Clinical trial results:
Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as monotherapy for patients with newly diagnosed partial-onset seizures: a double-blind, randomized, active-controlled, parallel-group, multicenter clinical study — Open-label ESL extension —

Summary

EudraCT number	2015-001243-36
Trial protocol	DE GB HU LT CZ LV PT BE FR ES SE EE AT BG SK FI HR IT
Global end of trial date	19 March 2019

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019
Summary attachment (see zip file)	BIA-2093-311/EXT (STUDY SYNOPSIS.pdf)

Trial information

Trial identification

Sponsor protocol code	BIA-2093-311/EXT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02484001
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BIAL - Portela & Ca, S.A.
Sponsor organisation address	À Av. Siderurgia Nacional, Coronado, Portugal, 4745-457
Public contact	Helena Gama, BIAL - Portela & Cª, S.A., 00351 229866100, helena.gama@bial.com
Scientific contact	Helena Gama, BIAL - Portela & Cª, S.A., 00351 229866100, helena.gama@bial.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 September 2018
Global end of trial reached?	Yes
Global end of trial date	19 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary: To confirm maintenance of efficacy of eslicarbazepine acetate (ESL, 800 mg to 1600 mg once daily [QD]) monotherapy during long-term treatment in adults (≥18 years) with recently diagnosed epilepsy experiencing partial-onset seizures.

Protection of trial subjects:

This study was conducted in compliance with International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice, including the archiving of essential documents.

Background therapy:

Concomitant AED therapy (1 or 2 AEDs).

Evidence for comparator: -

Actual start date of recruitment	21 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Bulgaria: 11
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	Czech Republic: 15
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Latvia: 13
Country: Number of subjects enrolled	Peru: 5

Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Romania: 19
Country: Number of subjects enrolled	Russian Federation: 54
Country: Number of subjects enrolled	Serbia: 11
Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	Ukraine: 13
Worldwide total number of subjects	207
EEA total number of subjects	111

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)	186
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adults (≥18 years) with recently diagnosed epilepsy experiencing partial-onset seizures who were under treatment in the double-blind study BIA-2093-311.

Pre-assignment

Screening details:

Subjects who met all inclusion criteria and none of the exclusion criteria. 207 subjects were enrolled to the trial and 1 subject was a screening failure.

Pre-assignment period milestones

Number of subjects started	207
Number of subjects completed	206

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Ineligibility: 1

Period 1

Period 1 title	Open-label ESL extension (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall ESL

Arm description:

Subjects already treated with ESL continued with their last evaluated dose (ESL 800 mg, 1200 mg or 1600 mg QD).
Subjects previously treated with CBZ-CR started with ESL 400 mg QD for one week followed by up-titration to the ESL target dose which was equivalent to the last evaluated CBZ-CR dose level (i.e. CBZ-CR 200 mg BID -> ESL 800 mg QD; CBZ-CR 400 mg BID -> ESL 1200 mg QD; CBZ-CR 600 mg BID -> ESL 1600 mg QD) in steps of 400 mg dose increase per week.

Arm type	Active comparator
Investigational medicinal product name	Eslicarbazepine acetate
Investigational medicinal product code	ESL
Other name	
Pharmaceutical forms	Tablet, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects already treated with ESL will continue with their last evaluated dose (ESL 800 mg, 1200 mg or 1600 mg QD).
Subjects previously treated with CBZ-CR will start with ESL 400 mg QD for one week followed by up-titration to the ESL target dose which is equivalent to the last evaluated CBZ-CR dose level (i.e. CBZ-CR 200 mg BID -> ESL 800 mg QD; CBZ-CR 400 mg BID -> ESL 1200 mg QD; CBZ-CR 600 mg BID -> ESL 1600 mg QD) in steps of 400 mg dose increase per week.
In case of new seizures, the ESL dose can be increased to a maximum dose of ESL 1600 mg QD [dose level C], depending on the investigator`s decision. Any up-titration should be performed in weekly steps of 400 mg.
If deemed necessary by the investigator, e.g. due to occurrence of adverse events, the dose of ESL can be reduced according to investigator’s discretion, as long as the dose remains in the range of 800 mg QD to 1600mg QD.
Down-titration of ESL as required should be performed in steps of 400 mg decrease per week.

Number of subjects in period 1[1]	Overall ESL
Started	206
Completed	172
Not completed	34
Adverse event, serious fatal	2
Consent withdrawn by subject	9
Physician decision	3
Hyponatremia <125 mmol/L	1
Adverse event, non-fatal	7
Subject non-compliance	4
Other	5
Adverse event, serious non-fatal	2
Lack of efficacy	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline period does not include 1 subject who was a screening failure.

Baseline characteristics

Reporting groups	
Reporting group title	Overall ESL

Reporting group description:

Subjects already treated with ESL continued with their last evaluated dose (ESL 800 mg, 1200 mg or 1600 mg QD).
Subjects previously treated with CBZ-CR started with ESL 400 mg QD for one week followed by up-titration to the ESL target dose which was equivalent to the last evaluated CBZ-CR dose level (i.e. CBZ-CR 200 mg BID -> ESL 800 mg QD; CBZ-CR 400 mg BID -> ESL 1200 mg QD; CBZ-CR 600 mg BID -> ESL 1600 mg QD) in steps of 400 mg dose increase per week.

Reporting group values	Overall ESL	Total	
Number of subjects	206	206	
Age Categorical			
Age Categorical Characteristic			
Units: Subjects			
In Utero	0	0	
Preterm newborn- gestational age < 37 wk	0	0	
Newborns (0-27days)	0	0	
Infants and toddlers (28days – 23months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 year)	0	0	
From 18 - 64 years	185	185	
From 65 – 84 years	21	21	
Over 85 years	0	0	
Age Continuous			
Age Continuous Characteristic			
Units: Years			
arithmetic mean	42.6		
standard deviation	± 15.89	-	
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	98	98	
Male	108	108	

End points

End points reporting groups

Reporting group title	Overall ESL

Reporting group description:

Subjects already treated with ESL continued with their last evaluated dose (ESL 800 mg, 1200 mg or 1600 mg QD).
Subjects previously treated with CBZ-CR started with ESL 400 mg QD for one week followed by up-titration to the ESL target dose which was equivalent to the last evaluated CBZ-CR dose level (i.e. CBZ-CR 200 mg BID -> ESL 800 mg QD; CBZ-CR 400 mg BID -> ESL 1200 mg QD; CBZ-CR 600 mg BID -> ESL 1600 mg QD) in steps of 400 mg dose increase per week.

Subject analysis set title	Overall ESL x Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects enrolled who received at least 1 dose of ESL during the open-label extension study.

Subject analysis set title	Overall ESL x FAS
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects enrolled and treated with at least 1 dose of ESL during the open-label extension study and date of withdrawal of ESL or last day of ESL intake available allowing to calculate the derived variables "time to treatment failure" or "treatment retention time" including censoring.

Subject analysis set title	Overall ESL x Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the OL FAS without any major protocol deviation. Subjects will be excluded from the PP set for the following reasons:
-Treated with ESL outside the range of 800-1600 mg QD except of treatment with ESL 400 mg QD during the first week of transition when switching from CBZ-CR treatment.
-Intake of prohibited therapies.
-Poor compliance for completion of the subject diary (i.e. they do not adequately report seizure information or diaries are not returned).
-Poor compliance for taking ESL (i.e. confirmed compliance <80% or >120% of the scheduled total dose).
-Other events occur that may have a relevant impact on the efficacy evaluations. Such study conditions, which may or may not represent a protocol deviation or violation, will be identified during the data review meeting.

Subject analysis set title	Overall ESL x Per Protocol Subset
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects of the OL PP set, excluding all subjects switching from CBZ-CR who discontinue the open-label extension study before they have completed CBZ-CR down-titration for any reasons not linked to efficacy.

Primary: Monthly failure rates of time to treatment failure (TTF) / treatment retention time (TRT)

End point title	Monthly failure rates of time to treatment failure (TTF) / treatment retention time (TRT)[1]

End point description:

Estimates of monthly failure rates of time to treatment failure (TTF) / treatment retention time (TRT).
Time to treatment failure (TTF) is defined as the time from OL Baseline (OL Visit 1) until withdrawal of ESL due to AE or lack of efficacy (i.e. inadequate seizure control) in subjects who received ESL already during the DB phase.
Treatment retention time (TRT) is defined as the time from OL Baseline (OL Visit 1) until withdrawal of ESL due to AE or lack of efficacy (i.e. inadequate seizure control) in all subjects including those subjects who received CBZ-CR during the DB phase.

End point type	Primary

End point timeframe:

Visit 1 untill the end of open-label ESL extension

Notes:

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

Justification: No statistical analyses have been performed for this primary end point.

End point values	Overall ESL x FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: Failure Probability				
number (confidence interval)				
+30 days	0.0049000000 (0.0007 to 0.0340)			
+60 days	0.0146 (0.0047 to 0.0445)			
+90 days	0.0194000000 (0.0073 to 0.0509)			
+120 days	0.0194000000 (0.0073 to 0.0509)			
+150 days	0.0194000000 (0.0073 to 0.0509)			
+180 days	0.0194000000 (0.0073 to 0.0509)			
+210 days	0.0194000000 (0.0073 to 0.0509)			
+240 days	0.0194000000 (0.0073 to 0.0509)			
+270 days	0.0194000000 (0.0073 to 0.0509)			
+300 days	0.0244000000 (0.0102 to 0.0576)			
+330 days	0.0293 (0.0133 to 0.0642)			
+360 days	0.0293 (0.0133 to 0.0642)			
+390 days	0.0394000000 (0.0199 to 0.0772)			
+420 days	0.0394000000 (0.0199 to 0.0772)			
+450 days	0.0394000000 (0.0199 to 0.0772)			
+480 days	0.0548000000 (0.0307 to 0.0968)			
+510 days	0.0548000000 (0.0307 to 0.0968)			

+540 days	0.0548000000 (0.0307 to 0.0968)			
+570 days	0.0548000000 (0.0307 to 0.0968)			
+600 days	0.0548000000 (0.0307 to 0.0968)			
+630 days	0.0548000000 (0.0307 to 0.0968)			
+660 days	0.0548000000 (0.0307 to 0.0968)			
+690 days	0.0548000000 (0.0307 to 0.0968)			
+720 days	0.0602000000 (0.0346 to 0.1037)			
+750 days	0.0602000000 (0.0346 to 0.1037)			

Statistical analyses

No statistical analyses for this end point

Primary: Monthly withdrawal rates of time to withdrawal for any reason TTW

End point title	Monthly withdrawal rates of time to withdrawal for any reason TTW[2]

End point description:

Estimates of monthly withdrawal rates of time to withdrawal for any reason is defined as the time from OL Baseline OL Visit 1 until withdrawal of ESL.

End point type	Primary

End point timeframe:

Visit 1 untill the end of open-label ESL extension

Notes:

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

End point values	Overall ESL x FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: Withdrawal Rate				
number (not applicable)				
+30 days	0.0049000000			
+60 days	0.0146			
+90 days	0.0194000000			
+120 days	0.0243000000			
+150 days	0.0291000000			
+180 days	0.0291000000			

+210 days	0.0340000000			
+240 days	0.0388000000			
+270 days	0.0388000000			
+300 days	0.0485000000			
+330 days	0.0534000000			
+360 days	0.0583000000			
+390 days	0.0777000000			
+420 days	0.0777000000			
+450 days	0.0825000000			
+480 days	0.1117000000			
+510 days	0.1165000000			
+540 days	0.1262000000			
+570 days	0.1311000000			
+600 days	0.1359000000			
+630 days	0.1359000000			
+660 days	0.1359000000			
+690 days	0.1505000000			
+720 days	0.1553000000			
+750 days	0.1746000000			

Statistical analyses

No statistical analyses for this end point

Primary: Seizure freedom

End point title	Seizure freedom[3]

End point description:

Number of subjects without seizures (seizure freedom) while treated during the open-label extension study.

End point type	Primary

End point timeframe:

Visit 1 untill the end of open-label ESL extension

Notes:

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

End point values	Overall ESL x FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: Seizure Freedom				
number (not applicable)				
Seizure Freedom	167			

Statistical analyses

No statistical analyses for this end point

Primary: Subjects with seizures by seizure type

End point title	Subjects with seizures by seizure type[4]

End point description:

The number of subjects with seizures while treated during the open-label extension study classified by seizure type.

End point type	Primary

End point timeframe:

Visit 1 untill the end of open-label ESL extension

Notes:

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

End point values	Overall ESL x FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: Subjects				
number (not applicable)				
Total seizures	39			
Simple partial	12			
Complex partial	17			
Partial evolving to secondary	19			
Generalized	2			
Unclassifiable	3			
Other seizure type	0			

Statistical analyses

No statistical analyses for this end point

Primary: Subjects with seizures by seizure duration

End point title	Subjects with seizures by seizure duration[5]

End point description:

The number of subjects with seizures while treated during the open-label extension study classified by seizure duration.

End point type	Primary

End point timeframe:

Visit 1 untill the end of open-label ESL extension

Notes:

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

End point values	Overall ESL x FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: Subjects				
number (not applicable)				
< 30 sec.	4			
≥ 30 sec. - < 1 min.	11			
≥ 1 min. - < 5 min.	26			
≥ 5 min.	17			
Unknown	1			
More than 1 day	0			
Ongoing	0			

Statistical analyses

No statistical analyses for this end point

Primary: Standardized seizure frequency

End point title	Standardized seizure frequency[6]

End point description:

Standardised seizure frequency (ssf), calculated as 28 days * (number of seizures in interval T/length of T in days) summarised by open-label ESL study.

End point type	Primary

End point timeframe:

Visit 1 untill the end of open-label ESL extension

Notes:

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

End point values	Overall ESL x FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: SSF				
number (standard deviation)				
OL Baseline	206			
OL Visit 2	204			
OL Treatment Visit 1	201			
OL Treatment Visit 2	199			
OL Treatment Visit 3	195			
OL Treatment Visit 4	191			
OL Treatment Visit 5	184			
OL Treatment Visit 6	178			
OL Treatment Visit 7	178			
OL EOS	172			
OL EDV	26			
OL PSV	193			

Statistical analyses

No statistical analyses for this end point

Primary: Number of responders

End point title	Number of responders[7]

End point description:

A responder is defined as a subject with ≥50% reduction in seizure frequency compared to the seizure frequency at double blind study Baseline.

End point type	Primary

End point timeframe:

Visit 1 untill the end of open-label ESL extension

Notes:

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

End point values	Overall ESL x FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: Subjects				
number (not applicable)				
OL Baseline	206			
OL Visit 2	201			
OL Treatment Visit 1	195			
OL Treatment Visit 2	193			
OL Treatment Visit 3	192			
OL Treatment Visit 4	191			
OL Treatment Visit 5	181			
OL Treatment Visit 6	175			
OL Treatment Visit 7	174			
OL EOS	171			
OL EDV	24			
OL PSV	186			
Overall	206			

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of responders

End point title	Frequency of responders[8]

End point description:

A responder is defined as a subject with ≥50% reduction in seizure frequency compared to the seizure frequency at double blind study Baseline.

End point type	Primary

End point timeframe:

Visit 1 untill the end of open-label ESL extension

Notes:

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

End point values	Overall ESL x FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: Percentage of responders				
number (not applicable)				
OL Baseline	100			
OL Visit 2	97.6			
OL Treatment Visit 1	94.7			
OL Treatment Visit 2	93.7			
OL Treatment Visit 3	93.2			
OL Treatment Visit 4	92.7			
OL Treatment Visit 5	87.9			
OL Treatment Visit 6	85			
OL Treatment Visit 7	84.5			
OL EOS	83			
OL EDV	11.7			
OL PSV	90.3			
Overall	100			

Statistical analyses

No statistical analyses for this end point

Primary: Quality of life assessed using the QOLIE-31

End point title	Quality of life assessed using the QOLIE-31[9]

End point description:

Score of the Quality of Life in Epilepsy Inventory-31 (QOLIE-31).

End point type	Primary

End point timeframe:

Visit 1 untill the end of open-label ESL extension

Notes:

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

End point values	Overall ESL x FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: QOLIE-31 Score				
number (standard deviation)				
OL Baseline	205			
OL Visit 2	201			
OL Treatment Visit 2	199			
OL Treatment Visit 4	191			
OL Treatment Visit 6	178			
OL EOS	172			
OL EDV	23			

Statistical analyses

No statistical analyses for this end point

Primary: Treatment satisfaction by the Subject

End point title	Treatment satisfaction by the Subject[10]

End point description:

Subject rating of treatment satisfaction (assessed on a 4-point-scale).

End point type	Primary

End point timeframe:

Visit 1 untill the end of open-label ESL extension

Notes:

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

End point values	Overall ESL x FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: Treatment satisfaction				
number (not applicable)				
OL Visit 2 x Very good	118			
OL Visit 2 x Good	79			
OL Visit 2 x Fair	6			
OL Visit 2 x Poor	1			
OL Treatment Visit 1 x Very good	129			
OL Treatment Visit 1 x Good	69			
OL Treatment Visit 1 x Fair	2			
OL Treatment Visit 1 x Poor	0			
OL Treatment Visit 1 x Missing	1			
OL Treatment Visit 2 x Very good	139			
OL Treatment Visit 2 x Good	54			
OL Treatment Visit 2 x Fair	6			
OL Treatment Visit 2 x Poor	0			
OL Treatment Visit 3 x Very good	140			

OL Treatment Visit 3 x Good	51			
OL Treatment Visit 3 x Fair	4			
OL Treatment Visit 3 x Poor	0			
OL Treatment Visit 4 x Very good	133			
OL Treatment Visit 4 x Good	55			
OL Treatment Visit 4 x Fair	3			
OL Treatment Visit 4 x Poor	0			
OL Treatment Visit 5 x Very good	130			
OL Treatment Visit 5 x Good	50			
OL Treatment Visit 5 x Fair	2			
OL Treatment Visit 5 x Poor	2			
OL Treatment Visit 6 x Very good	126			
OL Treatment Visit 6 x Good	48			
OL Treatment Visit 6 x Fair	4			
OL Treatment Visit 6 x Poor	0			
OL Treatment Visit 7 x Very good	122			
OL Treatment Visit 7 x Good	53			
OL Treatment Visit 7 x Fair	3			
OL Treatment Visit 7 x Poor	0			
OL EOS x Very good	121			
OL EOS x Good	49			
OL EOS x Fair	2			
OL EOS x Poor	0			
OL EDV x Very good	10			
OL EDV x Good	9			
OL EDV x Fair	5			
OL EDV x Poor	1			

Statistical analyses

No statistical analyses for this end point

Primary: Treatment satisfaction by the Investigator

End point title	Treatment satisfaction by the Investigator[11]

End point description:

Investigator rating of treatment satisfaction (assessed on a 4-point-scale).

End point type	Primary

End point timeframe:

Visit 1 untill the end of open-label ESL extension

Notes:

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

End point values	Overall ESL x FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: Treatment satisfaction				
number (not applicable)				
OL Visit 2 x Very good	128			
OL Visit 2 x Good	72			
OL Visit 2 x Fair	2			
OL Visit 2 x Poor	2			
OL Treatment Visit 1 x Very good	133			
OL Treatment Visit 1 x Good	64			
OL Treatment Visit 1 x Fair	3			
OL Treatment Visit 1 x Poor	0			
OL Treatment Visit 1 x Missing	1			
OL Treatment Visit 2 x Very good	140			
OL Treatment Visit 2 x Good	54			
OL Treatment Visit 2 x Fair	5			
OL Treatment Visit 2 x Poor	0			
OL Treatment Visit 3 x Very good	139			
OL Treatment Visit 3 x Good	53			
OL Treatment Visit 3 x Fair	3			
OL Treatment Visit 3 x Poor	0			
OL Treatment Visit 4 x Very good	137			
OL Treatment Visit 4 x Good	52			
OL Treatment Visit 4 x Fair	2			
OL Treatment Visit 4 x Poor	0			
OL Treatment Visit 5 x Very good	132			
OL Treatment Visit 5 x Good	49			
OL Treatment Visit 5 x Fair	3			
OL Treatment Visit 5 x Poor	0			
OL Treatment Visit 6 x Very good	130			
OL Treatment Visit 6 x Good	45			
OL Treatment Visit 6 x Fair	3			
OL Treatment Visit 6 x Poor	0			
OL Treatment Visit 7 x Very good	126			
OL Treatment Visit 7 x Good	49			
OL Treatment Visit 7 x Fair	3			
OL Treatment Visit 7 x Poor	0			
OL EOS x Very good	122			
OL EOS x Good	49			
OL EOS x Fair	14			
OL EOS x Poor	0			
OL EDV x Very good	12			
OL EDV x Good	7			
OL EDV x Fair	4			
OL EDV x Poor	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Visit 1 until post study visit (4 weeks after OL EOS or OL EDV).	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	Overall ESL x Safety
Reporting group description: Subjects in the Safety set treated with ESL	

Serious adverse events	Overall ESL x Safety		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 206 (8.25%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer recurrent			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder cancer			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic dilatation			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hypertension				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral haemorrhage				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cerebrovascular accident				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Partial seizures with secondary generalisation				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Seizure			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestinal haemorrhage			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mesenteric artery thrombosis			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal achalasia			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection viral			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall ESL x Safety		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	124 / 206 (60.19%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Thyroid neoplasm			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		

Vascular disorders			
Essential hypertension			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Arteriosclerosis			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	11 / 206 (5.34%)		
occurrences (all)	11		
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	3 / 206 (1.46%)		
occurrences (all)	3		
Asthenia			
subjects affected / exposed	5 / 206 (2.43%)		
occurrences (all)	5		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Allergy to plants			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Hypersensitivity			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	3 / 206 (1.46%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	6 / 206 (2.91%)		
occurrences (all)	6		
Pleurisy			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	4 / 206 (1.94%)		
occurrences (all)	5		
Lung disorder			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Sinus polyp			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Psychiatric disorders			
Acute stress disorder			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Alcohol abuse			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Disorientation			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Confusional state			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		

Bradyphrenia			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	3		
Irritability			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Mood disorder due to a general medical condition			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	3 / 206 (1.46%)		
occurrences (all)	3		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	4 / 206 (1.94%)		
occurrences (all)	4		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Blood chloride decreased			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Blood creatine phosphokinase increased			
subjects affected / exposed	13 / 206 (6.31%)		
occurrences (all)	15		
Blood creatinine decreased			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		

Blood lactate dehydrogenase increased				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Blood parathyroid hormone increased				
subjects affected / exposed	2 / 206 (0.97%)			
occurrences (all)	2			
Blood phosphorus decreased				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Blood pressure decreased				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Blood sodium decreased				
subjects affected / exposed	3 / 206 (1.46%)			
occurrences (all)	3			
Blood urea increased				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
International normalised ratio increased				
subjects affected / exposed	7 / 206 (3.40%)			
occurrences (all)	7			
Gamma-glutamyltransferase increased				
subjects affected / exposed	6 / 206 (2.91%)			
occurrences (all)	8			
C-reactive protein increased				
subjects affected / exposed	3 / 206 (1.46%)			
occurrences (all)	3			
Body mass index increased				
subjects affected / exposed	2 / 206 (0.97%)			
occurrences (all)	2			
N-telopeptide				
subjects affected / exposed	5 / 206 (2.43%)			
occurrences (all)	5			
Osteocalcin decreased				

subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Thyroid hormones decreased			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Thyroxine decreased			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Thyroxine free decreased			
subjects affected / exposed	3 / 206 (1.46%)		
occurrences (all)	3		
Weight decreased			
subjects affected / exposed	4 / 206 (1.94%)		
occurrences (all)	4		
Weight increased			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	4		
Hand fracture			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Foot fracture			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	2		
Craniocerebral injury			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Head injury			

subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Ligament rupture			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Muscle injury			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Overdose			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Rib fracture			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Upper limb fracture			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Tooth fracture			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Tongue injury			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Cardiac failure			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	2		
Coronary artery disease			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Cardiac failure chronic			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		

Left ventricular failure subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1			
Extrasystoles subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1			
Left ventricular hypertrophy subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1			
Supraventricular extrasystoles subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1			
Myocardial infarction subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1			
Ventricular extrasystoles subjects affected / exposed occurrences (all)	2 / 206 (0.97%) 2			
Nervous system disorders Amnesia subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1			
Ataxia subjects affected / exposed occurrences (all)	2 / 206 (0.97%) 2			
Balance disorder subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1			
Carpal tunnel syndrome subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1			
Cerebellar syndrome subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1			
Coordination abnormal				

subjects affected / exposed	2 / 206 (0.97%)			
occurrences (all)	2			
Disturbance in attention				
subjects affected / exposed	2 / 206 (0.97%)			
occurrences (all)	3			
Dizziness				
subjects affected / exposed	10 / 206 (4.85%)			
occurrences (all)	12			
Epilepsy				
subjects affected / exposed	4 / 206 (1.94%)			
occurrences (all)	4			
Drop attacks				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Headache				
subjects affected / exposed	10 / 206 (4.85%)			
occurrences (all)	17			
Hypoaesthesia				
subjects affected / exposed	3 / 206 (1.46%)			
occurrences (all)	8			
Hyporeflexia				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Memory impairment				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Hyperreflexia				
subjects affected / exposed	2 / 206 (0.97%)			
occurrences (all)	2			
Migraine				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Paraesthesia				
subjects affected / exposed	4 / 206 (1.94%)			
occurrences (all)	4			
Morton's neuralgia				

subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Migraine without aura			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Parkinson's disease			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Postictal paralysis			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Seizure			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	9 / 206 (4.37%)		
occurrences (all)	11		
Syncope			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	7		
Tension headache			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Eosinopenia			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	4 / 206 (1.94%)		
occurrences (all)	4		

Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	3 / 206 (1.46%)		
occurrences (all)	4		
Tinnitus			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Eye disorders			
Blepharospasm			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Conjunctivitis allergic			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Dry age-related macular degeneration			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Pterygium			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Myopia			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	2		
Eyelid dermatochalasis			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	3 / 206 (1.46%)		
occurrences (all)	3		
Visual impairment			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Gastrointestinal disorders			

Constipation				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Colitis ulcerative				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	2			
Colitis ischaemic				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Gastritis				
subjects affected / exposed	2 / 206 (0.97%)			
occurrences (all)	2			
Dyspepsia				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Duodenogastric reflux				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Dry mouth				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Gingival bleeding				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	2			
Large intestine polyp				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	4 / 206 (1.94%)			
occurrences (all)	6			
Pancreatitis chronic				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			

Salivary gland mucocoele subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1 2 / 206 (0.97%) 2		
Hepatobiliary disorders Biliary dyskinesia subjects affected / exposed occurrences (all) Cholelithiasis subjects affected / exposed occurrences (all) Steatohepatitis subjects affected / exposed occurrences (all)	 1 / 206 (0.49%) 1 1 / 206 (0.49%) 1 1 / 206 (0.49%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) Rash erythematous subjects affected / exposed occurrences (all) Skin depigmentation subjects affected / exposed occurrences (all) Skin exfoliation subjects affected / exposed occurrences (all)	 1 / 206 (0.49%) 1 1 / 206 (0.49%) 1 1 / 206 (0.49%) 1 1 / 206 (0.49%) 1		
Renal and urinary disorders Chromaturia subjects affected / exposed occurrences (all) Chronic kidney disease subjects affected / exposed occurrences (all) Haematuria	 1 / 206 (0.49%) 1 1 / 206 (0.49%) 1		

subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Renal artery thrombosis			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Renal cyst			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Urinary incontinence			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Hypothyroidism			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Primary hypothyroidism			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	11 / 206 (5.34%)		
occurrences (all)	11		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	3 / 206 (1.46%)		
occurrences (all)	3		
Musculoskeletal pain			

subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Osteoarthritis			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Posture abnormal			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Spinal osteoarthritis			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Infections and infestations			
Cystitis			
subjects affected / exposed	4 / 206 (1.94%)		
occurrences (all)	4		
Bronchitis			
subjects affected / exposed	7 / 206 (3.40%)		
occurrences (all)	8		
Erysipelas			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	4 / 206 (1.94%)		
occurrences (all)	5		
Herpes zoster			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	13 / 206 (6.31%)		
occurrences (all)	19		

Laryngitis				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Labyrinthitis				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Nasal herpes				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Otitis externa				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Otitis media acute				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	12 / 206 (5.83%)			
occurrences (all)	14			
Ophthalmic herpes zoster				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Oral herpes				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	3 / 206 (1.46%)			
occurrences (all)	3			
Pharyngitis bacterial				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Postoperative wound infection				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			
Pulpitis dental				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences (all)	1			

Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1		
Respiratory tract infection viral subjects affected / exposed occurrences (all)	4 / 206 (1.94%) 5		
Sinusitis subjects affected / exposed occurrences (all)	3 / 206 (1.46%) 4		
Tooth infection subjects affected / exposed occurrences (all)	2 / 206 (0.97%) 2		
Tonsillitis subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1		
Tinea cruris subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1		
Viral infection subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 206 (0.97%) 2		
Tracheitis subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1		
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1		
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1		
Diabetes mellitus			

subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Dyslipidaemia			
subjects affected / exposed	2 / 206 (0.97%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	3 / 206 (1.46%)		
occurrences (all)	3		
Hypoglycaemia			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Hypertriglyceridaemia			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Hypercholesterolaemia			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Obesity			
subjects affected / exposed	3 / 206 (1.46%)		
occurrences (all)	3		
Vitamin D deficiency			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Vitamin C deficiency			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		
Zinc deficiency			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported