Clinical trial results:
A PHASE 3 STUDY EVALUATING THE EFFECT OF PITAVASTATIN TO PREVENT CARDIOVASCULAR EVENTS IN HIV-1 INFECTED INDIVIDUALS

Summary

EudraCT number	2018-001285-41
Trial protocol	ES
Global end of trial date	21 August 2023

Results information

Result version number	v1 (current)
This version publication date	09 November 2024
First version publication date	09 November 2024

Trial information

Trial identification

Sponsor protocol code	EU5332

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02344290
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 119127, Secondary Protocol ID: EU5332

Notes:

Sponsors

Sponsor organisation name	NEAT ID Foundation
Sponsor organisation address	CHU Saint Pierre - PL 709 Rue Haute 322, Brussels, Belgium,
Public contact	Carl Fletcher, Neat ID Foundation, 0044 7494795982, selina.piper-b@rokcservices.com
Scientific contact	Carl Fletcher, Neat ID Foundation, 0044 7494795982, selina.piper-b@rokcservices.com
Sponsor organisation name	Massachusetts General Hospital
Sponsor organisation address	50 Staniford Street, Boston, MA , United States,
Public contact	REPRIEVE Project Manager, REPRIEVE Clinical Coordinating Center, 001 6177249109, mghreprievetrial@mgb.org
Scientific contact	REPRIEVE Project Manager, REPRIEVE Clinical Coordinating Center, 001 6177249109, mghreprievetrial@mgb.org

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	21 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 August 2023
Global end of trial reached?	Yes
Global end of trial date	21 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effects of pitavastatin as a primary prevention strategy for major adverse cardiovascular events (MACE) in HIV.

Protection of trial subjects:

The REPRIEVE protocol and the informed consent and any subsequent modifications were reviewed and approved by the IRB/EC responsible for oversight of the study. A signed consent form as obtained from the participant (or legal representative). The consent form described the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form was given to the participant or legal representative, and retained in the participant's record. Risks, including potential risks of pitavastatin, and protection against risk were described in the informed consent form.

All laboratory specimens, evaluation forms, reports, and other records that left the sites were identified by coded number only to maintain participant confidentiality. All records were kept locked. All computer entry and networking programs was done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NHLBI, NIAID, OHRP, and other local, US, and international regulatory entities as part of their duties, or the industry supporters or designee.

An independent DSMB empanelled by the NHLBI was responsible for oversight of the trial with respect to safety. The DSMB met every 6-9 months between 2015 and 2023

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	26 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 213
Country: Number of subjects enrolled	Haiti: 140
Country: Number of subjects enrolled	United States: 3787
Country: Number of subjects enrolled	Thailand: 590
Country: Number of subjects enrolled	India: 504
Country: Number of subjects enrolled	Canada: 131
Country: Number of subjects enrolled	Botswana: 281

Country: Number of subjects enrolled	Brazil: 1099
Country: Number of subjects enrolled	South Africa: 570
Country: Number of subjects enrolled	Uganda: 181
Country: Number of subjects enrolled	Zimbabwe: 125
Country: Number of subjects enrolled	Peru: 148
Worldwide total number of subjects	7769
EEA total number of subjects	213

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)	7624
From 65 to 84 years	145
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants living with HIV who were at risk of cardiovascular disease were randomly assigned to receive 4 mg of pitavastatin or placebo once a day for their entire study duration.

Pre-assignment

Screening details:

This study enrolled PWH who were on any ART regimen (ART was not provided by the study) for at least 6 months before study entry and were at low to moderate risk of CVD using the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline thresholds for recommended statin initiation.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pitavastatin

Arm description:

Participants received pitavastatin once a day for the entire time they were in study follow-up.

Arm type	Experimental
Investigational medicinal product name	Pitavastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet (4 mg) taken once daily, orally with or without food

Arm title	Placebo

Arm description:

Participants were randomly assigned to receive placebo tablet once a day for their entire study duration.

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

Dosage and administration details:

One tablet taken once daily, orally with or without food

Number of subjects in period 1	Pitavastatin	Placebo
Started	3888	3881
Completed	3201	3201
Not completed	687	680
Consent withdrawn by subject	315	324
Physician decision	25	25
Lost to follow-up	258	249
Unable to attend clinic	69	60
Site closure	15	19
not specified	5	3

Baseline characteristics

Reporting groups	
Reporting group title	Pitavastatin
Reporting group description:	
Participants received pitavastatin once a day for the entire time they were in study follow-up.	
Reporting group title	Placebo
Reporting group description:	
Participants were randomly assigned to receive placebo tablet once a day for their entire study duration.	

Reporting group values	Pitavastatin	Placebo	Total
Number of subjects	3888	3881	7769
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	50	50	
inter-quartile range (Q1-Q3)	45 to 55	45 to 55	-
Gender categorical Units: Subjects			
Female	1211	1208	2419
Male	2677	2673	5350
Race/Ethnicity			
Race was reported by the participants. “Other” race includes participants who identified as native or indigenous to the enrolment region, as having more than one race, or as having an unknown race.			
Units: Subjects			
Black	1569	1639	3208
White	1364	1340	2704
Asian	571	567	1138
Other	384	335	719
Global burden of disease Units: Subjects			
High Income	2044	2051	4095
Latin America and Caribbean	709	714	1423
Southeast or East Asia	304	286	590
South Asia	246	258	504
Sub-Saharan Africa	585	572	1157

Atherosclerotic Cardiovascular Disease (ASCVD) risk score			
10-Year Atherosclerotic Cardiovascular Disease (ASCVD) risk score is calculated based on age, sex, race, systolic blood pressure, total and high-density lipoprotein cholesterol, hypertension treatment, smoking history and presence of diabetes. It is measured on a continuous scale, with 0-<5% considered low risk, 5-<7.5% borderline risk, 7.5-<20% intermediate risk, and ≥20% high risk according to the American College of Cardiology and American Heart Association. More granular categories were used to describe REPRIEVE participants, given the eligibility criterion of low to moderate CVD risk.			
Units: Subjects			
0 - <2.5%	1096	1060	2156
2.5 - <5%	1030	1025	2055
5 - <7.5%	934	960	1894
7.5 - 10%	540	561	1101
≥10%	288	275	563
Nadir CD4 cell count Units: Subjects			
<200 cells/mm^3	1890	1911	3801
200 - 349 cells/mm^3	1019	1022	2041
≥350 cells/mm^3	839	825	1664
Unknown	140	123	263
CD4 cell count Units: Subjects			
≤500 cells/mm^3	1257	1253	2510
>500 cells/mm^3	2631	2628	5259
HIV-1 RNA			
The assays that were used for testing varied, including assays with a lower limit of quantification (LLQ) of 20 to 400 copies/mL			
Units: Subjects			
<LLQ	2641	2609	5250
LLQ - <400 copies/mL	305	312	617
≥400 copies/mL	63	67	130
Not available	879	893	1772
Pre-existing diabetes Units: Subjects			
Condition present	24	14	38
Condition absent	3864	3867	7731

Subject analysis sets

Subject analysis set title	All randomised participants
Subject analysis set type	Per protocol

Subject analysis set description:

All participants enrolled according to the randomized treatment group

Reporting group values	All randomised participants		
Number of subjects	7769		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female Male			
Race/Ethnicity			
Race was reported by the participants. "Other" race includes participants who identified as native or indigenous to the enrolment region, as having more than one race, or as having an unknown race.			
Units: Subjects			
Black White Asian Other			
Global burden of disease Units: Subjects			
High Income Latin America and Caribbean Southeast or East Asia South Asia Sub-Saharan Africa			
Atherosclerotic Cardiovascular Disease (ASCVD) risk score			
10-Year Atherosclerotic Cardiovascular Disease (ASCVD) risk score is calculated based on age, sex, race, systolic blood pressure, total and high-density lipoprotein cholesterol, hypertension treatment, smoking history and presence of diabetes. It is measured on a continuous scale, with 0-<5% considered low risk, 5-<7.5% borderline risk, 7.5-<20% intermediate risk, and ≥20% high risk according to the American College of Cardiology and American Heart Association. More granular categories were used to describe REPRIEVE participants, given the eligibility criterion of low to moderate CVD risk.			
Units: Subjects			
0 - <2.5% 2.5 - <5% 5 - <7.5% 7.5 - 10% ≥10%			
Nadir CD4 cell count Units: Subjects			
<200 cells/mm^3 200 - 349 cells/mm^3 ≥350 cells/mm^3 Unknown			
CD4 cell count Units: Subjects			

≤500 cells/mm^3 >500 cells/mm^3			
HIV-1 RNA			
The assays that were used for testing varied, including assays with a lower limit of quantification (LLQ) of 20 to 400 copies/mL			
Units: Subjects			
<LLQ LLQ - <400 copies/mL ≥400 copies/mL Not available			
Pre-existing diabetes Units: Subjects			
Condition present	38		
Condition absent	7731		

End points

End points reporting groups

Reporting group title	Pitavastatin
Reporting group description:	
Participants received pitavastatin once a day for the entire time they were in study follow-up.	
Reporting group title	Placebo
Reporting group description:	
Participants were randomly assigned to receive placebo tablet once a day for their entire study duration.	
Subject analysis set title	All randomised participants
Subject analysis set type	Per protocol
Subject analysis set description:	
All participants enrolled according to the randomized treatment group	

Primary: Incidence Rate of Major Adverse Cardiovascular Event (MACE)

End point title	Incidence Rate of Major Adverse Cardiovascular Event (MACE)
End point description:	
End point type	Primary
End point timeframe:	
From entry through end of study. Follow-up time varied depending on time of enrolment (the median follow-up time was 5.6 years).	

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	4.95 (4.07 to 6.03)	7.77 (6.64 to 9.08)		

Statistical analyses

Statistical analysis title	Incidence Rate of MACE
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.84

Notes:

[1] - Hazard ratio is shown as pitavastatin/placebo. Two-sided 95% repeated confidence interval that adjusts for interim looks according to the realized Lan and DeMets implementation of the O'Brien-Fleming sequential stopping boundary is presented.

Secondary: Incidence Rate of Cardiac Ischemia or Myocardial Infarction

End point title	Incidence Rate of Cardiac Ischemia or Myocardial Infarction

End point description:

Cardiac ischemia or myocardial infarction component of the primary composite MACE outcome. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated via cause-specific relative hazard (i.e. hazard ratio) of prescribed pitavastatin compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Deaths (without preceding event of interest) were treated as competing events and censored. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrolment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	1.48 (1.03 to 2.11)	2.65 (2.03 to 3.46)		

Statistical analyses

Statistical analysis title	Incidence Rate of Cardiac Ischemia
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.87

Secondary: Incidence Rate of Cerebrovascular Event (Stroke or TIA)

End point title	Incidence Rate of Cerebrovascular Event (Stroke or TIA)

End point description:

Cerebrovascular event (stroke or TIA) component of the primary composite MACE outcome. The incidence rates were

estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact.
The treatment effect was estimated via cause-specific relative hazard (i.e. hazard ratio) of prescribed pitavastatin
compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Deaths
(without preceding event of interest) were treated as competing events and censored. Treatment discontinuation was
ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrollment (the median follow-up time was
5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	1.53 (1.07 to 2.17)	2.46 (1.86 to 3.24)		

Statistical analyses

Statistical analysis title	Incidence Rate of Cerebrovascular Event
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.97

Secondary: Incidence Rate of Peripheral Arterial Ischemia

End point title	Incidence Rate of Peripheral Arterial Ischemia

End point description:

Peripheral arterial ischemia component of the primary composite MACE outcome. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated via cause-specific relative hazard (i.e. hazard ratio) of prescribed pitavastatin compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Deaths (without preceding event of interest) were treated as competing events and censored. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrollment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	0.10 (0.02 to 0.39)	0.15 (0.05 to 0.45)		

Statistical analyses

Statistical analysis title	Incidence Rate of Peripheral Arterial Ischemia
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	4.02

Secondary: Incidence Rate of Death From CV Causes

End point title	Incidence Rate of Death From CV Causes

End point description:

CV death component of the primary composite MACE outcome. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated via cause-specific relative hazard (i.e. hazard ratio) of prescribed pitavastatin compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Non-CV deaths and deaths from undetermined causes were treated as competing events and censored. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrollment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	0.69 (0.41 to 1.16)	0.98 (0.63 to 1.51)		

Statistical analyses

Statistical analysis title	Analysis 1 Incidence Rate of Death From CV Causes
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.38

Secondary: Incidence Rate of Death From CV or Undetermined Causes

End point title	Incidence Rate of Death From CV or Undetermined Causes

End point description:

CV or undetermined death component of the primary composite MACE outcome. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated via cause-specific relative hazard (i.e. hazard ratio) of prescribed pitavastatin compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Non-CV deaths were treated as competing events and censored. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrollment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	1.72 (1.23 to 2.39)	2.54 (1.94 to 3.33)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Incidence Rate of Death
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.03

Secondary: Incidence Rate of Cardiac Catheterization or Revascularization

End point title	Incidence Rate of Cardiac Catheterization or Revascularization

End point description:

Cardiac catheterization or revascularization component of the primary composite MACE outcome. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated via cause-specific relative hazard (i.e. hazard ratio) of prescribed pitavastatin compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Deaths (without preceding event of interest) were treated as competing events and censored. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrollment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	1.08 (0.71 to 1.64)	1.77 (1.27 to 2.45)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Incidence Rate of CC
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.05

Secondary: Incidence Rate of Carotid or Cerebrovascular Revascularization

End point title	Incidence Rate of Carotid or Cerebrovascular Revascularization

End point description:

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrollment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence Rate of MACE or Death

End point title	Incidence Rate of MACE or Death

End point description:

A composite outcome including MACE and death from any cause. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated via relative hazard (i.e. hazard ratio) of prescribed pitavastatin compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrolment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	9.31 (8.07 to 10.75)	12.02 (10.60 to 13.63)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Incidence Rate of MACE
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	0.94

Secondary: Incidence Rate of Death (All-cause)

End point title	Incidence Rate of Death (All-cause)

End point description:

Death from any cause. The incidence rates were estimated based on time to event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated via relative hazard (i.e. hazard ratio) of prescribed pitavastatin compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrolment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	6.18 (5.19 to 7.36)	6.99 (5.93 to 8.23)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Incidence Rate of Death
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.12

Secondary: Incidence Rate of Non-CV Clinical Diagnoses

End point title	Incidence Rate of Non-CV Clinical Diagnoses

End point description:

A composite of non-CV clinical diagnoses including: non-AIDS-defining cancers (excluding basal cell and squamous cell carcinomas of the skin), AIDS-defining events (based on Centers for Disease Control and Prevention [CDC] 2014 classification), end-stage renal disease, and end-stage liver disease. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated via cause-specific relative hazard (i.e. hazard ratio) of prescribed pitavastatin compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Deaths (without preceding event of interest) were treated as competing events and censored. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrolment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	9.17 (7.93 to 10.59)	9.90 (8.61 to 11.38)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Incidence Rate
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.13

Secondary: Incidence Rate of Non-AIDS-defining Cancer

End point title	Incidence Rate of Non-AIDS-defining Cancer

End point description:

Non-AIDS-defining cancer (excluding basal cell and squamous cell carcinomas of the skin) component of the composite non-CV clinical diagnoses outcome. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated via cause-specific relative hazard (i.e. hazard ratio) of prescribed pitavastatin compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Deaths (without preceding event of interest) were treated as competing events and censored. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrolment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	5.25 (4.34 to 6.36)	5.68 (4.74 to 6.83)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Non-AIDS-defining Cancer
Comparison groups	Pitavastatin v Placebo

Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.2

Secondary: Incidence Rate of Peripheral Arterial Revascularization

End point title	Incidence Rate of Peripheral Arterial Revascularization

End point description:

Peripheral arterial revascularization component of the primary composite MACE outcome. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated via cause-specific relative hazard (i.e. hazard ratio) of prescribed pitavastatin compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Deaths (without preceding event of interest) were treated as competing events and censored. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrolment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	0 (0 to 0)	0.29 (0.13 to 0.65)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Peripheral Arterial
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.54

Secondary: Incidence Rate of AIDS-defining Event

End point title	Incidence Rate of AIDS-defining Event

End point description:

AIDS-defining event component of the composite non-CV clinical diagnoses outcome. Events were captured based on the Centers for Disease Control and Prevention [CDC] 2014 classification. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated via cause-specific relative hazard (i.e. hazard ratio) of prescribed pitavastatin compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Deaths (without preceding event of interest) were treated as competing events and censored. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrollment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	3.36 (2.65 to 4.27)	3.55 (2.82 to 4.47)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 of AIDS-defining Event
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.31

Secondary: Incidence Rate of End-Stage Renal Disease

End point title	Incidence Rate of End-Stage Renal Disease

End point description:

End-stage renal disease (defined as initiation of dialysis or renal transplantation) component of the composite non-CV clinical diagnoses outcome. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated via cause-specific relative hazard (i.e. hazard ratio) of prescribed pitavastatin compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Deaths (without preceding event of interest) were treated as competing events and censored. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrollment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	0.15 (0.05 to 0.46)	0.24 (0.10 to 0.59)		

Statistical analyses

Statistical analysis title	Statistical Analysis for End-Stage Renal Disease
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	2.51

Secondary: Incidence Rate of End-Stage Liver Disease

End point title	Incidence Rate of End-Stage Liver Disease

End point description:

End-stage liver disease (defined as cirrhosis or hepatic decompensation requiring hospitalization) component of the composite non-CV clinical diagnoses outcome. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated via cause-specific relative hazard (i.e. hazard ratio) of prescribed pitavastatin compared to placebo from Cox proportional hazards models, stratified by screening CD4 count and sex. Deaths (without preceding event of interest) were treated as competing events and

censored. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrollment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 1000 person-years				
number (confidence interval 95%)	0.59 (0.33 to 1.04)	0.64 (0.37 to 1.10)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for End-Stage Liver Disease
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	2.02

Secondary: Incidence Rate of Non-fatal Serious Adverse Event

End point title	Incidence Rate of Non-fatal Serious Adverse Event

End point description:

Safety analysis outcome measure of non-fatal serious adverse event was defined by International Conference on Harmonisation (ICH) criteria. Fatal events were excluded as deaths were a secondary efficacy outcome (see outcome measure: incidence rate of death (all-cause)). The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated using incidence rate ratios from Poisson regression models (prescribed pitavastatin compared to placebo), adjusted for screening CD4 and sex. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrollment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 100 person-years				
number (confidence interval 95%)	4.17 (3.88 to 4.48)	4.18 (3.89 to 4.49)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Non-fatal SAE
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Incidence rate ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.1

Secondary: Incidence Rate of Diabetes

End point title	Incidence Rate of Diabetes

End point description:

Safety analysis outcome measure of diabetes was defined as new diagnosis of diabetes with initiation of anti-diabetic agent. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated using incidence rate ratios from Poisson regression models (prescribed pitavastatin compared to placebo), adjusted for screening CD4 and sex. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrolment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3864	3867		
Units: events per 100 person-years				
number (confidence interval 95%)	1.18 (1.04 to 1.34)	0.91 (0.79 to 1.06)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Rate of Diabetes
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7731
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Incidence rate ratio
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	1.57

Secondary: Incidence Rate of Myalgia, Muscle Weakness or Myopathy

End point title	Incidence Rate of Myalgia, Muscle Weakness or Myopathy

End point description:

Safety analysis outcome measure of myalgia, muscle weakness or myopathy which were grade 3 or higher or treatment-limiting. Grade 3 or higher includes grade 3 and 4 events, where grade 3 refers to severe and grade 4 to life-threatening according to DAIDS AE Grading Table (version 2.1). The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated using incidence rate ratios from Poisson regression models (prescribed pitavastatin compared to placebo), adjusted for screening CD4 and sex. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrolment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 100 person-years				
number (confidence interval 95%)	0.46 (0.38 to 0.56)	0.29 (0.23 to 0.38)		

Statistical analyses

Statistical analysis title	Analysis for Incidence Rate of Myalgia
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Incidence rate ratio
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	2.19

Secondary: Incidence Rate of Rhabdomyolysis

End point title	Incidence Rate of Rhabdomyolysis

End point description:

Safety analysis outcome measure of rhabdomyolysis which was grade 3 or higher or treatment-limiting. Grade 3 or higher includes grade 3 and 4 events, where grade 3 refers to severe and grade 4 to life-threatening, according to DAIDS AE Grading Table (version 2.1). The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated using incidence rate ratios from Poisson regression models (prescribed pitavastatin compared to placebo). Due to small number of events, there was no adjustment for screening CD4 and sex. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrolment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 100 person-years				
number (confidence interval 95%)	0.015 (0.005 to 0.046)	0.020 (0.007 to 0.052)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Rate of Rhabdomyolysis
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Incidence rate ratio
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	3.37

Secondary: Incidence Rate of Grade 3 or Higher ALT

End point title	Incidence Rate of Grade 3 or Higher ALT

End point description:

Safety analysis outcome measure of Grade 3 or higher alanine transaminase (ALT). Grade 3 or higher includes grade 3 and 4 events, where grade 3 refers to severe and grade 4 to life-threatening, according to DAIDS AE Grading Table (version 2.1). The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated using incidence rate ratios from Poisson regression models (prescribed pitavastatin compared to placebo). Due to small number of events, there was no adjustment for screening CD4 and sex. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrolment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 100 person-years				
number (confidence interval 95%)	0.059 (0.033 to 0.10)	0.044 (0.023 to 0.085)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Grade 3 or Higher ALT
Comparison groups	Pitavastatin v Placebo

Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Incidence rate ratio
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	3.18

Secondary: Incidence Rate of Adverse Event (AE)

End point title	Incidence Rate of Adverse Event (AE)

End point description:

Safety analysis outcome measure of any AE. AE collection included events of grade ≥3, those that were serious (defined by International Conference on Harmonisation (ICH) criteria) or treatment-limiting, and targeted diagnosis of diabetes. Grade ≥3 includes events that were grade 3 (serious) or grade 4 (life-threatening) per DAIDS AE Grading Table (version 2.1). Fatal events were excluded as deaths were a secondary efficacy outcome (see outcome measure: incidence rate of death (all-cause)). The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated using incidence rate ratios from Poisson regression models (prescribed pitavastatin compared to placebo), adjusted for screening CD4 and sex. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrollment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888	3881		
Units: events per 100 person-years				
number (confidence interval 95%)	8.83 (8.32 to 9.31)	8.49 (8.05 to 8.95)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Incidence Rate of AE
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Incidence rate ratio
Point estimate	1.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.12

Secondary: Fasting Low-density Lipoprotein Cholesterol (LDL-C)

End point title	Fasting Low-density Lipoprotein Cholesterol (LDL-C)

End point description:

LDL-C level was derived as LDL-C calculated according to the Friedewald formula at triglycerides ≤400 mg/dL, and direct LDL-C at triglycerides >400 to <500 mg/dL. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

At entry and months 12, 24, 36, 48, 60, 72, 84. Participants' follow-up time on study varied, depending on their time of enrolment.

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3682[2]	3667[3]		
Units: mg/dL				
median (inter-quartile range (Q1-Q3))				
Entry: LDL-C	107 (87 to 129)	106 (86 to 127)		
Month 12: LDL-C	74 (58 to 92)	105 (85 to 126)		
Month 24: LDL-C	75 (59 to 93)	104 (84 to 126)		
Month 36: LDL-C	73 (57 to 92)	104 (83 to 126)		
Month 48: LDL-C	73 (56 to 92)	103 (83 to 124)		
Month 60: LDL-C	73 (56 to 93)	103 (82 to 125)		
Month 72: LDL-C	74 (57 to 95)	101 (82 to 122)		
Month 84: LDL-C	75 (59 to 98)	98 (81 to 121)		

Notes:

[2] - Month(no. analysed):
12(3341)
24(3088)
36(2810)
48(2525)
60(2057)
72(1170)
84(492)

[3] - Month(no. analysed):
12(3321)
24(3122)
36(2792)
48(2526)
60(2053)

72(1114)
84(452)

Statistical analyses

No statistical analyses for this end point

Secondary: Fasting Non-high-density Lipoprotein Cholesterol (Non-HDL-C)

End point title	Fasting Non-high-density Lipoprotein Cholesterol (Non-HDL-C)

End point description:

Non-HDL cholesterol levels were calculated as total cholesterol minus HDL cholesterol. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

At entry and months 12, 24, 36, 48, 60, 72, 84. Participants' follow-up time on study varied, depending on their time of enrolment.

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3714[4]	3681[5]		
Units: mg/dL				
median (inter-quartile range (Q1-Q3))				
Entry: non-HDL-C	133 (110 to 158)	132 (108 to 157)		
Month 12: non-HDL-C	97 (80 to 118)	131 (108 to 156)		
Month 24: non-HDL-C	98 (80 to 121)	131 (108 to 156)		
Month 36: non-HDL-C	97 (78 to 118)	130 (107 to 154)		
Month 48: non-HDL-C	96 (77 to 119)	128 (106 to 154)		
Month 60: non-HDL-C	96 (78 to 120)	127 (104 to 153)		
Month 72: non-HDL-C	95 (78 to 121)	124 (104 to 150)		
Month 84: non-HDL-C	99 (80 to 124)	123 (101 to 151)		

Notes:

[4] - Mth: No Analysed
12:3367
24:3116
36:2835
48:2542
60:2073
72:1180
84:496

[5] - Mth: No Analysed
12:3354

24:3143
36:2816
48:2544
60:2074
72:1121
84:455

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence Rate of Serious COVID-19

End point title	Incidence Rate of Serious COVID-19

End point description:

Serious COVID-19 was defined as COVID-19 that resulted in hospitalization or death or was life-threatening as per the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline E2A definition. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated using incidence rate ratios from Poisson regression models (prescribed pitavastatin compared to placebo), adjusted for GBD region to account for regional differences. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From January 1, 2020 through end of study; the median follow-up time was 3.3 years.

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3451	3454		
Units: events per 100 person-years				
number (confidence interval 95%)	0.45 (0.34 to 0.59)	0.60 (0.48 to 0.77)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Rate of Serious COVID-1D
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	6905
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Incidence rate ratio
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.08

Secondary: Incidence Rate of COVID-19

End point title	Incidence Rate of COVID-19

End point description:

COVID-19 was defined as COVID-19 clinical diagnosis or positive test result (SARS-CoV-2 PCR or rapid antigen tests). The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The treatment effect was estimated using incidence rate ratios (prescribed pitavastatin compared to placebo) from Poisson regression models, adjusted for GBD region to account for regional differences. Treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy).

End point type	Secondary

End point timeframe:

From January 1, 2020 through end of study; the median follow-up time was 3.3 years.

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3451	3454		
Units: events per 100 person-years				
number (confidence interval 95%)	8.79 (8.22 to 9.39)	8.35 (7.80 to 8.93)		

Statistical analyses

Statistical analysis title	Statistical Anal. 1 for Incidence Rate of COVID-19
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	6905
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Incidence rate ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.16

Other pre-specified: Incidence Rate of MACE by Sex

End point title	Incidence Rate of MACE by Sex

End point description:

Subgroup analysis of the primary composite MACE outcome measure (as described above) by sex. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The Cox proportional hazards models described for the primary outcome above were expanded to include sex and interaction of sex and treatment, to evaluate modification of statin effect.

End point type	Other pre-specified

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrolment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888[6]	3881[7]		
Units: events per 1000 person-years				
number (confidence interval 95%)				
Among females	3.9 (2.7 to 5.8)	6.2 (4.6 to 8.4)		
Among males	5.5 (4.4 to 6.9)	8.5 (7.1 to 10.2)		

Notes:

[6] - 1211 females
2677 males
[7] - 1208 females
2673 males

Statistical analyses

Statistical analysis title	Analysis 1 for Incidence Rate of MACE by Sex

Statistical analysis description:

Evaluation of treatment effect modification by sex (i.e. pitavastatin effect differing in females compared to males).

Comparison groups	Placebo v Pitavastatin
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98 [8]
Method	Regression, Cox

Notes:

[8] - Treatment effect modification by sex was evaluated via interaction of treatment and sex in the Cox proportional hazards regression model.

Statistical analysis title	Analysis 2 for Incidence Rate of MACE by Sex

Statistical analysis description:

Evaluation of pitavastatin effect among females

Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.04

Statistical analysis title	Analysis 3 for Incidence Rate of MACE by Sex
Statistical analysis description:	
Evaluation of pitavastatin effect among males	
Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.86

Other pre-specified: Incidence Rate of MACE by Race

End point title	Incidence Rate of MACE by Race

End point description:

Subgroup analysis of the primary composite MACE outcome measure (as described above) by race. The incidence rates were estimated based on time to the first event using Poisson distribution, with follow-up time censored at last contact. The Cox proportional hazards models described for the primary outcome above were expanded to include race and interaction of race and treatment, to evaluate modification of statin effect.

End point type	Other pre-specified

End point timeframe:

From entry through end of study. Follow-up time varied depending on time of enrollment (the median follow-up time was 5.6 years).

End point values	Pitavastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3888[9]	3881[10]		
Units: events per 1000 person-years				
number (confidence interval 95%)				
Among Asians	1.6 (0.7 to 3.7)	7.0 (4.6 to 10.6)		
Among Blacks	5.8 (4.3 to 7.7)	8.7 (6.9 to 10.9)		
Among Whites	5.6 (4.1 to 7.7)	7.5 (5.7 to 9.9)		
Among Other	5.0 (2.7 to 9.4)	5.7 (3.1 to 10.6)		

Notes:

[9] - Among Asians: 571
Among Blacks: 1569
Among Whites: 1364
Among Other: 384

[10] - Among Asians: 567
Among Blacks: 1639
Among Whites: 1340
Among Other: 335

Statistical analyses

Statistical analysis title	Analysis 1 for Incidence Rate of MACE by Race

Statistical analysis description:

Evaluation of treatment effect modification by race (i.e. pitavastatin effect differing between races).

Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14 [11]
Method	Regression, Cox

Notes:

[11] - Treatment effect modification by race was evaluated via interaction of treatment and race in the Cox proportional hazards regression model.

Statistical analysis title	Analysis 2 for Incidence Rate of MACE by Race

Statistical analysis description:

Pitavastatin effect among Asians from subgroup analysis by race. Hazard ratio is shown as pitavastatin/placebo among Asians. Number analysed in Pitavastatin group 571, Number analysed in Placebo group 567

Comparison groups	Pitavastatin v Placebo
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.59

Statistical analysis title	Analysis 3 for Incidence Rate of MACE by Race

Statistical analysis description:

Pitavastatin effect among Blacks from subgroup analysis by race. Hazard ratio is shown as pitavastatin/placebo among Blacks. Number analysed in Pitavastatin group 1569, Number analysed in Placebo group 1639

Comparison groups	Placebo v Pitavastatin

Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.96

Statistical analysis title	Analysis 4 for Incidence Rate of MACE by Race

Statistical analysis description:

Pitavastatin effect among Whites from subgroup analysis by race. Hazard ratio is shown as pitavastatin/placebo among Whites. Number analysed in Pitavastatin group 1364, Number analysed in Placebo group 1340

Comparison groups	Placebo v Pitavastatin
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.13

Statistical analysis title	Analysis 5 for Incidence Rate of MACE by Race

Statistical analysis description:

Pitavastatin effect among Other race from subgroup analysis by race. Hazard ratio is shown as pitavastatin/placebo among Other race. Number analysed in Pitavastatin group 384, Number analysed in Placebo group 335

Comparison groups	Placebo v Pitavastatin
Number of subjects included in analysis	7769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	2.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From entry through end of study. Follow-up time varied depending on time of enrolment (the median follow-up time was 5.6 years)

Adverse event reporting additional description:

AE collection included events of grade ≥3, those that were serious (per ICH criteria) or treatment-limiting, and all new diagnoses of diabetes. Targeted clinical events for pitavastatin efficacy evaluation including death were not reported as AEs. The highest grade of each event type was recorded rather than the number of occurrences.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Pitavastatin

Reporting group description:

Participants received pitavastatin once a day for the entire time they were in study follow-up.

Reporting group title	Placebo

Reporting group description:

Participants were randomly assigned to receive placebo tablet once a day for their entire study duration.

Serious adverse events	Pitavastatin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	750 / 3888 (19.29%)	755 / 3881 (19.45%)	
number of deaths (all causes)	126	143	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal canal neoplasms malignant			
subjects affected / exposed	3 / 3888 (0.08%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphomas NEC			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct neoplasms malignant			

subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasms malignant			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone neoplasms unspecified malignancy			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast and nipple neoplasms benign			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast and nipple neoplasms malignant			
subjects affected / exposed	7 / 3888 (0.18%)	7 / 3881 (0.18%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burkitt’s lymphomas			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system neoplasms malignant NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix neoplasms malignant			
subjects affected / exposed	3 / 3888 (0.08%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal neoplasms malignant			

subjects affected / exposed	3 / 3888 (0.08%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine neoplasms malignant and unspecified NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extranodal marginal zone B-cell lymphomas (low grade B-cell)			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fallopian tube neoplasms malignant			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrous histiocytomas malignant			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder neoplasms malignant			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric neoplasms malignant			
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glial tumours malignant			
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gliomas benign			

subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasms malignant			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin’s disease NEC			
subjects affected / exposed	4 / 3888 (0.10%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal neoplasms malignant			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemias acute lymphocytic			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemias chronic myeloid			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip and oral cavity neoplasms malignant			
subjects affected / exposed	2 / 3888 (0.05%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liposarcomas malignant			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphomas unspecified NEC			

subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal neoplasms malignant			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to specified sites			
subjects affected / exposed	0 / 3888 (0.00%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myeloproliferative disorders (excl leukaemias)			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms malignant site unspecified NEC			
subjects affected / exposed	0 / 3888 (0.00%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system neoplasms unspecified malignancy NEC			
subjects affected / exposed	1 / 3888 (0.03%)	5 / 3881 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin’s lymphomas NEC			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell neoplasms malignant of the respiratory tract cell type specified			
subjects affected / exposed	3 / 3888 (0.08%)	6 / 3881 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oncologic complications and emergencies			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal, nasopharyngeal and tonsillar neoplasms malignant and unspecified			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian neoplasms benign			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian neoplasms malignant (excl germ cell)			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myelomas			
subjects affected / exposed	3 / 3888 (0.08%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic neoplasms malignant			
subjects affected / exposed	6 / 3888 (0.15%)	5 / 3881 (0.13%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasms malignant			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal pelvis and ureter neoplasms malignant			

subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Respiratory tract and pleural neoplasms malignant cell type unspecified NEC				
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)		
occurrences causally related to treatment / all	0 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Respiratory tract small cell carcinomas				
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Salivary gland neoplasms malignant				
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Skin melanomas (excl ocular)				
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Skin neoplasms benign				
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Skin neoplasms malignant and unspecified (excl melanoma)				
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Soft tissue neoplasms benign NEC				
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Uterine neoplasms benign			
subjects affected / exposed	3 / 3888 (0.08%)	5 / 3881 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval neoplasms malignant			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated and malignant hypertension			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysms and dissections			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic embolism and thrombosis			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse and shock			
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhages NEC			
subjects affected / exposed	2 / 3888 (0.05%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedemas			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-site specific embolism and thrombosis			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-site specific necrosis and vascular insufficiency NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism and thrombosis			
subjects affected / exposed	9 / 3888 (0.23%)	11 / 3881 (0.28%)	
occurrences causally related to treatment / all	0 / 9	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vasoconstriction, necrosis and vascular insufficiency			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose veins NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular hypertensive disorders NEC			
subjects affected / exposed	6 / 3888 (0.15%)	7 / 3881 (0.18%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular hypotensive disorders			
subjects affected / exposed	3 / 3888 (0.08%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitides NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Surgical and medical procedures			
Abdominal therapeutic procedures NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract and gallbladder therapeutic procedures			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac therapeutic procedures NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve therapeutic procedures			
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial therapeutic procedures			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric therapeutic procedures			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia repairs			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint therapeutic procedures			
subjects affected / exposed	2 / 3888 (0.05%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Laryngeal therapeutic procedures			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb therapeutic procedures			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile therapeutic procedures			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric therapies			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal therapeutic procedures			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine therapeutic procedures			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue therapeutic procedures NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spine and spinal cord therapeutic procedures			
subjects affected / exposed	2 / 3888 (0.05%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Therapeutic procedures NEC			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine therapeutic procedures			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortions spontaneous			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (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			
Asthenic conditions			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature altered			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile disorders			
subjects affected / exposed	5 / 3888 (0.13%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General signs and symptoms NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Healing abnormal NEC			

subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernias NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammations			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain and discomfort NEC			
subjects affected / exposed	16 / 3888 (0.41%)	24 / 3881 (0.62%)	
occurrences causally related to treatment / all	0 / 16	0 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcers NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Acute and chronic sarcoidosis			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergic conditions NEC			
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergies to foods, food additives, drugs and other chemicals			

subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic and anaphylactoid responses			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Criminal activity			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast disorders NEC			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix disorders NEC			
subjects affected / exposed	3 / 3888 (0.08%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menstruation and uterine bleeding NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menstruation with increased bleeding			
subjects affected / exposed	4 / 3888 (0.10%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian and fallopian tube cysts and neoplasms			

subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvis and broad ligament disorders NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate and seminal vesicles infections and inflammations			
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic neoplasms and hypertrophy			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive tract disorders NEC (excl neoplasms)			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular and epididymal disorders NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine disorders NEC			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvovaginal disorders NEC			
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Breathing abnormalities			
subjects affected / exposed	12 / 3888 (0.31%)	9 / 3881 (0.23%)	
occurrences causally related to treatment / all	0 / 12	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial conditions NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm and obstruction			
subjects affected / exposed	30 / 3888 (0.77%)	22 / 3881 (0.57%)	
occurrences causally related to treatment / all	0 / 30	0 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conditions associated with abnormal gas exchange			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coughing and associated symptoms			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal and adjacent sites disorders NEC (excl infections and neoplasms)			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract signs and symptoms			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal disorders			

subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal disorders NEC			
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parenchymal lung disorders NEC			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax and pleural effusions NEC			
subjects affected / exposed	7 / 3888 (0.18%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertensions			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedemas			
subjects affected / exposed	3 / 3888 (0.08%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombotic and embolic conditions			
subjects affected / exposed	11 / 3888 (0.28%)	21 / 3881 (0.54%)	
occurrences causally related to treatment / all	0 / 11	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failures (excl neonatal)			
subjects affected / exposed	6 / 3888 (0.15%)	6 / 3881 (0.15%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract disorders NEC			

subjects affected / exposed	0 / 3888 (0.00%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety symptoms			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorders			
subjects affected / exposed	2 / 3888 (0.05%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusion and disorientation			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deliria			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusional disorders			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusional symptoms			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressive disorders			

subjects affected / exposed	6 / 3888 (0.15%)	10 / 3881 (0.26%)	
occurrences causally related to treatment / all	0 / 6	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorders NEC			
subjects affected / exposed	10 / 3888 (0.26%)	6 / 3881 (0.15%)	
occurrences causally related to treatment / all	0 / 10	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood alterations with manic symptoms			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood disorders NEC			
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attacks and disorders			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder NEC			
subjects affected / exposed	8 / 3888 (0.21%)	6 / 3881 (0.15%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizoaffective and schizophreniform disorders			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia NEC			
subjects affected / exposed	1 / 3888 (0.03%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somatic symptom disorders			

subjects affected / exposed	3 / 3888 (0.08%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance related and addictive disorders			
subjects affected / exposed	9 / 3888 (0.23%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal and self-injurious behaviour			
subjects affected / exposed	33 / 3888 (0.85%)	28 / 3881 (0.72%)	
occurrences causally related to treatment / all	1 / 33	0 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device issues NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct infections and inflammations			
subjects affected / exposed	0 / 3888 (0.00%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis and cholelithiasis			
subjects affected / exposed	17 / 3888 (0.44%)	13 / 3881 (0.33%)	
occurrences causally related to treatment / all	0 / 17	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis and jaundice			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic and hepatobiliary disorders NEC			

subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzymes and function abnormalities			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic fibrosis and cirrhosis			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic vascular disorders			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular damage and hepatitis NEC			
subjects affected / exposed	0 / 3888 (0.00%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive bile duct disorders (excl neoplasms)			
subjects affected / exposed	1 / 3888 (0.03%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Structural and other bile duct disorders			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Carbohydrate tolerance analyses (incl diabetes)			

subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac function diagnostic procedures			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ECG investigations			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary function diagnostic procedures			
subjects affected / exposed	8 / 3888 (0.21%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	1 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Physical examination procedures and organ system status			
subjects affected / exposed	0 / 3888 (0.00%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet analyses			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Red blood cell analyses			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal function analyses			
subjects affected / exposed	4 / 3888 (0.10%)	5 / 3881 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skeletal and cardiac muscle analyses			

subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tissue enzyme analyses NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Triglyceride analyses			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular tests NEC (incl blood pressure)			
subjects affected / exposed	3 / 3888 (0.08%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell analyses			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal and gastrointestinal injuries NEC			
subjects affected / exposed	2 / 3888 (0.05%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental exposures to product			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral injuries NEC			
subjects affected / exposed	10 / 3888 (0.26%)	8 / 3881 (0.21%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chemical injuries			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest and respiratory tract injuries NEC			
subjects affected / exposed	4 / 3888 (0.10%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conditions caused by cold			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye injuries NEC			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractures and dislocations NEC			
subjects affected / exposed	7 / 3888 (0.18%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal and hepatobiliary procedural complications			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb fractures and dislocations			
subjects affected / exposed	43 / 3888 (1.11%)	50 / 3881 (1.29%)	
occurrences causally related to treatment / all	0 / 43	0 / 50	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle, tendon and ligament injuries			
subjects affected / exposed	3 / 3888 (0.08%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal procedural			

complications			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-site specific injuries NEC			
subjects affected / exposed	14 / 3888 (0.36%)	12 / 3881 (0.31%)	
occurrences causally related to treatment / all	0 / 14	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-site specific procedural complications			
subjects affected / exposed	2 / 3888 (0.05%)	7 / 3881 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdoses NEC			
subjects affected / exposed	4 / 3888 (0.10%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fractures and dislocations			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning and toxicity			
subjects affected / exposed	3 / 3888 (0.08%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product administration errors and issues			
subjects affected / exposed	0 / 3888 (0.00%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation injuries			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Site specific injuries NEC			

subjects affected / exposed	3 / 3888 (0.08%)	5 / 3881 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin injuries NEC			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractures, facial bone fractures and dislocations			
subjects affected / exposed	1 / 3888 (0.03%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord injuries NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fractures and dislocations			
subjects affected / exposed	4 / 3888 (0.10%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burns			
subjects affected / exposed	3 / 3888 (0.08%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic cage fractures and dislocations			
subjects affected / exposed	6 / 3888 (0.15%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac conduction disorders			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac signs and symptoms NEC			

subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disorders NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failures NEC			
subjects affected / exposed	5 / 3888 (0.13%)	6 / 3881 (0.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic coronary artery disorders			
subjects affected / exposed	7 / 3888 (0.18%)	10 / 3881 (0.26%)	
occurrences causally related to treatment / all	0 / 7	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failures			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valvular disorders			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Noninfectious pericarditis			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial disorders NEC			
subjects affected / exposed	1 / 3888 (0.03%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rate and rhythm disorders NEC			

subjects affected / exposed	3 / 3888 (0.08%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular arrhythmias			
subjects affected / exposed	8 / 3888 (0.21%)	6 / 3881 (0.15%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmias and cardiac arrest			
subjects affected / exposed	1 / 3888 (0.03%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Acute polyneuropathies			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alzheimer’s disease (incl subtypes)			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system aneurysms and dissections			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhages and cerebrovascular accidents			
subjects affected / exposed	5 / 3888 (0.13%)	9 / 3881 (0.23%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system vascular disorders NEC			

subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cervical spinal cord and nerve root disorders				
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Coordination and balance disturbances				
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cortical dysfunction NEC				
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cranial nerve disorders NEC				
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Dementia (excl Alzheimer’s type)				
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Demyelinating disorders NEC				
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Disturbances in consciousness NEC				
subjects affected / exposed	15 / 3888 (0.39%)	11 / 3881 (0.28%)		
occurrences causally related to treatment / all	0 / 15	0 / 11		
deaths causally related to treatment / all	0 / 0	0 / 0		
Encephalopathies NEC				

subjects affected / exposed	2 / 3888 (0.05%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathies toxic and metabolic			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial cranial nerve disorders			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizures			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headaches NEC			
subjects affected / exposed	6 / 3888 (0.15%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalic conditions			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increased intracranial pressure disorders			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal cord and nerve root disorders			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory loss (excl dementia)			

subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine headaches			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mononeuropathies			
subjects affected / exposed	3 / 3888 (0.08%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor neurone diseases			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological signs and symptoms NEC			
subjects affected / exposed	10 / 3888 (0.26%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 10	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuromuscular disorders NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic nerve disorders NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesias and dysaesthesias			

subjects affected / exposed	3 / 3888 (0.08%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis and paresis (excl cranial nerve)			
subjects affected / exposed	5 / 3888 (0.13%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson’s disease and parkinsonism			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral neuropathies NEC			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizures and seizure disorders NEC			
subjects affected / exposed	9 / 3888 (0.23%)	14 / 3881 (0.36%)	
occurrences causally related to treatment / all	0 / 9	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech and language abnormalities			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord and nerve root disorders NEC			
subjects affected / exposed	4 / 3888 (0.10%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Structural brain disorders NEC			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient cerebrovascular events			

subjects affected / exposed	3 / 3888 (0.08%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Behaviour and socialisation disturbances			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia deficiencies			
subjects affected / exposed	2 / 3888 (0.05%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemias NEC			
subjects affected / exposed	16 / 3888 (0.41%)	10 / 3881 (0.26%)	
occurrences causally related to treatment / all	0 / 16	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of chronic disorders			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathies			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenias NEC			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphatic system disorders NEC			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenias			

subjects affected / exposed	2 / 3888 (0.05%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenias			
subjects affected / exposed	3 / 3888 (0.08%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hearing losses			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inner ear signs and symptoms			
subjects affected / exposed	1 / 3888 (0.03%)	7 / 3881 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract conditions			
subjects affected / exposed	12 / 3888 (0.31%)	6 / 3881 (0.15%)	
occurrences causally related to treatment / all	0 / 12	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choroid and vitreous structural change, deposit and degeneration			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucomas (excl congenital)			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iris and uveal tract infections, irritations and inflammations			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Optic disc abnormalities NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic nerve bleeding and vascular disorders			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orbital infections, inflammations and irritations			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal structural change, deposit and degeneration			
subjects affected / exposed	3 / 3888 (0.08%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment and blindness (excl colour blindness)			
subjects affected / exposed	3 / 3888 (0.08%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernias NEC			
subjects affected / exposed	3 / 3888 (0.08%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute and chronic pancreatitis			
subjects affected / exposed	10 / 3888 (0.26%)	11 / 3881 (0.28%)	
occurrences causally related to treatment / all	0 / 10	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal and rectal disorders NEC			

subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal and rectal pains			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasms gastrointestinal (excl oral cavity)			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis (excl infective)			
subjects affected / exposed	4 / 3888 (0.10%)	8 / 3881 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic hernias			
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea (excl infective)			
subjects affected / exposed	9 / 3888 (0.23%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal and small intestinal stenosis and obstruction			
subjects affected / exposed	4 / 3888 (0.10%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcers and perforation			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric and oesophageal haemorrhages			

subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis (excl infective)			
subjects affected / exposed	8 / 3888 (0.21%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal and abdominal pains (excl oral and throat)			
subjects affected / exposed	5 / 3888 (0.13%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal atonic and hypomotility disorders NEC			
subjects affected / exposed	3 / 3888 (0.08%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammatory disorders NEC			
subjects affected / exposed	1 / 3888 (0.03%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal signs and symptoms NEC			
subjects affected / exposed	4 / 3888 (0.10%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stenosis and obstruction NEC			
subjects affected / exposed	5 / 3888 (0.13%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal ulcers and perforation, site unspecified			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal vascular occlusion and infarction			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival disorders, signs and symptoms NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids and gastrointestinal varices (excl oesophageal)			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernias			
subjects affected / exposed	8 / 3888 (0.21%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhages			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ulcers and perforation NEC			
subjects affected / exposed	1 / 3888 (0.03%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal stenosis and obstruction			

subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea and vomiting symptoms			
subjects affected / exposed	8 / 3888 (0.21%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-site specific gastrointestinal haemorrhages			
subjects affected / exposed	2 / 3888 (0.05%)	11 / 3881 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis and obstruction			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcers and perforation			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis (excl infective)			
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral soft tissue disorders NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal and retroperitoneal disorders			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal inflammations NEC			

subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland disorders NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernias			
subjects affected / exposed	3 / 3888 (0.08%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedemas			
subjects affected / exposed	3 / 3888 (0.08%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis and eczema			
subjects affected / exposed	2 / 3888 (0.05%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis ascribed to specific agent			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipodystrophies			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriatic conditions			

subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rashes, eruptions and exanthems NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue ulcerations			
subjects affected / exposed	1 / 3888 (0.03%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder disorders NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital and urinary tract disorders NEC			
subjects affected / exposed	2 / 3888 (0.05%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis and nephrotic syndrome			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathies and tubular disorders NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure and impairment			

subjects affected / exposed	25 / 3888 (0.64%)	24 / 3881 (0.62%)		
occurrences causally related to treatment / all	0 / 25	0 / 24		
deaths causally related to treatment / all	0 / 0	0 / 0		
Renal lithiasis				
subjects affected / exposed	4 / 3888 (0.10%)	4 / 3881 (0.10%)		
occurrences causally related to treatment / all	0 / 4	0 / 4		
deaths causally related to treatment / all	0 / 0	0 / 0		
Renal obstructive disorders				
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Renal vascular and ischaemic conditions				
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Structural and obstructive urethral disorders (excl congenital)				
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Urethral disorders NEC				
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Urinary abnormalities				
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Urinary tract lithiasis NEC				
subjects affected / exposed	3 / 3888 (0.08%)	2 / 3881 (0.05%)		
occurrences causally related to treatment / all	0 / 3	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Urinary tract signs and symptoms NEC				

subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal cortical hypofunctions			
subjects affected / exposed	4 / 3888 (0.10%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroid disorders			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior pituitary disorders			
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthropathies NEC			
subjects affected / exposed	3 / 3888 (0.08%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone disorders NEC			
subjects affected / exposed	8 / 3888 (0.21%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cartilage disorders			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture complications			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fractures NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorders NEC			
subjects affected / exposed	3 / 3888 (0.08%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint related disorders NEC			
subjects affected / exposed	4 / 3888 (0.10%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint related signs and symptoms			
subjects affected / exposed	4 / 3888 (0.10%)	6 / 3881 (0.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic bone disorders			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle infections and inflammations			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle pains			
subjects affected / exposed	2 / 3888 (0.05%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle related signs and symptoms NEC			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle weakness conditions			

subjects affected / exposed	2 / 3888 (0.05%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue pain and discomfort			
subjects affected / exposed	11 / 3888 (0.28%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 11	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathies			
subjects affected / exposed	4 / 3888 (0.10%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthropathies			
subjects affected / exposed	11 / 3888 (0.28%)	9 / 3881 (0.23%)	
occurrences causally related to treatment / all	0 / 11	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthropathies			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spine and neck deformities			
subjects affected / exposed	7 / 3888 (0.18%)	5 / 3881 (0.13%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial disorders			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon disorders			
subjects affected / exposed	0 / 3888 (0.00%)	5 / 3881 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal and gastrointestinal infections			

subjects affected / exposed	36 / 3888 (0.93%)	41 / 3881 (1.06%)	
occurrences causally related to treatment / all	0 / 36	0 / 41	
deaths causally related to treatment / all	0 / 0	0 / 0	
Actinomycotic infectious disorders			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoviral infections			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical mycobacterial infections			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infections NEC			
subjects affected / exposed	41 / 3888 (1.05%)	30 / 3881 (0.77%)	
occurrences causally related to treatment / all	0 / 41	0 / 30	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone and joint infections			
subjects affected / exposed	9 / 3888 (0.23%)	9 / 3881 (0.23%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast infections			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Caliciviral infections			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter infections			

subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infections			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system and spinal infections			
subjects affected / exposed	5 / 3888 (0.13%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridia infections			
subjects affected / exposed	5 / 3888 (0.13%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cryptococcal infections			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegaloviral infections			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental and oral soft tissue infections			
subjects affected / exposed	3 / 3888 (0.08%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infections			
subjects affected / exposed	0 / 3888 (0.00%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infections			

subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infections			
subjects affected / exposed	4 / 3888 (0.10%)	6 / 3881 (0.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye and eyelid infections			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female reproductive tract infections			
subjects affected / exposed	2 / 3888 (0.05%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flaviviral infections			
subjects affected / exposed	6 / 3888 (0.15%)	9 / 3881 (0.23%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infections NEC			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infections			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis virus infections			
subjects affected / exposed	3 / 3888 (0.08%)	6 / 3881 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary and spleen infections			

subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes viral infections			
subjects affected / exposed	7 / 3888 (0.18%)	7 / 3881 (0.18%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections NEC			
subjects affected / exposed	11 / 3888 (0.28%)	16 / 3881 (0.41%)	
occurrences causally related to treatment / all	0 / 11	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza viral infections			
subjects affected / exposed	11 / 3888 (0.28%)	10 / 3881 (0.26%)	
occurrences causally related to treatment / all	0 / 11	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Legionella infections			
subjects affected / exposed	0 / 3888 (0.00%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leptospira infections			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria infections			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract and lung infections			
subjects affected / exposed	71 / 3888 (1.83%)	66 / 3881 (1.70%)	
occurrences causally related to treatment / all	0 / 71	0 / 66	
deaths causally related to treatment / all	0 / 0	0 / 0	
Male reproductive tract infections			

subjects affected / exposed	4 / 3888 (0.10%)	7 / 3881 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle and soft tissue infections			
subjects affected / exposed	2 / 3888 (0.05%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neisseria infections			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nematode infections			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopox viral infections			
subjects affected / exposed	1 / 3888 (0.03%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae viral infections			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmodia infections			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis infections			
subjects affected / exposed	2 / 3888 (0.05%)	2 / 3881 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinoviral infections			

subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rickettsial infectious disorders NEC			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella infections			
subjects affected / exposed	2 / 3888 (0.05%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis, bacteraemia, viraemia and fungaemia NEC			
subjects affected / exposed	20 / 3888 (0.51%)	18 / 3881 (0.46%)	
occurrences causally related to treatment / all	0 / 20	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shigella infections			
subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin structures and soft tissue infections			
subjects affected / exposed	1 / 3888 (0.03%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infections			
subjects affected / exposed	4 / 3888 (0.10%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infections			
subjects affected / exposed	6 / 3888 (0.15%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxoplasma infections			

subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Treponema infections			
subjects affected / exposed	6 / 3888 (0.15%)	10 / 3881 (0.26%)	
occurrences causally related to treatment / all	0 / 6	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculous infections			
subjects affected / exposed	11 / 3888 (0.28%)	13 / 3881 (0.33%)	
occurrences causally related to treatment / all	0 / 11	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infections			
subjects affected / exposed	4 / 3888 (0.10%)	5 / 3881 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infections			
subjects affected / exposed	23 / 3888 (0.59%)	15 / 3881 (0.39%)	
occurrences causally related to treatment / all	0 / 23	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular infections			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infections NEC			
subjects affected / exposed	5 / 3888 (0.13%)	8 / 3881 (0.21%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Calcium metabolism disorders			
subjects affected / exposed	1 / 3888 (0.03%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus (incl subtypes)			

subjects affected / exposed	3 / 3888 (0.08%)	11 / 3881 (0.28%)	
occurrences causally related to treatment / all	0 / 3	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic complications NEC			
subjects affected / exposed	2 / 3888 (0.05%)	4 / 3881 (0.10%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic complications neurological			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorders of purine metabolism			
subjects affected / exposed	3 / 3888 (0.08%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Elevated triglycerides			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General nutritional disorders NEC			
subjects affected / exposed	7 / 3888 (0.18%)	6 / 3881 (0.15%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic conditions NEC			
subjects affected / exposed	4 / 3888 (0.10%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic conditions NEC			
subjects affected / exposed	2 / 3888 (0.05%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipid metabolism and deposit disorders NEC			

subjects affected / exposed	0 / 3888 (0.00%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidoses (excl diabetic acidoses)			
subjects affected / exposed	2 / 3888 (0.05%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic alkaloses			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phosphorus metabolism disorders			
subjects affected / exposed	1 / 3888 (0.03%)	0 / 3881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Potassium imbalance			
subjects affected / exposed	0 / 3888 (0.00%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sodium imbalance			
subjects affected / exposed	3 / 3888 (0.08%)	3 / 3881 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Total fluid volume decreased			
subjects affected / exposed	3 / 3888 (0.08%)	1 / 3881 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pitavastatin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	488 / 3888 (12.55%)	420 / 3881 (10.82%)	
Investigations			
Physical examination procedures and organ system status			
subjects affected / exposed	62 / 3888 (1.59%)	65 / 3881 (1.67%)	
occurrences (all)	62	65	
Renal function analyses			
subjects affected / exposed	125 / 3888 (3.22%)	122 / 3881 (3.14%)	
occurrences (all)	125	122	
Vascular disorders			
Vascular hypertensive disorders NEC			
subjects affected / exposed	37 / 3888 (0.95%)	50 / 3881 (1.29%)	
occurrences (all)	37	50	
Musculoskeletal and connective tissue disorders			
Muscle pains			
subjects affected / exposed	77 / 3888 (1.98%)	44 / 3881 (1.13%)	
occurrences (all)	77	44	
Musculoskeletal and connective tissue pain and discomfort			
subjects affected / exposed	40 / 3888 (1.03%)	43 / 3881 (1.11%)	
occurrences (all)	40	43	
Metabolism and nutrition disorders			
Diabetes mellitus (incl subtypes)			
subjects affected / exposed	238 / 3888 (6.12%)	184 / 3881 (4.74%)	
occurrences (all)	238	184	
General nutritional disorders NEC			
subjects affected / exposed	66 / 3888 (1.70%)	44 / 3881 (1.13%)	
occurrences (all)	66	44	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2015	Upper threshold for ASCVD risk score eligibility was increased from <7.5% to ≤10%; those between 7.5% and ≤10% had to have LDL <160 mg/dL
17 August 2016	Upper threshold for ASCVD risk score eligibility was increased from 10% to 15% along with corresponding changes in LDL thresholds.
01 February 2018	Future enrolment was restricted to exclude candidates with ASCVD risk score <2.5%
28 March 2018	Study sample size was increased by approximately 1000 participants (to 7500 participants); follow-up duration was increased by one year (to up to 7 years)
16 May 2018	Addition of the EU protocol
29 May 2018	Future enrolment was restricted to exclude candidates with ASCVD risk score <5%
01 April 2019	Vital status and endpoint follow-up after premature study discontinuation were implemented; follow-up was extended to 8 years; originally planned (tentative, if requested by DSMB) efficacy/futility look at 20% of information was removed
16 May 2022	Follow-up was extended until the study reaches its target of 288 primary MACE endpoints, or otherwise recommended for closure by the DSMB; COVID-19-related secondary objectives introduced with the REPRIEVE NOSI supplement were added

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The highest grade of each event type experienced by participants was reported, hence the number of occurrences recorded is the same as the number of subjects affected. Causality was attributed by site teams and may not reflect casual relatedness.

Notes: