



Clinical trial results:

A Multicenter Trial Comparing the Efficacy and Safety of Umeclidinium/Vilanterol 62.5/25 mcg Once Daily with Tiotropium 18 mcg Once Daily over 24 Weeks in Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Summary

EudraCT number	2012-003973-24
Trial protocol	HU BG ES
Global end of trial date	24 September 2013

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	09 July 2015

Trial information

Trial identification

Sponsor protocol code	ZEP117115
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01777334
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	04 November 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare the efficacy of umeclidinium/vilanterol (UMEC/VI) Inhalation Powder (62.5/25 micrograms [mcg]) once-daily with tiotropium (18 mcg) once-daily over 24 weeks for the treatment of subjects with Chronic Obstructive Pulmonary Disease (COPD).

Protection of trial subjects:

Several measures were taken to protect trial subjects: these included electrocardiogram (ECG) at screening, vital signs at all visits, adverse event monitoring throughout the study, frequent clinic visits (approximately every 4 weeks) to monitor subject status and safety, exclusion of subjects with clinically significant and uncontrolled medical conditions, and use of treatment arms where all subjects received pharmacologic treatment that was appropriate for their COPD.

Umeclidinium/Vilanterol (experimental arm) combination has an acceptable safety profile for use as it is supported by the results of previously performed clinical studies. Tiotropium is a marketed product and was administered as an active control according to the local label.

All subjects received active treatment with one of the two above mentioned medications during the treatment phase of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2013
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	Spain: 46
Country: Number of subjects enrolled	Bulgaria: 116
Country: Number of subjects enrolled	Germany: 171
Country: Number of subjects enrolled	Hungary: 136
Country: Number of subjects enrolled	Canada: 182
Country: Number of subjects enrolled	Romania: 121
Country: Number of subjects enrolled	Russian Federation: 107
Country: Number of subjects enrolled	United States: 292
Country: Number of subjects enrolled	Argentina: 20
Worldwide total number of subjects	1191
EEA total number of subjects	590

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)	697
From 65 to 84 years	488
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants (par.) who met the eligibility criteria at Screening (Visit 1) completed a 7- to 10-day Run-in Period and were then randomized to a 24-week Treatment Period. A total of 1191 par. were enrolled; 1053 par. were screened, and 905 par. were randomized and took at least one dose of randomized study medication.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind ^[1]
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

For further information on blinding reference the following publication: Maleki-Yazdi MR, Kaelin T, Richard N, Zvarich M, Church A. Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: results of a 24-week, randomized, controlled trial. *Respir Med.* 2014 Dec;108(12):1752-60
<http://www.ncbi.nlm.nih.gov/pubmed/25458157>

Arms

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

Arm description:

Participants received umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms (µg) once daily (QD) each morning via a dry powder inhaler (DPI) and placebo QD each morning via a DPI for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Umeclidinium bromide/vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Respiratory use

Dosage and administration details:

62.5/25 µg once daily via a dry powered inhaler (DPI)

Investigational medicinal product name	Placebo (for matching Tiotropium)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Respiratory use

Dosage and administration details:

Lactose with magnesium stearate administered once daily via a matching DPI

Arm title	TIO 18 µg
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Arm description:

Participants received tiotropium (TIO) 18 µg QD each morning via a DPI and placebo QD each morning via a DPI for 24 weeks.

Arm type	Active comparator
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Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Respiratory use
Dosage and administration details:	
1 8µg once daily via HandiHaler	
Investigational medicinal product name	Placebo (for matching UMEC/VI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Respiratory use
Dosage and administration details:	
Lactose administered once daily via matching HandiHaler	

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: For further information on blinding reference the following publication: Maleki-Yazdi MR, Kaelin T, Richard N, Zvarich M, Church A. Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: results of a 24-week, randomized, controlled trial. *Respir Med.* 2014 Dec;108(12):1752-60
<http://www.ncbi.nlm.nih.gov/pubmed/25458157>

Number of subjects in period 1^[2]	UMEC/VI 62.5/25 µg	TIO 18 µg
Started	454	451
Completed	401	388
Not completed	53	63
Adverse event, serious fatal	2	5
Consent withdrawn by subject	14	11
Adverse event, non-fatal	16	9
Lost to follow-up	3	2
Lack of efficacy	15	29
Protocol deviation	3	7

Notes:

[2] - 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: The baseline period includes only those enrolled participants who were randomized and took at least one dose of randomized study medication (n=905).

Baseline characteristics

Reporting groups

Reporting group title	UMEC/VI 62.5/25 µg
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Reporting group description:

Participants received umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms (µg) once daily (QD) each morning via a dry powder inhaler (DPI) and placebo QD each morning via a DPI for 24 weeks.

Reporting group title	TIO 18 µg
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Reporting group description:

Participants received tiotropium (TIO) 18 µg QD each morning via a DPI and placebo QD each morning via a DPI for 24 weeks.

Reporting group values	UMEC/VI 62.5/25 µg	TIO 18 µg	Total
Number of subjects	454	451	905
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	61.9	62.7	
standard deviation	± 8.41	± 8.5	-
Gender categorical			
Units: Subjects			
Female	144	148	292
Male	310	303	613
Race, Customized			
Units: Subjects			
White/Caucasian/European Heritage	438	442	880
African American/African Heritage	13	7	20
American Indian or Alaska Native	1	1	2
White - Arabic/North African Heritage	1	0	1
Mixed Race	1	1	2

End points

End points reporting groups

Reporting group title	UMEC/VI 62.5/25 µg
Reporting group description:	
Participants received umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms (µg) once daily (QD) each morning via a dry powder inhaler (DPI) and placebo QD each morning via a DPI for 24 weeks.	
Reporting group title	TIO 18 µg
Reporting group description:	
Participants received tiotropium (TIO) 18 µg QD each morning via a DPI and placebo QD each morning via a DPI for 24 weeks.	

Primary: Change from Baseline (BL) in trough forced expiratory volume in one second (FEV1) on Day 169 (Week 24)

End point title	Change from Baseline (BL) in trough forced expiratory volume in one second (FEV1) on Day 169 (Week 24)
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. Trough FEV1 measurements were taken electronically by spirometry on Days 2, 28, 56, 84, 112, 140, 168, and 169. Baseline is defined as the mean of the assessments made 30 minutes (min) pre-dose and 5 min pre-dose on Treatment Day 1. Trough FEV1 is defined as the mean of the FEV1 values obtained at 23 and 24 hours (hr) after the previous morning's dosing (ie., trough FEV1 on Day 169 is the mean of the FEV1 values obtained 23 and 24 hr after the morning dosing on Day 168). Change from Baseline at a particular visit was calculated as the trough FEV1 value at that visit minus the Baseline value. Analysis was performed using a repeated measures model with covariates of treatment, Baseline (mean of the two assessments made 30 min and 5 min pre-dose on Day 1), smoking status, center group, day, and day by Baseline and day by treatment interactions. ITT=Intent-to-Treat.	
End point type	Primary
End point timeframe:	
Baseline and Day 169	

End point values	UMEC/VI 62.5/25 µg	TIO 18 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400 ^[1]	388 ^[2]		
Units: Liters				
least squares mean (standard error)	0.205 (± 0.0114)	0.093 (± 0.0115)		

Notes:

[1] - ITT Population. Participants analyzed are those with data available at the presented time point.

[2] - ITT Population. Participants analyzed are those with data available at the presented time point.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	UMEC/VI 62.5/25 µg v TIO 18 µg

Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	< 0.001 ^[4]
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	0.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.081
upper limit	0.144

Notes:

[3] - Participants analyzed are those with data available at the presented time point; but, all participants without missing covariate information and with ≥ 1 post-Baseline measurement were included in the analysis. Least squares mean difference=UMEC/VI 62.5/25 μg minus TIO 18 μg .

[4] - Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Secondary: Change from Baseline (BL) in weighted mean (WM) 0-6 hour FEV1 obtained post-dose at Day 168

End point title	Change from Baseline (BL) in weighted mean (WM) 0-6 hour FEV1 obtained post-dose at Day 168
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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. The WM FEV1 was derived by calculating the area under the FEV1/time curve (AUC) using the trapezoidal rule, and then dividing the value by the time interval over which the AUC was calculated. The WM was calculated at Days 1, 84, and 168 using the 0-6-hour post-dose FEV1 measurements collected on that day, which included pre-dose (Day 1: mean of 30 minutes [min] and 5 min prior to dosing; other serial visits: mean of 23 and 24 hours after the previous morning dose) and post-dose at 15 min, 30 min, 1 hour, 3 hours, and 6 hours. Change from BL at a particular visit was calculated as the WM value at that visit minus the BL value. Analysis was performed using a repeated measures model with covariates of treatment, BL (mean of two assessments made 30 min and 5 min pre-dose on Day 1), smoking status, center group, day, and day by BL and day by treatment interactions.

End point type	Secondary
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End point timeframe:

Baseline and Day 168

End point values	UMEC/VI 62.5/25 μg	TIO 18 μg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404 ^[5]	387 ^[6]		
Units: Liters				
least squares mean (standard error)	0.276 (\pm 0.0124)	0.17 (\pm 0.0126)		

Notes:

[5] - ITT Population. Participants analyzed are those with data available at the presented time point.

[6] - ITT Population. Participants analyzed are those with data available at the presented time point.

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	UMEC/VI 62.5/25 μg v TIO 18 μg

Number of subjects included in analysis	791
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	0.105
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.071
upper limit	0.14

Notes:

[7] - Participants analyzed are those with data available at the presented time point; but, all participants without missing covariate information and with ≥ 1 post-Baseline measurement were included in the analysis. Least squares mean difference=UMEC/VI 62.5/25 µg minus TIO 18 µg.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious AEs were collected from the start of study medication until the end of treatment (up to 24 weeks).

Adverse event reporting additional description:

SAEs and non-serious AEs are reported for members of the ITT Population, comprised of all participants randomized to treatment who received at least one dose of randomized study drug during the Treatment Period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	UMEC/VI 62.5/25 µg
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Reporting group description:

Participants received umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms (µg) once daily (QD) each morning via a dry powder inhaler (DPI) and placebo QD each morning via a DPI for 24 weeks.

Reporting group title	TIO 18 µg
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Reporting group description:

Participants received tiotropium (TIO) 18 µg QD each morning via a DPI and placebo QD each morning via a DPI for 24 weeks.

Serious adverse events	UMEC/VI 62.5/25 µg	TIO 18 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 454 (3.52%)	17 / 451 (3.77%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			

subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal cancer			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arterial restenosis			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery restenosis			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Peripheral artery stenosis			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (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	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
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			
Death			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Sudden death			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 454 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 454 (0.44%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental disorder			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 454 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peritonitis			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 454 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 454 (0.22%)	0 / 451 (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	UMEC/VI 62.5/25 µg	TIO 18 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 454 (15.64%)	72 / 451 (15.96%)	
Nervous system disorders			
Headache			
subjects affected / exposed	40 / 454 (8.81%)	31 / 451 (6.87%)	
occurrences (all)	56	43	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 454 (2.86%)	15 / 451 (3.33%)	
occurrences (all)	15	17	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	28 / 454 (6.17%)	30 / 451 (6.65%)	
occurrences (all)	30	34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2012	Edit list of abbreviations; edit time and event table footnotes; modified wording regarding randomization criteria; reference added; minor protocol corrections addressed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported