo-immunotherapy phase). After completion of this chemo-immunotherapy phase, responding or stable subjects received study agent (i.e. without paclitaxel) every 4 weeks during the maintenance phase for an additional 12 injections.

Number of subjects in period 1	Paclitaxel + Placebo	Paclitaxel + 30 mg efti
Started	112	114
Randomisation Stage - Maintenance	54	60
Completed	2	2
Not completed	110	112
Adverse event, serious fatal	1	1
Physician decision	3	2
Consent withdrawn by subject	1	3
Adverse event, non-fatal	9	7
Symptomatic deterioration	5	5
1 Euthanasia + 1 Long Treatment Delay	-	2
Sponsor´s decision	1	-
Disease Progression	90	92

Baseline characteristics

Reporting groups	
Reporting group title	Paclitaxel + Placebo
Reporting group description:	
Placebo Arm: Paclitaxel (80 mg/m2 Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + placebo in a double-blinded fashion	
Reporting group title	Paclitaxel + 30 mg efti
Reporting group description:	
30 mg Efti Arm: Paclitaxel (80 mg/m2 Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + 30 mg Efti	

Reporting group values	Paclitaxel + Placebo	Paclitaxel + 30 mg efti	Total
Number of subjects	112	114	226
Age categorical Units: Subjects			
Adults (18-64 years)	71	76	147
From 65-87 years	41	38	79
Age continuous Units: years			
arithmetic mean	59.3	58.0	
standard deviation	± 11.36	± 11.93	-
Gender categorical Units: Subjects			
Female	112	114	226
Male	0	0	0
ECOG at Baseline			
ECOG performance status			
Units: Subjects			
ECOG 0	70	69	139
ECOG 1	42	44	86
ECOG 2	0	1	1
Visceral Disease			
Disease Overview Per Treatment Group at Baseline: Visceral Disease			
Units: Subjects			
Visceral Disease - Yes	104	103	207
Visceral Disease - No	8	11	19
Breast Cancer Subtype			
Breast Cancer Subtype – Retrospective Central Assessment The central pathology laboratory applied immunohistochemistry to confirm HR positivity, Ki-67 status, and HER2-neu status. Fluorescence in situ hybridisation analysis was performed on samples yielding positive HER2-neu result on immunohistochemistry.			
Units: Subjects			
no result	25	32	57
Luminal A	32	28	60
Luminal B	43	40	83
Luminal undefined	4	8	12
Triple negative	1	1	2
Undefined	6	5	11

HER2 positive	1	0	1
Number of Disease Sites at Screening			
Number of Disease Sites at Screening			
Units: Subjects			
1-2 disease sites	34	46	80
>2 disease sites	78	68	146
Location of Disease at Screening Bone			
Location of Disease at Screening			
Units: Subjects			
Bone	82	83	165
not Bone	30	31	61
Location of Disease at Screening Liver			
Location of Disease at Screening Liver			
Units: Subjects			
Liver	85	80	165
not Liver	27	34	61
Location of Disease at Screening Lymph Node			
Location of Disease at Screening Lymph Node			
Units: Subjects			
Lymph node	56	57	113
not Lymph node	56	57	113
Biomarker CA 15-3			
Biomarker CA 15-3			
Units: Subjects			
<30 arb units/L	20	19	39
≥30 arb units/L	88	92	180
not recorded	4	3	7
Lactate Dehydrogenase at Baseline			
Lactate Dehydrogenase at Baseline			
Units: Subjects			
Elevated (>250 U/L)	81	74	155
Non-Elevated (≤250 U/L)	30	39	69
not recorded	1	1	2
Monocytes at Baseline			
Units: Subjects			
<0.25 x 109 cells/L	22	25	47
≥0.25 x 109 cells/L	89	89	178
not recorded	1	0	1
Time Between Metastatic Stage 4 Diagnosis and Informed Consent (days)			
Time Between Metastatic Stage 4 Diagnosis and Informed Consent (days)			
Units: days			
median	668.0	262.5	
inter-quartile range (Q1-Q3)	55 to 1070	39 to 824	-
Body Mass Index			
Units: kg/m2			
median	24.9	24.7	
full range (min-max)	15.4 to 44.5	18.1 to 48.1	-

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) included all assigned/randomised subjects who received at least one dose of study drug (i.e., one dose of paclitaxel or one dose of efti or placebo). Subjects in this population were analysed according the treatment to which they were randomised. This population is the primary population for the analyses of efficacy endpoints.

Reporting group values	Full Analysis Set		
Number of subjects	226		
Age categorical			
Units: Subjects			
Adults (18-64 years)	147		
From 65-87 years	79		
Age continuous			
Units: years			
arithmetic mean	58.0		
standard deviation	± 11.93		
Gender categorical			
Units: Subjects			
Female	114		
Male	0		
ECOG at Baseline			
ECOG performance status			
Units: Subjects			
ECOG 0	139		
ECOG 1	86		
ECOG 2	1		
Visceral Disease			
Disease Overview Per Treatment Group at Baseline: Visceral Disease			
Units: Subjects			
Visceral Disease - Yes	207		
Visceral Disease - No	19		
Breast Cancer Subtype			
Breast Cancer Subtype – Retrospective Central Assessment The central pathology laboratory applied immunohistochemistry to confirm HR positivity, Ki-67 status, and HER2-neu status. Fluorescence in situ hybridisation analysis was performed on samples yielding positive HER2-neu result on immunohistochemistry.			
Units: Subjects			
no result	57		
Luminal A	60		
Luminal B	83		
Luminal undefined	12		
Triple negative	2		
Undefined	11		
HER2 positive	1		
Number of Disease Sites at Screening			
Number of Disease Sites at Screening			
Units: Subjects			
1-2 disease sites	80		
>2 disease sites	146		
Location of Disease at Screening Bone			

Location of Disease at Screening			
Units: Subjects			
Bone	165		
not Bone	61		
Location of Disease at Screening Liver			
Location of Disease at Screening Liver			
Units: Subjects			
Liver	165		
not Liver	61		
Location of Disease at Screening Lymph Node			
Location of Disease at Screening Lymph Node			
Units: Subjects			
Lymph node	113		
not Lymph node	113		
Biomarker CA 15-3			
Biomarker CA 15-3			
Units: Subjects			
<30 arb units/L	39		
≥30 arb units/L	180		
not recorded	7		
Lactate Dehydrogenase at Baseline			
Lactate Dehydrogenase at Baseline			
Units: Subjects			
Elevated (>250 U/L)	155		
Non-Elevated (≤250 U/L)	69		
not recorded	2		
Monocytes at Baseline Units: Subjects			
<0.25 x 109 cells/L	47		
≥0.25 x 109 cells/L	178		
not recorded	1		
Time Between Metastatic Stage 4 Diagnosis and Informed Consent (days)			
Time Between Metastatic Stage 4 Diagnosis and Informed Consent (days)			
Units: days			
median	741.8		
inter-quartile range (Q1-Q3)	41 to 944		
Body Mass Index Units: kg/m2			
median	24.7		
full range (min-max)	15.4 to 48.1		

End points

End points reporting groups

Reporting group title	Paclitaxel + Placebo

Reporting group description:

Placebo Arm:
Paclitaxel (80 mg/m2 Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + placebo in a double-blinded fashion

Reporting group title	Paclitaxel + 30 mg efti

Reporting group description:

30 mg Efti Arm:
Paclitaxel (80 mg/m2 Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + 30 mg Efti

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) included all assigned/randomised subjects who received at least one dose of study drug (i.e., one dose of paclitaxel or one dose of efti or placebo). Subjects in this population were analysed according the treatment to which they were randomised. This population is the primary population for the analyses of efficacy endpoints.

Primary: Progression-free survival (PFS) - BICR

End point title	Progression-free survival (PFS) - BICR

End point description:

PFS was defined as the number of days between the start date of Randomisation and the earliest date of documented disease progression, as defined by RECIST V1.1, or death without prior progression. For primary analysis an independent blinded review was performed, i.e., all imaging time points were reviewed by two independent reviewers according to RECIST 1.1. In case of discrepancy, a third reader (adjudicator) reviewed the images. Analysis incl. full analysis set.

End point type	Primary

End point timeframe:

PFS will be calculated as the time from the date of randomisation to the date of first documentation of disease progression (RECIST1.1) or date of death due to any cause, whichever occurs first.

End point values	Paclitaxel + Placebo	Paclitaxel + 30 mg efti		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	114		
Units: month				
median (confidence interval 95%)	7.29 (5.52 to 7.46)	7.29 (6.64 to 7.46)		

Statistical analyses

Statistical analysis title	Progression-Free Survival (BICR)
Comparison groups	Paclitaxel + Placebo v Paclitaxel + 30 mg efti

Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.341 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.3
Variability estimate	Standard deviation

Notes:

[1] - stratified by ECOG (0 versus 1)

Secondary: Overall Survival

End point title	Overall Survival

End point description:

OS was defined as the time between the date of the date of Randomisation and the date of death. For subjects without documentation of death, OS was censored on the last date the subject was known to be alive.

End point type	Secondary

End point timeframe:

Overall survival (OS) is defined as the time between the date of randomisation and the date of death from any cause.

End point values	Paclitaxel + Placebo	Paclitaxel + 30 mg efti		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	114		
Units: month				
median (confidence interval 95%)	17.54 (12.91 to 21.85)	20.37 (14.26 to 25.07)		

Statistical analyses

Statistical analysis title	Statistical Analysis OS
Comparison groups	Paclitaxel + Placebo v Paclitaxel + 30 mg efti
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.197
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.19
Variability estimate	Standard deviation

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective Response Rate (ORR) according to RECIST V1.1

End point type	Secondary

End point timeframe:

Radiological assessments according to RECIST 1.1. from screening onwards every 8 weeks until week 73, every 12 weeks thereafter.

End point values	Paclitaxel + Placebo	Paclitaxel + 30 mg efti		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	114		
Units: percent				
number (confidence interval 95%)	40.6 (31 to 51)	51.4 (42 to 61)		

Statistical analyses

Statistical analysis title	Overall Response Rate
Comparison groups	Paclitaxel + 30 mg efti v Paclitaxel + Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.118
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportion
Point estimate	11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	24
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening and then at each visit until end of PFS and OS follow up (every 12 weeks after end of treatment).

Adverse event reporting additional description:

According to NCI CTCAE V4.03. Reporting from ICF signature until 30 days after last study agent administration. Safety follow-up is to be performed until resolution of AEs/SAEs or for a minimum of 2 months after last study agent administration or until subject is receiving any other anti-cancer therapy or any other investigational therapy.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Paclitaxel + Placebo

Reporting group description:

Placebo Arm:
Paclitaxel (80 mg/m2 Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + placebo in a double-blinded fashion.

Reporting group title	Paclitaxel + 30 mg efti

Reporting group description:

30 mg Efti Arm:
Paclitaxel (80 mg/m2 Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + efti 30mg in a double-blinded fashion

Serious adverse events	Paclitaxel + Placebo	Paclitaxel + 30 mg efti	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 112 (19.64%)	22 / 114 (19.30%)	
number of deaths (all causes)	83	81	
number of deaths resulting from adverse events	3	2	
Surgical and medical procedures			
Thoracic outlet surgery			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast reconstruction			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopaedic procedure			

subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 112 (0.00%)	5 / 114 (4.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 112 (0.89%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	3 / 112 (2.68%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 112 (0.89%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Epistaxis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injection related reaction			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem infarction			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Headache			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			

subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatobiliary disease			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Erysipelas			
subjects affected / exposed	2 / 112 (1.79%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cellulitis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Paclitaxel + Placebo	Paclitaxel + 30 mg efti	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 112 (100.00%)	114 / 114 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 112 (9.82%)	14 / 114 (12.28%)	
occurrences (all)	47	38	
Hot flush			
subjects affected / exposed	3 / 112 (2.68%)	6 / 114 (5.26%)	
occurrences (all)	4	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	55 / 112 (49.11%)	53 / 114 (46.49%)	
occurrences (all)	85	104	
Injection site reaction			
subjects affected / exposed	4 / 112 (3.57%)	39 / 114 (34.21%)	
occurrences (all)	8	123	
Injection site erythema			
subjects affected / exposed	2 / 112 (1.79%)	35 / 114 (30.70%)	
occurrences (all)	2	101	
Oedema peripheral			
subjects affected / exposed	19 / 112 (16.96%)	8 / 114 (7.02%)	
occurrences (all)	29	12	
Pyrexia			

subjects affected / exposed	8 / 112 (7.14%)	17 / 114 (14.91%)	
occurrences (all)	10	38	
Injection site pain			
subjects affected / exposed	6 / 112 (5.36%)	12 / 114 (10.53%)	
occurrences (all)	10	23	
Influenza like illness			
subjects affected / exposed	4 / 112 (3.57%)	10 / 114 (8.77%)	
occurrences (all)	4	15	
Injection site induration			
subjects affected / exposed	0 / 112 (0.00%)	9 / 114 (7.89%)	
occurrences (all)	0	15	
Pain			
subjects affected / exposed	0 / 112 (0.00%)	9 / 114 (7.89%)	
occurrences (all)	0	11	
Injection site swelling			
subjects affected / exposed	0 / 112 (0.00%)	7 / 114 (6.14%)	
occurrences (all)	0	17	
Chest pain			
subjects affected / exposed	6 / 112 (5.36%)	6 / 114 (5.26%)	
occurrences (all)	8	6	
Chills			
subjects affected / exposed	3 / 112 (2.68%)	6 / 114 (5.26%)	
occurrences (all)	3	9	
Malaise			
subjects affected / exposed	7 / 112 (6.25%)	4 / 114 (3.51%)	
occurrences (all)	7	5	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	10 / 112 (8.93%)	16 / 114 (14.04%)	
occurrences (all)	11	17	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	22 / 112 (19.64%)	20 / 114 (17.54%)	
occurrences (all)	24	22	
Dyspnoea			

subjects affected / exposed	20 / 112 (17.86%)	16 / 114 (14.04%)	
occurrences (all)	31	20	
Epistaxis			
subjects affected / exposed	8 / 112 (7.14%)	8 / 114 (7.02%)	
occurrences (all)	11	9	
Dyspnoea exertional			
subjects affected / exposed	6 / 112 (5.36%)	2 / 114 (1.75%)	
occurrences (all)	6	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 112 (8.93%)	9 / 114 (7.89%)	
occurrences (all)	10	11	
Anxiety			
subjects affected / exposed	8 / 112 (7.14%)	4 / 114 (3.51%)	
occurrences (all)	8	4	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	34 / 112 (30.36%)	25 / 114 (21.93%)	
occurrences (all)	56	36	
Aspartate aminotransferase increased			
subjects affected / exposed	18 / 112 (16.07%)	16 / 114 (14.04%)	
occurrences (all)	26	39	
Alanine aminotransferase increased			
subjects affected / exposed	12 / 112 (10.71%)	10 / 114 (8.77%)	
occurrences (all)	18	33	
Blood alkaline phosphatase increased			
subjects affected / exposed	14 / 112 (12.50%)	9 / 114 (7.89%)	
occurrences (all)	15	13	
White blood cell count decreased			
subjects affected / exposed	11 / 112 (9.82%)	5 / 114 (4.39%)	
occurrences (all)	28	8	
Lymphocyte count decreased			
subjects affected / exposed	7 / 112 (6.25%)	3 / 114 (2.63%)	
occurrences (all)	8	5	
Neutrophil count decreased			

subjects affected / exposed	6 / 112 (5.36%)	2 / 114 (1.75%)	
occurrences (all)	9	4	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	28 / 112 (25.00%)	23 / 114 (20.18%)	
occurrences (all)	53	31	
Headache			
subjects affected / exposed	17 / 112 (15.18%)	21 / 114 (18.42%)	
occurrences (all)	19	24	
Peripheral sensory neuropathy			
subjects affected / exposed	22 / 112 (19.64%)	21 / 114 (18.42%)	
occurrences (all)	47	36	
Paraesthesia			
subjects affected / exposed	16 / 112 (14.29%)	14 / 114 (12.28%)	
occurrences (all)	27	23	
Dysgeusia			
subjects affected / exposed	12 / 112 (10.71%)	7 / 114 (6.14%)	
occurrences (all)	13	7	
Dizziness			
subjects affected / exposed	7 / 112 (6.25%)	6 / 114 (5.26%)	
occurrences (all)	9	7	
Polyneuropathy			
subjects affected / exposed	5 / 112 (4.46%)	6 / 114 (5.26%)	
occurrences (all)	5	8	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	21 / 112 (18.75%)	22 / 114 (19.30%)	
occurrences (all)	46	39	
Anaemia			
subjects affected / exposed	16 / 112 (14.29%)	18 / 114 (15.79%)	
occurrences (all)	26	39	
Leukopenia			
subjects affected / exposed	6 / 112 (5.36%)	3 / 114 (2.63%)	
occurrences (all)	10	8	
Gastrointestinal disorders			

Asthenia			
subjects affected / exposed	20 / 112 (17.86%)	16 / 114 (14.04%)	
occurrences (all)	35	29	
Nausea			
subjects affected / exposed	40 / 112 (35.71%)	44 / 114 (38.60%)	
occurrences (all)	55	81	
Diarrhoea			
subjects affected / exposed	41 / 112 (36.61%)	33 / 114 (28.95%)	
occurrences (all)	60	59	
Constipation			
subjects affected / exposed	20 / 112 (17.86%)	20 / 114 (17.54%)	
occurrences (all)	23	26	
Abdominal pain			
subjects affected / exposed	11 / 112 (9.82%)	17 / 114 (14.91%)	
occurrences (all)	14	26	
Vomiting			
subjects affected / exposed	13 / 112 (11.61%)	17 / 114 (14.91%)	
occurrences (all)	19	23	
Abdominal pain upper			
subjects affected / exposed	11 / 112 (9.82%)	10 / 114 (8.77%)	
occurrences (all)	13	13	
Stomatitis			
subjects affected / exposed	6 / 112 (5.36%)	8 / 114 (7.02%)	
occurrences (all)	11	8	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 112 (1.79%)	6 / 114 (5.26%)	
occurrences (all)	3	7	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	56 / 112 (50.00%)	46 / 114 (40.35%)	
occurrences (all)	84	67	
Rash			
subjects affected / exposed	12 / 112 (10.71%)	12 / 114 (10.53%)	
occurrences (all)	20	16	
Dry skin			

subjects affected / exposed	5 / 112 (4.46%)	8 / 114 (7.02%)	
occurrences (all)	5	8	
Nail disorder			
subjects affected / exposed	8 / 112 (7.14%)	8 / 114 (7.02%)	
occurrences (all)	11	10	
Pruritus			
subjects affected / exposed	7 / 112 (6.25%)	6 / 114 (5.26%)	
occurrences (all)	20	6	
Erythema			
subjects affected / exposed	10 / 112 (8.93%)	5 / 114 (4.39%)	
occurrences (all)	11	10	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 112 (11.61%)	14 / 114 (12.28%)	
occurrences (all)	18	16	
Pain in extremity			
subjects affected / exposed	8 / 112 (7.14%)	14 / 114 (12.28%)	
occurrences (all)	10	22	
Back pain			
subjects affected / exposed	16 / 112 (14.29%)	13 / 114 (11.40%)	
occurrences (all)	22	21	
Myalgia			
subjects affected / exposed	12 / 112 (10.71%)	10 / 114 (8.77%)	
occurrences (all)	20	14	
Musculoskeletal pain			
subjects affected / exposed	2 / 112 (1.79%)	6 / 114 (5.26%)	
occurrences (all)	2	7	
Bone pain			
subjects affected / exposed	9 / 112 (8.04%)	4 / 114 (3.51%)	
occurrences (all)	10	5	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	11 / 112 (9.82%)	11 / 114 (9.65%)	
occurrences (all)	13	13	
Nasopharyngitis			

subjects affected / exposed	16 / 112 (14.29%)	7 / 114 (6.14%)	
occurrences (all)	18	8	
Rhinitis			
subjects affected / exposed	4 / 112 (3.57%)	7 / 114 (6.14%)	
occurrences (all)	4	9	
Cystitis			
subjects affected / exposed	2 / 112 (1.79%)	6 / 114 (5.26%)	
occurrences (all)	2	9	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 112 (12.50%)	16 / 114 (14.04%)	
occurrences (all)	16	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 November 2016	• Primary analysis and long-term follow-up for OS was introduced; • Clarification on treatment/study duration, radiological assessments, contraception, subject criteria, safety reporting and dose adjustments of paclitaxel were given to harmonise between participating countries
10 May 2017	• Clarification on timing of radiological assessments, contraception method, safety reporting, statistical methods and analyses populations was given.
16 January 2018	• General update (contact details, table of content, abbreviations, references, footnotes, appendices linguistic improvements); • Clarification of inclusion and exclusion criteria incl. details on contraception; • Clarifications on study objectives, endpoints and study design including treatment and assessments; • Clarifications on study duration; • Clarification on safety reporting; • Clarification on statistical assumptions, sample size increase and specification of statistical analyses
12 March 2018	• General update (typographical corrections, clarifications, vendor contact details, update on clinical data of efti, update of link to RECIST V1.1 guidelines) • Update to study duration • Clarification on HBV screening requirements; • Explanation on the sequence of primary endpoint analysis; • Addition of two hypersensitivity reactions reported from the efti-P011 study added and related risk language updated; • Addition of management and discontinuation guidelines for hypersensitivity reactions; • Inclusion of local best clinical practice into assessment of safety criteria prior to paclitaxel administration

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

EudraCT results platform is not built to accommodate two stage trials. Results of the randomisation stage are presented in EudraCT.
Early conclusion of overall survival follow up due to data maturity.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30977393