Clinical trial results:
A Multi-center, Randomized, 52 Week Treatment, Double-blind, Triple-dummy, Parallel Group Study to Assess the Efficacy and Safety of QMF149 Compared to Mometasone Furoate in Patients With Asthma

Summary

EudraCT number	2015-002529-21
Trial protocol	GB EE LV DE LT HU CZ SK IE PL BG HR
Global end of trial date	28 June 2019

Results information

Result version number	v1 (current)
This version publication date	05 January 2020
First version publication date	05 January 2020

Trial information

Trial identification

Sponsor protocol code	CQVM149B2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02554786
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 Pharmaceuticals AG, +44 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals AG, +44 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000104-PIP20-16
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	28 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of either QMF149 150/160 µg delivered via Concept1 once daily (o.d.) (in the evening) to mometasone furoate (MF) 400 µg o.d (in the evening) delivered via Twisthaler® or QMF149 150/320 µg delivered via Concept1 o.d. (in the evening) to MF 800 µg delivered via Twisthaler® (delivered as 400 µg twice a day [b.i.d.]) in terms of trough forced expiratory volume in one second (trough FEV1) at 26 weeks in subjects with asthma.

Protection of trial subjects:

This study was conducted in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

Background therapy:

Fluticasone propionate received by all subjects during 2 weeks of Run-In Epoch until randomisation.

Evidence for comparator: -

Actual start date of recruitment	29 December 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 337
Country: Number of subjects enrolled	Serbia: 135
Country: Number of subjects enrolled	India: 203
Country: Number of subjects enrolled	Japan: 118
Country: Number of subjects enrolled	China: 127
Country: Number of subjects enrolled	Guatemala: 65
Country: Number of subjects enrolled	Mexico: 18
Country: Number of subjects enrolled	South Africa: 71
Country: Number of subjects enrolled	United States: 37
Country: Number of subjects enrolled	Egypt: 10
Country: Number of subjects enrolled	Korea, Republic of: 37
Country: Number of subjects enrolled	Poland: 111
Country: Number of subjects enrolled	Romania: 151
Country: Number of subjects enrolled	Slovakia: 101
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Croatia: 11
Country: Number of subjects enrolled	Bulgaria: 157
Country: Number of subjects enrolled	Czech Republic: 82

Country: Number of subjects enrolled	Estonia: 14
Country: Number of subjects enrolled	Germany: 197
Country: Number of subjects enrolled	Hungary: 170
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Latvia: 31
Country: Number of subjects enrolled	Lithuania: 19
Worldwide total number of subjects	2216
EEA total number of subjects	1058

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)	107
Adults (18-64 years)	1812
From 65 to 84 years	297
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in 316 investigative sites in 24 countries from 29 Dec 2015 to 28 Jun 2019.

Pre-assignment

Screening details:

3890 subjects were screened of which 2216 were randomised to 1 of the 5 treatment groups with a randomisation ratio of 1:1:1:1:1.

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, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	QMF149 150/320 µg

Arm description:

QMF149 (Indacaterol acetate/Mometasone furoate) 150/320 µg was delivered o.d. via Concept1 inhaler in the evening.

Arm type	Experimental
Investigational medicinal product name	Indacaterol acetate/Mometasone furoate
Investigational medicinal product code	
Other name	QMF149
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

150/320 µg, o.d. via Concept1 inhaler in the evening.

Arm title	QMF149 150/160 µg

Arm description:

QMF149 (Indacaterol acetate/Mometasone furoate) 150/160 µg was delivered o.d. via Concept1 inhaler in the evening.

Arm type	Experimental
Investigational medicinal product name	Indacaterol acetate/Mometasone furoate
Investigational medicinal product code	
Other name	QMF149
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

150/160 µg, o.d. via Concept1 inhaler in the evening.

Arm title	MF 800 µg

Arm description:

MF 800 µg of total daily dose (400 µg twice daily, in the morning and in the evening) was delivered via Twisthaler®.

Arm type	Active comparator

Investigational medicinal product name	Mometasone furoate
Investigational medicinal product code	
Other name	MF
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

400 µg twice daily, in the morning and in the evening via Twisthaler®.

Arm title	MF 400 µg

Arm description:

MF 400 µg was delivered o.d. via Twisthaler® in the evening.

Arm type	Active comparator
Investigational medicinal product name	Mometasone furoate
Investigational medicinal product code	
Other name	MF
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

MF 400 µg, o.d. via Twisthaler® in the evening.

Arm title	Salmeterol /fluticasone 50/500 µg

Arm description:

Salmeterol xinafoate/fluticasone propionate 50/500 µg was delivered twice daily (in the morning and in the evening) via Accuhaler®.

Arm type	Active comparator
Investigational medicinal product name	Salmeterol/fluticasone
Investigational medicinal product code	
Other name	Seretide
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

50/500 µg, twice daily in the morning and in the evening via Accuhaler®.

Number of subjects in period 1	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg
Started	445	439	442
Completed	410	413	412
Not completed	35	26	30
Physician decision	-	1	4
Technical problems	1	1	-
Adverse event, non-fatal	-	-	-
Death	-	-	-
Non-compliance with study treatment	-	1	1
Pregnancy	-	-	-
Lost to follow-up	4	3	4
Subject/guardian decision	29	17	18
Protocol deviation	1	3	3

Number of subjects in period 1	MF 400 µg	Salmeterol /fluticasone 50/500 µg
Started	444	446
Completed	403	416
Not completed	41	30
Physician decision	1	1
Technical problems	2	2
Adverse event, non-fatal	-	2
Death	1	-
Non-compliance with study treatment	-	1
Pregnancy	1	-
Lost to follow-up	2	2
Subject/guardian decision	30	20
Protocol deviation	4	2

Baseline characteristics

Reporting groups	
Reporting group title	QMF149 150/320 µg
Reporting group description:	
QMF149 (Indacaterol acetate/Mometasone furoate) 150/320 µg was delivered o.d. via Concept1 inhaler in the evening.	
Reporting group title	QMF149 150/160 µg
Reporting group description:	
QMF149 (Indacaterol acetate/Mometasone furoate) 150/160 µg was delivered o.d. via Concept1 inhaler in the evening.	

Reporting group title	MF 800 µg
Reporting group description:	
MF 800 µg of total daily dose (400 µg twice daily, in the morning and in the evening) was delivered via Twisthaler®.	
Reporting group title	MF 400 µg
Reporting group description:	
MF 400 µg was delivered o.d. via Twisthaler® in the evening.	
Reporting group title	Salmeterol /fluticasone 50/500 µg
Reporting group description:	
Salmeterol xinafoate/fluticasone propionate 50/500 µg was delivered twice daily (in the morning and in the evening) via Accuhaler®.	

Reporting group values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg
Number of subjects	445	439	442
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	22	20	21
Adults (18-64 years)	369	355	369
From 65-84 years	54	64	52
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	47.1	47.4	47.5
standard deviation	± 14.56	± 14.76	± 14.99
Gender categorical Units: Subjects			
Female	262	253	250
Male	183	186	192

Reporting group values	MF 400 µg	Salmeterol /fluticasone 50/500 µg	Total

Number of subjects	444	446	2216
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	22	22	107
Adults (18-64 years)	354	365	1812
From 65-84 years	68	59	297
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	48.7	48.9	
standard deviation	± 14.98	± 14.59	-
Gender categorical Units: Subjects			
Female	272	256	1293
Male	172	190	923

End points

End points reporting groups

Reporting group title	QMF149 150/320 µg
Reporting group description:	
QMF149 (Indacaterol acetate/Mometasone furoate) 150/320 µg was delivered o.d. via Concept1 inhaler in the evening.	

Reporting group title	QMF149 150/160 µg
Reporting group description:	
QMF149 (Indacaterol acetate/Mometasone furoate) 150/160 µg was delivered o.d. via Concept1 inhaler in the evening.	

Reporting group title	MF 800 µg
Reporting group description:	
MF 800 µg of total daily dose (400 µg twice daily, in the morning and in the evening) was delivered via Twisthaler®.	

Reporting group title	MF 400 µg
Reporting group description:	
MF 400 µg was delivered o.d. via Twisthaler® in the evening.	

Reporting group title	Salmeterol /fluticasone 50/500 µg
Reporting group description:	
Salmeterol xinafoate/fluticasone propionate 50/500 µg was delivered twice daily (in the morning and in the evening) via Accuhaler®.	

Primary: Trough Forced Expiratory Volume in One Second (Trough FEV1) at Week 26

End point title	Trough Forced Expiratory Volume in One Second (Trough FEV1) at Week 26[1]
End point description:	
Trough FEV1 was assessed by performing spirometric assessment. It is defined as average of the two FEV1 measurements taken 23 hr 15 min and 23 hr 45 min post-evening dose. FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing. Full Analysis Set (FAS) consisted of all subjects in the randomised (RAN) set who received at least one dose of study medication.	
End point type	Primary
End point timeframe:	
Week 26 (Day 184)	
Notes:	
[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The arm groups QMF149 150/320 µg, QMF149 150/160 µg, MF 800 µg and MF 400 µg were planned to be reported for this endpoint.	

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	395[2]	389[3]	372[4]	376[5]
Units: litre(s)				
least squares mean (standard error)	2.383 (± 0.0159)	2.387 (± 0.0160)	2.250 (± 0.0162)	2.176 (± 0.0162)

Notes:
[2] - Subjects analysed is number of subjects with data available for this endpoint point.
[3] - Subjects analysed is number of subjects with data available for this endpoint point.
[4] - Subjects analysed is number of subjects with data available for this endpoint point.
[5] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	767
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Least Squares mean (LS Mean)
Point estimate	0.132
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.088
upper limit	0.176
Variability estimate	Standard error of the mean
Dispersion value	0.0223

Statistical analysis title	QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	765
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.211
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.167
upper limit	0.255
Variability estimate	Standard error of the mean
Dispersion value	0.0224

Secondary: Asthma Control Questionnaire (ACQ-7) at Week 26

End point title	Asthma Control Questionnaire (ACQ-7) at Week 26[6]

End point description:
The ACQ-7 measured asthma symptom control and consisted of 7 items: 5 on symptom assessment, 1

on rescue bronchodilator use and 1 on airway calibre (FEV1 % predicted). All 7 questions of the ACQ-7 were equally weighted. Items 1-5 were scored along a 7-point response scale, where 0 = totally controlled and 6 = severely uncontrolled. Item 6 is scored between 0 = no rescue medication and 6 = More than 16 puffs/inhalations most days. The 7th item was scored by the investigator based on the FEV1 % predicted from the masterscope at the site (i.e., Score = 0 means > 95% of predicted FEV1, 1 = 90 – 95%, 2 = 80 – 89%, 3 = 70 – 79%, 4 = 60 – 69%, 5 = 50 – 59%, and Score = 6 means < 50% of predicted FEV1). The total score was calculated as the mean of all questions. FAS consisted of all subjects in the RAN set who received at least one dose of study.

End point type	Secondary

End point timeframe:

Week 26

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arm groups QMF149 150/320 µg, QMF149 150/160 µg, MF 800 µg and MF 400 µg were planned to be reported for this endpoint.

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	407[7]	407[8]	405[9]	393[10]
Units: score on a scale				
least squares mean (standard error)	1.267 (± 0.0350)	1.261 (± 0.0350)	1.439 (± 0.0352)	1.509 (± 0.0354)

Notes:

[7] - Subjects analysed is number of subjects with data available for this endpoint point.

[8] - Subjects analysed is number of subjects with data available for this endpoint point.

[9] - Subjects analysed is number of subjects with data available for this endpoint point.

[10] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	QMF149 vs MF

Statistical analysis description:

The comparison of QMF149 vs. MF was based on combined effects of QMF mid QMF high v Mf mid MF high.

Comparison groups	QMF149 150/160 µg v MF 400 µg v MF 800 µg v QMF149 150/320 µg
Number of subjects included in analysis	1612
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.209
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	-0.149
Variability estimate	Standard error of the mean
Dispersion value	0.031

Secondary: Trough FEV1 at Week 52

End point title	Trough FEV1 at Week 52

End point description:

Trough FEV1 was assessed by performing spirometric assessment. It is defined as average of the two FEV1 measurements taken 23 hr 15 min and 23 hr 45 min post-evening dose. FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Week 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	372[11]	383[12]	364[13]	369[14]
Units: litre(s)				
least squares mean (standard error)	2.386 (± 0.0168)	2.357 (± 0.0167)	2.249 (± 0.0170)	2.148 (± 0.0170)

Notes:

[11] - Subjects analysed is number of subjects with data available for this endpoint point.

[12] - Subjects analysed is number of subjects with data available for this endpoint point.

[13] - Subjects analysed is number of subjects with data available for this endpoint point.

[14] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	382[15]			
Units: litre(s)				
least squares mean (standard error)	2.338 (± 0.0167)			

Notes:

[15] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	736
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.136

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.183
Variability estimate	Standard error of the mean
Dispersion value	0.0235

Statistical analysis title	QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	752
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.209
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.163
upper limit	0.255
Variability estimate	Standard error of the mean
Dispersion value	0.0235

Statistical analysis title	QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	754
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.002
upper limit	0.094
Variability estimate	Standard error of the mean
Dispersion value	0.0234

Secondary: Pre-dose FEV1 at Weeks 4 and 12	
End point title	Pre-dose FEV1 at Weeks 4 and 12

End point description:

Pre-dose trough FEV1 is defined as average of the two FEV1 measurements taken 45 min and 15 min pre evening dose. It was assessed by performing spirometric assessment. FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Weeks 4 (Day 30) and 12 (Day 86)

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	430[16]	427[17]	430[18]	427[19]
Units: litre(s)				
least squares mean (standard error)				
Day 30 (n=430, 424, 421, 412, 435)	2.369 (± 0.0141)	2.367 (± 0.0142)	2.237 (± 0.0143)	2.171 (± 0.0143)
Day 86 (n=414, 414, 419, 398, 428)	2.368 (± 0.0148)	2.361 (± 0.0148)	2.245 (± 0.0148)	2.177 (± 0.0149)

Notes:

[16] - n represents number of subjects analysed at the given time point.

[17] - n represents number of subjects analysed at the given time point.

[18] - n represents number of subjects analysed at the given time point.

[19] - n represents number of subjects analysed at the given time point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	439[20]			
Units: litre(s)				
least squares mean (standard error)				
Day 30 (n=430, 424, 421, 412, 435)	2.333 (± 0.0141)			
Day 86 (n=414, 414, 419, 398, 428)	2.330 (± 0.0146)			

Notes:

[20] - n represents number of subjects analysed at the given time point.

Statistical analyses

Statistical analysis title	Day 30: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	860
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.132

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.094
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.0193

Statistical analysis title	Day 30: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	854
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.196
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.158
upper limit	0.234
Variability estimate	Standard error of the mean
Dispersion value	0.0194

Statistical analysis title	Day 30: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	Salmeterol /fluticasone 50/500 µg v QMF149 150/320 µg
Number of subjects included in analysis	869
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.0192
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.073
Variability estimate	Standard error of the mean
Dispersion value	0.0192

Statistical analysis title	Day 86: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg

Number of subjects included in analysis	860
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.083
upper limit	0.162
Variability estimate	Standard error of the mean
Dispersion value	0.0201

Statistical analysis title	Day 86: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	854
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.184
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.144
upper limit	0.224
Variability estimate	Standard error of the mean
Dispersion value	0.0202

Statistical analysis title	Day 86: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	869
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.076

Variability estimate	Standard error of the mean
Dispersion value	0.02

Secondary: Post Dose FEV1 (5 Minutes-1 Hour)

End point title	Post Dose FEV1 (5 Minutes-1 Hour)

End point description:

Post-dose FEV1 measurements were analyzed at 5 minutes, 15 minutes, 30 minutes and 1 hour. FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 52 (Day 364)

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	441[21]	434[22]	438[23]	438[24]
Units: litre(s)				
least squares mean (standard error)				
Day 1: 5 minutes (n=427,426,429,432,435)	2.279 (± 0.0084)	2.270 (± 0.0085)	2.138 (± 0.0085)	2.118 (± 0.0084)
Day 1: 15 minutes (n=434,425,433,433,441)	2.321 (± 0.0088)	2.312 (± 0.0089)	2.159 (± 0.0089)	2.137 (± 0.0089)
Day 1: 30 minutes (n=439,431,434,438,441)	2.338 (± 0.0095)	2.326 (± 0.0096)	2.162 (± 0.0096)	2.141 (± 0.0095)
Day 1: 1 hour (n=440,434,435,438,442)	2.343 (± 0.0100)	2.347 (± 0.0101)	2.166 (± 0.0101)	2.142 (± 0.0100)
Day 30: 5 minutes (n=428,420,419,411,435)	2.413 (± 0.0142)	2.406 (± 0.0144)	2.224 (± 0.0145)	2.174 (± 0.0145)
Day 30: 30 minutes(n=429,420,421,412,435)	2.432 (± 0.0143)	2.426 (± 0.0145)	2.238 (± 0.0146)	2.174 (± 0.0146)
Day 30: 1 hour (n=428,416,421,410,435)	2.448 (± 0.0145)	2.440 (± 0.0146)	2.257 (± 0.0147)	2.183 (± 0.0148)
Day 86:5 minutes (n=411,411,416,395,427)	2.411 (± 0.0150)	2.409 (± 0.0150)	2.248 (± 0.0150)	2.178 (± 0.0153)
Day 86: 30 minutes (n=412,411,417,395,426)	2.436 (± 0.0149)	2.431 (± 0.0149)	2.257 (± 0.0149)	2.179 (± 0.0152)
Day 86:1 hour (n=412,410,417,396,426)	2.456 (± 0.0151)	2.436 (± 0.0151)	2.269 (± 0.0151)	2.188 (± 0.0154)
Day 183: 5 minutes (n=404,399,400,385,409)	2.403 (± 0.0160)	2.406 (± 0.0161)	2.240 (± 0.0162)	2.163 (± 0.0164)
Day 183: 30 minutes (n=405,401,399,383,407)	2.426 (± 0.0163)	2.427 (± 0.0164)	2.250 (± 0.0165)	2.168 (± 0.0167)
Day 183: 1 hour (n=405,400,397,385,409)	2.432 (± 0.0161)	2.423 (± 0.0162)	2.253 (± 0.0163)	2.165 (± 0.0165)
Day 364: 5 minutes (n=375,389,380,374,403)	2.384 (± 0.0172)	2.379 (± 0.0169)	2.245 (± 0.0172)	2.130 (± 0.0173)
Day 364: 30 minutes (n=377,393,379,373,401)	2.408 (± 0.0171)	2.399 (± 0.0169)	2.253 (± 0.0172)	2.135 (± 0.0172)
Day 364:1 hour (n=378,393,379,375,402)	2.414 (± 0.0175)	2.390 (± 0.0172)	2.251 (± 0.0175)	2.128 (± 0.0176)

Notes:

[21] - n represents number of subjects analysed at the given time point.

[22] - n represents number of subjects analysed at the given time point.

[23] - n represents number of subjects analysed at the given time point.

[24] - n represents number of subjects analysed at the given time point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	442[25]			
Units: litre(s)				
least squares mean (standard error)				
Day 1: 5 minutes (n=427,426,429,432,435)	2.224 (± 0.0084)			
Day 1: 15 minutes (n=434,425,433,433,441)	2.278 (± 0.0088)			
Day 1: 30 minutes (n=439,431,434,438,441)	2.310 (± 0.0095)			
Day 1: 1 hour (n=440,434,435,438,442)	2.337 (± 0.0100)			
Day 30: 5 minutes (n=428,420,419,411,435)	2.360 (± 0.0142)			
Day 30: 30 minutes(n=429,420,421,412,435)	2.389 (± 0.0143)			
Day 30: 1 hour (n=428,416,421,410,435)	2.411 (± 0.0144)			
Day 86:5 minutes (n=411,411,416,395,427)	2.356 (± 0.0148)			
Day 86: 30 minutes (n=412,411,417,395,426)	2.398 (± 0.0147)			
Day 86:1 hour (n=412,410,417,396,426)	2.413 (± 0.0149)			
Day 183: 5 minutes (n=404,399,400,385,409)	2.359 (± 0.0160)			
Day 183: 30 minutes (n=405,401,399,383,407)	2.386 (± 0.0163)			
Day 183: 1 hour (n=405,400,397,385,409)	2.393 (± 0.0161)			
Day 364: 5 minutes (n=375,389,380,374,403)	2.358 (± 0.0168)			
Day 364: 30 minutes (n=377,393,379,373,401)	2.377 (± 0.0167)			
Day 364:1 hour (n=378,393,379,375,402)	2.383 (± 0.0171)			

Notes:

[25] - n represents number of subjects analysed at the given time point.

Statistical analyses

Statistical analysis title	Day 1: 5 minutes QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg

Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.142
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.119
upper limit	0.164
Variability estimate	Standard error of the mean
Dispersion value	0.0116

Statistical analysis title	Day 1: 5 minutes QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.152
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.129
upper limit	0.175
Variability estimate	Standard error of the mean
Dispersion value	0.0116

Statistical analysis title	Day 1:5 minutes QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.032
upper limit	0.078

Variability estimate	Standard error of the mean
Dispersion value	0.0116

Statistical analysis title	Day 1: 15 minutes QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.162
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.138
upper limit	0.186
Variability estimate	Standard error of the mean
Dispersion value	0.0122

Statistical analysis title	Day 1: 15 minutes QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.174
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.198
Variability estimate	Standard error of the mean
Dispersion value	0.0123

Statistical analysis title	Day 1:15 minutes QMF149 150/320 µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg

Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.044
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.068
Variability estimate	Standard error of the mean
Dispersion value	0.0122

Statistical analysis title	Day 1: 30 minutes QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.175
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.149
upper limit	0.201
Variability estimate	Standard error of the mean
Dispersion value	0.0132

Statistical analysis title	Day 1: 30 minutes QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.185
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.159
upper limit	0.211

Variability estimate	Standard error of the mean
Dispersion value	0.0132

Statistical analysis title	Day 1:30 minutes QMF149 150/320µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.053
Variability estimate	Standard error of the mean
Dispersion value	0.0132

Statistical analysis title	Day 1: 1 hour QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.178
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.205
Variability estimate	Standard error of the mean
Dispersion value	0.0139

Statistical analysis title	Day 1: 1 hour QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg

Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.205
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.177
upper limit	0.232
Variability estimate	Standard error of the mean
Dispersion value	0.0139

Statistical analysis title	Day 1: 1 hour QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.632
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.021
upper limit	0.034
Variability estimate	Standard error of the mean
Dispersion value	0.0139

Statistical analysis title	Day 30: 5 minutes QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.189
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.151
upper limit	0.226

Variability estimate	Standard error of the mean
Dispersion value	0.0192

Statistical analysis title	Day 30: 5 minutes QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.232
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.194
upper limit	0.27
Variability estimate	Standard error of the mean
Dispersion value	0.0194

Statistical analysis title	Day 30:5 minutes QMF149 150/320 µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.091
Variability estimate	Standard error of the mean
Dispersion value	0.0191

Statistical analysis title	Day 30: 30 minutes QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg

Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean
Point estimate	0.194
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.156
upper limit	0.232
Variability estimate	Standard error of the mean
Dispersion value	0.0194

Statistical analysis title	Day 30: 30 minutes QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.253
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.214
upper limit	0.291
Variability estimate	Standard error of the mean
Dispersion value	0.0196

Statistical analysis title	Day 30:30 minutes QMF149 150/320µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.005
upper limit	0.08

Variability estimate	Standard error of the mean
Dispersion value	0.0192

Statistical analysis title	Day 30: 1 hour QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.152
upper limit	0.229
Variability estimate	Standard error of the mean
Dispersion value	0.0196

Statistical analysis title	Day 30: 1 hour QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.258
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.219
upper limit	0.296
Variability estimate	Standard error of the mean
Dispersion value	0.0198

Statistical analysis title	Day 30: 1 hour QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg

Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.075
Variability estimate	Standard error of the mean
Dispersion value	0.0194

Statistical analysis title	Day 86: 5 minutes QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.163
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.123
upper limit	0.203
Variability estimate	Standard error of the mean
Dispersion value	0.0204

Statistical analysis title	Day 86: 5 minutes QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.231
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.191
upper limit	0.271

Variability estimate	Standard error of the mean
Dispersion value	0.0206

Statistical analysis title	Day 86: 5 minutes QMF149 150/320µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	0.095
Variability estimate	Standard error of the mean
Dispersion value	0.0203

Statistical analysis title	Day 86: 30 minutes QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.219
Variability estimate	Standard error of the mean
Dispersion value	0.0203

Statistical analysis title	Day 86: 30 minutes QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg

Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.252
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.211
upper limit	0.292
Variability estimate	Standard error of the mean
Dispersion value	0.0205

Statistical analysis title	Day 86:30 minutes QMF149 150/320µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.057
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.078
Variability estimate	Standard error of the mean
Dispersion value	0.0202

Statistical analysis title	Day 86: 1 hour QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.187
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.147
upper limit	0.227

Variability estimate	Standard error of the mean
Dispersion value	0.0205

Statistical analysis title	Day 86: 1 hour QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.249
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.208
upper limit	0.289
Variability estimate	Standard error of the mean
Dispersion value	0.0208

Statistical analysis title	Day 86: 1 hour QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.003
upper limit	0.083
Variability estimate	Standard error of the mean
Dispersion value	0.0205

Statistical analysis title	Day 183: 5 minutes QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg

Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.163
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.121
upper limit	0.206
Variability estimate	Standard error of the mean
Dispersion value	0.0217

Statistical analysis title	Day 183: 5 minutes QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.243
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.286
Variability estimate	Standard error of the mean
Dispersion value	0.0219

Statistical analysis title	Day 183:5 minutes QMF149 150/320µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.044
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.002
upper limit	0.087

Variability estimate	Standard error of the mean
Dispersion value	0.0216

Statistical analysis title	Day 183: 30 minutes QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.176
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.133
upper limit	0.22
Variability estimate	Standard error of the mean
Dispersion value	0.0222

Statistical analysis title	Day 183: 30 minutes QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.259
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.215
upper limit	0.303
Variability estimate	Standard error of the mean
Dispersion value	0.0224

Statistical analysis title	Day 183:30minutes QMF149 150/320µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg

Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	0.083
Variability estimate	Standard error of the mean
Dispersion value	0.0221

Statistical analysis title	Day 183: 1 hour QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.137
upper limit	0.223
Variability estimate	Standard error of the mean
Dispersion value	0.0219

Statistical analysis title	Day 183: 1 hour QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.259
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.215
upper limit	0.302

Variability estimate	Standard error of the mean
Dispersion value	0.0222

Statistical analysis title	Day 183: 1 hour QMF149 150/320µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	0.082
Variability estimate	Standard error of the mean
Dispersion value	0.0218

Statistical analysis title	Day 364: 5 minutes QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.139
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.094
upper limit	0.184
Variability estimate	Standard error of the mean
Dispersion value	0.0229

Statistical analysis title	Day 364: 5 minutes QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg

Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.249
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.205
upper limit	0.294
Variability estimate	Standard error of the mean
Dispersion value	0.0228

Statistical analysis title	Day 364:5 minutes QMF149 150/320µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.244
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.071
Variability estimate	Standard error of the mean
Dispersion value	0.0227

Statistical analysis title	Day 364: 30 minutes QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.155
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.2

Variability estimate	Standard error of the mean
Dispersion value	0.0228

Statistical analysis title	Day 364: 30 minutes QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.264
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.219
upper limit	0.308
Variability estimate	Standard error of the mean
Dispersion value	0.0227

Statistical analysis title	Day 364:30minutes QMF149 150/320µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.162
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.013
upper limit	0.076
Variability estimate	Standard error of the mean
Dispersion value	0.0226

Statistical analysis title	Day 364: 1 hour QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg

Number of subjects included in analysis	879
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.163
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.117
upper limit	0.209
Variability estimate	Standard error of the mean
Dispersion value	0.0234

Statistical analysis title	Day 364: 1 hour QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.262
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.216
upper limit	0.308
Variability estimate	Standard error of the mean
Dispersion value	0.0232

Statistical analysis title	Day 364: 1 hour QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.182
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.031
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.076

Variability estimate	Standard error of the mean
Dispersion value	0.0231

Secondary: Trough Forced Vital Capacity (FVC)

End point title	Trough Forced Vital Capacity (FVC)

End point description:

FVC is the total amount of air exhaled during the FEV test. Trough FVC is defined as average of the two FVC measurements taken 23 hr 15 min and 23 hr 45 min post-evening dose. It was assessed by performing spirometric assessment. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 52 (Day 365)

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	439[26]	433[27]	436[28]	441[29]
Units: litre(s)				
least squares mean (standard error)				
Day 2 (n=432,430,410,435,419)	3.342 (± 0.0173)	3.342 (± 0.0174)	3.256 (± 0.0177)	3.203 (± 0.0173)
Day 184 (n=395,389,372,376,391)	3.372 (± 0.0179)	3.387 (± 0.0180)	3.322 (± 0.0183)	3.246 (± 0.0182)
Day 365 (n=372,383,365,369,382)	3.394 (± 0.0182)	3.364 (± 0.0181)	3.319 (± 0.0184)	3.218 (± 0.0183)

Notes:

[26] - n represents number of subjects analysed at the given time point.

[27] - n represents number of subjects analysed at the given time point.

[28] - n represents number of subjects analysed at the given time point.

[29] - n represents number of subjects analysed at the given time point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	441[30]			
Units: litre(s)				
least squares mean (standard error)				
Day 2 (n=432,430,410,435,419)	3.344 (± 0.0176)			
Day 184 (n=395,389,372,376,391)	3.355 (± 0.0180)			
Day 365 (n=372,383,365,369,382)	3.358 (± 0.0182)			

Notes:
[30] - n represents number of subjects analysed at the given time point.

Statistical analyses

Statistical analysis title	Day 2: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	875
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.086
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.133
Variability estimate	Standard error of the mean
Dispersion value	0.0237

Statistical analysis title	Day 2: QMF149 150/160 µg vs MF 400 µg
Comparison groups	MF 400 µg v QMF149 150/160 µg
Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.139
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.093
upper limit	0.185
Variability estimate	Standard error of the mean
Dispersion value	0.0235

Statistical analysis title	Day 2: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg

Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.927
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.049
upper limit	0.044
Variability estimate	Standard error of the mean
Dispersion value	0.0237

Statistical analysis title	Day 184: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	875
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.098
Variability estimate	Standard error of the mean
Dispersion value	0.0246

Statistical analysis title	Day 184: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.141
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.093
upper limit	0.19

Variability estimate	Standard error of the mean
Dispersion value	0.0246

Statistical analysis title	Day 184: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.031
upper limit	0.065
Variability estimate	Standard error of the mean
Dispersion value	0.0244

Statistical analysis title	Day 365: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	875
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.027
upper limit	0.125
Variability estimate	Standard error of the mean
Dispersion value	0.0249

Statistical analysis title	Day 365: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg

Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.146
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.098
upper limit	0.195
Variability estimate	Standard error of the mean
Dispersion value	0.0248

Statistical analysis title	Day 365: QMF149 150/320µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.143
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.012
upper limit	0.085
Variability estimate	Standard error of the mean
Dispersion value	0.0248

Secondary: Trough Forced Expiratory Flow (FEF)Between 25% and 75% of FVC (FEF25-75)

End point title	Trough Forced Expiratory Flow (FEF)Between 25% and 75% of FVC (FEF25-75)

End point description:

FEF is the flow (or speed) of air coming out of the lung during the middle portion of a forced expiration. Trough FEF25-75% is defined as average of the two FEF25-75% measurements taken 23 hr 15 min and 23 hr 45 min post-evening dose. It was assessed by performing spirometric assessment. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 52 (Day 365)

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	439[31]	433[32]	436[33]	441[34]
Units: Liters/second(L/s)				
least squares mean (standard error)				
Day 2: (n=432,430,410,435,419)	1.644 (± 0.0186)	1.617 (± 0.0187)	1.455 (± 0.0191)	1.406 (± 0.0186)
Day 184: (n=395,389,372,376,391)	1.775 (± 0.0249)	1.738 (± 0.0250)	1.546 (± 0.0253)	1.473 (± 0.0254)
Day 365: (372,383,365,369,382)	1.745 (± 0.0259)	1.686 (± 0.0257)	1.530 (± 0.0261)	1.440 (± 0.0261)

Notes:

[31] - n represents number of subjects analysed at the given time point.

[32] - n represents number of subjects analysed at the given time point.

[33] - n represents number of subjects analysed at the given time point.

[34] - n represents number of subjects analysed at the given time point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	441[35]			
Units: Liters/second(L/s)				
least squares mean (standard error)				
Day 2: (n=432,430,410,435,419)	1.662 (± 0.0189)			
Day 184: (n=395,389,372,376,391)	1.692 (± 0.0250)			
Day 365: (372,383,365,369,382)	1.692 (± 0.0258)			

Notes:

[35] - n represents number of subjects analysed at the given time point.

Statistical analyses

Statistical analysis title	Day 2: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	875
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.189
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.139
upper limit	0.238
Variability estimate	Standard error of the mean
Dispersion value	0.0253

Statistical analysis title	Day 2: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.161
upper limit	0.259
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Day 2: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.475
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.067
upper limit	0.031
Variability estimate	Standard error of the mean
Dispersion value	0.0252

Statistical analysis title	Day 184: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	875
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.228

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.161
upper limit	0.296
Variability estimate	Standard error of the mean
Dispersion value	0.0345

Statistical analysis title	Day 184: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.265
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.197
upper limit	0.333
Variability estimate	Standard error of the mean
Dispersion value	0.0346

Statistical analysis title	Day 184: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.151
Variability estimate	Standard error of the mean
Dispersion value	0.0343

Statistical analysis title	Day 365: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg

Number of subjects included in analysis	875
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.215
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.145
upper limit	0.285
Variability estimate	Standard error of the mean
Dispersion value	0.0358

Statistical analysis title	Day 365: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.246
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.176
upper limit	0.316
Variability estimate	Standard error of the mean
Dispersion value	0.0357

Statistical analysis title	Day 365: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.139
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.017
upper limit	0.122

Variability estimate	Standard error of the mean
Dispersion value	0.0356

Secondary: Change From Baseline in Morning and Evening Peak Expiratory Flow Rate (PEF) Over 26 and 52 Weeks of Treatment

End point title	Change From Baseline in Morning and Evening Peak Expiratory Flow Rate (PEF) Over 26 and 52 Weeks of Treatment

End point description:

PEF is a person's maximum speed of expiration. All the subjects were instructed to record PEF twice daily using a mini Peak Flow Meter device, once in the morning (before taking the morning dose) and once approximately 12 h later in the evening (before taking the evening dose). At each time point, the subject was instructed to perform 3 consecutive manoeuvres within 10 minutes. These PEF values were captured in the e-PEF/diary. The best of 3 values were used. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Weeks 26 and 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443[36]	437[37]	440[38]	443[39]
Units: Liters/minute(L/min)				
least squares mean (standard error)				
Week 26: Mean morning PEF(n=418,419,430,422,426)	42.4 (± 2.15)	38.1 (± 2.15)	12.8 (± 2.13)	5.9 (± 2.14)
Week 26:Mean evening PEF(n=417,420,425,419,423)	32.5 (± 2.05)	30.4 (± 2.04)	7.7 (± 2.04)	0.0 (± 2.05)
Week 52:Mean morning PEF(n=415,420,427,422,424)	42.1 (± 2.24)	36.9 (± 2.22)	13.4 (± 2.21)	6.7 (± 2.22)
Week 52:Mean evening PEF(n=416,420,424,418,422)	31.2 (± 2.14)	28.7 (± 2.13)	7.4 (± 2.13)	-0.3 (± 2.14)

Notes:

[36] - n represents number of subjects analysed at the given time point.

[37] - n represents number of subjects analysed at the given time point.

[38] - n represents number of subjects analysed at the given time point.

[39] - n represents number of subjects analysed at the given time point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444[40]			
Units: Liters/minute(L/min)				
least squares mean (standard error)				
Week 26: Mean morning PEF(n=418,419,430,422,426)	29.1 (± 2.14)			
Week 26:Mean evening PEF(n=417,420,425,419,423)	23.9 (± 2.04)			
Week 52:Mean morning PEF(n=415,420,427,422,424)	28.3 (± 2.22)			

Week 52:Mean evening PEF(n=416,420,424,418,422)	22.1 (± 2.13)			

Notes:

[40] - n represents number of subjects analysed at the given time point.

Statistical analyses

Statistical analysis title	Wk 26: Mean morning QMF149 150/320 µg vs MF 800
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Linear Mixed Model (LMM)
Parameter estimate	LS Mean
Point estimate	29.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.8
upper limit	35.4
Variability estimate	Standard error of the mean
Dispersion value	2.96

Statistical analysis title	Wk 26: Mean morning QMF149 150/160 vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	32.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	26.4
upper limit	38.1
Variability estimate	Standard error of the mean
Dispersion value	2.97

Statistical analysis title	Wk 26:Mean morning QMF149 150/320µg v S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg

Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	13.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.5
upper limit	19.1
Variability estimate	Standard error of the mean
Dispersion value	2.97

Statistical analysis title	Wk 26:Mean evening QMF149 150/320µg vs MF 800µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	24.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.3
upper limit	30.3
Variability estimate	Standard error of the mean
Dispersion value	2.82

Statistical analysis title	Wk 26:Mean evening QMF149 150/160µg vs MF 400µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	30.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.8
upper limit	35.9

Variability estimate	Standard error of the mean
Dispersion value	2.83

Statistical analysis title	Wk 26:Mean evening QMF149 150/320µg v S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	LMM
Parameter estimate	LS Mean
Point estimate	8.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.1
upper limit	14.2
Variability estimate	Standard error of the mean
Dispersion value	2.83

Statistical analysis title	Wk 52:Mean morning QMF149 150/320µg vs MF 800µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	28.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.7
upper limit	34.8
Variability estimate	Standard error of the mean
Dispersion value	3.07

Statistical analysis title	Wk 52:Mean morning QMF149 150/160µg vs MF 400µg
Comparison groups	QMF149 150/160 µg v MF 400 µg

Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	30.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.2
upper limit	36.3
Variability estimate	Standard error of the mean
Dispersion value	3.07

Statistical analysis title	Wk 52:Mean morning QMF149 150/320µg v S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	13.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.7
upper limit	19.8
Variability estimate	Standard error of the mean
Dispersion value	3.08

Statistical analysis title	Wk 52:Mean evening QMF149 150/320µg vs MF 800µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	23.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	18
upper limit	29.5

Variability estimate	Standard error of the mean
Dispersion value	2.94

Statistical analysis title	Wk 52: Mean evening QMF149 150/160 vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	29.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.3
upper limit	34.8
Variability estimate	Standard error of the mean
Dispersion value	2.94

Statistical analysis title	Wk 52:Mean evening QMF149 150/320µg v S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	LMM
Parameter estimate	LS Mean
Point estimate	9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	14.9
Variability estimate	Standard error of the mean
Dispersion value	2.95

Secondary: ACQ-7 at Weeks 4, 12 and 52

End point title	ACQ-7 at Weeks 4, 12 and 52

End point description:

The ACQ-7 measured asthma symptom control and consists of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway calibre (FEV1 % predicted). All 7 questions of the ACQ-7 were equally weighted. Items 1-5 were scored along a 7-point response scale, where 0 = totally controlled and 6 = severely uncontrolled. Item 6 is scored between 0 = no rescue medication and 6 = More than 16 puffs/inhalations most days. The 7th item was scored by the investigator based on the

FEV1 % predicted from the masterscope at the site (i.e., Score = 0 means > 95% of predicted FEV1, 1 = 90 – 95%, 2 = 80 – 89%, 3 = 70 – 79%, 4 = 60 – 69%, 5 = 50 – 59%, and Score = 6 means < 50% of predicted FEV1). The total score was calculated as the mean of all questions. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Weeks 4, 12 and 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	429[41]	427[42]	431[43]	428[44]
Units: score on a scale				
least squares mean (standard error)				
Week 4 (n=426,422,429,425,437)	1.486 (± 0.0337)	1.533 (± 0.0338)	1.659 (± 0.0338)	1.730 (± 0.0337)
Week 12 (n=419,414,422,407,429)	1.394 (± 0.0347)	1.377 (± 0.0348)	1.523 (± 0.0348)	1.625 (± 0.0350)
Week 52 (n=385,397,387,377,405)	1.231 (± 0.0358)	1.183 (± 0.0356)	1.373 (± 0.0359)	1.449 (± 0.0361)

Notes:

[41] - n represents number of subjects analysed at the given time point.

[42] - n represents number of subjects analysed at the given time point.

[43] - n represents number of subjects analysed at the given time point.

[44] - n represents number of subjects analysed at the given time point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	439[45]			
Units: score on a scale				
least squares mean (standard error)				
Week 4 (n=426,422,429,425,437)	1.541 (± 0.0335)			
Week 12 (n=419,414,422,407,429)	1.445 (± 0.0345)			
Week 52 (n=385,397,387,377,405)	1.221 (± 0.0354)			

Notes:

[45] - n represents number of subjects analysed at the given time point.

Statistical analyses

Statistical analysis title	Week 4: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg

Number of subjects included in analysis	860
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.172
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.254
upper limit	-0.091
Variability estimate	Standard error of the mean
Dispersion value	0.0415

Statistical analysis title	Week 4: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.196
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.278
upper limit	-0.115
Variability estimate	Standard error of the mean
Dispersion value	0.0416

Statistical analysis title	Week 4: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.186
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.136
upper limit	0.026

Variability estimate	Standard error of the mean
Dispersion value	0.0414

Statistical analysis title	Week 12: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	860
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.129
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.214
upper limit	-0.044
Variability estimate	Standard error of the mean
Dispersion value	0.0431

Statistical analysis title	Week 12: QMF149 150/160 µg vs MF 400 µg
Comparison groups	MF 400 µg v QMF149 150/160 µg
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.248
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.333
upper limit	-0.162
Variability estimate	Standard error of the mean
Dispersion value	0.0435

Statistical analysis title	Week 12: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg

Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.232
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.136
upper limit	0.033
Variability estimate	Standard error of the mean
Dispersion value	0.0431

Statistical analysis title	Week 52: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	860
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.141
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.229
upper limit	-0.053
Variability estimate	Standard error of the mean
Dispersion value	0.0449

Statistical analysis title	Week 52: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.266
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.354
upper limit	-0.177

Variability estimate	Standard error of the mean
Dispersion value	0.045

Statistical analysis title	Week 52: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.824
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.078
upper limit	0.098
Variability estimate	Standard error of the mean
Dispersion value	0.0447

Secondary: Percentage of Subjects Achieving the Minimal Important Difference (MID) ACQ ≥ 0.5 at Weeks 26 and 52

End point title	Percentage of Subjects Achieving the Minimal Important Difference (MID) ACQ ≥ 0.5 at Weeks 26 and 52

End point description:

Change from baseline in ACQ-7 scores of ≤ 0.5 was defined as minimal clinically important difference and were considered clinically meaningful. The ACQ-7 measured asthma symptom control and consists of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway calibre (FEV1 % predicted). All 7 questions of the ACQ-7 were equally weighted. Items 1-5 were scored along a 7-point response scale, where 0 = totally controlled and 6 = severely uncontrolled. Item 6 is scored between 0 = no rescue medication and 6 = More than 16 puffs/inhalations most days. The 7th item was scored by the investigator based on the FEV1 % predicted from the masterscope at the site (i.e., Score = 0 means > 95% of predicted FEV1, 1 = 90 – 95%, 2 = 80 – 89%, 3 = 70 – 79%, 4 = 60 – 69%, 5 = 50 – 59%, and Score = 6 means < 50% of predicted FEV1). The total score was calculated as the mean of all questions. FAS consisted of all subjects in the RAN set who received at least one dose of study.

End point type	Secondary

End point timeframe:

Weeks 26 (Day 183) and 52 (Day 364)

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443[46]	437[47]	440[48]	443[49]
Units: percentage of subjects				
number (not applicable)				
Day 183 (n=407,407,405,393,410)	76.4	76.2	72.3	66.9
Day 364 (n=385,397,387,377,405)	77.7	82.1	73.6	69.2

Notes:
[46] - n represents number of subjects analysed at the given time point.
[47] - n represents number of subjects analysed at the given time point.
[48] - n represents number of subjects analysed at the given time point.
[49] - n represents number of subjects analysed at the given time point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444[50]			
Units: percentage of subjects				
number (not applicable)				
Day 183 (n=407,407,405,393,410)	75.9			
Day 364 (n=385,397,387,377,405)	77.3			

Notes:
[50] - n represents number of subjects analysed at the given time point.

Statistical analyses

Statistical analysis title	Day 183: QMF149 150/320 µg vs MF 800 µg
Comparison groups	MF 800 µg v QMF149 150/320 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	Logistic regression model
Parameter estimate	Odds ratio (OR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.81

Statistical analysis title	Day 183: QMF149 150/160 µg v MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logistic regression model
Parameter estimate	Odds ratio (OR)
Point estimate	1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.26
upper limit	2.37

Statistical analysis title	Day 183: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.746
Method	Logistic regression model
Parameter estimate	Odds ratio (OR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.46

Statistical analysis title	Day 364: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.088
Method	Logistic regression model
Parameter estimate	Odds ratio (OR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.87

Statistical analysis title	Day 364: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logistic regression model
Parameter estimate	Odds ratio (OR)
Point estimate	2.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.58
upper limit	3.17

Statistical analysis title	Day 364: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.771
Method	Logistic regression model
Parameter estimate	Odds ratio (OR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.49

Secondary: Change From Baseline in Percentage of Asthma Symptoms Free Days

End point title	Change From Baseline in Percentage of Asthma Symptoms Free Days

End point description:

All subjects were provided with an electronic diary (e-Diary) to record clinical symptoms. They were instructed to routinely complete the e-Diary twice daily at the same time each morning and again approximately 12 hours later in the evening. The e-Diary was reviewed at each visit until study completion. Asthma symptoms free days are days with no daytime symptoms, no night-time awakenings and no symptoms on awakening. The daytime asthma symptom score was based on the daily e-diary recordings by subjects with respect to shortness of breath, wheeze, cough, chest tightness, and impact on usual daily activities due to symptoms. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	401[51]	402[52]	408[53]	404[54]
Units: percentage of days				
least squares mean (standard error)	28.3 (± 1.72)	28.4 (± 1.72)	22.5 (± 1.72)	19.3 (± 1.72)

Notes:
[51] - Subjects analysed is number of subjects with data available for this endpoint point.
[52] - Subjects analysed is number of subjects with data available for this endpoint point.
[53] - Subjects analysed is number of subjects with data available for this endpoint point.
[54] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	405[55]			
Units: percentage of days				
least squares mean (standard error)	24.9 (± 1.72)			

Notes:
[55] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	QMF149 150/320 µg v MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	809
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Linear Mixed Model (LMM)
Parameter estimate	LS Mean
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	10.2
Variability estimate	Standard error of the mean
Dispersion value	2.29

Statistical analysis title	QMF149 150/160 µg v MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	806
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.6
upper limit	13.6

Variability estimate	Standard error of the mean
Dispersion value	2.29

Statistical analysis title	QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	806
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.135
Method	LMM
Parameter estimate	LS Mean
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	7.9
Variability estimate	Standard error of the mean
Dispersion value	2.29

Secondary: Change From Baseline in Percentage of Days With no Daytime Symptoms

End point title	Change From Baseline in Percentage of Days With no Daytime Symptoms

End point description:

All subjects were provided with an electronic diary (e-Diary) to record clinical symptoms. They were instructed to routinely complete the e-Diary twice daily at the same time each morning and again approximately 12 hours later in the evening. The e-Diary was reviewed at each visit until study completion. For days with no daytime symptoms, all 5 evening questions must have a score = 0 with respect to shortness of breath, wheeze, cough, chest tightness and impact on usual daily activities due to symptoms, each with scores from 0 (no problems) to 4 (very severe problems). FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	416[56]	420[57]	425[58]	419[59]
Units: percentage of days				
least squares mean (standard error)	28.0 (± 1.69)	28.0 (± 1.69)	23.0 (± 1.68)	20.0 (± 1.69)

Notes:

[56] - Subjects analysed is number of subjects with data available for this endpoint point.

[57] - Subjects analysed is number of subjects with data available for this endpoint point.

[58] - Subjects analysed is number of subjects with data available for this endpoint point.
[59] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	423[60]			
Units: percentage of days				
least squares mean (standard error)	24.8 (± 1.68)			

Notes:
[60] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	QMF149 150/320 µg v MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	841
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	LMM
Parameter estimate	LS Mean
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	9.4
Variability estimate	Standard error of the mean
Dispersion value	2.25

Statistical analysis title	QMF149 150/160 µg v MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	839
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.7
upper limit	12.5
Variability estimate	Standard error of the mean
Dispersion value	2.25

Statistical analysis title	QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	Salmeterol /fluticasone 50/500 µg v QMF149 150/320 µg
Number of subjects included in analysis	839
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.151
Method	LMM
Parameter estimate	LS Mean
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	7.7
Variability estimate	Standard error of the mean
Dispersion value	2.25

Secondary: Change From Baseline in Percentage of Nights With no Night-time Awakenings

End point title	Change From Baseline in Percentage of Nights With no Night-time Awakenings

End point description:

All subjects were provided with an electronic diary (e-Diary) to record clinical symptoms. They were instructed to routinely complete the e-Diary twice daily at the same time each morning and again approximately 12 hours later in the evening. The e-Diary was reviewed at each visit until study completion. The question asked for nights with no night-time awakenings was "How did you sleep last night?" had to be answered with "I did not wake up because of any breathing problems" with scores from 0 (no problem)-4 (very severe problems). FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	415[61]	420[62]	428[63]	422[64]
Units: percentage of nights				
least squares mean (standard error)	17.0 (± 1.28)	16.4 (± 1.27)	14.2 (± 1.27)	12.5 (± 1.27)

Notes:

[61] - Subjects analysed is number of subjects with data available for this endpoint point.

[62] - Subjects analysed is number of subjects with data available for this endpoint point.

[63] - Subjects analysed is number of subjects with data available for this endpoint point.

[64] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	424[65]			
Units: percentage of nights				
least squares mean (standard error)	16.1 (± 1.27)			

Notes:

[65] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	QMF149 150/320 µg v MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.104
Method	LMM
Parameter estimate	LS Mean
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	6.2
Variability estimate	Standard error of the mean
Dispersion value	1.72

Statistical analysis title	QMF149 150/160 µg v MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	842
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	LMM
Parameter estimate	LS Mean
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	7.3
Variability estimate	Standard error of the mean
Dispersion value	1.72

Statistical analysis title	QMF149 150/320 µg vs S/F 50/500 µg

Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	839
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.588
Method	LMM
Parameter estimate	LS Mean
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	4.3
Variability estimate	Standard error of the mean
Dispersion value	1.73

Secondary: Change From Baseline in Percentage of Mornings With no Symptoms on Awakening

End point title	Change From Baseline in Percentage of Mornings With no Symptoms on Awakening

End point description:

All subjects were provided with an electronic diary (e-Diary) to record clinical symptoms. They were instructed to routinely complete the e-Diary twice daily at the same time each morning and again approximately 12 hours later in the evening. The e-Diary was reviewed at each visit until study completion. The question asked for mornings with no symptoms on awakening was "Did you have asthma symptoms upon awakening in the morning?" to be answered with "None" with scores from 0 (no problem)-4 (very severe problems). FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	415[66]	420[67]	428[68]	422[69]
Units: percentage of mornings				
least squares mean (standard error)	25.5 (± 1.66)	22.9 (± 1.65)	19.1 (± 1.65)	14.1 (± 1.65)

Notes:

[66] - Subjects analysed is number of subjects with data available for this endpoint point.

[67] - Subjects analysed is number of subjects with data available for this endpoint point.

[68] - Subjects analysed is number of subjects with data available for this endpoint point.

[69] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	424[70]			

Units: percentage of mornings				
least squares mean (standard error)	20.7 (± 1.65)			

Notes:

[70] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	LMM
Parameter estimate	LS Mean
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	10.7
Variability estimate	Standard error of the mean
Dispersion value	2.19

Statistical analysis title	QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	842
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.6
upper limit	13.2
Variability estimate	Standard error of the mean
Dispersion value	2.19

Statistical analysis title	QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg

Number of subjects included in analysis	839
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	LMM
Parameter estimate	LS Mean
Point estimate	4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	9.1
Variability estimate	Standard error of the mean
Dispersion value	2.2

Secondary: Rescue Medication Usage

End point title	Rescue Medication Usage

End point description:

All subjectswere given salbutamol/albuterol to use as rescue medication throughout the study along with e-Diary to record rescue medication use. The number of puffs of rescue medication during the past 12 hours is recorded twice (morning/evening) by the subjects prior to taking study medication. The mean daily number of puffs of rescue medication use will be calculated for each subjects, done separately for morning (night-time), evening (daytime), and daily (night-time plus daytime) rescue medication use.
FAS consisted of all subjects in the RAN set who received at least one dose of study medication.
no. represents number.
NT represents night time.
dly represents daily
DT represents day time

End point type	Secondary

End point timeframe:

Up to Weeks 26 and 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443[71]	437[72]	440[73]	443[74]
Units: number of puffs				
least squares mean (standard error)				
Week1-26 Mean NT no. of puff n=418,419,430,422,426	-0.38 (± 0.028)	-0.27 (± 0.028)	-0.26 (± 0.028)	-0.19 (± 0.028)
Week1-26 Mean DT no. of puff n=417,420,427,419,424	-0.57 (± 0.035)	-0.46 (± 0.035)	-0.38 (± 0.035)	-0.34 (± 0.035)
Week1-26Mean dly no. of puff n=426,428,433,428,432	-0.96 (± 0.059)	-0.73 (± 0.059)	-0.65 (± 0.059)	-0.53 (± 0.059)
Week1-52Mean NT no. of puff n=415,420,428,422,424	-0.40 (± 0.029)	-0.30 (± 0.029)	-0.29 (± 0.028)	-0.20 (± 0.029)
Week1-52 Mean DT no. of puff n=416,420,425,419,423	-0.60 (± 0.035)	-0.51 (± 0.035)	-0.43 (± 0.035)	-0.36 (± 0.035)
Week1-52Mean dly no. of puff n=426,428,433,428,432	-1.00 (± 0.060)	-0.80 (± 0.060)	-0.72 (± 0.060)	-0.56 (± 0.060)

Notes:

[71] - n represents number of subjects analysed at the given time point.

[72] - n represents number of subjects analysed at the given time point.

[73] - n represents number of subjects analysed at the given time point.

[74] - n represents number of subjects analysed at the given time point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444[75]			
Units: number of puffs				
least squares mean (standard error)				
Week1-26 Mean NT no. of puff n=418,419,430,422,426	-0.34 (± 0.028)			
Week1-26 Mean DT no. of puff n=417,420,427,419,424	-0.53 (± 0.035)			
Week1-26Mean dly no. of puff n=426,428,433,428,432	-0.87 (± 0.059)			
Week1-52Mean NT no. of puff n=415,420,428,422,424	-0.35 (± 0.029)			
Week1-52 Mean DT no. of puff n=416,420,425,419,423	-0.55 (± 0.035)			
Week1-52Mean dly no. of puff n=426,428,433,428,432	-0.91 (± 0.060)			

Notes:

[75] - n represents number of subjects analysed at the given time point.

Statistical analyses

Statistical analysis title	Week1-26 Mean NT QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.039

Statistical analysis title	Week1-26 Mean NT QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg

Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.039

Statistical analysis title	Week1-26 Mean NT QMF149 150/320 µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.261
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.039

Statistical analysis title	Week1-26 Mean DT QMF149 150/320 µg vs MF 800µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	-0.09

Variability estimate	Standard error of the mean
Dispersion value	0.047

Statistical analysis title	Week1-26 Mean DT QMF149 150/160 µg vs MF 400µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.047

Statistical analysis title	Week1-26 Mean DT QMF149 150/320 µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.425
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.047

Statistical analysis title	Week1-26 Mean dly QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg

Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.081

Statistical analysis title	Week1-26 Mean dly QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.081

Statistical analysis title	Week1-26 Mean dly QMF149 150/320µg v S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	-0.07

Variability estimate	Standard error of the mean
Dispersion value	0.081

Statistical analysis title	Week1-52 Mean NT QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.039

Statistical analysis title	Week1-52 Mean NT QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	-0.02
Variability estimate	Standard error of the mean
Dispersion value	0.039

Statistical analysis title	Week1-52 Mean NT QMF149 150/320 µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg

Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.226
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.039

Statistical analysis title	Week1-52 Mean DT QMF149 150/320 µg vs MF 800µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	-0.07
Variability estimate	Standard error of the mean
Dispersion value	0.048

Statistical analysis title	Week1-52 Mean DT QMF149 150/160 µg vs MF 400µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	-0.05

Variability estimate	Standard error of the mean
Dispersion value	0.048

Statistical analysis title	Week1-52 Mean DT QMF149 150/320 µg vs S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.384
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.048

Statistical analysis title	Week1-52 Mean dly QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	-0.12
Variability estimate	Standard error of the mean
Dispersion value	0.081

Statistical analysis title	Week1-52 Mean dly QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg

Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	-0.07
Variability estimate	Standard error of the mean
Dispersion value	0.081

Statistical analysis title	Week1-52 Mean dly QMF149 150/320µg v S/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.245
Method	LMM
Parameter estimate	LS Mean
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.081

Secondary: Time to First Asthma Exacerbation by Exacerbation Category

End point title	Time to First Asthma Exacerbation by Exacerbation Category

End point description:

The exacerbation categories were: All (mild, moderate and severe) and combination of moderate or severe and severe. FAS consisted of all subjects in the RAN set who received at least one dose of study medication. Mod represents moderate, sev represents severe, asth represents asthma and exa represents exacerbation.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443[76]	437[77]	440[78]	443[79]
Units: days				
median (full range (min-max))				
Moderate or severe asthma exacerbation	366.0 (2 to 389)	366.0 (1 to 429)	366.0 (2 to 390)	364.0 (2 to 402)
Severe asthma exacerbation	367.0 (2 to 389)	366.0 (1 to 429)	366.0 (2 to 390)	366.0 (2 to 402)
All (mild, moderate or severe) asthma exacerbation	366.0 (2 to 389)	366.0 (1 to 429)	364.5 (2 to 390)	306.0 (2 to 402)

Notes:

[76] - Subjects analysed is number of subjects with data available for this endpoint point.

[77] - Subjects analysed is number of subjects with data available for this endpoint point.

[78] - Subjects analysed is number of subjects with data available for this endpoint point.

[79] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444[80]			
Units: days				
median (full range (min-max))				
Moderate or severe asthma exacerbation	366.0 (2 to 395)			
Severe asthma exacerbation	366.0 (3 to 395)			
All (mild, moderate or severe) asthma exacerbation	365.0 (2 to 394)			

Notes:

[80] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	Mod or sev asth exa:QMF149 150/320 µg v MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.72

Statistical analysis title	Mod or sev asth exa:QMF149 150/160 µg v MF 400 µg

Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.6

Statistical analysis title	Mod or sev asth exa:QMF149 150/160µg vS/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.209
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.12

Statistical analysis title	Sev asth exa:QMF149 150/320 µg v MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.81

Statistical analysis title	Sev asth exa:QMF149 150/160 µg v MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.63

Statistical analysis title	Sev asth exa:QMF149 150/320 µg v S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.115
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.09

Statistical analysis title	All asth exa :QMF149 150/320 µg v MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.82

Statistical analysis title	All asth exa :QMF149 150/160 µg v MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.6

Statistical analysis title	All asth exa:QMF149 150/320 µg v S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.185
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.08

Secondary: Time to First Hospitalization for Asthma Exacerbation

End point title	Time to First Hospitalization for Asthma Exacerbation

End point description:

The exacerbation categories were: All (mild, moderate and severe) and combination of moderate or severe and severe. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443[81]	437[82]	440[83]	443[84]
Units: days				
median (full range (min-max))	367 (2 to 389)	367 (1 to 429)	367 (2 to 390)	366 (2 to 402)

Notes:

[81] - Subjects analysed is number of subjects with data available for this endpoint point.

[82] - Subjects analysed is number of subjects with data available for this endpoint point.

[83] - Subjects analysed is number of subjects with data available for this endpoint point.

[84] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444[85]			
Units: days				
median (full range (min-max))	367 (3 to 395)			

Notes:

[85] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.337
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	2.03

Statistical analysis title	QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	1.11

Statistical analysis title	QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.599
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	9.7

Secondary: Annual Rate of Asthma Exacerbations by Exacerbation Category

End point title	Annual Rate of Asthma Exacerbations by Exacerbation Category

End point description:

The exacerbation categories were: All (mild, moderate and severe) and combination of moderate or severe and severe. FAS consisted of all subjects in the RAN set who received at least one dose of study medication. Mod represents moderate, sev represents severe, asth represents asthma and exa represents exacerbation.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443[86]	437[87]	440[88]	443[89]
Units: rate of exacerbations per year				
number (confidence interval 95%)				
Moderate or severe asthma exacerbation	0.25 (0.20 to 0.32)	0.27 (0.21 to 0.34)	0.39 (0.32 to 0.48)	0.56 (0.46 to 0.68)
Severe asthma exacerbation	0.13 (0.09 to 0.17)	0.13 (0.10 to 0.18)	0.18 (0.13 to 0.23)	0.29 (0.23 to 0.38)
All (mild, moderate,severe) asthma exacerbation	0.49 (0.41 to 0.60)	0.48 (0.40 to 0.59)	0.74 (0.62 to 0.88)	1.05 (0.89 to 1.24)

Notes:
[86] - Subjects analysed is number of subjects with data available for this endpoint point.
[87] - Subjects analysed is number of subjects with data available for this endpoint point.
[88] - Subjects analysed is number of subjects with data available for this endpoint point.
[89] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444[90]			
Units: rate of exacerbations per year				
number (confidence interval 95%)				
Moderate or severe asthma exacerbation	0.27 (0.22 to 0.34)			
Severe asthma exacerbation	0.14 (0.10 to 0.19)			
All (mild, moderate,severe) asthma exacerbation	0.52 (0.43 to 0.63)			

Notes:
[90] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	Mod or sev asth exa:QMF149 150/320 µg v MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Generalized linear model
Parameter estimate	Rate ratio
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.89

Statistical analysis title	Mod or sev asth exa:QMF149 150/160 µg v MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Generalized linear model
Parameter estimate	Rate ratio
Point estimate	0.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.64

Statistical analysis title	Mod or sev asth exa:QMF149 150/320µg vS/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.669
Method	Generalized linear model
Parameter estimate	Rate ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.29

Statistical analysis title	Sev asth exa:QMF149 150/320 µg v MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.108
Method	Generalized linear model
Parameter estimate	Rate ratio
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.08

Statistical analysis title	Sev asth exa:QMF149 150/160 µg v MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg

Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Generalized linear model
Parameter estimate	Rate ratio
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.67

Statistical analysis title	Sev asth exa:QMF149 150/320 µg v S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.597
Method	Generalized linear model
Parameter estimate	Rate ratio
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.37

Statistical analysis title	All asth exa :QMF149 150/320 µg v MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Generalized linear model
Parameter estimate	Rate ratio
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.87

Statistical analysis title	All asth exa :QMF149 150/160 µg v MF 400 µg

Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Generalized linear model
Parameter estimate	Rate ratio
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.59

Statistical analysis title	All asth exa:QMF149 150/320 µg v S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.681
Method	Generalized linear model
Parameter estimate	Rate ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.23

Secondary: Duration in Days of Asthma Exacerbations by Exacerbation Category

End point title	Duration in Days of Asthma Exacerbations by Exacerbation Category

End point description:

The exacerbation categories were: All (mild, moderate and severe) and combination of moderate or severe and severe. FAS consisted of all subjects in the RAN set who received at least one dose of study medication. Mod represents moderate, sev represents severe, asth represents asthma and exa represents exacerbation.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443[91]	437[92]	440[93]	443[94]
Units: days				
arithmetic mean (standard deviation)				
Moderate or severe asthma exacerbation	2.6 (± 10.60)	3.0 (± 12.53)	3.7 (± 11.40)	5.8 (± 13.98)
Severe asthma exacerbation	1.3 (± 6.02)	1.7 (± 8.48)	1.7 (± 6.07)	3.2 (± 9.16)
All (mild, moderate, severe) asthma exacerbation	5.4 (± 18.81)	5.0 (± 17.55)	6.9 (± 22.96)	10.1 (± 25.15)

Notes:

[91] - Subjects analysed is number of subjects with data available for this endpoint point.

[92] - Subjects analysed is number of subjects with data available for this endpoint point.

[93] - Subjects analysed is number of subjects with data available for this endpoint point.

[94] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444[95]			
Units: days				
arithmetic mean (standard deviation)				
Moderate or severe asthma exacerbation	3.1 (± 9.68)			
Severe asthma exacerbation	1.9 (± 7.76)			
All (mild, moderate, severe) asthma exacerbation	5.1 (± 14.48)			

Notes:

[95] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	Mod or sev asth exa:QMF149 150/320 µg v MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Van Elteren Test

Statistical analysis title	Mod or sev asth exa:QMF149 150/160 µg v MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Van Elteren Test

Statistical analysis title	Mod or sev asth exa:QMF149 150/160µg vS/F 50/500µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	Van Elteren Test

Statistical analysis title	Sev asth exa:QMF149 150/320 µg v MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	van Elteren test

Statistical analysis title	Sev asth exa:QMF149 150/160 µg v MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	van Elteren test

Statistical analysis title	Sev asth exa:QMF149 150/320 µg v S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	van Elteren test

Statistical analysis title	All asth exa :QMF149 150/320 µg v MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg

Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	van Elteren test

Statistical analysis title	All asth exa :QMF149 150/160 µg v MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	van Elteren test

Statistical analysis title	All asth exa:QMF149 150/320 µg v S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.074
Method	van Elteren test

Secondary: Percentage of Subjects With at Least One Asthma Exacerbation by Exacerbation Category

End point title	Percentage of Subjects With at Least One Asthma Exacerbation by Exacerbation Category

End point description:

The exacerbation categories were: All (mild, moderate and severe) and combination of moderate or severe and severe. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443	437	440	443
Units: percentage of subjects				
number (not applicable)				
Moderate or severe asthma exacerbation	14.9	16.9	26.1	32.5
Severe asthma exacerbation	8.1	9.8	14.5	20.1

Moderate asthma exacerbation	7.7	8.2	14.3	16.5
Mild asthma exacerbation	13.3	12.1	17.5	19.6
All (mild, moderate, severe) asthma exacerbation	25.5	25.6	36.1	44.5

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444			
Units: percentage of subjects				
number (not applicable)				
Moderate or severe asthma exacerbation	19.1			
Severe asthma exacerbation	11.9			
Moderate asthma exacerbation	9.2			
Mild asthma exacerbation	15.1			
All (mild, moderate, severe) asthma exacerbation	30.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Time in Days to Permanent Discontinuation of Study Medication Due to Asthma Exacerbations

End point title	Time in Days to Permanent Discontinuation of Study Medication Due to Asthma Exacerbations

End point description:

The exacerbation categories were: All (mild, moderate and severe) and combination of moderate or severe and severe. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443[96]	437[97]	440[98]	443[99]
Units: days				
median (full range (min-max))	367 (2 to 389)	367 (1 to 429)	367 (2 to 390)	366 (2 to 402)

Notes:

[96] - Subjects analysed is number of subjects with data available for this endpoint point.

[97] - Subjects analysed is number of subjects with data available for this endpoint point.

[98] - Subjects analysed is number of subjects with data available for this endpoint point.

[99] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444[100]			
Units: days				
median (full range (min-max))	367 (3 to 395)			

Notes:

[100] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.222
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	2.29

Statistical analysis title	QMF149 150/160 µg vs MF 400 µg
Statistical analysis description: 99999 indicates upper limit of CI and it was not estimable.	
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.992
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	99999

Statistical analysis title	QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.618
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	6.01

Secondary: Percentage of Subjects Who Permanently Discontinued Study Medication Due to Asthma Exacerbations

End point title	Percentage of Subjects Who Permanently Discontinued Study Medication Due to Asthma Exacerbations
End point description:	
FAS consisted of all subjects in the RAN set who received at least one dose of study medication.	
End point type	Secondary
End point timeframe:	
Up to Week 52	

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443[101]	437[102]	440[103]	443[104]
Units: percentage of subjects				
number (not applicable)	0.2	0	0.9	1.6

Notes:

[101] - Subjects analysed is number of subjects with data available for this endpoint point.

[102] - Subjects analysed is number of subjects with data available for this endpoint point.

[103] - Subjects analysed is number of subjects with data available for this endpoint point.

[104] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444[105]			
Units: percentage of subjects				
number (not applicable)	0.5			

Notes:

[105] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Amounts of Systemic Corticosteroids (in Doses) Used to Treat Asthma Exacerbations

End point title	Total Amounts of Systemic Corticosteroids (in Doses) Used to Treat Asthma Exacerbations

End point description:

The treatment of asthma exacerbations including the initiation of systemic corticosteroids were done according to investigator's or treating physician's medical judgement and in line with national and international recommendations. If systemic corticosteroids were required, a subject could return to the study after successfully completing a taper of approximately 7-10 days. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443[106]	437[107]	440[108]	443[109]
Units: milligram(s)				
arithmetic mean (standard deviation)	26 (± 136.92)	29.9 (± 124.98)	28 (± 95.18)	47.8 (± 139.98)

Notes:

[106] - Subjects analysed is number of subjects with data available for this endpoint point.

[107] - Subjects analysed is number of subjects with data available for this endpoint point.

[108] - Subjects analysed is number of subjects with data available for this endpoint point.

[109] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444[110]			
Units: milligram(s)				
arithmetic mean (standard deviation)	26.9 (± 114.36)			

Notes:

[110] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percentage of Rescue Medication Free Days

End point title	Change From Baseline in Percentage of Rescue Medication Free Days

End point description:

All subjects were given salbutamol/albuterol to use as rescue medication throughout the study along with e-Diary to record rescue medication use. Rescue medication free days is defined as any day where the subject did not use any puffs of rescue medication during daytime and night-time. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Weeks 26 and 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443[111]	437[112]	440[113]	443[114]
Units: percentage of days				
least squares mean (standard error)				
Weeks 1-26 (n=412, 416, 424, 414, 421)	31.5 (± 1.53)	27.4 (± 1.53)	21.4 (± 1.52)	19.1 (± 1.53)
Weeks 1-52 (n=408, 416, 420, 414, 416)	33.1 (± 1.55)	29.4 (± 1.54)	23.5 (± 1.54)	20.8 (± 1.54)

Notes:

[111] - n= Number of subjects analysed at the given time point.

[112] - n= Number of subjects analysed at the given time point.

[113] - n= Number of subjects analysed at the given time point.

[114] - n= Number of subjects analysed at the given time point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444[115]			
Units: percentage of days				
least squares mean (standard error)				
Weeks 1-26 (n=412, 416, 424, 414, 421)	27.4 (± 1.52)			
Weeks 1-52 (n=408, 416, 420, 414, 416)	28.8 (± 1.54)			

Notes:

[115] - n= Number of subjects analysed at the given time point.

Statistical analyses

Statistical analysis title	Weeks 1-26: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg

Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Linear Mixed Model (LMM)
Parameter estimate	LS Mean
Point estimate	10.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.2
upper limit	14.1
Variability estimate	Standard error of the mean
Dispersion value	2.02

Statistical analysis title	Weeks 1-26: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	12.3
Variability estimate	Standard error of the mean
Dispersion value	2.02

Statistical analysis title	Weeks 1-26: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	LMM
Parameter estimate	LS Mean
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	8

Variability estimate	Standard error of the mean
Dispersion value	2.02

Statistical analysis title	Weeks 1-52: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.7
upper limit	13.6
Variability estimate	Standard error of the mean
Dispersion value	2.03

Statistical analysis title	Weeks 1-52: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LMM
Parameter estimate	LS Mean
Point estimate	8.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.7
upper limit	12.6
Variability estimate	Standard error of the mean
Dispersion value	2.03

Statistical analysis title	Weeks 1-52: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg

Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	LMM
Parameter estimate	LS Mean
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	8.3
Variability estimate	Standard error of the mean
Dispersion value	2.04

Secondary: Asthma Quality of Life Questionnaire (AQLQ)

End point title	Asthma Quality of Life Questionnaire (AQLQ)

End point description:

AQLQ is a 32-item disease specific questionnaire designed to measure functional impairments that are most important to subjects with asthma, with a recall time of two weeks and each question to be answered on a 7-point scale (1-totally limited/problems all the time, 7-not at all limited/no problems). It consists of 4 domains:
• Symptoms = Mean of Items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30 (12 items)
• Activity limitation = Mean of Items 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32 (11 items)
• Emotional function = Mean of Items 7, 13, 15, 21, 27 (5 items)
• Environmental stimuli = Mean of Items 9, 17, 23, 26 (4 items)
• Overall Score = Mean of Items 1 to 32 (32 items)
FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 52 (Day 364)

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	428[116]	426[117]	431[118]	428[119]
Units: score on a scale				
least squares mean (standard error)				
Day 30 (n=427, 423, 430, 425, 436)	5.560 (± 0.0327)	5.498 (± 0.0328)	5.413 (± 0.0326)	5.374 (± 0.0327)
Day 86 (n=419, 416, 422, 406, 428)	5.618 (± 0.0356)	5.629 (± 0.0357)	5.564 (± 0.0355)	5.510 (± 0.0359)
Day 183 (n=406, 407, 405, 393, 410)	5.724 (± 0.0372)	5.738 (± 0.0372)	5.598 (± 0.0372)	5.581 (± 0.0376)
Day 254 (n=392, 395, 388, 385, 405)	5.761 (± 0.0383)	5.781 (± 0.0382)	5.689 (± 0.0383)	5.614 (± 0.0386)
Day 364 (n=384, 397, 389, 378, 405)	5.783 (± 0.0391)	5.832 (± 0.0388)	5.705 (± 0.0389)	5.641 (± 0.0394)

Notes:
[116] - n= Number of subjects analysed at the given time point.
[117] - n= Number of subjects analysed at the given time point.
[118] - n= Number of subjects analysed at the given time point.
[119] - n= Number of subjects analysed at the given time point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	438[120]			
Units: score on a scale				
least squares mean (standard error)				
Day 30 (n=427, 423, 430, 425, 436)	5.515 (± 0.0324)			
Day 86 (n=419, 416, 422, 406, 428)	5.592 (± 0.0352)			
Day 183 (n=406, 407, 405, 393, 410)	5.639 (± 0.0369)			
Day 254 (n=392, 395, 388, 385, 405)	5.700 (± 0.0378)			
Day 364 (n=384, 397, 389, 378, 405)	5.742 (± 0.0384)			

Notes:
[120] - n= Number of subjects analysed at the given time point.

Statistical analyses

Statistical analysis title	Day 30: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	859
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.147
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.056
upper limit	0.237
Variability estimate	Standard error of the mean
Dispersion value	0.0462

Statistical analysis title	Day 30: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg

Number of subjects included in analysis	854
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.123
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.032
upper limit	0.214
Variability estimate	Standard error of the mean
Dispersion value	0.0464

Statistical analysis title	Day 30: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	866
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.045
upper limit	0.135
Variability estimate	Standard error of the mean
Dispersion value	0.046

Statistical analysis title	Day 86: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	859
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.054
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.044
upper limit	0.153

Variability estimate	Standard error of the mean
Dispersion value	0.0503

Statistical analysis title	Day 86: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	854
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.118
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.019
upper limit	0.217
Variability estimate	Standard error of the mean
Dispersion value	0.0507

Statistical analysis title	Day 86: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	866
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.598
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.072
upper limit	0.125
Variability estimate	Standard error of the mean
Dispersion value	0.0501

Statistical analysis title	Day 183: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg

Number of subjects included in analysis	859
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.127
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.0526

Statistical analysis title	Day 183: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	854
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.156
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.053
upper limit	0.26
Variability estimate	Standard error of the mean
Dispersion value	0.0529

Statistical analysis title	Day 183: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	866
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.103
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.085
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.017
upper limit	0.188

Variability estimate	Standard error of the mean
Dispersion value	0.0525

Statistical analysis title	Day 254: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	859
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.188
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.035
upper limit	0.178
Variability estimate	Standard error of the mean
Dispersion value	0.0542

Statistical analysis title	Day 254: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	854
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.168
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.061
upper limit	0.274
Variability estimate	Standard error of the mean
Dispersion value	0.0543

Statistical analysis title	Day 254: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg

Number of subjects included in analysis	866
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.258
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.045
upper limit	0.166
Variability estimate	Standard error of the mean
Dispersion value	0.0538

Statistical analysis title	Day 364: QMF149 150/320 µg vs MF 800 µg
Comparison groups	QMF149 150/320 µg v MF 800 µg
Number of subjects included in analysis	859
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.154
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.079
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.187
Variability estimate	Standard error of the mean
Dispersion value	0.0552

Statistical analysis title	Day 364: QMF149 150/160 µg vs MF 400 µg
Comparison groups	QMF149 150/160 µg v MF 400 µg
Number of subjects included in analysis	854
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.191
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.082
upper limit	0.299

Variability estimate	Standard error of the mean
Dispersion value	0.0553

Statistical analysis title	Day 364: QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	866
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.455
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.067
upper limit	0.148
Variability estimate	Standard error of the mean
Dispersion value	0.0548

Secondary: Trough FEV1 Measured After 26 Weeks of Treatment

End point title	Trough FEV1 Measured After 26 Weeks of Treatment[121]

End point description:

Trough FEV1 was assessed by performing spirometric assessment. It is defined as average of the two FEV1 measurements taken 23 hr 15 min and 23 hr 45 min post-evening dose. FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Week 26

Notes:

[121] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arm groups QMF149 150/320 µg and Salmeterol/fluticasone 50/500 µg were planned to be reported for this endpoint.

End point values	QMF149 150/320 µg	Salmeterol /fluticasone 50/500 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395[122]	391[123]		
Units: litre(s)				
least squares mean (standard error)	2.383 (± 0.0159)	2.346 (± 0.0160)		

Notes:

[122] - Subjects analysed is number of subjects with data available for this endpoint point.

[123] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.101
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.0222

Secondary: Asthma Control as Assessed by the ACQ-7 After 26 Weeks Treatment

End point title	Asthma Control as Assessed by the ACQ-7 After 26 Weeks Treatment[124]

End point description:

The ACQ-7 measured asthma symptom control and consisted of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway calibre (FEV1 % predicted). All 7 questions of the ACQ-7 were equally weighted. Items 1-5 were scored along a 7-point response scale, where 0 = totally controlled and 6 = severely uncontrolled. Item 6 is scored between 0 = no rescue medication and 6 = More than 16 puffs/inhalations most days. The 7th item was scored by the investigator based on the FEV1 % predicted from the masterscope at the site (i.e., Score = 0 means > 95% of predicted FEV1, 1 = 90 – 95%, 2 = 80 – 89%, 3 = 70 – 79%, 4 = 60 – 69%, 5 = 50 – 59%, and Score = 6 means < 50% of predicted FEV1). The total score was calculated as the mean of all questions. FAS consisted of all subjects in the RAN set who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Week 26

Notes:

[124] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arm groups QMF149 150/320 µg and Salmeterol/fluticasone 50/500 µg were planned to be reported for this endpoint.

End point values	QMF149 150/320 µg	Salmeterol /fluticasone 50/500 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	407[125]	410[126]		
Units: score on a scale				
least squares mean (standard error)	1.267 (± 0.0350)	1.322 (± 0.0349)		

Notes:

[125] - Subjects analysed is number of subjects with data available for this endpoint point.

[126] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

Statistical analysis title	QMF149 150/320 µg vs S/F 50/500 µg
Comparison groups	QMF149 150/320 µg v Salmeterol /fluticasone 50/500 µg
Number of subjects included in analysis	817
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.214
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.054
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.031
Variability estimate	Standard error of the mean
Dispersion value	0.0437

Secondary: Percentage of Subjects With Composite Endpoint of Serious Asthma Outcomes

End point title	Percentage of Subjects With Composite Endpoint of Serious Asthma Outcomes

End point description:

A composite endpoint of serious asthma outcomes is defined as asthma-related hospitalisation, asthma-related intubation, or asthma-related death and was reviewed by the Adjudication Committee. Safety Set consisted of all subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443[127]	437[128]	440[129]	443[130]
Units: percentage of subjects				
number (not applicable)	0.7	0.5	1.6	1.8

Notes:

[127] - Subjects analysed is number of subjects with data available for this endpoint point.

[128] - Subjects analysed is number of subjects with data available for this endpoint point.

[129] - Subjects analysed is number of subjects with data available for this endpoint point.

[130] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444[131]			
Units: percentage of subjects				
number (not applicable)	0.5			

Notes:

[131] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AE) and Serious Adverse Events (SAE)

End point title	Percentage of Subjects With Adverse Events (AE) and Serious Adverse Events (SAE)

End point description:

An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign including abnormal laboratory findings, symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria: is fatal or life-threatening, results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, requires in subjects hospitalization or prolongation of existing hospitalization or is medically significant, i.e. defined as an event that jeopardizes the subjects or may require medical or surgical intervention. The Safety Set consisted of all subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Approximately up to 56 weeks

End point values	QMF149 150/320 µg	QMF149 150/160 µg	MF 800 µg	MF 400 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	443[132]	437[133]	440[134]	443[135]
Units: percentage of subjects				
number (not applicable)				
Adverse Events(AEs)	64.6	66.8	70.0	72.2
Serious Adverse Events(SAEs)	4.7	4.6	4.8	7.0

Notes:

[132] - Subjects analysed is number of subjects with data available for this endpoint point.

[133] - Subjects analysed is number of subjects with data available for this endpoint point.

[134] - Subjects analysed is number of subjects with data available for this endpoint point.

[135] - Subjects analysed is number of subjects with data available for this endpoint point.

End point values	Salmeterol /fluticasone 50/500 µg			
Subject group type	Reporting group			
Number of subjects analysed	444[136]			
Units: percentage of subjects				
number (not applicable)				
Adverse Events(AEs)	65.3			
Serious Adverse Events(SAEs)	4.7			

Notes:

[136] - Subjects analysed is number of subjects with data available for this endpoint point.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Serious adverse events: From first dose up to 30 days post last dose (approximately 56 weeks) Other adverse events: From first dose up to 7 days post last dose (approximately 53 weeks)	
Adverse event reporting additional description:	
Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	QMF 150/320
Reporting group description: QMF 150/320	
Reporting group title	QMF 150/160
Reporting group description: QMF 150/160	
Reporting group title	MF 800
Reporting group description: MF 800	
Reporting group title	MF 400
Reporting group description: MF 400	
Reporting group title	S/F 50/500
Reporting group description: S/F 50/500	

Serious adverse events	QMF 150/320	QMF 150/160	MF 800
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 443 (4.74%)	20 / 437 (4.58%)	21 / 440 (4.77%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			

subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cancer			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical dysplasia			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cervix enlargement			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal prolapse			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asphyxia			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	3 / 443 (0.68%)	2 / 437 (0.46%)	6 / 440 (1.36%)
occurrences causally related to treatment / all	1 / 4	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chronic rhinosinusitis with nasal polyps			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrothorax			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental device ingestion			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye injury			

subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound complication			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			

subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 443 (0.45%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebellar haematoma			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			

subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine with aura			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral artery aneurysm			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Corneal deposits			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic ischaemic neuropathy			

subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric polyps			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritable bowel syndrome			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 443 (0.23%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Angioedema			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis atopic			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urethral			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydroureter			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric stenosis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral stenosis			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Goitre			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteoporosis			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 443 (0.23%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complicated appendicitis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis salmonella			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			

subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 443 (0.23%)	3 / 437 (0.69%)	5 / 440 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	1 / 443 (0.23%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sialoadenitis			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection bacterial			

subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 443 (0.00%)	1 / 437 (0.23%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 443 (0.00%)	0 / 437 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	MF 400	S/F 50/500	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 443 (7.00%)	21 / 444 (4.73%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			

subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 443 (0.23%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cervix enlargement			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asphyxia			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	8 / 443 (1.81%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic rhinosinusitis with nasal polyps			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septum deviation			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental device ingestion			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye injury			

subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	2 / 443 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar haematoma			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			

subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine with aura			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral artery aneurysm			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Corneal deposits			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic ischaemic neuropathy			

subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
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	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Angioedema			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis atopic			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urethral			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydroureter			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Goitre			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteoporosis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complicated appendicitis			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			

subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 443 (0.00%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 443 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sialoadenitis			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			

subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 443 (0.00%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 443 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 443 (0.00%)	1 / 444 (0.23%)	
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: 2 %

Non-serious adverse events	QMF 150/320	QMF 150/160	MF 800
Total subjects affected by non-serious adverse events			
subjects affected / exposed	228 / 443 (51.47%)	233 / 437 (53.32%)	263 / 440 (59.77%)
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 443 (2.26%)	14 / 437 (3.20%)	13 / 440 (2.95%)
occurrences (all)	12	17	14
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 443 (5.87%)	21 / 437 (4.81%)	24 / 440 (5.45%)
occurrences (all)	39	24	37
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	3 / 443 (0.68%)	9 / 437 (2.06%)	5 / 440 (1.14%)
occurrences (all)	4	9	5
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	112 / 443 (25.28%)	113 / 437 (25.86%)	157 / 440 (35.68%)
occurrences (all)	211	202	308
Cough			
subjects affected / exposed	8 / 443 (1.81%)	9 / 437 (2.06%)	12 / 440 (2.73%)
occurrences (all)	9	9	13
Oropharyngeal pain			
subjects affected / exposed	11 / 443 (2.48%)	6 / 437 (1.37%)	8 / 440 (1.82%)
occurrences (all)	12	7	8
Rhinitis allergic			
subjects affected / exposed	5 / 443 (1.13%)	11 / 437 (2.52%)	7 / 440 (1.59%)
occurrences (all)	5	11	7
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 443 (2.03%)	17 / 437 (3.89%)	9 / 440 (2.05%)
occurrences (all)	9	21	13
Infections and infestations			
Bronchitis			
subjects affected / exposed	20 / 443 (4.51%)	22 / 437 (5.03%)	22 / 440 (5.00%)
occurrences (all)	22	25	27
Gastroenteritis			
subjects affected / exposed	4 / 443 (0.90%)	9 / 437 (2.06%)	4 / 440 (0.91%)
occurrences (all)	4	9	4
Influenza			
subjects affected / exposed	12 / 443 (2.71%)	13 / 437 (2.97%)	19 / 440 (4.32%)
occurrences (all)	13	13	22
Nasopharyngitis			
subjects affected / exposed	50 / 443 (11.29%)	58 / 437 (13.27%)	78 / 440 (17.73%)
occurrences (all)	66	87	96
Pharyngitis			
subjects affected / exposed	10 / 443 (2.26%)	11 / 437 (2.52%)	12 / 440 (2.73%)
occurrences (all)	10	12	13

Respiratory tract infection viral			
subjects affected / exposed	10 / 443 (2.26%)	16 / 437 (3.66%)	14 / 440 (3.18%)
occurrences (all)	11	21	23
Rhinitis			
subjects affected / exposed	10 / 443 (2.26%)	10 / 437 (2.29%)	9 / 440 (2.05%)
occurrences (all)	10	12	9
Upper respiratory tract infection			
subjects affected / exposed	22 / 443 (4.97%)	27 / 437 (6.18%)	40 / 440 (9.09%)
occurrences (all)	29	33	54
Upper respiratory tract infection bacterial			
subjects affected / exposed	5 / 443 (1.13%)	7 / 437 (1.60%)	6 / 440 (1.36%)
occurrences (all)	6	10	7
Viral infection			
subjects affected / exposed	7 / 443 (1.58%)	8 / 437 (1.83%)	11 / 440 (2.50%)
occurrences (all)	9	8	12
Viral upper respiratory tract infection			
subjects affected / exposed	7 / 443 (1.58%)	11 / 437 (2.52%)	21 / 440 (4.77%)
occurrences (all)	9	15	31

Non-serious adverse events	MF 400	S/F 50/500	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	290 / 443 (65.46%)	239 / 444 (53.83%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 443 (2.48%)	6 / 444 (1.35%)	
occurrences (all)	12	7	
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 443 (5.19%)	22 / 444 (4.95%)	
occurrences (all)	32	28	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 443 (0.90%)	9 / 444 (2.03%)	
occurrences (all)	4	9	
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	194 / 443 (43.79%)	137 / 444 (30.86%)	
occurrences (all)	418	233	
Cough			
subjects affected / exposed	15 / 443 (3.39%)	8 / 444 (1.80%)	
occurrences (all)	16	9	
Oropharyngeal pain			
subjects affected / exposed	9 / 443 (2.03%)	8 / 444 (1.80%)	
occurrences (all)	11	8	
Rhinitis allergic			
subjects affected / exposed	11 / 443 (2.48%)	7 / 444 (1.58%)	
occurrences (all)	12	8	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 443 (1.13%)	8 / 444 (1.80%)	
occurrences (all)	5	12	
Infections and infestations			
Bronchitis			
subjects affected / exposed	21 / 443 (4.74%)	17 / 444 (3.83%)	
occurrences (all)	25	18	
Gastroenteritis			
subjects affected / exposed	6 / 443 (1.35%)	8 / 444 (1.80%)	
occurrences (all)	6	9	
Influenza			
subjects affected / exposed	10 / 443 (2.26%)	15 / 444 (3.38%)	
occurrences (all)	11	17	
Nasopharyngitis			
subjects affected / exposed	82 / 443 (18.51%)	47 / 444 (10.59%)	
occurrences (all)	108	70	
Pharyngitis			
subjects affected / exposed	12 / 443 (2.71%)	14 / 444 (3.15%)	
occurrences (all)	18	15	
Respiratory tract infection viral			
subjects affected / exposed	12 / 443 (2.71%)	13 / 444 (2.93%)	
occurrences (all)	18	18	
Rhinitis			

subjects affected / exposed	5 / 443 (1.13%)	8 / 444 (1.80%)	
occurrences (all)	6	8	
Upper respiratory tract infection			
subjects affected / exposed	37 / 443 (8.35%)	38 / 444 (8.56%)	
occurrences (all)	55	57	
Upper respiratory tract infection bacterial			
subjects affected / exposed	14 / 443 (3.16%)	8 / 444 (1.80%)	
occurrences (all)	14	8	
Viral infection			
subjects affected / exposed	7 / 443 (1.58%)	6 / 444 (1.35%)	
occurrences (all)	8	7	
Viral upper respiratory tract infection			
subjects affected / exposed	20 / 443 (4.51%)	21 / 444 (4.73%)	
occurrences (all)	31	26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2015	This amendment was made in order to comply with the Health Authorities requirements received after finalisation of the protocol version 00 regarding the paediatric population before finalisation of the Paediatric Investigational Plan. As this protocol includes adolescent patients, the following changes were made: 1.Modify the Section Discontinuation of study treatment in order to permanently discontinue study drug for any adolescent patients after one asthma exacerbation requiring hospitalisation 2.Modify inclusion criteria number 4 and 5 in Section Inclusion criteria and in the protocol summary to change the requirement of previous treatment of "any" dose of long-acting β2-adrenergic agonist/inhaled corticosteroids (LABA/ICS) to "low" dose of LABA/ICS.Also patients should qualify for treatment with medium or high dose LABA/ICS (GINA 2015 step≥ 3). The Section Supportive analyses was modified accordingly for the subgroup analysis Following changes and revisions were also made: 1.Change ACQ-5 to be given to the patients and site to ACQ-7 on Table of Assessment for Patients who Discontinue Study Treatment prematurely,Table of assessment,Section Health Status (Patient Reported Outcomes) and Section ACQ-7 at Weeks 4,12 and 52. Derivation of rescue medication from e-diary (6th item on ACQ) and FEV1 (7th item on ACQ) was not performed 2.Specification in Section Treatment exposure and compliance that the patient had entered on the e-diary the compliance of study drug once a week 3.Update on Section Electronic Diary in order to be aligned with Section Treatment exposure and compliance 4.Update on Section Peak Expiratory Flow (PEF) in order to clarify the PEF measurement start and update Table of assessment accordingly 5.Clarify in Section Euro QoL 5 Dimension (EQ-5D-5L) that it was validated in adults and adolescent 6.Update of the questions of Appendix 8:Patient Asthma Control e-Diary for the Patient Asthma diary in order to align to the exacerbations definition
01 October 2015	The purpose of this amendment was to modify the ACQ score inclusion criteria from ACQ≥2 to ACQ≥1.5 based on the feedback from an external expert advisory board in September 2015. Initial threshold of ≥2 was defined based on internal modelling and simulation data as well as published literature. However, expert advisory board members suggested that a threshold of 1.5 is a more clinically meaningful for the patient population. Additionally, there was precedent for this threshold in recent asthma studies. The Protocol Summary, Section Study Design, Section Rationale for dosing, Section Risk and Benefits, Section Inclusion criteria, Section Supportive analysis were updated accordingly.
08 September 2016	The rationale for this amendment was changing the E-Diary Alert handling during run-in epoch due to asthma worsening. If an asthma worsening alert was observed during the run-in epoch, the patients were discontinued regardless of clinical context and the investigator's judgment. This amendment allowed investigator's discretion in determining the clinical significance of asthma worsening e-diary alerts during the run-in epoch and allowed the investigator to make the most appropriate decision as to whether patients continued in the study or were discontinued. If asthma worsening was confirmed as clinically significant by investigator, patients were discontinued. A combination of e-diary alerts and investigator's judgment helped ensure that the most appropriate patients were enrolled in the study, while maintaining rigorous monitoring and assessment of patient safety.

14 February 2017	1.Modification of inclusion criteria for baseline ICS and ICS/LABA requirements and upper limit of FEV1 threshold. This was based on investigator feedback of real world asthma populations and intended to address variability in baseline FEV1 as well as evolving treatment patterns, whereby patient medications are more rapidly up-titrated in response to symptoms. This helped identify previously ineligible patients who potentially benefited from treatment with medium to high fixed dose combination of ICS/LABA. 2.The sample size was revised based on the re-estimation of drop-out rate at Week 26 at which time the primary and key secondary objectives were evaluated (Section Population and Section Safety Monitoring Analyses).
17 January 2018	1.Conduct primary analysis after all patients have completed at least 26 weeks treatment (V207): The primary and key secondary endpoints of this study were trough FEV1 and ACQ-7, respectively after 26 weeks of treatment, while the entire study treatment period was 52 weeks. Novartis had decided to perform primary analysis once all patients had completed 26 weeks of treatment (Visit 207) or prematurely withdrawn from the study. Two separate CSRs were written: CSR I was completed for the primary analyses once all patients had completed the assessments after 26 weeks of treatment or prematurely withdrawn from the study. It consisted of primary and key secondary objectives as well as other pre-specified objectives up to and including Week 26. CSR II was completed once all patients had completed 52 weeks of treatment plus 30 day follow up or prematurely withdrawn from the study. CSR II consisted of primary and secondary objectives analysed in CSR I in addition to all other objectives evaluated after 26 weeks and up to 52 weeks (plus follow up). 2.Modification of analysis of key secondary endpoint, ACQ-7: The key secondary objective was modified to demonstrate the benefit of indacaterol (QAB149) 150 µg monotherapy on ACQ-7. This was achieved by demonstrating superiority of combined medium and high QMF149 doses to combined medium and high MF doses, respectively in terms of ACQ-7 after 26 weeks of treatment. The analysis was performed only if the individual treatment comparisons were significant for the primary endpoint, trough FEV1 at week 26 (i.e., there was an evidence of efficacy of both doses of QMF149 over respective MF doses in terms of trough FEV1).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported