Clinical trial results:
A randomized, double-blind, 12-week treatment, parallel-group study to evaluate the efficacy and safety of QMF149(150 g/160 g o.d.) compared with salmeterol xinafoate/fluticasone propionate (50 g/500 g b.i.d.) in patients with chronic obstructive pulmonary disease.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2012-001172-12
Trial protocol	HU GR BG BE SE FI PL ES DK
Global end of trial date	25 September 2013
Results information	
Result version number	v1 (current)
This version publication date	07 July 2018
First version publication date	07 July 2018

Trial information

Trial identification	
Sponsor protocol code	CQMF149F2202
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01636076
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	25 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 September 2013
Global end of trial reached?	Yes
Global end of trial date	25 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate QMF149 (150/160 µg, od) delivered via Concept1 device is at least non- inferior to salmeterol xinafoate/fluticasone propionate (50/500 µg bid) delivered via Accuhaler® in terms of trough FEV1 after 12 weeks of treatment. Trough refers to the mean of FEV1 at 23 h 10 min and 23 h 45 min after the morning dose.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

At the start of Screening (Visit 1), all patients were provided with a short acting β2-agonist (salbutamol or albuterol) which they were instructed to use throughout the study as rescue medication. Nebulized salbutamol was not allowed as rescue medication throughout the entire trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 November 2012
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	Australia: 31
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Bulgaria: 53
Country: Number of subjects enrolled	Denmark: 35
Country: Number of subjects enrolled	Finland: 14
Country: Number of subjects enrolled	Germany: 62
Country: Number of subjects enrolled	Greece: 34
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Hungary: 66
Country: Number of subjects enrolled	Israel: 68
Country: Number of subjects enrolled	Malaysia: 13
Country: Number of subjects enrolled	Poland: 86

Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	South Africa: 64
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Sweden: 33
Country: Number of subjects enrolled	Thailand: 37
Worldwide total number of subjects	629
EEA total number of subjects	412

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)	350
From 65 to 84 years	278
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 117 centres in 18 countries

Pre-assignment

Screening details:

982 patients screened, 629 patients randomized

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	QMF149

Arm description:

QMF149 (Indacaterol acetate/Mometasone furoate) 150/160 µg o.d. delivered via Concept1 device

Arm type	Experimental
Investigational medicinal product name	QMF 149
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

QMF149 was supplied to the investigators by Novartis Drug Supply Management (DSM) as dry powder FDC formulation at dose strengths of Indacaterol acetate/Mometasone furoate 150/160 µg. QMF149 was administered once daily in the morning via Concept1 device as a single dose dry powder inhaler (SDDPI).

Arm title	Salmeterol xinafoate/fluticasone propionate

Arm description:

Salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d, delivered via Accuhaler®

Arm type	Active comparator
Investigational medicinal product name	xinafoate/fluticasone propionate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

Salmeterol xinafoate/fluticasone propionate as dry powder of 50/500 µg dose strengths were locally sourced. Salmeterol xinafoate/fluticasone propionate 50/500 µg bid, delivered via Accuhaler®.

Number of subjects in period 1	QMF149	Salmeterol xinafoate/fluticasone propionate
Started	316	313
Completed	299	288
Not completed	17	25
Physician decision	1	1
Consent withdrawn by subject	7	10
Adverse event, non-fatal	6	11
Non-compliance with study treatment	1	1
Terminated by sponsor	1	1
Lost to follow-up	1	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	QMF149
Reporting group description:	
QMF149 (Indacaterol acetate/Mometasone furoate) 150/160 µg o.d. delivered via Concept1 device	
Reporting group title	Salmeterol xinafoate/fluticasone propionate
Reporting group description:	
Salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d, delivered via Accuhaler®	

Reporting group values	QMF149	Salmeterol xinafoate/fluticasone propionate	Total
Number of subjects	316	313	629
Age categorical Units: Subjects			
Adults (18 - <65)	173	177	350
adults (65 - <85)	142	136	278
adults (>=85)	1	0	1
Age Continuous | Units: years			
arithmetic mean	64.8	64.1	
standard deviation	± 7.74	± 7.89	-
Gender, Male/Female Units: Participants			
Male	233	227	460
Female	83	86	169

End points

End points reporting groups

Reporting group title	QMF149
Reporting group description:	
QMF149 (Indacaterol acetate/Mometasone furoate) 150/160 µg o.d. delivered via Concept1 device	
Reporting group title	Salmeterol xinafoate/fluticasone propionate
Reporting group description:	
Salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d, delivered via Accuhaler®	

Primary: Mixed Model for Repeated Measures (MMRM): Between-treatment comparisons for trough FEV1 (L) on Day 85

End point title	Mixed Model for Repeated Measures (MMRM): Between-treatment comparisons for trough FEV1 (L) on Day 85
End point description:	
Spirometry is conducted according to the global standard. Trough FEV1 is defined as the average of the 23 hour 10 minute and 23 hour 45 minute post dose FEV1 readings.	
End point type	Primary
End point timeframe:	
12 weeks	

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: Liters				
least squares mean (standard error)				
Full analysis set (n=291,282)	1.27 (± 0.0124)	1.215 (± 0.0124)		
Per protocol set (n=259,251)	1.277 (± 0.0136)	1.228 (± 0.0137)		

Statistical analyses

Statistical analysis title	Mixed Model for Repeated Measures
Comparison groups	QMF149 v Salmeterol xinafoate/fluticasone propionate
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.056

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0277
upper limit	0.0833
Variability estimate	Standard error of the mean
Dispersion value	0.0142

Secondary: Trough FEV1 after first dose and after 4 and 12 weeks of treatment

End point title	Trough FEV1 after first dose and after 4 and 12 weeks of treatment

End point description:

Spirometry is conducted according to the global standard. FEV1 is measured at pre-dose and post dose up to 1 hours on Day 1 and Day 28; 24 hours post-dose on Day 29 and 85. In a subset of approximately 60 patients, FEV1 is measured up to 20 hours postdose on Day 28 and Day 84.

End point type	Secondary

End point timeframe:

Day 1 and Day 85

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: Liters				
arithmetic mean (standard error)				
Baseline Day 2 (n=286, 302)	1.147 (± 0.0237)	1.167 (± 0.0264)		
Day 2 (n=286, 302)	1.216 (± 0.0106)	1.243 (± 0.0104)		
Baseline Day 29 (n=293, 296)	1.148 (± 0.0236)	1.178 (± 0.0266)		
Day 29 (n=293,296)	1.277 (± 0.0119)	1.247 (± 0.0119)		
Day 84 baseline (n=289,287)	1.144 (± 0.024)	1.187 (± 0.0267)		
Day 84 (n=289,287)	1.269 (± 0.0139)	1.208 (± 0.0139)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mixed Model for Repeated Measures (MMRM): Between-treatment comparisons for FEV1 (L), by visit and timepoint

End point title	Mixed Model for Repeated Measures (MMRM): Between-treatment comparisons for FEV1 (L), by visit and timepoint

End point description: Within treatment LS Mean	
End point type	Secondary
End point timeframe: Day 1 through day 85	

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: liter				
least squares mean (standard error)				
Absolute Value Day 1/5min (n=290,298)	1.254 (± 0.0069)	1.198 (± 0.0068)		
Absolute Value Day 1/30 min (n=294,306)	1.281 (± 0.0079)	1.25 (± 0.0087)		
Absolute Value Day 1/60min (n=300,303)	1.281 (± 0.0087)	1.256 (± 0.0087)		
Absolute Value Day 2/ 23 hr 10 min (n=288,295)	1.213 (± 0.0108)	1.239 (± 0.0107)		
Absolute Value Day 2/ 23 hr 45 min (n=297,305)	1.215 (± 0.0106)	1.244 (± 0.0105)		
Absolute Value Day 28/ -50min (n=288,295)	1.265 (± 0.0132)	1.287 (± 0.0139)		
Absolute Value Day 28/ -15min (n=292,290)	1.287 (± 0.0132)	1.235 (± 0.014)		
Absolute Value Day 28/ 5min (n=290,289)	1.329 (± 0.0113)	1.268 (± 0.0113)		
Absolute Value Day 28/ 30min (n=293,290)	1.352 (± 0.0118)	1.298 (± 0.0118)		
Absolute Value Day 28/ 60min (n=292,290)	1.353 (± 0.0123)	1.298 (± 0.0122)		
Absolute Value Day 29/ 23 hr 10 min (n=285,292)	1.269 (± 0.0118)	1.242 (± 0.0117)		
Absolute Value Day 29/ 23 hr 45 min (n=290,295)	1.281 (± 0.0123)	1.254 (± 0.0122)		
Absolute Value Day 84/ -50 min (n=286,278)	1.259 (± 0.014)	1.195 (± 0.0141)		
Absolute Value Day 84/ -15 min (n=282,285)	1.282 (± 0.0146)	1.222 (± 0.0147)		
Absolute Value Day 84/ 5 min (n=280,279)	1.336 (± 0.0128)	1.243 (± 0.0128)		
Absolute Value Day 84/ 30 min (n=286,280)	1.352 (± 0.0124)	1.277 (± 0.0124)		
Absolute Value Day 84/ 60 min (n=287,281)	1.351 (± 0.0128)	1.283 (± 0.0128)		
Absolute Value Day 84/ 23 hr 10 min (n=292,291)	1.264 (± 0.0125)	1.212 (± 0.0125)		
Absolute Value Day 84/ 23 hr 45 min (n=291,285)	1.273 (± 0.0125)	1.221 (± 0.0126)		

Statistical analyses

No statistical analyses for this end point

Secondary: Forced vital capacity (FVC) at each timepoint

End point title	Forced vital capacity (FVC) at each timepoint

End point description:

Spirometry is conducted according to the global standard. FVC is measured at pre-dose and post dose up to 4 hour on Day 1, Day 28, and Day 84, at post dose 12 hour, 23 hour 10 minute and 23 hour 45 minutes on Day 2 and Day 29, and at pre-dose 50 min and 15 min on Day 2, Day 28, and Day 84.

End point type	Secondary

End point timeframe:

Day 1, Day 2, Day 28, Day , Day 29, Day 84, Day 85

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: liters				
arithmetic mean (standard deviation)				
Baseline (n=316,313)	2.46 (± 0.6969)	2.481 (± 0.7209)		
Day 1/ 5 min (n=299,298) Change	0.179 (± 0.2165)	0.06 (± 0.1404)		
Day 1/ 30 min (n=302,306) Change	0.207 (± 0.2279)	0.129 (± 0.1953)		
Day 1/ 60 min (n=308,303) Change	0.222 (± 0.2472)	0.152 (± 0.2287)		
Day 1/ 4 hr (n=302,297) Change	0.217 (± 0.2847)	0.183 (± 0.2611)		
Day 2/ 23hr 10 min (n=297,296) Change	0.089 (± 0.2518)	0.092 (± 0.2896)		
Day 2/ 23hr 45 min (n=307,306) Change	0.083 (± 0.2583)	0.092 (± 0.2815)		
Day 28 / -50 min (n=295,296) Change	0.132 (± 0.2806)	0.068 (± 0.2814)		
Day 28 / -15 min (n=300,291) Change	0.161 (± 0.309)	0.072 (± 0.2892)		
Day 28 / 5 min (n=297,290) Change	0.238 (± 0.3163)	0.122 (± 0.3068)		
Day 28 / 30 min (n=301,291) Change	0.263 (± 0.3169)	0.168 (± 0.3166)		
Day 28 / 60 min (n=299,292) Change	0.279 (± 0.3261)	0.189 (± 0.335)		
Day 29 / 23hr 10 min (n=293,293) Change	0.121 (± 0.2955)	0.084 (± 0.2817)		
Day 29 /23hr 45 min (n=299,296) Change	0.133 (± 0.3132)	0.097 (± 0.2965)		
Day 84 / -50min (n=295,279) Change	0.125 (± 0.2979)	0.019 (± 0.357)		
Day 84 /-15 min (n=291,286) Change	0.144 (± 0.3234)	0.049 (± 0.3519)		
Day 84 / 5 min (n=288,290) Change	0.229 (± 0.337)	0.076 (± 0.3729)		

Day 84 /30 min (n=295,281) Change	0.255 (± 0.3344)	0.12 (± 0.3537)		
Day 84 / 60 min (n=296,282) Change	0.272 (± 0.3295)	0.159 (± 0.3648)		
Day 85 / 23 hr 10 min (n=302,292) Change	0.113 (± 0.3132)	0.022 (± 0.3482)		
Day 85 / 23 hr 45 min (n=301,286) Change	0.126 (± 0.3206)	0.035 (± 0.362)		

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1/FVC at each timepoint

End point title	FEV1/FVC at each timepoint

End point description:

Spirometry is conducted according to the global standard. FEV1/FVC is measured at pre-dose and post dose up to 4 hour on Day 1, Day 28, and Day 84, at post dose 12 hour, 23 hour 10 minute and 23 hour 45 minutes on Day 2 and Day 29, and at pre-dose 50 min and 15 min on Day 2, Day 28, and Day 84.

End point type	Secondary

End point timeframe:

Day 1, Day 2, Day 28, Day , Day 29, Day 84, Day 85

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: FEV1/ FVC (%)				
arithmetic mean (standard deviation)				
Baseline (n=316, 313)	46.786 (± 10.0306)	46.859 (± 10.0392)		
Day 1 / 5 min (n=299, 298) change	0.488 (± 2.9633)	0.047 (± 2.1366)		
Day 1 / 30 min (n=302,306) change	0.955 (± 3.0166)	0.879 (± 2.7281)		
Day 1 / 60 min (n=308,303) change	1.112 (± 3.1413)	1.182 (± 3.0612)		
Day 1 / 4 hr (n=302, 297) change	1.045 (± 3.3917)	1.397 (± 3.2407)		
Day 2 / 23 Hr 10 min (n=297,296) change	0.503 (± 3.345)	1.042 (± 3.2074)		
Day 2 / 23 Hr 45 min (n=307,306) change	0.583 (± 3.4552)	1.319 (± 3.1977)		
Day 28 / -50 min (n=295,296) change	1.463 (± 3.7864)	1.14 (± 3.89)		
Day 28 / -15 min (n=300,291) change	1.837 (± 3.9769)	1.495 (± 3.7597)		
Day 28 / 5 min (n=297,290) change	1.951 (± 4.0512)	1.581 (± 4.006)		
Day 28 / 30 min (n=301,291) change	2.296 (± 4.4904)	1.873 (± 4.2723)		

Day 28 / 60 min (n=299,292) change	2.525 (± 4.3228)	2.06 (± 4.4398)		
Day 28 / 4 hr (n=44,45) change	4.034 (± 5.2622)	2.322 (± 4.0257)		
Day 28 / 11hr 10 min (n=47,44) change	2.553 (± 4.026)	1.909 (± 3.9389)		
Day 28 / 11hr 45 min (n=43,42) change	2.791 (± 4.1708)	2.476 (± 4.3978)		
Day 28 / 16 hr (n=40,41) change	2.25 (± 3.4006)	2.305 (± 4.3111)		
Day 28 / 20 hr (n=43,44) change	2.535 (± 3.5379)	2.25 (± 3.9935)		
Day 29 / 23 hr 10 min (n=293,293) change	1.771 (± 4.073)	1.319 (± 3.82)		
Day 29 / 23 hr 45 min (n=299,296) change	2 (± 4.0562)	1.566 (± 3.9704)		
Day 84 / -50 min (n=295,279) change	1.449 (± 4.1145)	1.068 (± 4.1776)		
Day 84 / -15 min (n=291,286) change	2.155 (± 4.0673)	1.584 (± 4.3278)		
Day 84 / 5 min (n=288,280) change	2.332 (± 4.1032)	1.796 (± 4.231)		
Day 84 / 30 min (n=295,281) change	2.42 (± 4.3561)	2.062 (± 4.3941)		
Day 84 / 60 min (n=296,282) change	2.571 (± 4.4128)	2.067 (± 4.3512)		
Day 84 / 4 hr (n=45,44) change	2.389 (± 3.7079)	2.682 (± 4.3269)		
Day 84 / 11hr 10 min (n=45,43) change	1.944 (± 4.0833)	2.105 (± 3.8754)		
Day 84 / 11 hr 45 min (n=39,39) change	2.538 (± 3.7895)	2.295 (± 4.1147)		
Day 84 / 16 hr (n=41,39) change	1.415 (± 4.0588)	1.962 (± 3.6981)		
Day 84 / 20 hr (n=44,43) change	2.364 (± 4.0539)	1.837 (± 3.7713)		
Day 84 / 23 hr 10 min (n=302,292) change	1.856 (± 4.4315)	1.414 (± 4.0356)		
Day 84 / 23 hr 45 min (n=301,286) change	2.098 (± 4.3676)	1.593 (± 4.211)		

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 (L) on Day 1 between-treatment comparisons of AUC (5min – 4h)

End point title	FEV1 (L) on Day 1 between-treatment comparisons of AUC (5min – 4h)

End point description:

Spirometry is conducted according to the global standard. FEV1 AUC (5 min-4 h), Scheduled (not actual) time points are to be used. The standardized AUC(5 min – 4 h) for FEV1 will be summarized by treatment. LS mean is within treatment

End point type	Secondary

End point timeframe:

Day 1

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: Liters / hour				
least squares mean (standard error)				
Day 1 baseline (n=303,311)	1.142 (± 0.0233)	1.169 (± 0.0259)		
Day 1 post (n=303,311)	1.277 (± 0.0086)	1.26 (± 0.0085)		

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 AUC (5 min-4 h),

End point title	FEV1 AUC (5 min-4 h),

End point description:

Spirometry is conducted according to the global standard. FEV1 AUC (5 min-4 h), (5 min-24 h) is measured after the first dose on Day 1 and on Day 28 and Day 84 in a subset of approximately 60 patients. Scheduled (not actual) time points are to be used. The interpretation of FEV1 at time 0 is the baseline value at the randomization visit and the latest pre-dose value (-50 min or -15 min) at subsequent visits. The standardized AUC(5 min – 4 h) for FEV1 will be summarized by treatment. The same will be repeated for standardized AUC for FEV1 between 5 min and 24 hours post morning dose.

End point type	Secondary

End point timeframe:

Day 1(Baseline), Day 28, Day 84

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Liters				
least squares mean (standard error)				
Day 1 baseline (n=46,47)	1.302 (± 0.0278)	1.331 (± 0.0282)		
Day 28 (n=45,46)	1.41 (± 0.0353)	1.355 (± 0.0355)		
Day 84 (n=44,46)	1.387 (± 0.0401)	1.372 (± 0.0401)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mixed Model for Repeated Measures (MMRM): Between-treatment comparisons for AUC (5 min – 23 h 45 min) for FEV1 (L) on Day 28 and Day 84 (Full analysis set, 24-h profiling subgroup)

End point title	Mixed Model for Repeated Measures (MMRM): Between-treatment comparisons for AUC (5 min – 23 h 45 min) for FEV1 (L) on Day 28 and Day 84 (Full analysis set, 24-h profiling subgroup)

End point description:

Spirometry is conducted according to the global standard. FEV1 AUC (5 min-4 h), (5 min-24 h) is measured after the first dose on Day 1 and on Day 28 and Day 84 in a subset of approximately 60 patients. Scheduled (not actual) time points are to be used. The interpretation of FEV1 at time 0 is the baseline value at the randomization visit and the latest pre-dose value (-50 min or -15 min) at subsequent visits. The standardized AUC(5 min – 4 h) for FEV1 will be summarized by treatment. The same will be repeated for standardized AUC for FEV1 between 5 min and 24 hours post morning dose.

End point type	Secondary

End point timeframe:

Day 28, Day 84

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Liter/hour				
least squares mean (standard error)				
Day 28 (n=45,46)	1.352 (± 0.0428)	1.298 (± 0.0431)		
Day 85 (n=47,47)	1.317 (± 0.0454)	1.303 (± 0.0459)		

Statistical analyses

No statistical analyses for this end point

Secondary: The usage of rescue medication (short acting β2-agonist)

End point title	The usage of rescue medication (short acting β2-agonist)

End point description:

Participants record the number of puffs of rescue medication taken in the previous 12 hours each morning and evening throughout the 12 week treatment period.

End point type	Secondary

End point timeframe:

12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: Number of puffs				
least squares mean (standard error)				
Daily Change Weeks 1-12 (n-281,274)	-1.064 (± 0.1615)	-0.593 (± 0.1621)		
Daytime Change Weeks 1-12 (n=276-272)	-0.625 (± 0.1021)	-0.3 (± 0.1026)		
Nighttime Change Weeks 1-12 (n=281,271)	-0.452 (± 0.0748)	-0.308 (± 0.0751)		

Statistical analyses

No statistical analyses for this end point

Secondary: % of days with no rescue medication use

End point title	% of days with no rescue medication use

End point description:

Participants record the number of puffs of rescue medication taken in the previous 12 hours each morning and evening throughout the 12 week treatment period. % days shows the difference between groups in the frequency of the need for rescue medication

End point type	Secondary

End point timeframe:

12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	274		
Units: % of days				
number (not applicable)	8.796	2.538		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient reported outcome measures: SGRQ (St. George’s Respiratory Questionnaire)

End point title	Patient reported outcome measures: SGRQ (St. George’s Respiratory Questionnaire)

End point description:

A Total and three component scores are calculated: Symptoms; Activity; Impacts. Each component of

the questionnaire is scored separately:The score for each component is calculated separately by dividing the summed weights by the maximum possible weight for that component and expressing the result as a percentage: Score = 100 x Summed weights from all positive items in that component divided by Sum of weights for all items in that component The Total score is calculated in similar way: Score = 100 x Summed weights from all positive items in the questionnaire divided by Sum of weights for all items in the questionnaire Sum of maximum possible weights for each component and Total: Symptoms 566.2 Activity 982.9 Impacts 1652.8 Total (sum of maximum for all three components) 3201.9 The proportion of patients who achieve a clinically important improvement from baseline of at least 4 units in the total SGRQ will be analyzed. The higher the score the more symptoms of disease are present.

End point type	Secondary

End point timeframe:

4 and 12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: Total Score				
arithmetic mean (standard deviation)				
Baseline (n=314, 308)	43.05 (± 18.515)	42.28 (± 17.941)		
Day 28 Baseline (n=304,295)	42.87 (± 18.392)	42.47 (± 18.051)		
Day 28 Post (n=304,295)	40.95 (± 18.527)	42.18 (± 18.101)		
Day 28 Change (n=304,295)	-1.92 (± 11.383)	-0.29 (± 12.145)		
Day 84 Baseline (n=297,284)	42.57 (± 18.322)	42.03 (± 18.099)		
Day 84 Post (n=297,284)	39.81 (± 19.057)	41.01 (± 18.553)		
Day 84 Change (n=297,284)	-2.76 (± 13.062)	-1.02 (± 12.178)		

Statistical analyses

No statistical analyses for this end point

Secondary: Analysis of the proportion of subjects with a clinically important improvement of >=1 point in the TDI (Transitional Dyspnoea Index) focal score by visit

End point title	Analysis of the proportion of subjects with a clinically important improvement of >=1 point in the TDI (Transitional Dyspnoea Index) focal score by visit

End point description:

A TDI focal score of ≥1 is considered to be a clinically important improvement from baseline. Analysis of the proportion of subjects with a clinically important improvement of >=1 point in the TDI focal score, by visit

End point type	Secondary

End point timeframe:

4 and 12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: (% patient) showing clinical improvement				
number (not applicable)				
Day 28 Change from baseline (n=291,294)	43.3	40.5		
Day 84 Change from baseline (n=287,283)	52.6	45.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient reported outcome measures: COPD Assessment Test

End point title	Patient reported outcome measures: COPD Assessment Test

End point description:

It consists of eight items, each presented as a semantic 6-point differential scale, providing a total score out of 40. A higher score indicates a worse health status. Scores of 0 - 10, 11 - 20, 21 - 30 and 31 - 40 represent a mild, moderate, severe or very severe clinical impact of COPD upon the patient.

End point type	Secondary

End point timeframe:

Baseline, 4 and 12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 311,308)	16.3 (± 7.6)	16.2 (± 7.48)		
Day 28 baseline (n=303,298)	16.2 (± 7.58)	16.2 (± 7.48)		
Day 28 Post (n=303,298)	15.8 (± 7.63)	16.8 (± 7.75)		
Day 28 Change (n=303,298)	-0.4 (± 5.56)	0.6 (± 4.94)		
Day 84 Baseline (n=295,285)	15.9 (± 7.54)	16.1 (± 8.38)		
Day 84 Post (n=295,285)	15.5 (± 7.56)	16.3 (± 8.38)		
Day 84 change (n=295,285)	-0.4 (± 5.77)	0.2 (± 5.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient reported outcome measures: Medical Outcome Study (MOS) sleep scale

End point title	Patient reported outcome measures: Medical Outcome Study (MOS) sleep scale

End point description:

MOS Consists of 12 items to measure 6 sleep dimensions: initiation (time to fall asleep), quantity (hours of sleep each night), maintenance , respiratory problems, perceived adequacy, somnolence (the last 4 items reported using a 6- item Likert scale ranging from "All of the time" to "None of the time"). The time frame for the responses is "the past 4 weeks." Each patient reported outcome is measured at the start of study treatment and after 4 and 12 weeks of treatment. Score range. The range for the 12-item version is 12–71.

End point type	Secondary

End point timeframe:

Baseline, 4 and 12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	296		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Sleep disturbance Baseline (n=299,295)	49.6423 (± 8.50059)	49.9292 (± 8.5133)		
Sleep disturbance Day 28 Baseline (n=290,285)	49.6833 (± 8.57069)	49.7616 (± 8.49307)		
Sleep disturbance Day 28 post (n=290,285)	50.9323 (± 8.9254)	50.0858 (± 8.7711)		
Sleep disturbance Day 28 change (n=290,285)	1.249 (± 5.67591)	0.3242 (± 6.63156)		
Sleep disturbance Day 84 Baseline (n=283,274)	49.7622 (± 8.611)	49.6634 (± 8.41228)		
Sleep disturbance Day 84 Post (n=283,274)	50.7508 (± 9.22016)	50.238 (± 9.07204)		
Sleep disturbance Day 84 Change (n=283,274)	0.9887 (± 6.52972)	0.5745 (± 6.45362)		
Sleep snoring Baseline (n=299,295)	48.8815 (± 9.32313)	49.8895 (± 9.18885)		
Sleep snoring Day 28 Baseline (n=290,285)	48.8234 (± 9.40239)	49.7733 (± 9.2303)		
Sleep snoring Day 28 Post (n=290,285)	49.3476 (± 9.37744)	49.5067 (± 9.39012)		
Sleep snoring Day 28 change(n=290,285)	0.5241 (± 6.70023)	-0.2667 (± 7.06825)		

Sleep snoring Day 84 Baseline (n=283,274)	48.8414 (± 9.29113)	49.6385 (± 9.19681)		
Sleep snoring Day 84 post (n=283,274)	49.4591 (± 9.29113)	49.6108 (± 9.51632)		
Sleep snoring Day 84 change (n=283,274)	0.6177 (± 7.42456)	-0.0277 (± 8.266668)		
Sleep shortness of breath Baseline (n=302,295)	44.5221 (± 13.28329)	45.4259 (± 11.5156)		
Sleep shortness of breath D 28 Bseline(n=293,285)	44.6348 (± 13.1571)	45.3292 (± 11.48556)		
Sleep shortness of breath D 28 post (n=293,285)	45.8814 (± 11.85664)	45.5774 (± 11.65379)		
Sleep shortness of breath D 28 change (n=293,285)	1.2466 (± 12.21272)	0.2481 (± 11.44262)		
Sleep shortness of breath D 84 Bseline (n=287,274)	44.8645 (± 12.99605)	45.318 (± 11.37006)		
Sleep shortness of breath D 84 post (n=287,274)	45.7676 (± 13.20151)	45.7049 (± 11.8491)		
Sleep shortness of breath D 84 change (n=287,274)	0.9031 (± 12.11351)	0.387 (± 10.97093)		
Sleep adequacy baseline (n=300,295)	54.9999 (± 9.85865)	54.9725 (± 9.41704)		
Sleep adequacy baseline D 28 (n=291,285)	55.0531 (± 9.80609)	55.0679 (± 9.30955)		
Sleep adequacy Post D 28 (n=291,285)	55.2032 (± 10.04281)	54.8296 (± 10.21011)		
Sleep adequacy Change D 28 (n=291,285)	0.1501 (± 9.8392)	-0.2383 (± 9.2125)		
Sleep adequacy baseline D 84 (n=284,274)	55.2125 (± 9.81055)	55.1084 (± 9.20723)		
Sleep adequacy Post D 84 (n=284,274)	55.2467 (± 10.00283)	54.5424 (± 9.96705)		
Sleep adequacy change D 84 (n=284,274)	0.0342 (± 8.81793)	-0.5659 (± 8.578)		
Sleep somnolence baseline (n=302,296)	47.6646 (± 9.56376)	49.1709 (± 9.56807)		
Sleep somnolence baseline D28 (n=290,285)	47.8711 (± 9.4894)	49.1092 (± 9.58808)		
Sleep somnolence post D28 (n=290,285)	48.4429 (± 9.93046)	48.6761 (± 10.1785)		
Sleep somnolence change D28 (n=290,285)	0.5718 (± 7.91162)	-0.4331 (± 8.67719)		
Sleep somnolence baseline D84 (n=284,274)	47.7821 (± 9.53639)	48.9335 (± 9.55603)		
Sleep somnolence post D84 (n=284,274)	48.2568 (± 10.36223)	49.0461 (± 9.54132)		
Sleep somnolence change D84 (n=284,274)	0.4747 (± 8.11292)	0.1126 (± 7.83662)		
Sleep Index 1 Baseline (n=300,295)	50.4795 (± 9.72203)	50.8382 (± 9.16082)		
Sleep Index 1 Baseline D28 (n=290,285)	50.6034 (± 9.67464)	50.7911 (± 9.13425)		
Sleep Index 1 Post D28 (n=290,285)	51.4799 (± 9.86137)	50.7836 (± 10.02742)		
Sleep Index 1 Change D28 (n=290,285)	0.8764 (± 7.0396)	-0.0074 (± 7.73909)		
Sleep Index 1 Baseline D84 (n=284,274)	50.7327 (± 9.64776)	50.6951 (± 9.09626)		
Sleep Index 1 Post D84 (n=284,274)	51.359 (± 10.16584)	50.9888 (± 9.54642)		
Sleep Index 1 Change D84 (n=284,274)	0.6263 (± 7.22742)	0.2938 (± 7.08082)		

Sleep Index 2 baseline (n=299,295)	50.461 (± 9.14154)	51.0701 (± 8.62899)		
Sleep Index 2 baseline D 28 (n=289,285)	50.572 (± 9.15508)	50.9923 (± 8.60656)		
Sleep Index 2 Post D 28 (n=289,285)	51.5578 (± 9.43365)	51.0116 (± 9.33837)		
Sleep Index 2 Change D 28 (n=289,285)	0.9858 (± 6.00711)	0.0193 (± 6.99119)		
Sleep Index 2 Baseline D 84 (n=283,274)	50.688 (± 9.16092)	50.8848 (± 8.58893)		
Sleep Index 2 Post D 84 (n=283,274)	51.4615 (± 9.79518)	51.1511 (± 9.09673)		
Sleep Index 2 Change D 84 (n=283,274)	0.7735 (± 6.66709)	0.2663 (± 6.29393)		
Sleep quantity Baseline (n=301,295)	6.5565 (± 1.44169)	6.6203 (± 1.34895)		
Sleep quantity Baseline D28(n=292,285)	6.5702 (± 1.44879)	6.6351 (± 1.35775)		
Sleep quantity Post D28(n=292,285)	6.5717 (± 1.54708)	6.6246 (± 1.463566)		
Sleep quantity Change D28(n=292,285)	0.0015 (± 1.0739)	-0.0105 (± 1.10691)		
Sleep quantity Baseline D84(n=285,274)	6.5456 (± 1.42402)	6.6496 (± 1.345)		
Sleep quantity Post D84(n=285,274)	6.5561 (± 1.4378)	6.6569 (± 1.37648)		
Sleep quantity Change D84(n=285,274)	0.0105 (± 1.1227)	0.0073 (± 1.18906)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary Statistics of COPD Exacerbations over12 weeks as defined by Chronic Pulmonary Disease Tool (EXACT)

End point title	Summary Statistics of COPD Exacerbations over12 weeks as defined by Chronic Pulmonary Disease Tool (EXACT)

End point description:

The EXACT is a 14-item electronic questionnaire designed to detect the frequency, severity, and duration of exacerbations in patients with COPD.

End point type	Secondary

End point timeframe:

12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: COPD exacerbation per participant				
arithmetic mean (standard deviation)	0.2 (± 0.49)	0.3 (± 0.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first COPD exacerbation

End point title	Time to first COPD exacerbation

End point description:

Time-to-event variables will be analyzed by the Kaplan-Meier estimates and the stratified Cox proportional hazard model by smoking status and COPD severity. The model will include treatment and country as factors, and FEV1 prior to inhalation and FEV1 15 min post inhalation of salbutamol/albuterol as covariates. The reported measure will detail the percentage of participants that were event free of a specified event.

End point type	Secondary

End point timeframe:

12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: Percentage of participants event free				
number (confidence interval)				
Mild COPD exacerbation	99.3 (98.4 to 100)	98.7 (97.4 to 100)		
Moderate COPD exacerbation	94.5 (92 to 97.1)	88.5 (84.9 to 92.1)		
Severe COPD exacerbation	98 (96.5 to 99.6)	98.3 (96.9 to 99.8)		
Moderate or Severe COPD exacerbation	92.9 (89.9 to 95.7)	86.8 (82.9 to 90.6)		
Any(mild, moderate,severe)	92.2 (89.2 to 95.2)	85.8 (81.9 to 89.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual rate of COPD exacerbations

End point title	Annual rate of COPD exacerbations

End point description:

Time-to-event variables will be analyzed by the Kaplan-Meier estimates and the stratified Cox

proportional hazard model by smoking status and COPD severity. The model will include treatment and country as factors, and FEV1 prior to inhalation and FEV1 15 min post inhalation of salbutamol/albuterol as covariates.

End point type	Secondary

End point timeframe:

12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: COPD Exacerbations per year				
number (confidence interval)				
Model based estimates	0.354 (0.221 to 0.5663)	0.659 (0.4523 to 0.9592)		
Actual rate exacerbations per year	0.39 (-99999.9 to 99999.9)	0.73 (-99999.9 to 99999.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration (in days) of COPD exacerbations

End point title	Duration (in days) of COPD exacerbations

End point description:

Duration and number of the COPD exacerbation will be analyzed by the negative binomial regression model including treatment, country, smoking status, and COPD severity as factors and FEV1 prior to inhalation and FEV1 15 min post inhalation of salbutamol/albuterol as covariates.

End point type	Secondary

End point timeframe:

12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: Days				
arithmetic mean (standard deviation)	1.4 (± 6.59)	2 (± 6.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients exacerbation free at 12 weeks

End point title	Percentage of patients exacerbation free at 12 weeks

End point description:

Time-to-event variables will be analyzed by the Kaplan-Meier estimates and the stratified Cox proportional hazard model by smoking status and COPD severity. The model will include treatment and country as factors, and FEV1 prior to inhalation and FEV1 15 min post inhalation of salbutamol/albuterol as covariates. The reported measure will detail the percentage of participants that were event free of a specified event.

End point type	Secondary

End point timeframe:

12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: Percentage of participants				
number (not applicable)	92.4	85.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Time (in days) to permanent study discontinuation due to COPD exacerbation

End point title	Time (in days) to permanent study discontinuation due to COPD exacerbation

End point description:

Time-to-event variables will be analyzed by the Kaplan-Meier estimates and the stratified Cox proportional hazard model by smoking status and COPD severity. The model will include treatment and country as factors, and FEV1 prior to inhalation and FEV1 15 min post inhalation of salbutamol/albuterol as covariates.

End point type	Secondary

End point timeframe:

12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316[1]	313[2]		
Units: Days				

median (inter-quartile range (Q1-Q3))	9999.9 (-99999.9 to 99999.9)	9999.9 (-99999.9 to 99999.9)		

Notes:

[1] - number of observations is too small to project time to event

[2] - number of observations is too small to project time to event

Statistical analyses

No statistical analyses for this end point

Secondary: The percentage of patients who permanently discontinued due to COPD exacerbation

End point title	The percentage of patients who permanently discontinued due to COPD exacerbation

End point description:

Time-to-event variables will be analyzed by the Kaplan-Meier estimates and the stratified Cox proportional hazard model by smoking status and COPD severity. The model will include treatment and country as factors, and FEV1 prior to inhalation and FEV1 15 min post inhalation of salbutamol/albuterol as covariates.

End point type	Secondary

End point timeframe:

12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: Percentage participants				
number (not applicable)	0.6	1.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Total amount (in doses) of systemic corticosteroid used to treat COPD exacerbation during the 12 week treatment period

End point title	Total amount (in doses) of systemic corticosteroid used to treat COPD exacerbation during the 12 week treatment period

End point description:

Total amount (in doses) of systemic corticosteroid used to treat COPD exacerbation will be summarized descriptively by treatment group per each systemic corticosteroid.

End point type	Secondary

End point timeframe:

12 weeks

End point values	QMF149	Salmeterol xinafoate/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	313		
Units: (Prednisolone dose equivalents) mg				
arithmetic mean (standard deviation)				
IM Hydrocortisone (mg) (n=1,0)	100 (± 0)	0 (± 0)		
IV dexamethasone (mg) (n=0,1)	0 (± 0)	4 (± 0)		
IV Hydrocortisone (mg) (n=0,1)	0 (± 0)	100 (± 0)		
IV Hydrocortisone sodium succinate (mg) (n=2,0)	400 (± 282.843)	0 (± 0)		
IV methylprenisolone sodium succinate(mg)(n=1,0)	250 (± 0)	0 (± 0)		
IV methylprenisolone sodium succinate(ug)(n=0,1)	0 (± 0)	80 (± 0)		
IV prednisolone (mg) (n=0,1)	0 (± 0)	250 (± 0)		
Oral Budesonide (mg) (n=0,1)	0 (± 0)	20 (± 0)		
Oral methylprenisolone (mg) (n=7,13)	16.57 (± 11.414)	20.31 (± 9.586)		
Oral prednisolone (mg) (n=8,28)	24.38 (± 9.52)	23.93 (± 13.06)		
Oral prednisone (mg) (n=8,16)	31.25 (± 11.26)	25.31 (± 11.176)		
Oral prednisone (ug) (n=0,1)	0 (± 0)	10 (± 0)		
Inhalation budesonide (mL)(n=0,1)	0 (± 0)	0.5 (± 0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	SALM/FLUT
Reporting group description:	
SALM/FLUT	
Reporting group title	QMF149
Reporting group description:	
QMF149	

Serious adverse events	SALM/FLUT	QMF149	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 313 (6.07%)	10 / 316 (3.16%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
ELECTROCARDIOGRAM T WAVE INVERSION			
subjects affected / exposed	2 / 313 (0.64%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PLEURAL MESOTHELIOMA MALIGNANT			
subjects affected / exposed	1 / 313 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
UPPER LIMB FRACTURE			

subjects affected / exposed	1 / 313 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	2 / 313 (0.64%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 313 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
INTRACRANIAL ANEURYSM			
subjects affected / exposed	1 / 313 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TEMPORAL LOBE EPILEPSY			
subjects affected / exposed	1 / 313 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TENSION HEADACHE			
subjects affected / exposed	1 / 313 (0.32%)	0 / 316 (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			
MALAISE			
subjects affected / exposed	0 / 313 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
COLITIS			

subjects affected / exposed	1 / 313 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	1 / 313 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 313 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER HAEMORRHAGE			
subjects affected / exposed	1 / 313 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOCHEZIA			
subjects affected / exposed	0 / 313 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 313 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	1 / 313 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ATELECTASIS			
subjects affected / exposed	1 / 313 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	5 / 313 (1.60%)	6 / 316 (1.90%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
COUGH			
subjects affected / exposed	0 / 313 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	1 / 313 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
OSTEOARTHRITIS			
subjects affected / exposed	0 / 313 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
LOBAR PNEUMONIA			
subjects affected / exposed	1 / 313 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCISION SITE INFECTION			
subjects affected / exposed	0 / 313 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	0 / 313 (0.00%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	0 / 313 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPUTUM PURULENT			
subjects affected / exposed	0 / 313 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	SALM/FLUT	QMF149	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 313 (13.74%)	19 / 316 (6.01%)	
Respiratory, thoracic and mediastinal disorders			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	43 / 313 (13.74%)	19 / 316 (6.01%)	
occurrences (all)	49	21	

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

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: