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Novartis Clinical Trial Results

Sponsor

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Generic Drug Name

Indacaterol acetate/mometasone furoate/QMF149

Trial Indication(s)

Asthma

Protocol Number

CQVM149B2301

Protocol Title

A multi-center, randomized, 52 week treatment, double-blind, triple-dummy, parallel-group study to assess the efficacy and safety of QMF149 compared with mometasone furoate in patients with asthma.

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

29-Dec-2015 to 28-Jun-2019

Reason for Termination

Not applicable.

Study Design/Methodology

A 52-week treatment, randomized, double-blind, triple-dummy, parallel-group design. At the screening visit, informed consent was obtained, and current asthma and non-asthma medications were reviewed and adjusted. All patients must have used inhaled medium or high dose corticosteroids and/or low dose long-acting β2-adrenergic agonist/inhaled corticosteroids (LABA/ICS) for at least 3 months and on a stable dose for at least 1 month prior to Visit 1 (Screening).

At Visit 101, all patients received open- label fluticasone propionate 100 µg b.i.d. delivered via Accuhaler® (if not available in a specific country, open-label fluticasone propionate 125 µg b.i.d. via metered dose inhaler or fluticasone low dose equivalent could be used throughout the Run-In epoch and stopped at Visit 102 (end of Run-In epoch).

Patients meeting the eligibility criteria at the end of Run-in were randomized to 1 of 5 treatment groups: (QMF149 150/160 µg o.d. or QMF149 150/320 µg o.d., delivered via the Concept1 device, MF 400 µg o.d. (medium MF dose) and MF 800 µg (administered as 400 µg b.i.d.) (high MF dose) both delivered via Twisthaler®, or salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d. (Seretide®) delivered via Accuhaler®. The 52-week treatment period was followed by a 30-day Follow-up.

Centers

The study was conducted in 24 countries (at 316 sites): Bulgaria (14), China (24), Croatia (4), Czech Republic (14), Egypt (2), Estonia (2), Germany (45), Guatemala (6), Hungary (22), India (18), Ireland (1), Japan (20), Latvia (5), Lithuania (4), Mexico (4), Poland (13), Republic of Korea (6), Romania (19), Russian Federation (39), Serbia (5), Slovakia (20), South Africa (6), United Kingdom (3), United States (20).

Objectives:

Primary objective(s)

Primary Objective: The primary objective was to demonstrate the superiority of QMF149 150/160 µg delivered via Concept1 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® (administered as 400 µg b.i.d.) in terms of trough forced expiratory volume in one second (trough FEV1) after 26 weeks of treatment in patients with asthma.

Secondary objective(s)

The key secondary objective was to demonstrate the superiority of QMF149 (150/160 µg and 150/320 µg combined) to MF (400 µg and 800 µg combined) in terms of Asthma Control Questionnaire (ACQ-7) after 26 weeks of treatment in patients with asthma.

Test Product (s), Dose(s), and Mode(s) of Administration

QMF149 (indacaterol acetate/MF) was supplied to the Investigators as powder in hard capsules 150/160 µg and 150/320 µg to be delivered via Concept1 inhaler.

Statistical Methods

The comparisons of QMF149 doses: medium (150/160 µg o.d.) and high (150/320 µg o.d.) delivered via Concept1, versus the 2 corresponding MF doses, medium (400 µg o.d.) and high (800 µg, administered as 400 µg b.i.d.) delivered via Twisthaler® were evaluated by testing the following null hypothesis (H0) versus the alternative hypothesis (Ha):

H0: QMF149 treatment group is equal to the MF treatment group in trough FEV1 at Week 26

Ha:

QMF149 treatment group is not equal to the MF treatment group in trough FEV1 at Week 26

The primary variable was analyzed using a mixed model for repeated measure (MMRM) on the FAS. The model contains treatment, age (12 to 17 or ≥18 years), region, visit (Days 2, 184 and 365), and treatment-by-visit interaction as fixed effects with baseline FEV1 measurement, baseline-by-visit interaction, FEV1 prior to inhalation and FEV1 within 15 to 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility) as covariates, and center nested within region as a random effect. The estimated adjusted treatment difference (QMF149--MF) was displayed along with the associated standard error, 2-sided 95% confidence interval, and p-value (2-sided).

The key secondary endpoint was analyzed using the same MMRM model (including all available visits) on the FAS as used for the primary analysis but included baseline ACQ-7 score instead of baseline FEV1.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

-Patients with a diagnosis of asthma, for a period of at least 1 year prior to Visit 1 (Screening)
-Patients who have used medium or high dose ICS or low dose of LABA/ICS combinations for asthma for at least 3 months and at stable doses for at least 1 month prior to Visit 1
- Patients must have ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (prior to double-blind treatment) and qualify for treatment with medium or high dose LABA/ICS
-Pre-bronchodilator ≥ 50% FEV1 of < 85 % of the predicted normal value for the patient after withholding bronchodilators at both Visit 101 and 102, according to ATS/ERS criteria.
-Withholding period of bronchodilators prior to spirometry: SABA for ≥ 6 hours and FDC or free combinations of ICS/LABA for ≥ 48 hours, SAMA for ≥ 8 hours, xanthines >=07 days

-A one-time repeat/re-testing of percent predicted FEV1 (prebronchodilator FEV1) is allowed at Visit 101 and at Visit 102. Spacer devices are permitted for reversibility testing only.
-Patients who demonstrate an increase in FEV1 of 12% and 200 mL within 30 minutes after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at Visit 101
All patients must perform a reversibility test at Visit 101
If reversibility is not demonstrated at Visit 101:
- Reversibility should be repeated once-
- Patients may be permitted to enter the study with historical evidence of reversibility that was performed according to ATS/ERS guidelines within 2 years prior to Visit 1
- Alternatively, patients may be permitted to enter the study with a historical positive bronchoprovocation test that was performed within 2 years prior to Visit 1.

Exclusion Criteria:
-Patients who have smoked or inhaled tobacco products within the 6 month period prior to Visit 1, or who have a smoking history of greater than 10 pack years. This includes use of nicotine inhalers such as e-cigarettes at the time of Visit 1
-Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of Visit 1 (Screening)
-Patients who have ever required intubation for a severe asthma attack/exacerbation.
-Patients who have a clinical condition which is likely to be worsened by ICS administration (e.g. glaucoma, cataract and fragility fractures) who are according to investigator's medical judgment at risk participating in the study).
-Patients who have had a respiratory tract infection or asthma worsening as determined by the investigator within 4 weeks prior to Visit 1 (Screening) or between Visit 1 and Visit 102. Patients may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening.
-Patients with a history of chronic lung diseases other than asthma, including (but not limited to) COPD, sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis and active tuberculosis.
-Patients with severe narcolepsy and/or insomnia.
-Patients who have a clinically significant ECG abnormality at Visit 101 (Start of Run- In epoch) and at any time between Visit 101 and Visit 102 (including unscheduled ECG). ECG evidence of myocardial infarction at Visit 101 (via central reader) should be clinically assessed by the investigator with supportive documentation
-Patients with a history of hypersensitivity to lactose, any of the study drugs or to similar drugs within the class including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof

-Patients who have not achieved an acceptable spirometry results at Visit 101 in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) criteria for acceptability and repeatability (rescreening allowed only once). Repeat spirometry may be allowed once in an ad-hoc visit if the spirometry did not qualify due to ATS/ERS criteria. If the patient fails the repeat assessment, the patient may be rescreened once
-Patients on Maintenance Immunotherapy (desensitization) for allergies or less than 3 months prior to Visit 101 or patients on Maintenance Immunotherapy for more than 3 months prior to Visit 101 but expected to change throughout the course of the study.
-Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment and for 30 days after stopping of study treatment.
- LAMA use within 3 months prior to Visit 101

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Participant Flow Table

Patient disposition (All screened patients)

Disposition Reason	QMF149 150/320 n (%)	QMF149 150/160 n (%)	MF 800 n (%)	MF 400 n (%)	S/F 50/500 n (%)	Total n (%)
Screened						3890
Randomized	445	439	442	444	446	2216
Treatment phase completer	410 (92.1)	413 (94.1)	412 (93.2)	403 (90.8)	416 (93.3)	2054 (92.7)
Premature discontinuation of treatment phase	35 (7.9)	26 (5.9)	30 (6.8)	41 (9.2)	30 (6.7)	162 (7.3)
Primary reason for premature discontinuation of treatment phase						
Subject/guardian decision	29 (6.5)	17 (3.9)	18 (4.1)	30 (6.8)	20 (4.5)	114 (5.1)
Lost to follow-up	4 (0.9)	3 (0.7)	4 (0.9)	2 (0.5)	2 (0.4)	15 (0.7)
Protocol deviation	1 (0.2)	3 (0.7)	3 (0.7)	4 (0.9)	2 (0.4)	13 (0.6)
Technical problems	1 (0.2)	1 (0.2)	0	2 (0.5)	1 (0.2)	5 (0.2)
Adverse event	0	0	0	0	2 (0.4)	2 (0.1)
Death	0	0	0	1 (0.2)	0	1 (0.0)
Non-compliance with study treatment	0	1 (0.2)	1 (0.2)	0	1 (0.2)	3 (0.1)
Physician decision	0	1 (0.2)	4 (0.9)	1 (0.2)	1 (0.2)	7 (0.3)
Pregnancy	0	0	0	1 (0.2)	1 (0.2)	2 (0.1)

The primary reason for discontinuation is summarized as given by the investigator on the Treatment Phase Disposition eCRF.

Reasons are ordered by descending frequency of the QMF 150/320 group.

Percentages are based on the number of randomized patients.

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Baseline Characteristics

Demographics (Randomized set)

Variable Statistic/Category	QMF149 150/320 N=445	QMF149 150/160 N=439	MF 800 N=442	MF 400 N=444	S/F 50/500 N=446	Total N=2216
Age (years)						
n	445	439	442	444	446	2216
Mean (SD)	47.1 (14.56)	47.4 (14.76)	47.5 (14.99)	48.7 (14.98)	48.9 (14.59)	47.9 (14.78)
Median	48.0	49.0	50.0	50.0	52.0	49.5
Min - Max	12 - 75	12 - 74	12 - 75	12 - 74	12 - 74	12 - 75
Age group in years, n (%)						
12-17	22 (4.9)	20 (4.6)	21 (4.8)	22 (5.0)	22 (4.9)	107 (4.8)
18-64	369 (82.9)	355 (80.9)	369 (83.5)	354 (79.7)	365 (81.8)	1812 (81.8)
>= 65	54 (12.1)	64 (14.6)	52 (11.8)	68 (15.3)	59 (13.2)	297 (13.4)
Gender, n (%)						
Male	183 (41.1)	186 (42.4)	192 (43.4)	172 (38.7)	190 (42.6)	923 (41.7)
Female	262 (58.9)	253 (57.6)	250 (56.6)	272 (61.3)	256 (57.4)	1293 (58.3)
Race, n (%)						
Caucasian	313 (70.3)	311 (70.8)	318 (71.9)	312 (70.3)	305 (68.4)	1559 (70.4)
Black	5 (1.1)	2 (0.5)	4 (0.9)	8 (1.8)	4 (0.9)	23 (1.0)
Asian	97 (21.8)	98 (22.3)	98 (22.2)	98 (22.1)	102 (22.9)	493 (22.2)
Native American	13 (2.9)	14 (3.2)	11 (2.5)	18 (4.1)	12 (2.7)	68 (3.1)
Pacific Islander	1 (0.2)	0	0	0	0	1 (0.0)
Other	16 (3.6)	14 (3.2)	11 (2.5)	8 (1.8)	23 (5.2)	72 (3.2)

Age is calculated based on imputed day and month, since only year of birth is collected.

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Primary Outcome Result(s)

Trough FEV1 (L): MMRM of absolute value and change from baseline by visit (FAS)

						---- Treatment difference ----		
Visit	Treatment	n	Absolute value LS Mean (SE)	Change from baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
Baseline	All		2.101					
Day 2	QMF 150/320	432	2.314 (0.0117)	0.212 (0.0117)	QMF 150/320 - MF 800	0.136 (0.0163)	(0.104, 0.168)	<.001
					QMF 150/320 - S/F 50/500	-0.002 (0.0162)	(-0.034, 0.030)	0.914
	QMF 150/160	430	2.308 (0.0118)	0.206 (0.0118)	QMF 150/160 - MF 400	0.180 (0.0161)	(0.149, 0.212)	<.001
	MF 800	410	2.178 (0.0120)	0.077 (0.0120)				
	MF 400	435	2.127 (0.0117)	0.026 (0.0117)				
	S/F 50/500	419	2.316 (0.0119)	0.214 (0.0119)				
Day 184	QMF 150/320	395	2.383 (0.0159)	0.281 (0.0159)	QMF 150/320 - MF 800	0.132 (0.0223)	(0.088, 0.176)	<.001
					QMF 150/320 - S/F 50/500	0.036 (0.0222)	(-0.007, 0.080)	0.101
	QMF 150/160	389	2.387 (0.0160)	0.286 (0.0160)	QMF 150/160 - MF 400	0.211 (0.0224)	(0.167, 0.255)	<.001
	MF 800	372	2.250 (0.0162)	0.149 (0.0162)				
	MF 400	376	2.176 (0.0162)	0.075 (0.0162)				
	S/F 50/500	391	2.346 (0.0160)	0.245 (0.0160)				
Day 365	QMF 150/320	372	2.386 (0.0168)	0.284 (0.0168)	QMF 150/320 - MF 800	0.136 (0.0235)	(0.090, 0.183)	<.001
					QMF 150/320 - S/F 50/500	0.048 (0.0234)	(0.002, 0.094)	0.040
	QMF 150/160	383	2.357 (0.0167)	0.255 (0.0167)	QMF 150/160 - MF 400	0.209 (0.0235)	(0.163, 0.255)	<.001
	MF 800	364	2.249 (0.0170)	0.148 (0.0170)				
	MF 400	369	2.148 (0.0170)	0.046 (0.0170)				

	S/F 50/500	382	2.338 (0.0167)	0.236 (0.0167)

Number of patients included in the analysis: QMF149 150/320: n=439, QMF149 150/160: n=433, MF 800: n=436, MF 400: n=441, S/F 50/500: n=441

n: n is the number of patients with data at respective visit. Estimates from the MMRM model consider the full time course data and not only those at respective visit.

Secondary Outcome Result(s)

ACQ-7: MMRM of absolute value and change from baseline by visit (FAS)

						---- Treatment difference ----		
Visit	Treatment	n	Absolute value LS Mean (SE)	Change from baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
Baseline	All		2.298					
Day 183	QMF 150/320	407	1.267 (0.0350)	-1.030 (0.0350)	QMF 150/320 - MF 800	-0.171 (0.0437)	(-0.257, -0.086)	<.001
					QMF 150/320 - S/F 50/500	-0.054 (0.0437)	(-0.140, 0.031)	0.214
	QMF 150/160	407	1.261 (0.0350)	-1.036 (0.0350)	QMF 150/160 - MF 400	-0.248 (0.0439)	(-0.334, -0.162)	<.001
	QMF	814	1.264 (0.0273)	-1.033 (0.0273)	QMF - MF	-0.209 (0.0310)	(-0.270, -0.149)	<.001
	MF 800	405	1.439 (0.0352)	-0.859 (0.0352)				
	MF 400	393	1.509 (0.0354)	-0.789 (0.0354)				
	MF	798	1.474 (0.0277)	-0.824 (0.0277)				
	S/F 50/500	410	1.322 (0.0349)	-0.976 (0.0349)				
Day 364	QMF 150/320	385	1.231 (0.0358)	-1.066 (0.0358)	QMF 150/320 - MF 800	-0.141 (0.0449)	(-0.229, -0.053)	0.002
					QMF 150/320 - S/F 50/500	0.010 (0.0447)	(-0.078, 0.098)	0.824
	QMF 150/160	397	1.183 (0.0356)	-1.114 (0.0356)	QMF 150/160 - MF 400	-0.266 (0.0450)	(-0.354, -0.177)	<.001

QMF	782	1.207 (0.0278)	-1.090 (0.0278)	QMF - MF	-0.203 (0.0318)	(-0.266, -0.141)	<.001
MF 800	387	1.373 (0.0359)	-0.925 (0.0359)				
MF 400	377	1.449 (0.0361)	-0.849 (0.0361)				
MF	764	1.411 (0.0281)	-0.887 (0.0281)				
S/F 50/500	405	1.221 (0.0354)	-1.076 (0.0354)				

Number of patients included in the analysis: QMF149 150/320: n=429, QMF149 150/160: n=427, MF 800: n=431, MF 400: n=428, S/F 50/500: n=439
n: n is the number of patients with data at respective visit. Estimates from the MMRM model consider the full time course data and not only those at respective visit.

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Trough FEV1 (L): MMRM of absolute value and change from baseline by visit (FAS)

						---- Treatment difference ----		
Visit	Treatment	n	Absolute value LS Mean (SE)	Change from baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
Baseline	All		2.101					
Day 2	QMF 150/320	432	2.314 (0.0117)	0.212 (0.0117)	QMF 150/320 - MF 800	0.136 (0.0163)	(0.104, 0.168)	<.001
					QMF 150/320 - S/F 50/500	-0.002 (0.0162)	(-0.034, 0.030)	0.914
	QMF 150/160	430	2.308 (0.0118)	0.206 (0.0118)	QMF 150/160 - MF 400	0.180 (0.0161)	(0.149, 0.212)	<.001
	MF 800	410	2.178 (0.0120)	0.077 (0.0120)				
	MF 400	435	2.127 (0.0117)	0.026 (0.0117)				
	S/F 50/500	419	2.316 (0.0119)	0.214 (0.0119)				
Day 184	QMF 150/320	395	2.383 (0.0159)	0.281 (0.0159)	QMF 150/320 - MF 800	0.132 (0.0223)	(0.088, 0.176)	<.001
					QMF 150/320 - S/F 50/500	0.036 (0.0222)	(-0.007, 0.080)	0.101
	QMF 150/160	389	2.387 (0.0160)	0.286 (0.0160)	QMF 150/160 - MF 400	0.211 (0.0224)	(0.167, 0.255)	<.001
	MF 800	372	2.250 (0.0162)	0.149 (0.0162)				
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	S/F 50/500	391	2.346 (0.0160)	0.245 (0.0160)				
Day 365	QMF 150/320	372	2.386 (0.0168)	0.284 (0.0168)	QMF 150/320 - MF 800	0.136 (0.0235)	(0.090, 0.183)	<.001
					QMF 150/320 - S/F 50/500	0.048 (0.0234)	(0.002, 0.094)	0.040
	QMF 150/160	383	2.357 (0.0167)	0.255 (0.0167)	QMF 150/160 - MF 400	0.209 (0.0235)	(0.163, 0.255)	<.001
	MF 800	364	2.249 (0.0170)	0.148 (0.0170)				
	MF 400	369	2.148 (0.0170)	0.046 (0.0170)				
	S/F 50/500	382	2.338 (0.0167)	0.236 (0.0167)				

Number of patients included in the analysis: QMF149 150/320: n=439, QMF149 150/160: n=433, MF 800: n=436, MF 400: n=441, S/F 50/500: n=441

n: n is the number of patients with data at respective visit. Estimates from the MMRM model consider the full time course data and not only those at respective visit.

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Mean evening PEF (L/min) during Weeks 1 - 52: Linear Mixed Model (LMM) of change from baseline (FAS)

					Treatment difference		
Treatment	n	Baseline Raw Mean	Change from Baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
All	2100	333.5					
QMF 150/320	416	335.1	31.2 (2.14)	QMF 150/320 - MF 800	23.7 (2.94)	(18.0, 29.5)	<.001
				QMF 150/320 - S/F 50/500	9.1 (2.95)	(3.3, 14.9)	0.002
QMF 150/160	420	336.8	28.7 (2.13)	QMF 150/160 - MF 400	29.1 (2.94)	(23.3, 34.8)	<.001
MF 800	424	337.6	7.4 (2.13)				
MF 400	418	331.0	-0.3 (2.14)				
S/F 50/500	422	327.2	22.1 (2.13)				

n = number of patients included in the analysis.
Baseline raw means are not from the model.

Mean morning PEF (L/min) during Weeks 1 - 52: Linear Mixed Model (LMM) of change from baseline (FAS)

					Treatment difference		
Treatment	n	Baseline Raw Mean	Change from Baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
All	2108	321.8					
QMF 150/320	415	322.8	42.1 (2.24)	QMF 150/320 - MF 800	28.7 (3.07)	(22.7, 34.8)	<.001
				QMF 150/320 - S/F 50/500	13.8 (3.08)	(7.7, 19.8)	<.001
QMF 150/160	420	323.9	36.9 (2.22)	QMF 150/160 - MF 400	30.2 (3.07)	(24.2, 36.3)	<.001
MF 800	427	327.1	13.4 (2.21)				
MF 400	422	320.1	6.7 (2.22)				
S/F 50/500	424	315.2	28.3 (2.22)				

n = number of patients included in the analysis.
Baseline raw means are not from the model.

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Overview of the number of patients with asthma exacerbations, by exacerbation category (FAS)

Type of exaoerbation	QMF149 150/320 N=443 n (%)	QMF149 150/160 N=437 n (%)	MF 800 N=440 n (%)	MF 400 N=443 n (%)	S/F 50/500 N=444 n (%)
Moderate or severe asthma exacerbation	66 (14.9)	74 (16.9)	115 (26.1)	144 (32.5)	85 (19.1)
Severe asthma exacerbation	36 (8.1)	43 (9.8)	64 (14.5)	89 (20.1)	53 (11.9)
Moderate asthma exacerbation	34 (7.7)	36 (8.2)	63 (14.3)	73 (16.5)	41 (9.2)
Mild asthma exacerbation	59 (13.3)	53 (12.1)	77 (17.5)	87 (19.6)	67 (15.1)
All (mild, moderate, severe) asthma exacerbation	113 (25.5)	112 (25.6)	159 (36.1)	197 (44.5)	136 (30.6)
Asthma exacerbation requiring hospitalization	3 (0.7)	1 (0.2)	6 (1.4)	7 (1.6)	2 (0.5)
Asthma exacerbation causing permanent discontinuation of study drug	1 (0.2)	0	4 (0.9)	7 (1.6)	2 (0.5)

Asthma exacerbations starting between first dose and one day after date of last treatment are included.
All analyses are based on data reported on the 'Asthma Exacerbation Episodes' eCRF.

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Rate of asthma exacerbations, by exacerbation category (FAS)

Exacerbation category Treatment	n	Annualized rate (95% CI)	Comparison	Rate ratio	(95% CI)	p-value
Moderate or severe asthma exacerbation						
QMF 150/320 (N=443)	443	0.25 (0.20, 0.32)	QMF 150/320 / MF 800	0.65	(0.48, 0.89)	0.008
			QMF 150/320 / S/F 50/500	0.93	(0.67, 1.29)	0.669
QMF 150/160 (N=437)	437	0.27 (0.21, 0.34)	QMF 150/160 / MF 400	0.47	(0.35, 0.64)	<.001
QMF (N=880)	880	0.26 (0.22, 0.31)	QMF / MF	0.56	(0.45, 0.69)	<.001
MF 800 (N=440)	440	0.39 (0.32, 0.48)				
MF 400 (N=443)	443	0.56 (0.46, 0.68)				
MF (N=883)	883	0.47 (0.41, 0.54)				
S/F 50/500 (N=444)	444	0.27 (0.22, 0.34)				
Severe asthma exacerbation						
QMF 150/320 (N=443)	443	0.13 (0.09, 0.17)	QMF 150/320 / MF 800	0.71	(0.47, 1.08)	0.108
			QMF 150/320 / S/F 50/500	0.89	(0.58, 1.37)	0.597
QMF 150/160 (N=437)	437	0.13 (0.10, 0.18)	QMF 150/160 / MF 400	0.46	(0.31, 0.67)	<.001
QMF (N=880)	880	0.13 (0.10, 0.16)	QMF / MF	0.57	(0.43, 0.76)	<.001
MF 800 (N=440)	440	0.18 (0.13, 0.23)				
MF 400 (N=443)	443	0.29 (0.23, 0.38)				
MF (N=883)	883	0.23 (0.19, 0.28)				
S/F 50/500 (N=444)	444	0.14 (0.10, 0.19)				
All (mild, moderate, severe) asthma exacerbation						
QMF 150/320 (N=443)	443	0.49 (0.41, 0.60)	QMF 150/320 / MF 800	0.67	(0.52, 0.87)	0.002
			QMF 150/320 / S/F 50/500	0.95	(0.72, 1.23)	0.681
QMF 150/160 (N=437)	437	0.48 (0.40, 0.59)	QMF 150/160 / MF 400	0.46	(0.36, 0.59)	<.001
QMF (N=880)	880	0.49 (0.43, 0.56)	QMF / MF	0.55	(0.46, 0.66)	<.001
MF 800 (N=440)	440	0.74 (0.62, 0.88)				
MF 400 (N=443)	443	1.05 (0.89, 1.24)				
MF (N=883)	883	0.88 (0.78, 0.99)				
S/F 50/500 (N=444)	444	0.52 (0.43, 0.63)				

n = number of patients included in the analysis

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Cox regression of time to first asthma exacerbation, by exacerbation category (FAS)

Exacerbation category Treatment	n/M (%)	Comparison	Hazard Ratio	(95% CI)	p-value
Moderate or severe asthma exacerbation					
QMF 150/320 (N=443)	66/ 443 (14.9)	QMF 150/320 / MF 800	0.53	(0.39, 0.72)	<.001
		QMF 150/320 / S/F 50/500	0.81	(0.59, 1.12)	0.209
QMF 150/160 (N=437)	74/ 437 (16.9)	QMF 150/160 / MF 400	0.45	(0.34, 0.60)	<.001
QMF (N=880)	140/ 880 (15.9)	QMF / MF	0.49	(0.40, 0.60)	<.001
MF 800 (N=440)	115/ 440 (26.1)				
MF 400 (N=443)	144/ 443 (32.5)				
MF (N=883)	259/ 883 (29.3)				
S/F 50/500 (N=444)	85/ 444 (19.1)				
Severe asthma exacerbation					
QMF 150/320 (N=443)	36/ 443 (8.1)	QMF 150/320 / MF 800	0.54	(0.36, 0.81)	0.003
		QMF 150/320 / S/F 50/500	0.71	(0.47, 1.09)	0.115
QMF 150/160 (N=437)	43/ 437 (9.8)	QMF 150/160 / MF 400	0.44	(0.30, 0.63)	<.001
QMF (N=880)	79/ 880 (9.0)	QMF / MF	0.49	(0.37, 0.64)	<.001
MF 800 (N=440)	64/ 440 (14.5)				
MF 400 (N=443)	89/ 443 (20.1)				
MF (N=883)	153/ 883 (17.3)				
S/F 50/500 (N=444)	53/ 444 (11.9)				
All (mild, moderate, severe) asthma exacerbation					
QMF 150/320 (N=443)	113/ 443 (25.5)	QMF 150/320 / MF 800	0.66	(0.51, 0.82)	<.001
		QMF 150/320 / S/F 50/500	0.84	(0.66, 1.08)	0.185
QMF 150/160 (N=437)	112/ 437 (25.6)	QMF 150/160 / MF 400	0.48	(0.38, 0.60)	<.001
QMF (N=880)	225/ 880 (25.6)	QMF / MF	0.55	(0.47, 0.66)	<.001
MF 800 (N=440)	159/ 440 (36.1)				
MF 400 (N=443)	197/ 443 (44.5)				
MF (N=883)	356/ 883 (40.3)				
S/F 50/500 (N=444)	136/ 444 (30.6)				

n: The number of patients with at least one type of asthma exacerbation.
M: The number of patients included in the analysis. N: Number of patients in the analysis set.

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Proportion of patients with an improvement of at least 0.5 units in the ACQ-7 score, by visit (FAS)

Visit Treatment	n/M (%)	Comparison	Odds Ratio	95% CI	p-value
Day 183					
QMF 150/320 (N=443)	311/407 (76.4)	QMF 150/320 / MF 800	1.31	(0.95, 1.81)	0.094
		QMF 150/320 / S/F 50/500	1.06	(0.76, 1.46)	0.746
QMF 150/160 (N=437)	310/407 (76.2)	QMF 150/160 / MF 400	1.73	(1.26, 2.37)	<.001
QMF (N=880)	621/814 (76.3)	QMF / MF	1.51	(1.20, 1.89)	<.001
MF 800 (N=440)	293/405 (72.3)				
MF 400 (N=443)	263/393 (66.9)				
MF (N=883)	556/798 (69.7)				
S/F 50/500 (N=444)	311/410 (75.9)				
Day 364					
QMF 150/320 (N=443)	299/385 (77.7)	QMF 150/320 / MF 800	1.34	(0.96, 1.87)	0.088
		QMF 150/320 / S/F 50/500	1.05	(0.75, 1.49)	0.771
QMF 150/160 (N=437)	326/397 (82.1)	QMF 150/160 / MF 400	2.24	(1.58, 3.17)	<.001
QMF (N=880)	625/782 (79.9)	QMF / MF	1.73	(1.36, 2.20)	<.001
MF 800 (N=440)	285/387 (73.6)				
MF 400 (N=443)	261/377 (69.2)				
MF (N=883)	546/764 (71.5)				
S/F 50/500 (N=444)	313/405 (77.3)				

n: The number of patients with an improvement of at least 0.5 units, i.e. a decrease of >= 0.5 units in ACQ-7.
M: The number of patients with data at the respective visit. N: Number of patients in the analysis set.

NOVARTIS

Asthma Quality of Life Questionnaire (AQLQ-S) overall score: MMRM of absolute value and change from baseline at Week 52 (FAS)

						---- Treatment difference ----		
Visit	Treatment	n	Absolute value LS Mean (SE)	Change from baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
Baseline	All		4.971					
Day 183	QMF 150/320	406	5.724 (0.0372)	0.754 (0.0372)	QMF 150/320 - MF 800	0.127 (0.0526)	(0.023, 0.230)	0.016
					QMF 150/320 - S/F 50/500	0.085 (0.0525)	(-0.017, 0.188)	0.103
	QMF 150/160	407	5.738 (0.0372)	0.767 (0.0372)	QMF 150/160 - MF 400	0.156 (0.0529)	(0.053, 0.260)	0.003
	MF 800	405	5.598 (0.0372)	0.627 (0.0372)				
	MF 400	393	5.581 (0.0376)	0.611 (0.0376)				
	S/F 50/500	410	5.639 (0.0369)	0.668 (0.0369)				
Day 364	QMF 150/320	384	5.783 (0.0391)	0.813 (0.0391)	QMF 150/320 - MF 800	0.079 (0.0552)	(-0.030, 0.187)	0.154
					QMF 150/320 - S/F 50/500	0.041 (0.0548)	(-0.067, 0.148)	0.455
	QMF 150/160	397	5.832 (0.0388)	0.861 (0.0388)	QMF 150/160 - MF 400	0.191 (0.0553)	(0.082, 0.299)	<.001
	MF 800	389	5.705 (0.0389)	0.734 (0.0389)				
	MF 400	378	5.641 (0.0394)	0.670 (0.0394)				
	S/F 50/500	405	5.742 (0.0384)	0.772 (0.0384)				

Number of patients included in the analysis: QMF149 150/320: n=428, QMF149 150/160: n=426, MF 800: n=431, MF 400: n=428, S/F 50/500: n=438

n: n is the number of patients with data at respective visit. Estimates from the MMRM model consider the full time course data and not only those at respective visit.

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Mean daily number of puffs of rescue medication during Weeks 1-52: Linear Mixed Model (LMM) of change from baseline (FAS)

					——— Treatment difference ———		
Treatment	n	Baseline Raw Mean	Change from Baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
All	2147	1.63					
QMF 150/320	426	1.57	-1.00 (0.060)	QMF 150/320 - MF 800	-0.28 (0.081)	(-0.44,-0.12)	<.001
				QMF 150/320 - S/F 50/500	-0.09 (0.081)	(-0.25,0.06)	0.245
QMF 150/160	428	1.62	-0.80 (0.060)	QMF 150/160 - MF 400	-0.23 (0.081)	(-0.39,-0.07)	0.004
MF 800	433	1.54	-0.72 (0.060)				
MF 400	428	1.70	-0.56 (0.060)				
S/F 50/500	432	1.70	-0.91 (0.060)				

n = number of patients included in the analysis.
Baseline raw means are not from the model.

Percentage of rescue medication free days during Weeks 1 – 52: Linear Mixed Model (LMM) of change from baseline (FAS)

					——— Treatment difference ———		
Treatment	n	Baseline Raw Mean	Change from Baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
All	2074	43.9					
QMF 150/320	408	43.4	33.1 (1.55)	QMF 150/320 - MF 800	9.6 (2.03)	(5.7, 13.6)	<.001
				QMF 150/320 - S/F 50/500	4.3 (2.04)	(0.3, 8.3)	0.034
QMF 150/160	416	42.9	29.4 (1.54)	QMF 150/160 - MF 400	8.6 (2.03)	(4.7, 12.6)	<.001
MF 800	420	46.9	23.5 (1.54)				
MF 400	414	43.7	20.8 (1.54)				
S/F 50/500	416	42.6	28.8 (1.54)				

n = number of patients included in the analysis.
Baseline raw means are not from the model.

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Percentage of nights with no night-time awakenings during Weeks 1-52: Linear Mixed Model (LMM) of change from baseline (FAS)

					——— Treatment difference ———		
Treatment	n	Baseline Raw Mean	Change from Baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
All	2109	65.9					
QMF 150/320	415	66.0	17.0 (1.28)	QMF 150/320 - MF 800	2.8 (1.72)	(-0.6, 6.2)	0.104
				QMF 150/320 - S/F 50/500	0.9 (1.73)	(-2.5, 4.3)	0.588
QMF 150/160	420	65.5	16.4 (1.27)	QMF 150/160 - MF 400	3.9 (1.72)	(0.5, 7.3)	0.024
MF 800	428	66.7	14.2 (1.27)				
MF 400	422	66.3	12.5 (1.27)				
S/F 50/500	424	65.2	16.1 (1.27)				

n = number of patients included in the analysis.
Baseline raw means are not from the model.

Mean total daily symptom score during Weeks 1 - 52: Linear Mixed Model (LMM) of change from baseline (FAS)

					——— Treatment difference ———		
Treatment	n	Baseline Raw Mean	Change from Baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
All	2020	2.01					
QMF 150/320	401	1.96	-0.91 (0.051)	QMF 150/320 - MF 800	-0.15 (0.067)	(-0.28,-0.02)	0.027
				QMF 150/320 - S/F 50/500	-0.08 (0.067)	(-0.22,0.05)	0.209
QMF 150/160	402	2.04	-0.88 (0.051)	QMF 150/160 - MF 400	-0.32 (0.067)	(-0.45,-0.19)	<.001
MF 800	408	1.98	-0.76 (0.051)				
MF 400	404	1.99	-0.56 (0.051)				
S/F 50/500	405	2.07	-0.83 (0.051)				

n = number of patients included in the analysis.
Baseline raw means are not from the model.

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Percentage of asthma symptom-free days during Weeks 1 - 52: Linear Mixed Model (LMM) of change from baseline (FAS)

					Treatment difference		
Treatment	n	Baseline Raw Mean	Change from Baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
All	2020	14.2					
QMF 150/320	401	16.0	28.3 (1.72)	QMF 150/320 - MF 800	5.8 (2.29)	(1.3, 10.2)	0.012
				QMF 150/320 - S/F 50/500	3.4 (2.29)	(-1.1, 7.9)	0.135
QMF 150/160	402	12.3	28.4 (1.72)	QMF 150/160 - MF 400	9.1 (2.29)	(4.6, 13.6)	<.001
MF 800	408	15.1	22.5 (1.72)				
MF 400	404	13.3	19.3 (1.72)				
S/F 50/500	405	14.2	24.9 (1.72)				

n = number of patients included in the analysis.
Baseline raw means are not from the model.

NOVARTIS

Safety Results

AEs (including asthma exacerbations) by primary SOC (Safety set)

Primary system organ class	QMF149 160/320 N=443, exp.=414.6 yrs n (IR)	QMF149 160/160 N=437, exp.=416.3 yrs n (IR)	MF 800 N=440, exp.=414.8 yrs n (IR)	MF 400 N=443, exp.=402.9 yrs n (IR)	S/F 50/500 N=444, exp.=421.9 yrs n (IR)
Patients with at least one AE	**286 (122.7)**	**282 (131.0)**	**308 (149.3)**	**320 (166.3)**	**290 (130.6)**
Infections and infestations	159 (49.2)	189 (62.5)	215 (76.1)	212 (76.8)	187 (60.5)
Respiratory, thoracic and mediastinal disorders	148 (45.0)	142 (43.5)	182 (60.8)	214 (80.0)	160 (49.4)
Nervous system disorders	35 (8.9)	34 (8.6)	37 (9.4)	32 (8.3)	31 (7.6)
Musculoskeletal and connective tissue disorders	31 (7.8)	42 (10.8)	25 (6.3)	22 (5.6)	34 (8.5)
Gastrointestinal disorders	29 (7.3)	36 (9.0)	32 (8.0)	24 (6.2)	45 (11.4)
Injury, poisoning and procedural complications	22 (5.5)	13 (3.2)	16 (3.9)	14 (3.5)	19 (4.6)
Investigations	22 (5.5)	26 (6.5)	24 (5.9)	22 (5.6)	31 (7.7)
Skin and subcutaneous tissue disorders	21 (5.2)	5 (1.2)	9 (2.2)	18 (4.5)	13 (3.1)
Vascular disorders	15 (3.7)	22 (5.4)	15 (3.7)	14 (3.5)	7 (1.7)
Cardiac disorders	13 (3.2)	12 (2.9)	10 (2.4)	15 (3.8)	12 (2.9)
General disorders and administration site conditions	12 (2.9)	13 (3.2)	15 (3.7)	19 (4.8)	20 (4.9)
Metabolism and nutrition disorders	11 (2.7)	7 (1.7)	6 (1.5)	12 (3.0)	10 (2.4)
Eye disorders	7 (1.7)	9 (2.2)	2 (0.5)	5 (1.2)	4 (1.0)
Blood and lymphatic system disorders	5 (1.2)	10 (2.4)	4 (1.0)	9 (2.3)	4 (1.0)
Renal and urinary disorders	5 (1.2)	9 (2.2)	4 (1.0)	6 (1.5)	5 (1.2)
Hepatobiliary disorders	4 (1.0)	4 (1.0)	0	6 (1.5)	4 (1.0)
Psychiatric disorders	4 (1.0)	5 (1.2)	3 (0.7)	4 (1.0)	4 (1.0)
Immune system disorders	3 (0.7)	6 (1.5)	2 (0.5)	8 (2.0)	1 (0.2)
Reproductive system and breast disorders	3 (0.7)	6 (1.5)	5 (1.2)	5 (1.3)	4 (1.0)
Ear and labyrinth disorders	2 (0.5)	3 (0.7)	5 (1.2)	2 (0.5)	5 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.5)	5 (1.2)	0	5 (1.3)	5 (1.2)
Endocrine disorders	1 (0.2)	2 (0.5)	2 (0.5)	1 (0.2)	2 (0.5)
Pregnancy, puerperium and perinatal conditions	1 (0.2)	1 (0.2)	0	1 (0.2)	2 (0.5)
Social circumstances	1 (0.2)	0	0	0	0
Congenital, familial and genetic disorders	0	1 (0.2)	0	2 (0.5)	0

Product issues	0	1 (0.2)	0	0	0

exp. = exposure in total number of patient-years.
n = number of patients with at least one event.
IR = incidence rate per 100 patient-years (= 100 * number of patients with at least one event / total exposure in patient-years). For patients with an event, exposure is only counted until the first onset event date.
Primary system organ classes are presented in descending order of frequency in the QMF149 150/320 group.
A patient with multiple AEs is counted only once in the 'at least one AE' row.
A patient with multiple AEs within a system organ class is counted only once in that system organ class.
Only AEs reported whilst on study drug or within 7 days of the last dose (within 30 days for SAEs) are included.
MedDRA version 22.0 has been used for the reporting of adverse events.

Most frequent AEs (IR of at least 2.0 per 100 patient-years in any treatment group including asthma exacerbations) by PT (Safety set)

Preferred term	QMF149 150/320 N=443, exp.=414.6 yrs n (IR)	QMF149 150/160 N=437, exp.=416.3 yrs n (IR)	MF 800 N=440, exp.=414.8 yrs n (IR)	MF 400 N=443, exp.=402.9 yrs n (IR)	S/F 60/600 N=444, exp.=421.9 yrs n (IR)
Patients with at least one AE	286 (122.7)	292 (131.0)	308 (149.3)	320 (166.3)	290 (130.6)
Asthma	113 (32.4)	113 (32.7)	159 (49.9)	198 (71.4)	137 (40.4)
Nasopharyngitis	50 (12.9)	58 (15.1)	78 (20.9)	82 (22.7)	47 (11.9)
Headache	26 (6.5)	21 (5.2)	24 (6.0)	24 (6.1)	22 (5.4)
Upper respiratory tract infection	22 (5.5)	27 (6.7)	40 (10.2)	37 (9.7)	38 (9.5)

Bronchitis	20 (5.0)	22 (5.4)	22 (5.5)	21 (5.3)	17 (4.1)
Influenza	12 (2.9)	13 (3.2)	19 (4.7)	10 (2.5)	15 (3.6)
Oropharyngeal pain	11 (2.7)	6 (1.5)	8 (1.9)	9 (2.3)	8 (1.9)
Hypertension	10 (2.4)	14 (3.4)	13 (3.2)	11 (2.8)	6 (1.4)
Pharyngitis	10 (2.4)	11 (2.7)	12 (2.9)	12 (3.0)	14 (3.4)
Respiratory tract infection viral	10 (2.4)	16 (3.9)	14 (3.4)	12 (3.0)	13 (3.1)
Rhinitis	10 (2.4)	10 (2.4)	9 (2.2)	5 (1.3)	8 (1.9)
Back pain	9 (2.2)	17 (4.2)	9 (2.2)	6 (1.5)	8 (1.9)
Cough	8 (1.9)	9 (2.2)	12 (2.9)	15 (3.8)	8 (1.9)
Viral infection	7 (1.7)	8 (1.9)	11 (2.7)	7 (1.8)	6 (1.4)
Viral upper respiratory tract infection	7 (1.7)	11 (2.7)	21 (5.2)	20 (5.1)	21 (5.1)
Respiratory tract infection	5 (1.2)	4 (1.0)	3 (0.7)	8 (2.0)	8 (1.9)
Rhinitis allergic	5 (1.2)	11 (2.7)	7 (1.7)	11 (2.8)	7 (1.7)
Upper respiratory tract infection bacterial	5 (1.2)	7 (1.7)	7 (1.7)	14 (3.5)	8 (1.9)
Gastroenteritis	4 (1.0)	9 (2.2)	4 (1.0)	6 (1.5)	8 (1.9)
Sinusitis	4 (1.0)	6 (1.5)	8 (1.9)	8 (2.0)	5 (1.2)
Diarrhoea	3 (0.7)	9 (2.2)	5 (1.2)	4 (1.0)	9 (2.2)
Lower respiratory tract infection	3 (0.7)	5 (1.2)	7 (1.7)	8 (2.0)	6 (1.4)

exp. = exposure in total number of patient-years.

n = number of patients with at least one event.

IR = incidence rate per 100 patient-years (= 100 * number of patients with at least one event / total exposure in patient-years). For patients with an event, exposure is only counted until the first onset event date.

Preferred terms are sorted in descending order of frequency in the QMF149 150/320 group.

A patient with multiple AEs is counted only once in the "at least one AE" row.

A patient with multiple AEs with the same preferred term is counted only once for that preferred term.

Only AEs reported whilst on study drug or within 7 days of the last dose (within 30 days for SAEs) are included.

MedDRA Version 22.0 has been used for the reporting of adverse events.

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AEs (including asthma exacerbations) suspected to be study drug-related (investigator reported), by PT, with an IR of at least 0.5 per 100 patient-years in any treatment group (Safety set)

Preferred term	QMF149 160/320 N=443, exp.=414.6 yrs n (IR)	QMF149 160/160 N=437, exp.=416.3 yrs n (IR)	MF 800 N=440, exp.=414.8 yrs n (IR)	MF 400 N=443, exp.=402.9 yrs n (IR)	S/F 60/600 N=444, exp.=421.8 yrs n (IR)
Patients with at least one AE suspected to be study drug-related	37 (9.4)	28 (7.0)	25 (6.3)	30 (7.7)	32 (8.0)
Dysphonia	5 (1.2)	4 (1.0)	2 (0.5)	2 (0.5)	3 (0.7)
Asthma	3 (0.7)	3 (0.7)	5 (1.2)	13 (3.3)	9 (2.2)
Pharyngitis	2 (0.5)	1 (0.2)	0	1 (0.2)	2 (0.5)
Weight increased	2 (0.5)	0	0	0	0
Cough	1 (0.2)	2 (0.5)	2 (0.5)	1 (0.2)	1 (0.2)
Headache	1 (0.2)	0	1 (0.2)	2 (0.5)	0
Oral candidiasis	1 (0.2)	2 (0.5)	2 (0.5)	5 (1.2)	3 (0.7)
Oropharyngeal pain	1 (0.2)	3 (0.7)	1 (0.2)	3 (0.7)	2 (0.5)
Throat irritation	1 (0.2)	2 (0.5)	0	0	0
Upper respiratory tract infection	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.5)	2 (0.5)
Blood creatinine increased	0	0	0	0	2 (0.5)
Hypertension	0	1 (0.2)	2 (0.5)	0	1 (0.2)
Influenza like illness	0	0	0	1 (0.2)	3 (0.7)
Non-cardiac chest pain	0	1 (0.2)	0	2 (0.5)	0
Palpitations	0	1 (0.2)	2 (0.5)	0	0
Upper respiratory tract infection bacterial	0	0	0	1 (0.2)	2 (0.5)

exp. = exposure in total number of patient-years.
n = number of patients with at least one event.
IR = incidence rate per 100 patient-years (= 100 * number of patients with at least one event / total exposure in patient-years). For patients with an event, exposure is only counted until the first onset event date.
Preferred terms are sorted in descending order of frequency in the QMF149 150/320 group.
A patient with multiple AEs is counted only once in the "at least one AE" row.
A patient with multiple AEs with the same preferred term is counted only once for that preferred term.
Only AEs reported whilst on study drug or within 7 days of the last dose (within 30 days for SAEs) are included.
Relationship to study drug is considered as suspected for those events where "Reasonable possibility that AE is related to study treatment" is answered by the investigator as "Yes", "Yes, investigational treatment", "Yes, other study treatment (non-investigational)", or "Yes, both and/or indistinguishable".
MedDRA Version 22.0 has been used for the reporting of adverse events.

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SAEs (including asthma exacerbations) by primary SOC (Safety set)

Primary system organ class	QMF149 160/320 N=443, exp.=414.6 yrs n (IR)	QMF149 160/180 N=437, exp.=416.3 yrs n (IR)	MF 800 N=440, exp.=414.8 yrs n (IR)	MF 400 N=443, exp.=402.9 yrs n (IR)	S/F 60/600 N=444, exp.=421.8 yrs n (IR)
Patients with at least one SAE	21 (5.2)	20 (5.0)	21 (5.2)	31 (8.0)	21 (5.1)
Infections and infestations	5 (1.2)	7 (1.7)	10 (2.4)	2 (0.5)	5 (1.2)
Cardiac disorders	3 (0.7)	0	1 (0.2)	1 (0.2)	2 (0.5)
Injury, poisoning and procedural complications	3 (0.7)	1 (0.2)	2 (0.5)	5 (1.2)	3 (0.7)
Musculoskeletal and connective tissue disorders	3 (0.7)	2 (0.5)	1 (0.2)	2 (0.5)	0
Respiratory, thoracic and mediastinal disorders	3 (0.7)	4 (1.0)	8 (1.9)	10 (2.5)	3 (0.7)
Gastrointestinal disorders	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)
Eye disorders	1 (0.2)	1 (0.2)	0	1 (0.2)	0
Hepatobiliary disorders	1 (0.2)	1 (0.2)	0	0	0
Nervous system disorders	1 (0.2)	1 (0.2)	3 (0.7)	1 (0.2)	1 (0.2)
Renal and urinary disorders	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Vascular disorders	1 (0.2)	1 (0.2)	0	1 (0.2)	0
Ear and labyrinth disorders	0	0	0	1 (0.2)	0
Endocrine disorders	0	0	0	0	1 (0.2)
Investigations	0	0	1 (0.2)	1 (0.2)	1 (0.2)
Metabolism and nutrition disorders	0	0	1 (0.2)	1 (0.2)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	3 (0.7)	3 (0.7)
Psychiatric disorders	0	0	0	0	1 (0.2)
Reproductive system and breast disorders	0	2 (0.5)	0	2 (0.5)	1 (0.2)
Skin and subcutaneous tissue disorders	0	0	0	2 (0.5)	0

exp. = exposure in total number of patient-years.
n = number of patients with at least one event.
IR = incidence rate per 100 patient-years (= 100 * number of patients with at least one event / total exposure in patient-years). For patients with an event, exposure is only counted until the first onset event date.
Primary system organ classes are presented in descending order of frequency in the QMF149 150/320 group.
A patient with multiple SAEs is counted only once in the "at least one SAE" row.
A patient with multiple SAEs within a system organ class is counted only once for that system organ class.
Only SAEs reported whilst on study drug or within 30 days of the last dose are included.
MedDRA Version 22.0 has been used for the reporting of adverse events.

NOVARTIS

SAEs (including asthma exacerbations) by PT, with an IR of at least 0.5 per 100 patient-years in any treatment group (Safety set)

Preferred term	QMF149 160/320 N=443, exp.=414.6 yrs n (IR)	QMF149 150/160 N=437, exp.=416.3 yrs n (IR)	MF 800 N=440, exp.=414.8 yrs n (IR)	MF 400 N=443, exp.=402.8 yrs n (IR)	S/F 50/500 N=444, exp.=421.8 yrs n (IR)
Patients with at least one SAE	21 (5.2)	20 (5.0)	21 (5.2)	31 (8.0)	21 (5.1)
Asthma	3 (0.7)	2 (0.5)	6 (1.5)	8 (2.0)	2 (0.5)
Acute myocardial infarction	2 (0.5)	0	0	0	1 (0.2)
Pneumonia	1 (0.2)	3 (0.7)	5 (1.2)	2 (0.5)	0
Peritonitis	0	0	1 (0.2)	0	3 (0.7)
Rib fracture	0	0	0	2 (0.5)	0

exp. = exposure in total number of patient-years.

n = number of patients with at least one event.

IR = incidence rate per 100 patient-years (= 100 * number of patients with at least one event / total exposure in patient-years). For patients with an event, exposure is only counted until the first onset event date.

Preferred terms are sorted in descending order of frequency in the QMF149 150/320 group.

A patient with multiple SAEs is counted only once in the 'at least one SAE' row.

A patient with multiple SAEs with the same preferred term is counted only once for that preferred term.

Only SAEs reported whilst on study drug or within 30 days of the last dose are included.

MedDRA Version 22.0 has been used for the reporting of adverse events.

NOVARTIS

AEs (including asthma exacerbations) leading to permanent discontinuation of study treatment, by PT with an IR of at least 0.5 per 100 patient-years in any treatment group (Safety set)

Preferred term	QMF149 160/320 N=443, exp.=414.6 yrs n (IR)	QMF149 150/160 N=437, exp.=416.3 yrs n (IR)	MF 800 N=440, exp.=414.8 yrs n (IR)	MF 400 N=443, exp.=402.9 yrs n (IR)	S/F 60/600 N=444, exp.=421.9 yrs n (IR)
Patients with at least one AE leading to permanent discontinuation of study drug	9 (2.2)	3 (0.7)	12 (2.9)	16 (4.0)	11 (2.6)
Asthma	1 (0.2)	0	4 (1.0)	7 (1.7)	2 (0.5)
Angioedema	0	0	0	2 (0.5)	0
Dysphonia	0	0	0	2 (0.5)	0
Electrocardiogram QT prolonged	0	0	2 (0.5)	0	1 (0.2)

exp. = exposure in total number of patient-years.

n = number of patients with at least one event.

IR = incidence rate per 100 patient-years (= 100 * number of patients with at least one event / total exposure in patient-years). For patients with an event, exposure is only counted until the first onset event date.

Preferred terms are sorted in descending order of frequency in the QMF149 150/320 group.

A patient with multiple AEs is counted only once in the "at least one AE" row.

A patient with multiple AEs with the same preferred term is counted only once for that preferred term.

Only AEs reported whilst on study drug or within 7 days of the last dose (within 30 days for SAEs) are included.

MedDRA Version 22.0 has been used for the reporting of adverse events.

Other Relevant Findings

AEs of special interest by risk category (Safety set)

Intubation hospitalization and death due to asthma related events	3 (0.7)	1 (0.2)	6 (1.5)	8 (2.0)	2 (0.5)
Liver toxicity	8 (1.9)	7 (1.7)	9 (2.2)	12 (3.0)	12 (2.9)
Medication error: Device interchangeability or Swallowing of capsules	0	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Paradoxical bronchospasm	0	0	2 (0.5)	3 (0.7)	0
QTc prolongation and interaction with drugs known to prolong QTc interval	2 (0.5)	2 (0.5)	3 (0.7)	0	2 (0.5)
Reduced bone mineral density	2 (0.5)	0	0	2 (0.5)	1 (0.2)

exp. = exposure in total number of patient-years.

n = number of patients with at least one event.

IR = incidence rate per 100 patient-years (= 100 * number of patients with at least one event / total exposure in patient-years). For patients with an event, exposure is only counted until the first onset event date.

Risks are presented in alphabetical order. * = (incl brady- and tachyarrhythmias).

A patient with multiple AEs with the same risk is counted only once for that risk category.

Only AEs reported whilst on study drug or within 7 days of the last dose (within 30 days for SAEs) are included.

MedDRA Version 22.0 has been used for the reporting of adverse events.

Conclusion:

The totality of evidence for QMF149 demonstrates the benefit of adding indacaterol to mometasone furoate in a fixed dose combination therapy for patients with poorly controlled asthma. Both QMF149 doses (150/160 µg and 150/320 µg) demonstrated clinically meaningful improvements over corresponding MF doses and the persistence of efficacy for lung function, symptom control, and reduction of exacerbations. Improvements in adolescents were also observed and consistent with the overall population. QMF149 was well tolerated without evidence of an increased risk compared with the known safety profile of the individual monotherapy components or to salmeterol/fluticasone 50/500 µg b.i.d.

Date of Clinical Trial Report

24-Sept-2019