



Clinical trial results:

An Open-Label, Rollover Study to Evaluate the Long Term Safety and Efficacy of VX-770 in Subjects with Cystic Fibrosis

Summary

EudraCT number	2009-012997-11
Trial protocol	FR IE CZ GB DE
Global end of trial date	12 May 2014

Results information

Result version number	v1 (current)
This version publication date	28 June 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	VX08-770-105
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01117012
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States, 02210-1862
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000335-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 July 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of long-term Ivacaftor (VX-770) treatment in subjects with cystic fibrosis (CF).

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 July 2010
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	Canada: 10
Country: Number of subjects enrolled	United States: 105
Country: Number of subjects enrolled	Australia: 30
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Ireland: 14
Worldwide total number of subjects	192
EEA total number of subjects	47

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)	34

Adolescents (12-17 years)	40
Adults (18-64 years)	118
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with Cystic Fibrosis (CF) who had completed the Study VX08-770-102 (Study 102/NCT00909532) and Study VX08-770-103 (Study 103/NCT00909727), were enrolled in this Study VX08-770-105 (Study 105/NCT01117012).

Pre-assignment

Screening details:

A total of 192 subjects were enrolled. Efficacy results are presented as per the treatment received in previous study (Placebo/Ivacaftor [VX-770]).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/VX-770

Arm description:

Subjects who received placebo during the parent study (Study 102 or 103), received VX-770 150 mg tablet orally twice daily q12h.

Arm type	Experimental
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

150 milligram (mg) tablet orally twice daily (q12h).

Arm title	VX-770/VX-770
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Arm description:

Subjects who received VX-770 during the parent study (Study 102 or 103), received VX-770 150 mg tablet orally q12h.

Arm type	Experimental
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg tablet orally twice daily q12h.

Number of subjects in period 1	Placebo/VX-770	VX-770/VX-770
Started	89	103
Completed	81	98
Not completed	8	5
Consent withdrawn by subject	3	-
Adverse Event	-	1
Death	1	1
Undefined	4	3

Baseline characteristics

Reporting groups

Reporting group title	Placebo/VX-770
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Reporting group description:

Subjects who received placebo during the parent study (Study 102 or 103), received VX-770 150 mg tablet orally twice daily q12h.

Reporting group title	VX-770/VX-770
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Reporting group description:

Subjects who received VX-770 during the parent study (Study 102 or 103), received VX-770 150 mg tablet orally q12h.

Reporting group values	Placebo/VX-770	VX-770/VX-770	Total
Number of subjects	89	103	192
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	22 ± 10.94	23.2 ± 11.55	-
Gender categorical Units: Subjects			
Female	44	58	102
Male	45	45	90

End points

End points reporting groups

Reporting group title	Placebo/VX-770
Reporting group description: Subjects who received placebo during the parent study (Study 102 or 103), received VX-770 150 mg tablet orally twice daily q12h.	
Reporting group title	VX-770/VX-770
Reporting group description: Subjects who received VX-770 during the parent study (Study 102 or 103), received VX-770 150 mg tablet orally q12h.	
Subject analysis set title	VX-770
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who received VX-770 150 mg tablet orally q12h in Study 105.	

Primary: Number of Subjects With Non-Serious Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Non-Serious Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[1]
End point description: Adverse Event: any untoward medical occurrence in a subject during the study, including any unfavorable and unintended sign, symptom, or disease whether or not it was considered to be study drug related. This included any newly occurring event or previous condition that increased in severity or frequency after obtaining informed consent and assent (where applicable). SAE: medical event or condition, which resulted in any of following, regardless of its relationship to the study drug: death, life threatening adverse experience, in-patient hospitalization/prolonged hospitalization, persistent/significant disability/incapacity, congenital anomaly/birth defect, important medical event. Non-Serious AEs included all AEs except SAEs. Analysis was performed in Safety Set defined as all subjects who received at least 1 dose of study drug during Study 105.	
End point type	Primary
End point timeframe: Study 105: Day 1 up to Week 168	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No inferential statistics was planned for this study.

End point values	VX-770			
Subject group type	Subject analysis set			
Number of subjects analysed	192			
Units: Subjects				
number (not applicable)				
Non-Serious AEs	190			
SAEs	70			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Decline From Study 105 Baseline in Percent

Predicted Forced Expiratory Volume in 1 Second (FEV1) Through Week 96

End point title	Annualized Rate of Decline From Study 105 Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Through Week 96
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Predicted FEV1 (for age, gender, and height) was calculated using the Knudson method. Baseline was defined as Study 105 Day 15. Analysis was performed in Full Analysis Set defined as all subjects who were enrolled and received at least 1 dose of study drug during Study 105.

End point type	Secondary
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End point timeframe:

Study 105: Baseline through Week 96

End point values	Placebo/VX-770	VX-770/VX-770		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	103		
Units: percent predicted of FEV1 per year				
least squares mean (confidence interval 95%)	-0.3 (-2.47 to 1.86)	-1.23 (-2.1 to -0.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Study 105 Baseline in Percent Predicted FEV1 Through Week 96

End point title	Absolute Change From Study 105 Baseline in Percent Predicted FEV1 Through Week 96
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Predicted FEV1 (for age, gender, and height) was calculated using the Knudson method. Baseline was defined as the most recent measurement prior to intake of the first dose of study drug in Study 105. Absolute Change at Week 48 and Week 96 are reported. Analysis was performed in Full Analysis Set.

End point type	Secondary
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End point timeframe:

Study 105: Baseline through Week 96

End point values	Placebo/VX-770	VX-770/VX-770		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	99		
Units: percent predicted of FEV1				
arithmetic mean (standard deviation)				
Absolute Change at Week 48 (n = 85, 99)	9.2585 (± 9.63822)	-0.4422 (± 8.62332)		

Absolute Change at Week 96 (n = 76, 97)	9.8194 (\pm 11.22812)	0.1581 (\pm 9.01629)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Study 105 Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score Through Week 96

End point title	Absolute Change From Study 105 Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score Through Week 96
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End point description:

The CFQ-R is a validated subject-reported outcome measuring health-related quality of life for subjects with cystic fibrosis. Respiratory domain assessed respiratory symptoms (for example, coughing, congestion, wheezing), score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life. Absolute Change at Week 48 and Week 96 are reported. Analysis was performed in Full Analysis Set.

End point type	Secondary
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End point timeframe:

Study 105: Baseline through Week 96

End point values	Placebo/VX-770	VX-770/VX-770		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	99		
Units: units on a scale				
arithmetic mean (standard deviation)				
Absolute Change at Week 48 (n = 86, 99)	7.43 (\pm 16.6)	-1.94 (\pm 16.55)		
Absolute Change at Week 96 (n = 77, 97)	10.05 (\pm 15.254)	0.77 (\pm 14.305)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Pulmonary Exacerbation Event Rate

End point title	Annualized Pulmonary Exacerbation Event Rate
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End point description:

Annualized event rate was calculated by regression with negative binomial distribution. Analysis was performed in Full Analysis Set.

End point type	Secondary
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End point timeframe:

Study 105: Day 1 through Week 96

End point values	Placebo/VX-770	VX-770/VX-770		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	103		
Units: events per year				
number (not applicable)	0.463	0.658		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Duration of Pulmonary Exacerbation Events

End point title	Annualized Duration of Pulmonary Exacerbation Events
End point description: Analysis was performed in Full Analysis Set.	
End point type	Secondary
End point timeframe: Study 105: Day 1 through Week 96	

End point values	Placebo/VX-770	VX-770/VX-770		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	103		
Units: Days per year				
arithmetic mean (standard deviation)	10.89 (± 20.124)	17.27 (± 30.974)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Study 105 Baseline in Weight Through Week 96

End point title	Absolute Change From Study 105 Baseline in Weight Through Week 96
End point description: Weight is a measurement of nutritional status. Absolute change in weight, measured in kilograms (kg), at Week 48 and Week 96 are reported. Analysis was performed in Full Analysis Set.	
End point type	Secondary
End point timeframe: Study 105: Baseline through Week 96	

End point values	Placebo/VX-770	VX-770/VX-770		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	99		
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
Absolute Change at Week 48 (n = 86, 99)	4.03 (± 3.677)	1.26 (± 3.844)		
Absolute Change at Week 96 (n = 76, 97)	4.93 (± 5.577)	2.62 (± 5.909)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study 105: Day 1 through Week 168

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	VX-770
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Reporting group description:

All subjects who received VX-770 150 mg tablet orally q12h in Study 105.

Serious adverse events	VX-770		
Total subjects affected by serious adverse events			
subjects affected / exposed	70 / 192 (36.46%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Device occlusion			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			

subjects affected / exposed	7 / 192 (3.65%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Bullous lung disease			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Depression suicidal			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Chest X-ray abnormal			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoglobin decreased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary function test decreased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Road traffic accident			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hemiplegic migraine			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemic seizure			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			

subjects affected / exposed	2 / 192 (1.04%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	2 / 192 (1.04%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Anal fissure				
subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Distal ileal obstruction syndrome				
subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				

subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal tubular disorder			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	42 / 192 (21.88%)		
occurrences causally related to treatment / all	2 / 88		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspergilloma			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lobar pneumonia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung abscess			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection pseudomonal			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection viral			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	VX-770		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	190 / 192 (98.96%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Fibroadenoma of breast			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Flushing			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Thrombophlebitis superficial			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	35 / 192 (18.23%)		
occurrences (all)	47		
Fatigue			
subjects affected / exposed	13 / 192 (6.77%)		
occurrences (all)	16		
Catheter site pain			
subjects affected / exposed	7 / 192 (3.65%)		
occurrences (all)	8		
Chest pain			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	6		
Influenza like illness			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	6		
Non-cardiac chest pain			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	6		
Pain			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	8		
Chills			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Malaise			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Asthenia			

subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Chest discomfort			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Injection site pain			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Adverse drug reaction			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Catheter site swelling			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Drug interaction			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Exercise tolerance decreased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Infusion site pain			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Medical device pain			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	2		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	9 / 192 (4.69%)		
occurrences (all)	38		
Drug hypersensitivity			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Hypersensitivity			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	4		

Allergy to animal subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Reproductive system and breast disorders			
Dysmenorrhoea subjects affected / exposed occurrences (all)	6 / 192 (3.13%) 22		
Breast mass subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Cervix inflammation subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Dyspareunia subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Erectile dysfunction subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Menorrhagia subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Menstruation irregular subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Metrorrhagia subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Ovarian cyst subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Pelvic pain subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 2		
Vaginal haemorrhage			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	86 / 192 (44.79%)		
occurrences (all)	166		
Oropharyngeal pain			
subjects affected / exposed	39 / 192 (20.31%)		
occurrences (all)	58		
Nasal congestion			
subjects affected / exposed	26 / 192 (13.54%)		
occurrences (all)	34		
Haemoptysis			
subjects affected / exposed	24 / 192 (12.50%)		
occurrences (all)	57		
Productive cough			
subjects affected / exposed	24 / 192 (12.50%)		
occurrences (all)	45		
Rales			
subjects affected / exposed	19 / 192 (9.90%)		
occurrences (all)	33		
Sputum increased			
subjects affected / exposed	17 / 192 (8.85%)		
occurrences (all)	25		
Rhinorrhoea			
subjects affected / exposed	16 / 192 (8.33%)		
occurrences (all)	29		
Sinus congestion			
subjects affected / exposed	14 / 192 (7.29%)		
occurrences (all)	15		
Wheezing			
subjects affected / exposed	14 / 192 (7.29%)		
occurrences (all)	22		
Dyspnoea			

subjects affected / exposed	10 / 192 (5.21%)		
occurrences (all)	13		
Epistaxis			
subjects affected / exposed	9 / 192 (4.69%)		
occurrences (all)	10		
Pleuritic pain			
subjects affected / exposed	9 / 192 (4.69%)		
occurrences (all)	14		
Respiratory tract congestion			
subjects affected / exposed	9 / 192 (4.69%)		
occurrences (all)	13		
Respiration abnormal			
subjects affected / exposed	8 / 192 (4.17%)		
occurrences (all)	9		
Nasal polyps			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	8		
Asthma			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	6		
Paranasal sinus hypersecretion			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	6		
Rhinitis allergic			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	6		
Nasal discharge discolouration			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	6		
Pharyngeal erythema			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Rhonchi			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	5		
Dysphonia			

subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Nasal inflammation			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	4		
Increased viscosity of bronchial secretion			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Nasal oedema			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Nasal turbinate abnormality			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	3		
Sputum discoloured			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Throat irritation			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Tonsillar hypertrophy			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	4		
Allergic cough			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Atelectasis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Bronchial obstruction			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Dyspnoea exertional			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		

Nasal discomfort			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Paranasal sinus mucosal hypertrophy			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Pharyngeal oedema			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Pleurisy			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Pneumothorax			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Prolonged expiration			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Sneezing			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	2		
Tonsillar inflammation			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	11 / 192 (5.73%)		
occurrences (all)	12		
Depression			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Insomnia			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	6		
Sleep disorder			

subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	3		
Abnormal dreams			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Adjustment disorder			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Attention deficit/hyperactivity disorder			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Mood swings			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Phagophobia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Investigations			
Bacterial test positive			
subjects affected / exposed	16 / 192 (8.33%)		
occurrences (all)	20		
Weight decreased			
subjects affected / exposed	13 / 192 (6.77%)		
occurrences (all)	14		
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 192 (4.69%)		
occurrences (all)	13		
Pulmonary function test decreased			
subjects affected / exposed	8 / 192 (4.17%)		
occurrences (all)	8		
Alanine aminotransferase increased			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	11		
Fungal test positive			

subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	6		
Glucose urine present			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	7		
Vitamin D decreased			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	6		
Blood glucose increased			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	6		
Prothrombin time prolonged			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	5		
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	5		
Hepatic enzyme increased			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Liver function test abnormal			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	6		
Blood bilirubin increased			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	7		
Blood creatinine increased			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Culture throat positive			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Forced expiratory volume decreased			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		

White blood cell count increased subjects affected / exposed occurrences (all)	3 / 192 (1.56%) 3		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Blood glucose decreased subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Blood iron decreased subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Blood urine present subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 3		
Body temperature increased subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Breath sounds abnormal subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Cardiac murmur subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 3		
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Eosinophil count increased subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Neutrophil count increased subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Platelet count increased subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		

Protein urine present			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Spirometry abnormal			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Blood albumin increased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Blood bilirubin unconjugated increased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Blood calcium increased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	2		
Blood cortisol increased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Blood immunoglobulin E increased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Blood pressure increased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	2		
Blood urea increased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Clostridium test positive			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Coagulation factor increased			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Electrocardiogram T wave peaked			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Gastrointestinal examination abnormal			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Haemoglobin increased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Monocyte count increased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Nitrite urine present			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Peak expiratory flow rate decreased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Serum ferritin decreased			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Sputum abnormal			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Urine leukocyte esterase			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Urine leukocyte esterase positive			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		

Weight increased subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Injury, poisoning and procedural complications			
Procedural pain subjects affected / exposed occurrences (all)	5 / 192 (2.60%) 5		
Laceration subjects affected / exposed occurrences (all)	4 / 192 (2.08%) 4		
Ligament sprain subjects affected / exposed occurrences (all)	4 / 192 (2.08%) 4		
Contusion subjects affected / exposed occurrences (all)	3 / 192 (1.56%) 4		
Arthropod sting subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Excoriation subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Hand fracture subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Joint dislocation subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Meniscus lesion subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Muscle strain subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 3		
Skeletal injury			

subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Wrist fracture			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Arthropod bite			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Chest injury			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Corneal abrasion			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Fibula fracture			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Foot fracture			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Foreign body in eye			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	4		
Incision site pain			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Ligament rupture			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Muscle injury			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Muscle rupture			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Post procedural complication			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Post procedural swelling			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Post-traumatic pain			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Radius fracture			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Rib fracture			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Scratch			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Soft tissue injury			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Stab wound			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Sternal injury			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Tendon rupture			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Tongue injury			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Cystic fibrosis related diabetes			

subjects affected / exposed occurrences (all)	4 / 192 (2.08%) 4		
Cataract congenital subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Cystic fibrosis pancreatic subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Cardiac disorders			
Palpitations subjects affected / exposed occurrences (all)	3 / 192 (1.56%) 3		
Tachycardia subjects affected / exposed occurrences (all)	3 / 192 (1.56%) 3		
Angina pectoris subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Intracardiac thrombus subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Left ventricular dysfunction subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	45 / 192 (23.44%) 90		
Dizziness subjects affected / exposed occurrences (all)	12 / 192 (6.25%) 15		
Sinus headache subjects affected / exposed occurrences (all)	7 / 192 (3.65%) 9		
Hypoaesthesia			

subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	8		
Lethargy			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	5		
Paraesthesia			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Migraine			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	5		
Convulsion			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Syncope			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Ageusia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Burning sensation			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Epilepsy			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Memory impairment			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	5		
Coagulopathy			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		

Neutrophilia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Polycythaemia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	6		
Vertigo			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Cerumen impaction			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Deafness			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Ear discomfort			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Ear pruritus			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Middle ear inflammation			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Tympanic membrane hyperaemia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Eye disorders			

Conjunctivitis			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	7		
Vision blurred			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Conjunctivitis allergic			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Eye pruritus			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Lens disorder			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	2		
Meibomian gland dysfunction			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Myopia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Ocular vascular disorder			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Visual acuity reduced			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Visual impairment			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Vitreous floaters			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	23 / 192 (11.98%)		
occurrences (all)	28		
Constipation			
subjects affected / exposed	22 / 192 (11.46%)		
occurrences (all)	27		
Diarrhoea			
subjects affected / exposed	21 / 192 (10.94%)		
occurrences (all)	22		
Vomiting			
subjects affected / exposed	21 / 192 (10.94%)		
occurrences (all)	23		
Abdominal pain upper			
subjects affected / exposed	19 / 192 (9.90%)		
occurrences (all)	31		
Nausea			
subjects affected / exposed	19 / 192 (9.90%)		
occurrences (all)	24		
Dyspepsia			
subjects affected / exposed	9 / 192 (4.69%)		
occurrences (all)	11		
Gastrooesophageal reflux disease			
subjects affected / exposed	9 / 192 (4.69%)		
occurrences (all)	9		
Flatulence			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	8		
Toothache			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	6		
Abdominal distension			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	5		
Rectal haemorrhage			

subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Distal ileal obstruction syndrome			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	4		
Abdominal discomfort			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Haemorrhoids			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Steatorrhoea			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	3		
Duodenitis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Gastric hypomotility			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Gastrointestinal hypomotility			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Gingival pain			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Impaired gastric emptying			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Inguinal hernia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Irritable bowel syndrome			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Lip dry			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Lip swelling			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Tooth impacted			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Umbilical hernia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Cholelithiasis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	13 / 192 (6.77%)		
occurrences (all)	14		
Acne			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	5		
Alopecia			

subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Dermatitis contact			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Night sweats			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Pruritus			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Rash erythematous			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	5		
Dry skin			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	4		
Sunburn			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Urticaria			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	5		
Drug eruption			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Rash generalised			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Rash papular			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Skin wrinkling			

subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Dermal cyst			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Ecchymosis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Onychoclasia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Photosensitivity reaction			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Pruritus generalised			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Rash follicular			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Skin fissures			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Skin odour abnormal			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	7		
Nephrolithiasis			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	4		
Polyuria			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Cystitis interstitial			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Glycosuria			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Hypertonic bladder			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Renal colic			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Renal cyst			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Adrenal suppression			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	26 / 192 (13.54%)		
occurrences (all)	34		
Back pain			
subjects affected / exposed	14 / 192 (7.29%)		
occurrences (all)	15		
Musculoskeletal chest pain			
subjects affected / exposed	7 / 192 (3.65%)		
occurrences (all)	9		
Pain in extremity			
subjects affected / exposed	7 / 192 (3.65%)		
occurrences (all)	8		
Musculoskeletal pain			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	5		
Myalgia			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Joint swelling			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Muscle spasms			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Neck pain			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Arthritis			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Arthropathy			

subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	4		
Fibromyalgia			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Intervertebral disc protrusion			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	3		
Osteoarthritis			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Clubbing			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Costochondritis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Osteopenia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Periarthritis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Tendon pain			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Tendonitis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Groin pain			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	94 / 192 (48.96%)		
occurrences (all)	231		
Upper respiratory tract infection			
subjects affected / exposed	65 / 192 (33.85%)		
occurrences (all)	144		
Nasopharyngitis			
subjects affected / exposed	39 / 192 (20.31%)		
occurrences (all)	67		
Sinusitis			
subjects affected / exposed	29 / 192 (15.10%)		
occurrences (all)	41		
Gastroenteritis			
subjects affected / exposed	13 / 192 (6.77%)		
occurrences (all)	16		
Rhinitis			
subjects affected / exposed	10 / 192 (5.21%)		
occurrences (all)	15		
Influenza			
subjects affected / exposed	9 / 192 (4.69%)		
occurrences (all)	9		
Urinary tract infection			
subjects affected / exposed	9 / 192 (4.69%)		
occurrences (all)	11		
Respiratory tract infection viral			
subjects affected / exposed	8 / 192 (4.17%)		
occurrences (all)	11		
Tonsillitis			
subjects affected / exposed	8 / 192 (4.17%)		
occurrences (all)	8		
Oral candidiasis			

subjects affected / exposed	7 / 192 (3.65%)		
occurrences (all)	8		
Respiratory tract infection			
subjects affected / exposed	7 / 192 (3.65%)		
occurrences (all)	14		
Bronchitis			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	14		
Candidiasis			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	13		
Gastroenteritis viral			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	6		
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 192 (3.13%)		
occurrences (all)	7		
Oral herpes			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	6		
Pharyngitis			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	6		
Vulvovaginal mycotic infection			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	6		
Bacterial disease carrier			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	5		
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Ear infection			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		

Pneumonia			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Acute sinusitis			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	4		
Cellulitis			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Cystitis			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Otitis media			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	4		
Pseudomonas infection			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Tooth abscess			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Viral infection			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences (all)	3		
Conjunctivitis infective			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Folliculitis			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Herpes zoster			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Laryngitis			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		

Lower respiratory tract infection subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Oropharyngeal candidiasis subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Otitis externa subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Tracheobronchitis subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2		
Alveolar osteitis subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Bacteraemia subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Body tinea subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Diverticulitis subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Erythema migrans subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Fungal skin infection subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		
Furuncle subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1		

Gastritis viral			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Genital candidiasis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Genital herpes			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Genital infection fungal			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Herpes simplex			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Herpes simplex ophthalmic			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Infection parasitic			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Labyrinthitis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Mycobacterial infection			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Nail bed infection bacterial			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Oesophageal candidiasis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		

Onychomycosis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Pharyngitis streptococcal			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Pneumonia staphylococcal			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Rhinotracheitis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Serratia infection			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Vaginitis bacterial			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Varicella			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Wound infection staphylococcal			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	6		
Hypoglycaemia			
subjects affected / exposed	5 / 192 (2.60%)		
occurrences (all)	5		
Glucose tolerance impaired			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Hyperglycaemia			

subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Vitamin D deficiency			
subjects affected / exposed	4 / 192 (2.08%)		
occurrences (all)	4		
Hypokalaemia			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Iron deficiency			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Vitamin K deficiency			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences (all)	2		
Dehydration			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Electrolyte imbalance			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Hypovitaminosis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Increased appetite			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Insulin resistance			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Lactose intolerance			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Vitamin A deficiency			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		
Zinc deficiency			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2010	The Data Monitoring Committee (DMC) was removed for this study. Two interim analyses were added.
11 June 2010	Changes in study procedures regarding liver function testing were made.
26 July 2010	The DMC was reinstated as a safety monitoring measure for this study. Criteria for subject discontinuation were updated.
10 November 2010	Frequency of liver function test was changed.
23 May 2011	Frequency of liver function test was changed.
26 March 2012	Ophthalmologic examination (OE) was added. A third interim analysis was added.
05 October 2012	Additional OEs were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported