Clinical trial results:
A phase IIIB, 24-week randomised, double-blind study to compare closed triple therapy (FF/UMEC/VI) with open triple therapy (FF/VI + UMEC), in subjects with chronic obstructive pulmonary disease (COPD)

Summary

EudraCT number	2015-005212-14
Trial protocol	ES FR RO IT
Global end of trial date	23 May 2017

Results information

Result version number	v1
This version publication date	11 May 2018
First version publication date	11 May 2018

Trial information

Trial identification

Sponsor protocol code	200812

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	20 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of FF/UMEC/VI with FF/VI + UMEC on lung function after 24 weeks of treatment

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 June 2016
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	Mexico: 112
Country: Number of subjects enrolled	Argentina: 131
Country: Number of subjects enrolled	Australia: 112
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 162
Country: Number of subjects enrolled	Italy: 75
Country: Number of subjects enrolled	Japan: 102
Country: Number of subjects enrolled	Korea, Republic of: 69
Country: Number of subjects enrolled	Poland: 122
Country: Number of subjects enrolled	Romania: 120
Country: Number of subjects enrolled	Russian Federation: 215
Country: Number of subjects enrolled	Spain: 60
Worldwide total number of subjects	1311
EEA total number of subjects	570

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)	533
From 65 to 84 years	766
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

This was a 24-week, randomized, double-blind, parallel group multicenter study to compare closed triple therapy Fluticasone Furoate/ Umeclidinium/ Vilanterol Trifenatate (FF/UMEC/VI) with open triple therapy (FF/VI + UMEC), in participants with chronic obstructive pulmonary disease (COPD). This study was conducted across 12 countries.

Pre-assignment

Screening details:

A total of 1311 participants were pre-screened, of which 1278 participants were screened (33 pre-screen failures). There were 175 screen failures and 48 Run-in failures. A total of 1055 participants were randomized and received the study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	FF/UMEC/VI 100/62.5/25

Arm description:

Participants received FF/UMEC/VI, 100 micrograms (mcg)/62.5 mcg/25 mcg via ELLIPTA dry powder inhaler (DPI) once daily in morning and placebo inhalation powder via ELLIPTA DPI, once daily in the morning. Participants also received albuterol/salbutamol as a rescue medication when needed during the treatment period.

Arm type	Experimental
Investigational medicinal product name	FF/UMEC/VI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received FF/UMEC/VI, 100 mcg/62.5 mcg/25 mcg inhalation powder via the DPI, once daily in the morning.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received placebo inhalation powder via the DPI, once daily in the morning.

Investigational medicinal product name	Albuterol/salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received albuterol/salbutamol as a rescue medication via metered-dose inhaler (MDI) with a spacer which was used when needed during the study

Arm title	FF/VI 100/25 + UMEC 62.5

Arm description:

Participants received FF/VI, 100 mcg/25 mcg via ELLIPTA DPI once daily in morning and UMEC 62.5 mcg inhalation powder via ELLIPTA DPI, once daily in the morning. Participants also received albuterol/salbutamol as a rescue medication when needed during the treatment period.

Arm type	Active comparator
Investigational medicinal product name	FF/VI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received FF/VI, 100 mcg/25 mcg inhalation powder via the DPI, once daily in the morning.

Investigational medicinal product name	UMEC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received UMEC 62.5 mcg inhalation powder via the DPI, once daily in the morning.

Investigational medicinal product name	Albuterol/salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received albuterol/salbutamol as a rescue medication via metered-dose inhaler (MDI) with a spacer which was used when needed during the study

Number of subjects in period 1[1]	FF/UMEC/VI 100/62.5/25	FF/VI 100/25 + UMEC 62.5
Started	527	528
Completed	497	496
Not completed	30	32
Physician decision	1	1
Consent withdrawn by subject	6	17
Adverse event, non-fatal	21	11
Lost to follow-up	1	2
Lack of efficacy	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 1311 participants were pre-screened, of which 1278 participants were screened (33 pre-screen failures). There were 175 screen failures and 48 Run-in failures. A total of 1055 participants were randomized and received the study treatment.

Baseline characteristics

Reporting groups	
Reporting group title	FF/UMEC/VI 100/62.5/25
Reporting group description:	
Participants received FF/UMEC/VI, 100 micrograms (mcg)/62.5 mcg/25 mcg via ELLIPTA dry powder inhaler (DPI) once daily in morning and placebo inhalation powder via ELLIPTA DPI, once daily in the morning. Participants also received albuterol/salbutamol as a rescue medication when needed during the treatment period.	
Reporting group title	FF/VI 100/25 + UMEC 62.5
Reporting group description:	
Participants received FF/VI, 100 mcg/25 mcg via ELLIPTA DPI once daily in morning and UMEC 62.5 mcg inhalation powder via ELLIPTA DPI, once daily in the morning. Participants also received albuterol/salbutamol as a rescue medication when needed during the treatment period.	

Reporting group values	FF/UMEC/VI 100/62.5/25	FF/VI 100/25 + UMEC 62.5	Total
Number of subjects	527	528	1055
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	66.7	65.9	
standard deviation	± 8.46	± 8.77	-
Gender categorical			
Units: Subjects			
Female	136	134	270
Male	391	394	785
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	18	14	32
Asian - East Asian Heritage	29	30	59
Asian - Japanese Heritage	41	38	79
Asian - South East Asian Heritage	2	0	2
White - Arabic/North African Heritage	1	4	5
White - White/Caucasian/European Heritage	416	416	832
American Indian/Alaska Native and Asian and White	0	1	1
American Indian or Alaska Native and White	20	25	45

End points

End points reporting groups

Reporting group title	FF/UMEC/VI 100/62.5/25

Reporting group description:

Participants received FF/UMEC/VI, 100 micrograms (mcg)/62.5 mcg/25 mcg via ELLIPTA dry powder inhaler (DPI) once daily in morning and placebo inhalation powder via ELLIPTA DPI, once daily in the morning. Participants also received albuterol/salbutamol as a rescue medication when needed during the treatment period.

Reporting group title	FF/VI 100/25 + UMEC 62.5

Reporting group description:

Participants received FF/VI, 100 mcg/25 mcg via ELLIPTA DPI once daily in morning and UMEC 62.5 mcg inhalation powder via ELLIPTA DPI, once daily in the morning. Participants also received albuterol/salbutamol as a rescue medication when needed during the treatment period.

Primary: Change from Baseline in trough forced expiratory volume in one second (FEV1) at 24 weeks

End point title	Change from Baseline in trough forced expiratory volume in one second (FEV1) at 24 weeks

End point description:

FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. It was measured using centralized spirometry. FEV1 values at Week 0, pre-dose were considered as Baseline values. Change from Baseline was calculated by substracting Baseline value from the value at indicated time point. Modified Per Protocol (mPP) Population was used which comprised of all participants in the Intent-to-Treat (ITT) Population, who do not have a full protocol deviation considered to impact efficacy. Data following a moderate/severe COPD exacerbation or pneumonia was excluded from analysis due to the potential impact of the exacerbation or the medications used to treat it. Participants with partial protocol deviations considered to impact efficacy were included in the mPP Population but had their data excluded from analysis from the time of deviation onwards. Analysis was performed using a mixed model repeated measures (MMRM) method.

End point type	Primary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25	FF/VI 100/25 + UMEC 62.5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307[1]	287[2]		
Units: Liter				
least squares mean (standard error)				
Liter	0.113 (± 0.0112)	0.095 (± 0.0116)		

Notes:

[1] - mPP Population

[2] - mPP Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

MMRM method included covariates of Baseline FEV1, stratum (number of long-acting bronchodilators per

day during the run-in: 0/1 or 2), visit, geographical region, treatment, visit by treatment and visit by Baseline interaction.

Comparison groups	FF/UMEC/VI 100/62.5/25 v FF/VI 100/25 + UMEC 62.5
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Mean difference (final values)
Point estimate	0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.013
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.0161

Notes:

[3] - If the lower bound of the two-sided 95% confidence interval around the (FF/UMEC/VI versus FF/VI+UMEC) treatment difference is above -50 milliliter (mL) then FF/UMEC/VI was to be considered non-inferior to FF/VI+UMEC.

Secondary: Percentage of responders based on the Saint (St) George Respiratory Questionnaire (SGRQ) Total Score at Week 24

End point title	Percentage of responders based on the Saint (St) George Respiratory Questionnaire (SGRQ) Total Score at Week 24

End point description:

SGRQ is a disease-specific questionnaire designed to measure impact of respiratory disease and its treatment on health related quality of life (HRQoL) of participants with COPD. It contains 14 questions with a total of 40 items grouped into domains (Symptoms, Activity and Impacts). SGRQ total score was calculated as 100 multiplied by summed weights from all positive items divided by sum of weights for all items in questionnaire. Higher score indicates poor HRQoL. Response was defined as an SGRQ total score of >=4 units below Baseline. Non response was defined as a SGRQ total score <4 units below Baseline or a missing SGRQ total score with no subsequent on treatment scores. ITT Population comprised of randomized participants, excluding those who were randomized in error. A participant who was screened or run-in failure and also randomized was considered to be randomized in error. Analysis was performed using a generalized linear mixed model with a logit link function.

End point type	Secondary

End point timeframe:

Week 24

End point values	FF/UMEC/VI 100/62.5/25	FF/VI 100/25 + UMEC 62.5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	489[4]	483[5]		
Units: Percentage of Participants				
Percentage of Participants	50	51		

Notes:

[4] - ITT Population

[5] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis included covariates of treatment group, stratum (number of long-acting bronchodilators per day

during the run-in: 0/1 or 2), geographical region, visit, Baseline, Baseline by visit and treatment by visit interactions.

Comparison groups	FF/VI 100/25 + UMEC 62.5 v FF/UMEC/VI 100/62.5/25
Number of subjects included in analysis	972
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.2

Secondary: Change from Baseline in SGRQ Total Score at Week 24

End point title	Change from Baseline in SGRQ Total Score at Week 24

End point description:

SGRQ is a disease-specific questionnaire designed to measure impact of respiratory disease and its treatment on HRQoL of participants with COPD. It contains 14 questions with a total of 40 items grouped into domains (Symptoms, Activity and Impacts). SGRQ total score was calculated as 100 multiplied by summed weights from all positive items divided by sum of weights for all items in questionnaire. Higher score indicates poor HRQoL. Values at Week 0, pre-dose were considered as Baseline values. Change from Baseline was calculated by substracting Baseline value from the value at indicated time point. Analysis was performed using a MMRM method including covariates of Baseline SGRQ Total score, stratum (number of long-acting bronchodilators per day during the run-in: 0/1 or 2), visit, geographical region, treatment, visit by treatment and visit by Baseline interaction.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25	FF/VI 100/25 + UMEC 62.5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	489[6]	483[7]		
Units: Scores on SGRQ scale				
least squares mean (standard error)				
Scores on SGRQ scale	-5.841 (± 0.5870)	-4.935 (± 0.5904)		

Notes:

[6] - ITT Population

[7] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis performed using a repeated measures model with covariates of Baseline SGRQ, stratum (number of long-acting bronchodilators per day during the run-in: 0/1 or 2), visit, geographical region, treatment, visit by treatment and visit by Baseline interaction.

Comparison groups	FF/UMEC/VI 100/62.5/25 v FF/VI 100/25 + UMEC 62.5

Number of subjects included in analysis	972
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.906
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	0.728
Variability estimate	Standard error of the mean
Dispersion value	0.8327

Secondary: Percentage of responders based on Transitional Dyspnea Index (TDI) focal score at Week 24

End point title	Percentage of responders based on Transitional Dyspnea Index (TDI) focal score at Week 24

End point description:

The TDI measures changes in the participant's dyspnea. TDI focal score was calculated as the sum of the ratings recorded for each of the 3 individual scales (Functional Impairment, Magnitude of Task, Magnitude of Effort). Each of these scales had a possible score ranging from -6 to +6. TDI focal score was calculated as the sum of the 3 individual scores and then divided by 2 (so the range of the TDI focal score is -9 to +9). The lower the score, the more deterioration in severity of dyspnea. If a score is missing for any of the three scales, then the TDI focal score was set to missing. A participant was considered as a responder if the on-treatment TDI focal score was at least 1 unit at that visit. Non-response was defined as a TDI focal score of less than 1 unit or a missing TDI focal score with no subsequent non-missing on-treatment scores. Analysis was performed using a generalized linear mixed model with a logit link function.

End point type	Secondary

End point timeframe:

Week 24

End point values	FF/UMEC/VI 100/62.5/25	FF/VI 100/25 + UMEC 62.5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	482[8]	481[9]		
Units: Percentage of Participants				
Percentage of Participants	56	56		

Notes:

[8] - ITT Population

[9] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Include covariates of treatment group, stratum (number of long-acting bronchodilators/ day during the run-in: 0/1 or 2), geographical region, visit, Baseline dyspnea index (BDI) focal score, BDI focal score/ visit and treatment/ visit interactions.

Comparison groups	FF/VI 100/25 + UMEC 62.5 v FF/UMEC/VI 100/62.5/25

Number of subjects included in analysis	963
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.25

Secondary: TDI focal score at Week 24

End point title	TDI focal score at Week 24

End point description:

The TDI measures changes in the participant's dyspnoea. TDI focal score was calculated as the sum of the ratings recorded for each of the 3 individual scales (Functional Impairment, Magnitude of Task, Magnitude of Effort). Each of these scales had a possible score ranging from -6 to +6. TDI focal score was calculated as the sum of the 3 individual scores and then divided by 2 (so the range of the TDI focal score is -9 to +9). If a score is missing for any of the three scales, then the TDI focal score was set to missing. Analysis was performed using a repeated measures model.

End point type	Secondary

End point timeframe:

Week 24

End point values	FF/UMEC/VI 100/62.5/25	FF/VI 100/25 + UMEC 62.5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	482[10]	481[11]		
Units: Scores on TDI scale				
least squares mean (standard error)				
Scores on TDI scale	2.029 (± 0.1252)	1.892 (± 0.1254)		

Notes:

[10] - ITT Population

[11] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis included covariates of BDI focal score, stratum (number of long-acting bronchodilators per day during the run-in: 0/1 or 2), visit, geographical region, treatment, visit by treatment and visit by BDI Focal score interactions.

Comparison groups	FF/UMEC/VI 100/62.5/25 v FF/VI 100/25 + UMEC 62.5

Number of subjects included in analysis	963
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	0.137
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.211
upper limit	0.485
Variability estimate	Standard error of the mean
Dispersion value	0.1773

Secondary: Time to first moderate or severe exacerbation

End point title	Time to first moderate or severe exacerbation

End point description:

COPD exacerbations were identified based on the investigator's clinical judgment. Worsening symptoms of COPD that required treatment with oral/systemic corticosteroids and/or antibiotics were considered as moderate exacerbation. Worsening symptoms of COPD that required treatment with in-subject hospitalization was considered as severe exacerbation. Hazard ratio and 95% confidence interval (CI) is from a Cox proportional hazards model with covariates of treatment group, sex, exacerbation history (0, 1, >=2 moderate/severe exacerbations, prior year), smoking status (screening), stratum (number of long-acting bronchodilators per day during the run-in: 0/1 or 2), geographical region and percent predicted FEV1 at Baseline.

End point type	Secondary

End point timeframe:

Up to 27 weeks

End point values	FF/UMEC/VI 100/62.5/25	FF/VI 100/25 + UMEC 62.5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	527[12]	528[13]		
Units: Days				
Days	166	150		

Notes:

[12] - ITT Population

[13] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis was performed using a Cox proportional hazards model.

Comparison groups	FF/VI 100/25 + UMEC 62.5 v FF/UMEC/VI 100/62.5/25

Number of subjects included in analysis	1055
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.12

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious AEs (nSAEs) were collected from start of study treatment (Week 0) until Week 25 including 1 Week of follow-up.

Adverse event reporting additional description:

On-treatment SAEs and nSAEs were reported for ITT Population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	FF/VI 100/25 + UMEC 62.5

Reporting group description:

Participants received FF/VI, 100 mcg/25 mcg via ELLIPTA DPI once daily in morning and UMEC 62.5 mcg inhalation powder via ELLIPTA DPI, once daily in the morning. Participants also received albuterol/salbutamol as a rescue medication when needed during the treatment period.

Reporting group title	FF/UMEC/VI 100/62.5/25

Reporting group description:

Participants received FF/UMEC/VI, 100 mcg/62.5 mcg/25 mcg via ELLIPTA DPI once daily in morning and placebo inhalation powder via ELLIPTA DPI, once daily in the morning. Participants also received albuterol/salbutamol as a rescue medication when needed during the treatment period.

Serious adverse events	FF/VI 100/25 + UMEC 62.5	FF/UMEC/VI 100/62.5/25	
Total subjects affected by serious adverse events			
subjects affected / exposed	60 / 528 (11.36%)	55 / 527 (10.44%)	
number of deaths (all causes)	5	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiosarcoma			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign hepatic neoplasm			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (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			
Chest pain			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Death			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Vaginal prolapse			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
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			
Acute pulmonary oedema			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	32 / 528 (6.06%)	24 / 527 (4.55%)	
occurrences causally related to treatment / all	0 / 38	0 / 28	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			

subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 528 (0.38%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Organic brain syndrome			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
X-ray abnormal			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femoral neck fracture			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
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 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 528 (0.19%)	2 / 527 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Aortic valve incompetence			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 528 (0.00%)	2 / 527 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 528 (0.19%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 528 (0.19%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Degenerative aortic valve disease			

subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prinzmetal angina			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain injury			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intensive care unit acquired weakness			

subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis hypertrophic			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal hypomotility			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cholecystitis acute			
subjects affected / exposed	1 / 528 (0.19%)	2 / 527 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudarthrosis			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cholecystitis infective			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			

subjects affected / exposed	2 / 528 (0.38%)	3 / 527 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 528 (0.19%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	13 / 528 (2.46%)	9 / 527 (1.71%)	
occurrences causally related to treatment / all	0 / 13	0 / 10	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pneumonia bacterial			
subjects affected / exposed	2 / 528 (0.38%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (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 bacterial			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal infection			

subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic shock syndrome			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (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			
Dehydration			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 528 (0.00%)	1 / 527 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 528 (0.19%)	0 / 527 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	FF/VI 100/25 + UMEC 62.5	FF/UMEC/VI 100/62.5/25	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 528 (23.67%)	122 / 527 (23.15%)	
Nervous system disorders			
Headache			
subjects affected / exposed	33 / 528 (6.25%)	32 / 527 (6.07%)	
occurrences (all)	54	56	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	52 / 528 (9.85%)	56 / 527 (10.63%)	
occurrences (all)	61	69	
Upper respiratory tract infection			
subjects affected / exposed	24 / 528 (4.55%)	18 / 527 (3.42%)	
occurrences (all)	29	19	
Influenza			
subjects affected / exposed	17 / 528 (3.22%)	16 / 527 (3.04%)	
occurrences (all)	17	17	
Pharyngitis			
subjects affected / exposed	16 / 528 (3.03%)	12 / 527 (2.28%)	
occurrences (all)	18	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2016	Amendment 1 (Global): 1. Synopsis, Section 1 and Overall Design, Section 4.1: Text updated to include the requirement for an early withdrawal study for participants who stop study treatment early. 2. Time and Events Table, Section 7.1: Scheduling of pulse oximetry corrected and scheduling of genetics sample collection revised. 3. Appendix 3 - Genetics Research: Text corrected to include combinations of study medications used in the protocol and the scheduled visit for sample collection revised. Appendix 8 – Hair Sample, Scalp & Finger Secretion pharmacokinetics (PK) Sub-Study: Discrepancy regarding the timing of sample collection corrected.
11 February 2016	Amendment 2 (South Korea only): Appendix 6 updated, for South Korea, with study medication labeling and information regarding study equipment.
29 June 2016	Amendment 3 (Global excluding South Korea): 1. Minor discrepancies corrected and clarifications made to some of the footnotes in the Time and Events Table. 2. The requirement of two views (poster anterior and lateral) for Screening chest x-rays and chest x-rays for suspected pneumonias and moderate/severe exacerbations specified. 3. Reference section updated. 4. A minor update to the wording for when the genetics sample can be collected made in the Time and Events Table and Appendix 3.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported