Clinical trial results:
A multi-center, randomized, 12-week treatment, doubleblind study to assess the efficacy and safety of QMF149 (150/80 g) compared with mometasone furoate (MF) Twisthaler® (200 g) in adult and adolescent patients with asthma

Summary

EudraCT number	2016-000472-22
Trial protocol	DE EE IT SE LT SK LV HU BG PL
Global end of trial date	30 November 2018

Results information

Result version number	v1 (current)
This version publication date	14 June 2019
First version publication date	14 June 2019

Trial information

Trial identification

Sponsor protocol code	CQVM149B2303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02892344
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharmaceutical, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 November 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of QMF149 150/80 µg o.d. (in the evening) delivered via Concept1 compared with MF 200 µg o.d. (in the evening) delivered via Twisthaler in terms of trough FEV1 after 12 weeks of treatment in adults and adolescents

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 2017
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	Bulgaria: 40
Country: Number of subjects enrolled	Chile: 12
Country: Number of subjects enrolled	Colombia: 7
Country: Number of subjects enrolled	Estonia: 24
Country: Number of subjects enrolled	Germany: 111
Country: Number of subjects enrolled	Hungary: 116
Country: Number of subjects enrolled	India: 73
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Japan: 52
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 25
Country: Number of subjects enrolled	Latvia: 44
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Peru: 54
Country: Number of subjects enrolled	Philippines: 11
Country: Number of subjects enrolled	Poland: 50
Country: Number of subjects enrolled	Russian Federation: 34
Country: Number of subjects enrolled	Slovakia: 80
Country: Number of subjects enrolled	South Africa: 23

Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	Vietnam: 22
Worldwide total number of subjects	802
EEA total number of subjects	475

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)	64
Adults (18-64 years)	630
From 65 to 84 years	108
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study used a 12-week treatment, randomized, double-blind, double-dummy, parallel-group design. The 12 week treatment epoch was followed by a 30 day Follow-up epoch.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	QMF149 150/80 µg

Arm description:

QMF149 150/80 microgram o.d. delivered via Concept1

Arm type	Experimental
Investigational medicinal product name	QMF149 150/80 µg
Investigational medicinal product code	QMF149 150/80 µg
Other name	QMF149 150/80 µg
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Oral use

Dosage and administration details:

QMF149 150/80 µg o.d. delivered via Concept1

Arm title	MF 200 µg

Arm description:

MF 200 microgram o.d. delivered via Twisthaler®

Arm type	Active comparator
Investigational medicinal product name	MF 200 µg
Investigational medicinal product code	MF 200 µg
Other name	MF 200 µg
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Oral use

Dosage and administration details:

MF 200 µg o.d. delivered via a Twisthaler

Number of subjects in period 1	QMF149 150/80 µg	MF 200 µg
Started	398	404
Full analysis set	395	399
Completed	394	383
Not completed	4	21

Physician decision	-	2
Adverse event, non-fatal	1	8
Technical problems	-	1
Protocol deviation	3	4
Non-compliance with study treatment	-	1
Lost to follow-up	-	1
Subject/guardian decision	-	4

Baseline characteristics

Reporting groups	
Reporting group title	QMF149 150/80 µg
Reporting group description:	
QMF149 150/80 microgram o.d. delivered via Concept1	
Reporting group title	MF 200 µg
Reporting group description:	
MF 200 microgram o.d. delivered via Twisthaler®	

Reporting group values	QMF149 150/80 µg	MF 200 µg	Total
Number of subjects	398	404	802
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)	31	33	64
Adults (18-64 years)	312	318	630
From 65-84 years	55	53	108
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	46.1	45.1	
standard deviation	± 16.26	± 16.27	-
Sex: Female, Male Units: Subjects			
Female	247	241	488
Male	151	163	314
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	98	101	199
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	5	6
White	262	265	527
More than one race	0	0	0
Unknown or Not Reported	37	33	70

End points

End points reporting groups	
Reporting group title	QMF149 150/80 µg
Reporting group description:	
QMF149 150/80 microgram o.d. delivered via Concept1	
Reporting group title	MF 200 µg
Reporting group description:	
MF 200 microgram o.d. delivered via Twisthaler®	

Primary: trough FEV1	
End point title	trough FEV1
End point description:	
demonstrate the superiority of QMF149 150/80 microgram o.d. (in the evening) delivered via Concept1 compared with MF 200 microgram o.d. (in the evening) delivered via Twisthaler® in terms of trough FEV1 after 12 weeks of treatment in adults and adolescents. Forced Expiratory Volume in 1 second (FEV1) is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured by spirometry.	
End point type	Primary
End point timeframe:	
week 12	

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	377	375		
Units: Liters				
least squares mean (standard error)	2.562 (± 0.0134)	2.379 (± 0.0134)		

Statistical analyses

Statistical analysis title	Trough FEV1
Comparison groups	QMF149 150/80 µg v MF 200 µg
Number of subjects included in analysis	752
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.182

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.148
upper limit	0.217

Secondary: ACQ-7

End point title	ACQ-7

End point description:

ACQ-7 is an asthma control questionnaire (scoring 5 symptoms, FEV1 entered by the investigator and daily rescue bronchodilator use entered by the patient) validated to evaluate different levels of asthma control. the ACQ-7 was used to assess improvements in asthma symptom control. The ACQ-7, a seven-item disease-specific instrument developed and validated to assess asthma control in patients in clinical trials as well as in individuals in clinical practice, was provided to the site. All seven items were then scored on a 7-point Likert scale, with 0 indicating total control and 6 indicating no control. The questions were equally weighted and the total score was the mean of the seven items. The first 6 questions of the ACQ-7 were completed by the patient while the last question (question 7) was completed by the study investigator using spirometry data generated by the spirometry equipment.

End point type	Secondary

End point timeframe:

week 12

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	375	369		
Units: Units on a scale				
least squares mean (standard error)	1.323 (± 0.0411)	1.540 (± 0.0411)		

Statistical analyses

Statistical analysis title	ACQ-7
Comparison groups	QMF149 150/80 µg v MF 200 µg
Number of subjects included in analysis	744
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.218
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.293
upper limit	-0.143

Secondary: trough FEV1 at day 2

End point title	trough FEV1 at day 2

End point description:

Forced Expiratory Volume in 1 second (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

End point type	Secondary

End point timeframe:

Day 2

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	389	393		
Units: Liters				
least squares mean (standard error)	2.490 (± 0.0108)	2.358 (± 0.0108)		

Statistical analyses

Statistical analysis title	trough FEV1 at day 2
Comparison groups	QMF149 150/80 µg v MF 200 µg
Number of subjects included in analysis	782
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.132
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.105
upper limit	0.158

Secondary: Pre-dose FEV1 at week 4

End point title	Pre-dose FEV1 at week 4

End point description:

Pre-dose FEV1 is defined as the mean of -45 min and -15 min FEV1 values pre-evening dose

End point type	Secondary

End point timeframe:

week 4

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	389	386		
Units: Liters				
least squares mean (standard error)	2.545 (± 0.0132)	2.369 (± 0.0131)		

Statistical analyses

Statistical analysis title	Pre-dose FEV1 at week 4
Comparison groups	QMF149 150/80 µg v MF 200 µg
Number of subjects included in analysis	775
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.176
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.145
upper limit	0.207

Secondary: FVC over 12 weeks

End point title	FVC over 12 weeks

End point description:

FVC is the total amount of air exhaled during the FEV test. Forced Vital Capacity (FVC) and Forced Expiratory Flow between 25% and 75% of FVC (FEF25-75) will be measured

End point type	Secondary

End point timeframe:

week 12

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	383	379		
Units: Liters				
least squares mean (standard error)				
Pre dose trough FVC	3.453 (± 0.0169)	3.353 (± 0.0169)		

Pre-dose trough FEF25-75%	2.030 (± 0.0228)	1.742 (± 0.0228)		

Statistical analyses

Statistical analysis title	Pre-dose trough FEF25-75%
Statistical analysis description: Pre-dose trough FEF25-75%	
Comparison groups	QMF149 150/80 µg v MF 200 µg
Number of subjects included in analysis	762
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.288
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.231
upper limit	0.345

Statistical analysis title	Pre-dose trough FVC
Statistical analysis description: Pre-dose trough FVC	
Comparison groups	QMF149 150/80 µg v MF 200 µg
Number of subjects included in analysis	762
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.061
upper limit	0.139

Secondary: PEF over 4 and 12 weeks

End point title	PEF over 4 and 12 weeks

End point description:

Morning and Evening Peak Expiratory Flow Rate (PEF) will be measured. PEF is the peak expiratory flow,

the maximum speed of expiration

End point type	Secondary

End point timeframe:
week 12

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	404		
Units: L/min				
least squares mean (standard error)				
Mean Morning PEF(n=382, 382)	31.0 (± 1.98)	3.8 (± 1.97)		
Mean Evening PEF(n=386,386)	26.8 (± 1.84)	0.7 (± 1.84)		

Statistical analyses

Statistical analysis title	Mean Morning PEF
Statistical analysis description: Mean Morning PEF	
Comparison groups	QMF149 150/80 µg v MF 200 µg
Number of subjects included in analysis	802
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	27.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.1
upper limit	32.4

Statistical analysis title	Mean Evening PEF
Statistical analysis description: Mean Evening PEF	
Comparison groups	QMF149 150/80 µg v MF 200 µg
Number of subjects included in analysis	802
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	26.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	21
upper limit	31.2

Secondary: Percentage of patients with ACQ-7 MID at week 12

End point title	Percentage of patients with ACQ-7 MID at week 12

End point description:

MID is Minimum Important Difference. ACQ-7 is an asthma control questionnaire (scoring 5 symptoms, FEV1 entered by the investigator and daily rescue bronchodilator use entered by the patient) validated to evaluate different levels of asthma control. Percent of patients achieving the minimal important difference (MID) in ACQ-7 (i.e. at least 0.5 decrease from baseline) will be measured.

End point type	Secondary

End point timeframe:

week 12

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	375	370		
Units: Percentage				
number (not applicable)	74.7	64.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Daily e-diary over 12 weeks

End point title	Daily e-diary over 12 weeks

End point description:

Percentage of asthma symptoms free days, the percentage of nights without nighttime awakenings, and the percentage of mornings without symptoms on awakening as recorded by daily electronic Diary (e-Diary) over 12 weeks of treatment

End point type	Secondary

End point timeframe:

week 12

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	404		
Units: Percentage				
least squares mean (standard error)				
% of nights with no night-time awakenings	13.4 (± 1.37)	8.7 (± 1.36)		
% of mornings with no symptoms on awakening	14.7 (± 1.53)	11.2 (± 1.53)		
% of asthma symptom-free days	17.1 (± 1.68)	14.4 (± 1.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: ACQ-7 at week 4

End point title	ACQ-7 at week 4

End point description:

ACQ-7 is an asthma control questionnaire (scoring 5 symptoms, FEV1 entered by the investigator and daily rescue bronchodilator use entered by the patient) validated to evaluate different levels of asthma control

End point type	Secondary

End point timeframe:

week 4

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	372	378		
Units: Units on a scale				
least squares mean (standard error)	1.454 (± 0.0408)	1.658 (± 0.0406)		

Statistical analyses

Statistical analysis title	ACQ-7 at week 4
Comparison groups	QMF149 150/80 µg v MF 200 µg
Number of subjects included in analysis	750
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.204

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.277
upper limit	-0.131

Secondary: Rescue medication use over 12 weeks

End point title	Rescue medication use over 12 weeks
End point description:	
Rescue salbutamol/albuterol usage (mean daily, nighttime and daytime use) from e-Diary recordings over 12 weeks of treatment	
End point type	Secondary
End point timeframe:	
week 12	

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	404		
Units: Number of puffs of rescue medication				
least squares mean (standard error)				
Night-time number of puffs of rescue medication	-0.26 (± 0.025)	-0.16 (± 0.025)		
Daytime number of puffs of rescue medication	-0.39 (± 0.033)	-0.24 (± 0.032)		

Statistical analyses

Statistical analysis title	Night-time number of puffs of rescue medication
Statistical analysis description:	
Night-time number of puffs of rescue medication	
Comparison groups	QMF149 150/80 µg v MF 200 µg
Number of subjects included in analysis	802
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	-0.05

Statistical analysis title	Daytime number of puffs of rescue medication
Statistical analysis description: Daytime number of puffs of rescue medication	
Comparison groups	QMF149 150/80 µg v MF 200 µg
Number of subjects included in analysis	802
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	-0.08

Secondary: Percentage of rescue medication free days over 12 weeks	
End point title	Percentage of rescue medication free days over 12 weeks
End point description: Percentage of rescue medication free days over 12 weeks of treatment period	
End point type	Secondary
End point timeframe: week 12	

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384	385		
Units: Percentage				
least squares mean (standard error)	22.2 (± 1.81)	14.1 (± 1.80)		

Statistical analyses

Statistical analysis title	Percentage of rescue medication free days
Comparison groups	QMF149 150/80 µg v MF 200 µg

Number of subjects included in analysis	769
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	11.8

Secondary: Quality of life assessed by AQLQ-S 12

End point title	Quality of life assessed by AQLQ-S 12

End point description:

The AQLQ-S +12 is a 32-item disease specific questionnaire designed to measure functional impairments that were most important to patients with asthma. It consists of 4 domains: symptoms, emotions, exposure to environmental stimuli and activity limitation

End point type	Secondary

End point timeframe:

week 12

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	381	379		
Units: Score				
least squares mean (standard error)	5.779 (± 0.0475)	5.630 (± 0.0473)		

Statistical analyses

Statistical analysis title	Quality of life assessed by AQLQ-S 12
Comparison groups	QMF149 150/80 µg v MF 200 µg
Number of subjects included in analysis	760
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.149

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.064
upper limit	0.234

Secondary: Asthma exacerbation over 12 weeks

End point title	Asthma exacerbation over 12 weeks

End point description:

The exacerbation categories are: mild, moderate, severe and the combination of moderate or severe. Time to first asthma exacerbation by exacerbation category. Annual rate of asthma exacerbations by exacerbation category.

End point type	Secondary

End point timeframe:

Week 12

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	399		
Units: Number of patients				
Mild asthma exacerbation	11	29		
Moderate asthma exacerbation	7	23		
Severe asthma exacerbation	3	11		
Moderate or severe asthma exacerbation	10	32		

Statistical analyses

No statistical analyses for this end point

Secondary: The Annual Rate of Asthma Exacerbations (Moderate or Severe) Over the 12 Week Treatment Period

End point title	The Annual Rate of Asthma Exacerbations (Moderate or Severe) Over the 12 Week Treatment Period

End point description:

Annual incidence rate of asthma exacerbation by severity of exacerbation. The number of asthma exacerbation is used to calculate annual incidence rate. A severe asthma exacerbation is SCS (Systemic Corticosteroids) use ≥3 days and hospitalization or emergency department visit (greater than 24 h) or death due to asthma. A moderate asthma exacerbation is SCS use ≥3 days either as an outpatient or in emergency department visits (less than or equal to 24 h). Worsening of asthma not requiring more than 3 days of SCS or hospitalization/emergency room will be considered mild asthma exacerbations

End point type	Secondary

End point timeframe:

Week 12

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	394	397		
Units: Number of exacerbation				
number (not applicable)				
Moderate or severe asthma exacerbation	0.08	0.31		
All (mild, moderate, severe) asthma exacerbation	0.20	0.67		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first Asthma Exacerbations (Moderate or Severe) Over the 12 Week Treatment Period

End point title	Time to first Asthma Exacerbations (Moderate or Severe) Over the 12 Week Treatment Period

End point description:

Defined as the number of days from start of treatment up to the first date when an asthma exacerbation occurs.

End point type	Secondary

End point timeframe:

Week 12

End point values	QMF149 150/80 µg	MF 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	394	397		
Units: Count of participants				
number (not applicable)	10	32		

Statistical analyses

Statistical analysis title	The annual rate of asthma exacerbations
Comparison groups	QMF149 150/80 µg v MF 200 µg

Number of subjects included in analysis	791
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.59

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	MF 200
Reporting group description:	
MF 200	
Reporting group title	QMF149 150/80
Reporting group description:	
QMF149 150/80	

Serious adverse events	MF 200	QMF149 150/80	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 399 (1.75%)	5 / 396 (1.26%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	0 / 399 (0.00%)	1 / 396 (0.25%)	
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			
Ankle fracture			
subjects affected / exposed	1 / 399 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 399 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Incisional hernia			
subjects affected / exposed	0 / 399 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 399 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Appendix disorder			
subjects affected / exposed	1 / 399 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental cyst			
subjects affected / exposed	0 / 399 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 399 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 399 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	0 / 399 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess oral			
subjects affected / exposed	0 / 399 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 399 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 399 (0.50%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 399 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MF 200	QMF149 150/80	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 399 (26.57%)	69 / 396 (17.42%)	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	10 / 399 (2.51%)	5 / 396 (1.26%)	
occurrences (all)	12	5	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 399 (2.26%)	4 / 396 (1.01%)	
occurrences (all)	9	4	
Respiratory, thoracic and mediastinal			

disorders			
Asthma			
subjects affected / exposed	60 / 399 (15.04%)	20 / 396 (5.05%)	
occurrences (all)	79	24	
Cough			
subjects affected / exposed	4 / 399 (1.00%)	5 / 396 (1.26%)	
occurrences (all)	4	6	
Dysphonia			
subjects affected / exposed	2 / 399 (0.50%)	5 / 396 (1.26%)	
occurrences (all)	2	5	
Dyspnoea			
subjects affected / exposed	4 / 399 (1.00%)	0 / 396 (0.00%)	
occurrences (all)	4	0	
Rhinitis allergic			
subjects affected / exposed	0 / 399 (0.00%)	4 / 396 (1.01%)	
occurrences (all)	0	4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 399 (1.25%)	1 / 396 (0.25%)	
occurrences (all)	5	1	
Influenza			
subjects affected / exposed	4 / 399 (1.00%)	4 / 396 (1.01%)	
occurrences (all)	4	4	
Nasopharyngitis			
subjects affected / exposed	19 / 399 (4.76%)	17 / 396 (4.29%)	
occurrences (all)	21	19	
Pharyngitis			
subjects affected / exposed	2 / 399 (0.50%)	5 / 396 (1.26%)	
occurrences (all)	2	5	
Sinusitis			
subjects affected / exposed	5 / 399 (1.25%)	5 / 396 (1.26%)	
occurrences (all)	5	5	
Upper respiratory tract infection			
subjects affected / exposed	10 / 399 (2.51%)	4 / 396 (1.01%)	
occurrences (all)	10	4	
Viral upper respiratory tract infection			

subjects affected / exposed occurrences (all)	5 / 399 (1.25%) 5	1 / 396 (0.25%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2017	Adjust the approach to asthma worsening eDiary alerts during the Run-in epoch. It was earlier stated in the protocol, that if an asthma worsening alert is observed during the Run-in epoch, the patients must be discontinued regardless of clinical context and investigator judgment. This protocol amendment allowed investigators to use their discretion in determining the clinical significance of asthma worsening eDiary alerts during the Run-in epoch. This allowed the investigator to make the most appropriate decision as to whether patients may continue in the study or be discontinued. If asthma worsening alert was confirmed as clinically significant by the investigator, patients should be discontinued. A combination of eDiary alerts and investigator judgment was expected to help ensure that the most appropriate patients were enrolled in the study, while maintaining rigorous monitoring and assessment of patient safety
20 March 2018	The assumptions for Study B2303 key secondary endpoint, ACQ-7 treatment difference, were originally based on data from QMF149 Study A2210. In study A2210, the observed mean difference after 12 weeks of treatment (QMF149 vs MF) was −0.21 with 95% CI (−0.28, −0.15). Based on the upper limit of the CI, a treatment difference of −0.15 was chosen as a conservative estimate, which was used to determine the sample size of Study B2303. However, upon recent evaluation of the treatment difference of Study A2210, it was decided to adopt an ACQ-7 treatment difference of −0.18. This treatment difference is the upper limit of the one-sided 80% CI and more appropriately reflects the expected improvement in ACQ-7 for the patient population of Study B2303. Reflecting the revised assumptions, the sample size re-estimation has allowed for a reduction from 1000 to approximately 750 patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported