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Original Research

Cardiovascular safety of mometasone/indacaterol and mometasone/indacaterol/glycopyrronium once-daily fixed-dose combinations in asthma: pooled analysis of phase 3 trials

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ABSTRACT

Objective: To evaluate cardiovascular safety of two new inhaled fixed-dose combinations for treatment of asthma: (i) the inhaled corticosteroid/long-acting beta2-agonist (ICS/LABA) mometasone furoate/indacaterol acetate (MF/IND), (ii) the ICS/LABA/long-acting muscarinic antagonist (LAMA) MF/IND/glycopyrronium bromide (GLY).

Methods: Patient-level data were pooled from four randomized trials, including 52-week studies PALLADIUM (n = 2216) and IRIDIUM (n = 3092), 24-week study ARGON (n = 1426), and 12-week study QUARTZ (n = 802). Cardio-/cerebrovascular (CCV) event frequencies were examined in the following comparisons: (1) LABA effect: pooled-dose MF/IND vs. pooled-dose MF; (2) LAMA effect: pooled-dose MF/IND/GLY vs. pooled-dose MF/IND; (3) ICS-dose effects: (a) high-dose MF/IND vs. medium-dose MF/IND, (b) high-dose MF/IND/GLY vs. medium-dose MF/IND/GLY; (4) intra-class effects: (a) high-dose MF/IND vs. Fluticasone/Salmeterol (F/S), (b) high-dose MF/IND/GLY vs. F/S + Tiotropium (TIO). Risk estimates (percentage of patients with ≥1 CCV event) and risk differences (RDs) with 95% confidence intervals (CIs) were calculated for each comparison.

Results: The frequency of CCV events was low, without notable differences between comparison groups. Risk estimates and corresponding RDs (95% CIs) were as follows: (1) pooled-dose MF/IND = 2.35%, pooled-dose MF = 2.18%, RD = 0.17% (−1.00%, 1.34%); (2) pooled-dose MF/IND/GLY = 3.65%, pooled-dose MF/IND = 3.77%, RD = −0.12% (−1.63%, 1.39%); (3a) high-dose MF/IND = 3.69%, medium-dose MF/IND = 3.35%, RD = 0.34% (−1.25%, 1.94%); (3b) high-dose MF/IND/GLY = 2.84%, medium-dose MF/IND/GLY = 2.02%, RD = 0.82% (−0.49%, 2.13%); (4a) high-dose MF/IND = 3.69%, F/S = 2.82%, RD = 0.87% (−0.66%, 2.40%); (4b) high-dose MF/IND/GLY = 1.26%, F/S + TIO = 1.05%, RD = 0.21% (−1.26%, 1.68%).

Conclusions: There was no evidence of increased cardiovascular risk attributable to the addition of IND to MF or addition of GLY to MF/IND. Similarly, no evidence of increased cardiovascular risk was observed with an increase in the ICS-dose or relative to F/S ± TIO.

1. Introduction

A fixed-dose combination of an inhaled corticosteroid (ICS) with a long-acting β2-agonist (LABA) is a widely accepted treatment option for asthma patients whose symptoms are not adequately controlled on ICS maintenance therapy alone [1]. When adequate asthma management is not achieved with an ICS/LABA combination at recommended doses, a long-acting muscarinic antagonist (LAMA) can be added to the ICS/LABA treatment regimen [1].

Indacaterol (IND) is a LABA currently licensed for use in chronic obstructive pulmonary disease (COPD). Due to its rapid onset of action

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Table 1
Overview of phase 3 controlled studies contributing key safety data.

Study (duration)	Intervention arms	ICS Dose	N	GINA Step	Reference
PALLADIUM (52 weeks)	MF/IND 160/150 μg od C1	Medium	437	3	van Zyl-Smit et al. (2020) [2]
	MF/IND 320/150 μg od C1	High	443		NCT02554786
	MF 400 μg od TH	Medium	443		
	MF 400 μg bid TH	High	440		
	F/S 500/50 μg bid AC	High	444		
IRIDIUM (52 weeks)	MF/IND/GLY 80/150/50 μg od C1	Medium	617	≥4	Kerstjens et al. (2020) [3]
	MF/IND/GLY 160/150/50 μg od C1	High	616		NCT02571777
	MF/IND 160/150 μg od C1	Medium	608		
	MF/IND 320/150 μg od C1	High	613		
	F/S 500/50 μg bid AC	High	618		
ARGON (24 weeks)	MF/IND/GLY 80/150/50 μg od C1	Medium	474	≥4	Gessner et al. (2020) [4]
	MF/IND/GLY 160/150/50 μg od C1	High	476		NCT03158311
	F/S 500/50 μg bid AC + TIO 5 μg od RS	High	475		
QUARTZ (12 weeks)	MF/IND 80/150 μg od C1	Low	396	2/3	Kornmann et al. (2020) [5]
	MF 200 μg od TH	Low	399		NCT02892344

N = number of patients (sample size) in the safety analysis set; IND = indacaterol acetate; GLY = glycopyrronium bromide; MF = mometasone furoate; F/S = fluticasone propionate/salmeterol xinafoate; TIO = tiotropium bromide; C1 = Concept1 device (Breezhaler®), TH = Twisthaler®, AC = Accuhaler®, RS = Respimat®; ICS = inhaled corticosteroid; GINA = Global Initiative for Asthma; od = once daily; bid = twice daily (bis in die).
Note: Medium dose ICS in MF/IND and MF/IND/GLY is defined based on comparable pharmacokinetic and efficacy parameters (equipotency) whereas the nominal doses are dissimilar. The same applies to the high dose ICS in MF/IND and MF/IND/GLY (see Kerstjens et al., 2020 for further details).

which is sustained for 24 h, IND was also developed and recently approved for treatment of asthma as a once-daily fixed-dose combination with an ICS compound mometasone furoate (MF), and as a once-daily fixed-dose combination with MF and glycopyrronium bromide (GLY), a LAMA licensed for use in COPD. Details of the clinical development program, key efficacy results and basic safety findings were reported elsewhere [2–5].

Because beta2-adrenergic and muscarinic receptors are present in the heart [6–8], both LABA and LAMA drug classes can potentially contribute to occurrence of clinically significant adverse cardiovascular events in asthma patients. Despite biological plausibility, accumulating evidence from randomized clinical trials in COPD indicates that LABA and LAMA compounds do not increase the risk of serious adverse cardiovascular events or all-cause mortality [9–16]. Assessment of cardiovascular safety of LABA and LAMA products based on published asthma trials is more difficult because adverse cardiovascular events are not consistently reported in publications due to their low frequency. Asthma patients tend to have much lower baseline prevalence of cardiovascular risk factors than patients enrolled in COPD trials, which results in low incidence of adverse cardiovascular events [17].

Due to the historical concerns related to cardiovascular adverse effects of LABA and LAMA drug classes, a detailed analysis of cardiovascular safety of MF/IND and MF/IND/GLY was performed in the present clinical development program in asthma. This article provides a description of cardiovascular safety profiles of MF/IND and MF/IND/GLY fixed-dose combination therapies in asthma.

2. Methods

Phase 3 trials contributing safety data to the present analysis are listed in Table 1, including two 52-week studies (PALLADIUM and IRIDIUM), a 24-week study (ARGON), and a 12-week study (QUARTZ). Because asthma is a new indication for MF/IND and MF/IND/GLY, the only trials eligible for inclusion in this analysis are those completed during our clinical development program (Table 1). No additional studies are available from published literature. Studies IRIDIUM and ARGON allowed for more severe asthma at baseline compared with studies PALLADIUM and QUARTZ (Table 1). The IND and GLY doses were the same in all intervention arms containing IND and GLY, respectively (Table 1). The MF (ICS) dose varied between the studies and intervention arms, as shown in Table 1. Evaluation of cardiovascular safety of MF/IND and MF/IND/GLY was based on analysis of adverse event frequencies in the comparisons defined in Table 2, based on pooling of individual patient-level data from the respective trials.

The purpose of Comparison 1 (MF/IND versus MF) was to identify the IND (LABA) component effect of the MF/IND combination. Comparison 2 (MF/IND/GLY versus MF/IND) estimated the effect of the GLY (LAMA) component of MF/IND/GLY. Comparisons 3a and 3b examined the effect of doubling the dose of ICS (MF) components of the MF/IND and MF/IND/GLY combinations, respectively. Comparisons 4a and 4b explored potential intra-class effects of the high-dose MF/IND versus a comparator high-dose ICS/LABA (F/S), and of the high-dose MF/IND/GLY versus an ICS/LABA + LAMA combination comparator with a high-dose ICS (F/S + Tio). All data pools defined in Table 2 preserve the effect of randomization, resulting in unbiased effect estimates, because for each of the six comparisons, treatment and control groups were pooled from the same trials maintaining the same treatment-to-control allocation ratio [18].

Comparisons 1 and 2 were seen as the main comparisons for evaluation of cardiovascular safety of MF/IND and MF/IND/GLY due to the mechanistic plausibility of LABA and LAMA class effects on the cardiovascular system. A dose effect of the MF component in Comparisons 3a and 3b, and the intra-class effects in Comparisons 4a and 4b are less likely based on the mechanistic considerations alone. These effects were nevertheless explored to assess whether the observed data were in agreement with the current state of knowledge.

The following adverse event endpoints were examined in the comparisons defined above: (i) cardio-/cerebrovascular (CCV) events: any category, (ii) cardiac serious adverse events (SAEs), (iii) cerebrovascular events, (iv) cardiovascular (cardiac or cerebrovascular) death, and (v) death from any cause. The cause of death was adjudicated by an external independent adjudication committee. These definitions of analysis endpoints were chosen because they could be applied uniformly to each of the four studies, thus allowing for the pooled analysis.

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system. The composite endpoint "CCV events: any category" consisted of cardiovascular adverse events of special interest (AESI) terms, defined by Standard MedDRA Queries (SMQs) "ischemic heart disease", "myocardial infarction", "cerebrovascular events", and "cardiac failure", and Custom MedDRA queries (CMQs) representing cardiac arrhythmia terms ("atrial fibrillation", "bradyarrhythmia", "repolarization abnormalities", "conduction abnormalities", "ectopics", "tachyarrhythmias", and "non-specific cardiac arrhythmia terms"). A CMQ consisting of preferred terms "sudden death" and "sudden cardiac death" was also considered an AESI and included in the analysis as a CCV event. The frequencies of individual

Table 2
Safety analysis comparisons.

Comparison	Treatment	Control	Studies	Effect
1	All doses MF/IND N = 1276 (921.0 yrs)	All doses MF N = 1282 (908.7 yrs)	PALLADIUM/QUARTZ	IND (LABA)
2	Medium + High dose MF/IND/GLY N = 1233 (1159.7 yrs)	Medium + High dose MF/IND N = 1221 (1152.0 yrs)	IRIDIUM	GLY (LAMA)
3a	High dose MF/IND N = 1056 (993.4 yrs)	Medium dose MF/IND N = 1045 (988.5 yrs)	PALLADIUM/IRIDIUM	MF (ICS) dose
3b	High dose MF/IND/GLY N = 1092 (801.3 yrs)	Medium dose MF/IND/GLY N = 1091 (791.8 yrs)	IRIDUM/ARGON	MF (ICS) dose
4a	High dose MF/IND N = 1056 (993.4 yrs)	High dose F/S N = 1062 (997.5 yrs)	PALLADIUM/IRIDIUM	Intra-class
4b	High dose MF/IND/GLY N = 476 (217.5 yrs)	High dose F/S + TIO N = 475 (215.1 yrs)	ARGON	Intra-class

IND = indacaterol acetate; GLY = glycopyrronium bromide; MF = mometasone furoate; F/S = fluticasone propionate/salmeterol xinafoate; TIO = tiotropium bromide; N = number of patients in the safety analysis set (patient-years of exposure); ICS = inhaled corticosteroid.

CCV terms were calculated by intervention arm within each of the four studies.

Because each treatment group in each comparison in Table 2 had the same distribution of exposure time as its corresponding control group (i.e., the exposure time was not affected by treatment), analysis of adverse event frequencies was based on incidence proportions, without exposure adjustment. An incidence proportion is the number of patients with the adverse event divided by the baseline sample size. Risk estimates in each comparison group were expressed as percentages (i.e., incidence proportion × 100%). Treatment effect estimates were defined as differences in incidence proportions (treatment minus control) × 100%. Confidence intervals (CIs) for the risk differences were constructed based on the method of Agresti and Caffo [19], which results in valid inference with large or small event counts [19,20].

In addition to the analysis of adverse events, the following cardiovascular parameters were examined in each intervention arm of the four studies: pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg), and Fridericia's QTc interval (msec). Distributions of

Table 3
Baseline distribution of cardiovascular risk factors, by study.

	PALLADIUM N = 2216 (2069.5 yrs)	IRIDIUM N = 3092 (2887.3 yrs)	ARGON N = 1426 (648.5 yrs)	QUARTZ N = 802 (182.1 yrs)
Age (years)				
Mean (SD)	47.9 (14.8)	52.2 (12.7)	52.5 (13.3)	45.6 (16.3)
Median	49.5	54.0	54.0	48.0
Min - Max	12–75	17–75	18–82	12–75
Age group in years, n (%)				
12-17	107 (4.8)	2 (0.1)	0 (0.0)	64 (8.0)
18-64	1812 (81.8)	2521 (81.5)	1137 (79.7)	630 (78.6)
≥ 65	297 (13.4)	569 (18.4)	289 (20.3)	108 (13.5)
Gender, n (%)				
Male	923 (41.7)	1174 (38.0)	524 (36.7)	314 (39.2)
Female	1293 (58.3)	1918 (62.0)	902 (63.3)	488 (60.8)
Race, n (%)				
Caucasian	1559 (70.4)	2287 (74.0)	1184 (83.0)	527 (65.7)
Black	23 (1.0)	17 (0.5)	14 (1.0)	6 (0.7)
Asian	493 (22.2)	671 (21.7)	103 (7.2)	199 (24.8)
Other*	141 (6.4)	116 (3.8)	125 (8.8)	70 (8.7)
History of heart disease, n (%)				
Cardiac disorders (SOC)	153 (6.9)	314 (10.2)	124 (8.7)	45 (5.6)
Myocardial ischaemia (PT)	39 (1.8)	101 (3.3)	26 (1.8)	11 (1.4)
Angina pectoris (PT)	19 (0.9)	63 (2.0)	17 (1.2)	3 (0.4)
Coronary artery disease (PT)	26 (1.2)	55 (1.8)	29 (2.0)	5 (0.6)
Other risk factors, n (%)				
Cerebrovascular accident (PT)	4 (0.2)	9 (0.3)	5 (0.4)	3 (0.4)
BMI > 30 kg/m^2	562 (25.4)	1015 (32.8)	541 (37.9)	187 (23.3)
Hypertension (PT)	670 (30.2)	1044 (33.8)	537 (37.7)	183 (22.8)
Type 2 diabetes mellitus (PT)	85 (3.8)	240 (7.8)	121 (8.5)	35 (4.4)
Hypercholesterolemia (PT)	89 (4.0)	130 (4.2)	95 (6.7)	26 (3.2)
Hyperlipidemia (PT)	51 (2.3)	78 (2.5)	30 (2.1)	17 (2.1)
Dyslipidemia (PT)	57 (2.6)	156 (5.0)	53 (3.7)	26 (3.2)
Former smoker	404 (18.2)	612 (19.8)	308 (21.6)	107 (13.3)
Current smoker	0 (0.0)	0 (0.0)	31 (2.2)	0 (0.0)

N = number of randomized patients (treatment patient-years); SOC = System Organ Class of Cardiac Disorders with the three most common preferred terms; PT = preferred term; SD = standard deviation; BMI = Body Mass Index.
*Including Native American, American Indian, Pacific Islander, and Alaska Native.

Table 4
Estimated treatment effects on cardiovascular risk endpoints.

Comparison Endpoint	Treatment Patients with event (%)	Control Patients with event (%)	Difference in % (95% CI)
1. LABA effect	**MF/IND (N = 1276)**	**MF (N = 1282)**	
CCV events: any category	30 (2.35)	28 (2.18)	0.17 (−1.00, 1.34)
Cardiac SAEs	3 (0.24)	2 (0.16)	0.08 (−0.33, 0.48)
Cerebrovascular events	2 (0.16)	4 (0.31)	−0.16 (−0.59, 0.28)
CCV Death	0 (0.00)	0 (0.00)	0.00 (−0.22, 0.22)
All-cause mortality	0 (0.00)	1 (0.08)	−0.08 (−0.34, 0.19)
2. LAMA effect	**MF/IND/GLY (N = 1233)**	**MF/IND (N = 1221)**	
CCV events: any category	45 (3.65)	46 (3.77)	−0.12 (−1.63, 1.39)
Cardiac SAEs	5 (0.41)	13 (1.06)	−0.66 (−1.37, 0.05)
Cerebrovascular events	5 (0.41)	8 (0.66)	−0.25 (−0.87, 0.37)
CCV Death	3 (0.24)	2 (0.16)	0.08 (−0.34, 0.50)
All-cause mortality	3 (0.24)	4 (0.33)	−0.08 (−0.56, 0.39)
3a. ICS dose effect	**MF-H/IND (N = 1056)**	**MF-M/IND (N = 1045)**	
CCV events: any category	39 (3.69)	35 (3.35)	0.34 (−1.25, 1.94)
Cardiac SAEs	9 (0.85)	7 (0.67)	0.18 (−0.61, 0.97)
Cerebrovascular events	7 (0.66)	3 (0.29)	0.38 (−0.27, 1.02)
CCV Death	2 (0.19)	0 (0.00)	0.19 (−0.18, 0.56)
All-cause mortality	4 (0.38)	0 (0.00)	0.38 (−0.08, 0.83)
3b. ICS dose effect	**MF-H/IND/GLY (N = 1092)**	**MF-M/IND/GLY (N = 1091)**	
CCV events: any category	31 (2.84)	22 (2.02)	0.82 (−0.49, 2.13)
Cardiac SAEs	4 (0.37)	3 (0.27)	0.09 (−0.45, 0.63)
Cerebrovascular events	3 (0.27)	2 (0.18)	0.09 (−0.38, 0.56)
CCV Death	2 (0.18)	1 (0.09)	0.09 (−0.31, 0.49)
All-cause mortality	2 (0.18)	1 (0.09)	0.09 (−0.31, 0.49)
4a. Intra-class effect	**MF-H/IND (N = 1056)**	**F/S (N = 1062)**	
CCV events: any category	39 (3.69)	30 (2.82)	0.87 (−0.66, 2.40)
Cardiac SAEs	9 (0.85)	5 (0.47)	0.38 (−0.36, 1.12)
Cerebrovascular events	7 (0.66)	4 (0.38)	0.29 (−0.38, 0.95)
CCV Death	2 (0.19)	0 (0.00)	0.19 (−0.18, 0.56)
All-cause mortality	4 (0.38)	0 (0.00)	0.38 (−0.07, 0.83)
4b. Intra-class effect	**MF-H/IND/GLY (N = 476)**	**F/S + TIO (N = 475)**	
CCV events: any category	6 (1.26)	5 (1.05)	0.21 (−1.26, 1.68)
Cardiac SAEs	1 (0.21)	1 (0.21)	0.00 (−0.82, 0.82)
Cerebrovascular events	0 (0.00)	2 (0.42)	−0.42 (−1.24, 0.40)
CCV Death	0 (0.00)	1 (0.21)	−0.21 (−0.92, 0.50)
All-cause mortality	0 (0.00)	1 (0.21)	−0.21 (−0.92, 0.50)

IND = indacaterol acetate; MF = mometasone furoate (–M = medium dose, –H = high dose); F/S = fluticasone propionate/salmeterol xinafoate; CCV = cardio-/cerebrovascular events; Cardiac SAE = serious adverse events in the System Organ Class (SOC) "Cardiac Disorders"; CI = confidence interval computed by the method of Agresti and Caffo (2000).

the minimum and maximum subject-specific post-baseline values of these parameters in each intervention arm were summarized with means, medians, interquartile ranges, and numbers and percentages of subjects with a clinically notable value. Clinically notable values are defined in Supplementary Table 1 (Appendix).

3. Results

Baseline distribution of cardiovascular risk factors, by study is presented in Table 3. Study-specific frequencies of incident cardiovascular AESIs, clinically notable values, and distributions of post-baseline vital signs and QTc measurements are presented by intervention arm in Supplementary Tables 1 through 8 (Appendix). Treatment effect estimates on the key cardiovascular endpoints are provided in Table 4.

The incidence of cardiovascular adverse events was low in all comparison groups in Table 4. These analyses did not reveal any differences in the adverse event frequencies between the comparison groups, beyond those expected to arise by chance (Table 4). Distributions of individual AESI terms, clinically notable values, vital signs and QTc measurements were also very similar in all intervention arms in each trial (Supplementary Tables 1 through 8 - Appendix). None of the fatal cases in Table 4 were considered to be related to study treatment by investigators. Individual fatal cases were described in the original publications from the respective studies [2–4], and are also listed in Supplementary Listing 1 (Appendix).

4. Discussion

This analysis of phase 3 trials did not find evidence of increased cardiovascular risk attributable to the addition of IND to MF or addition of GLY to MF/IND. Similarly, no evidence of increased cardiovascular risk was observed with an increase in the ICS-dose or relative to F/S ± TIO. These findings are in agreement with other evidence on cardiovascular safety of these drugs, as reviewed in the following sections.

4.1. LABA effects

Absence of the IND (LABA) effect in Comparison 1 is consistent with findings from an earlier phase 2 trial in asthma, were a fixed-dose combination of IND maleate 500 μg od/MF 400 μg od (n = 749) was compared with MF 400 μg od (n = 759) [21]. Both interventions were administered via the Twisthaler device. With a median treatment duration of 13 months, cardiac AEs were reported in 12 patients (1.6%) on MF/IND versus 20 patients (2.6%) on MF. Cardiac SAEs occurred in 2 patients (0.3%) on MF/IND versus 5 patients (0.7%) on MF. There were no deaths in the MF/IND arm and 1 non-CV death in the MF arm [21]. This phase 2 trial was not formally incorporated in our pooled analysis of the LABA effects (Comparison 1) due to the differences between this study and the phase 3 trials in the IND formulation (maleate versus acetate) and delivery (Twisthaler versus Breezhaler). Nevertheless, findings from the phase 2 study provide important supporting information on cardiovascular safety of the MF/IND fixed-dose combination in asthma.

In 2010, the US Food and Drug Administration (FDA) mandated that companies marketing LABAs for asthma perform 26-week randomized trials of their ICS/LABA products versus the respective ICS controls, with the primary endpoint of asthma-related intubation or death [22–25]. Because the cause of death was described for all fatal cases, the incidence of cardiovascular death can be quantified based on the published data (Supplementary Table 9). These trials are noteworthy for their large sample sizes, with more than 5000 patients per arm, with the exception of NCT01845025, which was terminated early due to removal of the respective product from the market for commercial reasons unrelated to safety.

Cumulatively, in the four studies listed in Supplementary Table 9, there were 16 deaths in 17,960 patients treated with ICS/LABA (0.09%), including 5 CV deaths (0.03%) versus 18 deaths in 17,966 patients treated with ICS (0.10%), including 9 CV deaths (0.05%). These findings do not support the hypothesis that LABAs as a class increase all-cause mortality through cardiovascular effects or by any other mechanism, when used concomitantly with ICS in asthma.

This conclusion is also in agreement with findings from recent cumulative reviews of ICS/LABA vs. ICS trials in asthma focused on specific LABA products formoterol [26] and salmeterol [27], where overall mortality rate in the ICS/LABA arms was not significantly different from the rate in the ICS arms, and was equal to 1 death per 1000 patients treated for 26 weeks (i.e., 2 deaths per 1000 patient-years, with the same estimate for ICS/formoterol and ICS/salmeterol products).

A true biological effect of LABA products on serious cardiovascular events and mortality, if present in asthma, would also be expected in COPD, considering the high prevalence of cardiovascular risk factors and comorbidities in COPD patients. Estimates of LABA effects on cardiovascular risk and overall mortality in COPD trials are summarized in Supplementary Table 10, with a focus on meta-analyses/pooled analyses of randomized trials, which provide the most precise and most reliable effect estimates. Large recently completed trials (>1000 patients per arm with ≥1 year of treatment) not yet included in published meta-analyses or pooled analyses were also listed in the table. The pooled analysis estimates reported by Wedzicha et al. (2014) [13] in the LABA effects section of this table were based specifically on placebo-controlled trials of IND. These findings do not support the hypothesis of increased risk of cardiovascular adverse events or mortality attributable to IND or LABA as a class.

4.2. LAMA effects

Cardiovascular safety of the LAMAs in asthma can be examined based on the pooled analysis of placebo-controlled trials of tiotropium, reported in the Tiotropium Respimat New Drug Application (NDA) Clinical Review (US FDA 2015) [28]. This analysis did not show evidence of increased cardiovascular risk attributable to tiotropium. As in other asthma trials, cardiovascular SAEs were rare, without significant differences between the comparison groups (Supplementary Table 11).

Estimates of LAMA effects on cardiovascular risk and overall mortality in COPD trials are summarized in Supplementary Table 10. The pooled analysis estimates reported by Wedzicha et al. (2014) [13] in the LAMA and LABA/LAMA effects section of this table were based on placebo-controlled trials of GLY and IND/GLY, respectively. These findings do not support the hypothesis of increased risk of cardiovascular adverse events or mortality attributable to GLY or IND/GLY use in COPD or to LAMA and LABA/LAMA drug classes more generally. These results are consistent with findings from our Comparison 2 (Table 4), where no GLY (LAMA) effect was observed.

4.3. ICS-dose effects and intra-class effects

Comparisons 3a and 3b (ICS-dose effects) and Comparisons 4a and 4b (intra-class effects) did not reveal any differences in the adverse event frequencies between the comparison groups, beyond those expected to arise by chance (Table 4). Results from the ICS-dose comparisons are consistent with findings from a meta-analysis of 31 trials in COPD, where the frequency of cardiovascular events was not different between the ICS-treated and control groups (risk ratio = 0.99; 95% CI: 0.93 to 1.06) [29]. Intra-class effects are also not expected based on data external to the present clinical development program. In the FLAME trial of IND/GLY (n = 1680) versus F/S (n = 1682) in COPD, during the 52-weeks of treatment, the composite endpoint of adjudicated fatal/non-fatal major adverse cardiovascular events (myocardial infarction, unstable angina, stroke, revascularization or hospitalization for heart failure) occurred in 32 patients (2%) on IND/GLY versus 31 patients (2%) on F/S, cardiovascular death occurred in 9 patients (0.5%) on IND/GLY versus 11 patients (0.7%) on F/S, and all-cause mortality occurred in 24 patients (1.4%) on IND/GLY versus 24 patients (1.4%) on F/S [14]. Thus, IND/GLY was not associated with increased risk of serious adverse cardiovascular events or mortality compared with F/S. Similarly, cardiovascular safety profile of IND/GLY did not differ from that of TIO in the COPD trials [13,30].

4.4. Observational data

While findings from clinical trials do not support the hypothesis of increased cardiovascular risk attributable to inhaled LABA or LAMA products, some observational studies in COPD reported an association of LABA and/or LAMA use with adverse cardiovascular outcomes [31–33]. Unfortunately, observational evidence of this association is difficult to interpret due to the high risk of bias resulting from confounding by indication. Respiratory and systemic effects of COPD progression are known to contribute to the development of cardiovascular disease through several pathophysiological pathways [34,35], while also influencing the choice of bronchodilation therapy, resulting in addition or discontinuation of specific drug products. Furthermore, deteriorating cardiovascular status may cause worsening of the respiratory symptoms, triggering a change in COPD therapy. Specifically, worsening dyspnoea due to unrecognized ventricular dysfunction may be attributed to poor control of COPD, triggering intensification of COPD therapy, such as addition of a second bronchodilator or a fixed-dose combination [36–39], which results in a non-causal association of adverse cardiovascular events with the COPD medication.

This confounding bias cannot be fully eliminated by adjustment for baseline characteristics in observational studies using matching or other statistical techniques because even among patients with nominally identical medical histories, the rates of subsequent disease progression naturally vary. Those with a deteriorating pulmonary and/or cardiac function are likely to receive a second bronchodilator or a fixed-dose combination (for worsening respiratory symptoms), while the more stable patients are likely to remain on monotherapy. As was noted by several authors [16,40], this type of bias significantly complicates interpretation of cardiovascular safety findings from observational studies of long-acting bronchodilators.

For example, in a large nested case-control study of 65,966 COPD patients on ICS/LABA therapy, initiation of tiotropium was associated with increased risk of adverse cardiovascular events, with a relative risk of 1.88 (95% CI: 1.44–2.46) during the first month [33]. These findings do not have a causal interpretation due to confounding by indication. Addition of a LAMA such as tiotropium to prior treatment in COPD patients on ICS/LABA generally occurs as a result of inadequate control of respiratory symptoms on prior therapy, which can be a manifestation of worsening COPD and/or deteriorating cardiovascular health. This bias would not be present in randomized trials. In fact, in a large meta-analysis of placebo-controlled trials, tiotropium was not associated with increased risk of cardiac adverse events (RR = 0.93; 95% CI: 0.85, 1.02), major adverse cardiovascular events (RR = 0.87; 95% CI: 0.75, 1.01), or mortality (RR = 0.90; 95% CI: 0.79, 1.01) [15].

Due to the bias inherent to observational studies of cardiovascular adverse effects of inhaled LABA and LAMA products, the present review

was largely focused on data from clinical trials. Despite their generally robust designs, clinical trials of the LABA and LAMA compounds have some limitations that need to be recognized.

4.5. Limitations

First, most clinical trials, including the four studies used in the present analysis excluded patients with unstable cardiovascular status at baseline, per exclusion criteria specified in the study protocols [2–5]. Thus, the study findings might not be generalizable to patients with very high cardiovascular risk at baseline. Nevertheless, many clinically significant baseline cardiovascular risk factors that are highly prevalent in the real-world settings were also well represented in the four studies, including hypertension, BMI>30, and smoking history (Table 3). Furthermore, cardiovascular safety of LABA and LAMA products has been well established in COPD trials with high baseline prevalence of cardiovascular disease (Supplementary Table 10). For example, the SUMMIT trial (N = 16,485) and the ASCENT-COPD trial (N = 3630) by design enrolled only patients with high cardiovascular risk at baseline, and found no evidence of adverse cardiovascular effects attributable to LABA or LAMA use, respectively [12,16].

Second, none of the phase 3 trials included in the present analysis had treatment duration exceeding the 1-year period. Hence, long-term safety beyond 1-year of exposure could not be directly evaluated in these studies. However, the large phase 2 study of MF/IND versus MF with more than 1500 patients had a treatment duration of up to 20 months, with a median of 13 months [21]. Thus, more than half of the subjects in this study had the study drug exposure >1 year, without any evidence of increased cardiovascular risk attributable to MF/IND. It is also re-assuring that neither IND nor GLY or the MF dose had any discernable effects on the pulse rate, blood pressure or the QTc interval in any of the studies. Therefore, long-term adverse effects mediated by these cardiovascular parameters are unlikely. It should also be noted that some of the placebo-controlled trials of LABA and LAMA products in COPD had follow-up substantially exceeding 52 weeks. For example, in Halpin et al.'s (2015) meta-analysis [15], the largest of the placebo-controlled tiotropium (LAMA) trials had approximately 3000 patients per arm, with a treatment duration of up to 4 years. The ASCENT-COPD trial of aclidinium (LAMA) versus placebo enrolled more than 1800 patients per arm with a treatment duration of up to 3 years [16]. Similarly, in the SUMMIT trial investigating the effect of vilanterol (LABA) with or without fluticasone (ICS) versus placebo, more than 4000 patients were enrolled per arm, with the treatment duration of up to 4 years [12]. These studies did not reveal any evidence of increased cardiovascular risk attributable to long-term LABA or LAMA use (Supplementary Table 10).

Finally, the present analysis is somewhat limited by the small number of incident cardiovascular events, which precludes any meaningful subgroup analysis, due to the low precision of estimation within subgroups. This limitation is shared by other asthma trials. Nevertheless, our findings are in agreement with similar results reported from the COPD trials, where the counts of incident cardiovascular adverse events were orders of magnitude larger than in the present analysis, and baseline cardiovascular risk factors were much more prevalent [11–16,30,41].

In summary, the present analysis did not find evidence of increased cardiovascular risk attributable to the addition of IND to MF or addition of GLY to MF/IND. Similarly, no evidence of increased cardiovascular risk was observed with an increase in the ICS-dose or relative to F/S ± TIO. These findings are in agreement with the current state of knowledge on cardiovascular safety of ICS/LABA and ICS/LABA/LAMA drug classes.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ES, PD, and AP are employees of Novartis Pharmaceuticals Corporation, East Hanover, USA. DJ, EA, MH, and DB are employees of Novartis Pharma AG, Basel, Switzerland. RNvZ-S reports receiving personal fees from Aspen–GlaxoSmithKline, Pfizer, Roche, AstraZeneca, Novartis, Merck Sharp & Dohme, and Cipla, outside of the submitted work. HAMK reports grants and fees for consultancy or advisory board participation and for unrestricted research grants from Novartis, as well as from GlaxoSmithKline, Boehringer and Chiesi, outside of the submitted work. All were paid to his institution. CG reports receiving personal fees for advisory board and honoraria for academic talks from GSK, Pfizer, AstraZeneca, Roche, Novartis, BMS, MSD, Berlin-Chemie, Chiesi, Boehringer Ingelheim, and Sanofi, outside of the submitted work. OK's institution received fees for conducting the study as participating site; OK reports personal fees from Sanofi, Boehringer Ingelheim, Novartis, AstraZeneca and GlaxoSmithKline outside the submitted work.

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Appendix A. Supplementary data

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