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Review

Dose bridging data for mometasone furoate in once-daily fixed-dose inhaled combinations of mometasone furoate/indacaterol and mometasone furoate/ indacaterol/glycopyrronium in patients with asthma

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ABSTRACT

Once-daily (o.d.) fixed-dose combinations of mometasone furoate/indacaterol acetate (MF/IND) and mometasone furoate/indacaterol acetate/glycopyrronium bromide (MF/IND/GLY), both delivered via the Breezhaler® device, are approved for the maintenance treatment of asthma. Across these fixed-dose combinations, while the doses of bronchodilators remain the same, the nominal doses of mometasone furoate in micrograms differ.

This article presents the steps followed in bridging the mometasone furoate doses at the corresponding dose strengths in the mometasone furoate formulation delivered via the Twisthaler® and mometasone furoate/ indacaterol acetate and mometasone furoate/indacaterol acetate/glycopyrronium bromide formulations delivered via the Breezhaler®. These were: (i) bridging the mometasone furoate doses in the Twisthaler® (previously approved) to mometasone furoate doses in the Breezhaler®; (ii) bridging the mometasone furoate doses in the Breezhaler® to mometasone furoate/indacaterol acetate and mometasone furoate/indacaterol acetate/glycopyrronium bromide formulation.

Following this stepwise approach, it was determined that mometasone furoate 80 μg o.d. (medium-dose strength) and 160 μg o.d. (high-dose strength) in mometasone furoate/indacaterol acetate/glycopyrronium bromide formulation provided comparable inhaled corticosteroid efficacy to mometasone furoate 160 μg o.d. (medium-dose strength) and 320 μg o.d. (high-dose strength) in the mometasone furoate/indacaterol acetate formulation, respectively.

These doses were used in the PLATINUM Phase III clinical program that investigated the efficacy and safety of mometasone furoate/indacaterol acetate and mometasone furoate/indacaterol acetate/glycopyrronium bromide combinations in patients with asthma.

1. Introduction

The Global Initiative for Asthma (GINA) [1] strategy recommends treatment with a combination of inhaled corticosteroid (ICS) and long-acting β_2-agonist (LABA) in patients with moderate-to-severe asthma, with a step-up/step-down approach based on the level of asthma control. Patients who receive ICS/LABA show improved asthma control compared with patients treated with ICS alone [2]. In addition,

Abbreviations: AUC, area under the plasma concentration curve; b.i.d., twice-daily; C_{max}, maximum peak plasma concentration; C_{trough}, trough plasma concentration; FDC, fixed-dose combinations; FEV_1, forced expiratory volume in 1 second; GLY, glycopyrronium bromide; ICS, inhaled corticosteroid; IND, indacaterol acetate; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MF, mometasone furoate; o.d., once-daily; PD, pharmacodynamic; PK, pharmacokinetic; T_{max}, maximum concentration after drug administration.

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add-on therapy with a long-acting muscarinic antagonist (LAMA) is suggested in patients inadequately controlled on ICS/LABA [3]. Most currently available inhaled treatment options for asthma require a twice-daily (b.i.d.) dosing regimen and are administered with two or more inhalers. Although the available fixed-dose combinations (FDCs) of LABA and ICS are effective in the management of asthma [4,5], a substantial proportion of patients (approximately 35%–46 %) remain uncontrolled on currently available therapies [6]. Once-daily FDCs of mometasone furoate/indacaterol acetate (MF/IND; ICS/LABA) and mometasone furoate/indacaterol acetate/glycopyrronium bromide (MF/IND/GLY; ICS/LABA/LAMA), all delivered via the Breezhaler®, have recently been approved by various health authorities world-wide for the treatment of asthma. Both MF/IND and MF/IND/GLY have been developed with different MF doses so that it is possible to tailor the treatment to a patient's needs depending on the level of asthma control required. The bronchodilator dose of IND is the same for all FDCs. Indacaterol acetate and GLY as mono-components and as an FDC (delivered via the Breezhaler®) are approved for maintenance therapy in chronic obstructive pulmonary disease (COPD) in most regions at the same doses as MF/IND and MF/IND/GLY [7–9]. Mometasone furoate (delivered via the Twisthaler®) was approved for treatment of asthma several years earlier [10]. A recent population pharmacokinetic (PK) analysis found that IND and GLY had similar PK profiles across formulations, while MF displayed comparable PK profiles for corresponding medium- or high-dose inhaled corticosteroids [11]. The Breezhaler® is a dose-confirming unit-dose dry powder inhaler.

Here we present an overview of the stepwise dose bridging approach and data that demonstrate the comparability of MF doses at the corresponding dose strengths in the MF formulation delivered via the Twisthaler® device and MF/IND and MF/IND/GLY delivered via the Breezhaler® device.

2. Main text

2.1. Outline of the stepwise bridging approach

As the Twisthaler® and the Breezhaler® are inhalation devices with different characteristics, two sequential bridging work packages were conducted which comprised of: (i) the bridging from MF doses in the Twisthaler® to MF doses in the Breezhaler® as monotherapy and (ii) the identification and confirmation of corresponding doses in the combination products. The first work package included a single-dose PK study in healthy subjects [12], *in vitro* fine particle mass adjustments, and a pharmacodynamic (PD) study in patients [13]. The second work package comprised the identification and confirmation of the matching doses of the components in the FDC, in which the MF doses in MF/IND and MF/IND/GLY were determined via *in vitro* assessments and studies to evaluate potential PK/biopharmaceutical interactions between IND, GLY, and MF when combined for delivery via the Breezhaler® [17] and further evaluated using population PK analysis of the Phase III studies [1,11,14].

2.2. Single-dose PK study

A single-dose PK study in 24 healthy subjects investigated systemic exposure to MF delivered via the Twisthaler® (MF dose of 400 μg) versus Breezhaler® (MF dose range of 50–400 μg); the estimated dose of MF Breezhaler® that provided systemic exposure comparable to the approved MF Twisthaler® dose of 400 μg was 195 μg [12]. An *in vitro* dose adjustment for MF from 195 μg to 160 μg was then carried out because a small increase in the delivered dose was observed with the second and subsequent doses of MF administered via the Breezhaler® due to the drug substance coating effect of the inner plastic surfaces of the inhaler with the first dose delivered from a new, unused inhaler. Based on the linear relationship between dose and systemic exposure in the single-dose PK study and *in vitro* fine particle mass adjustment, MF 160 μg delivered via the Breezhaler® as monotherapy was defined as comparable to MF 400 μg dose delivered via the Twisthaler® as monotherapy. Consequently, MF 80 μg and MF 320 μg delivered via the Breezhaler® were calculated and projected to be the MF doses corresponding to MF 200 μg and MF 800 μg doses delivered via the Twisthaler®, and these doses were tested for clinical efficacy.

2.3. Multiple-dose PD and PK studies

A randomized, 4-week clinical study in 739 adults and adolescents with persistent asthma assessed the clinical efficacy of the corresponding 200/80 μg and 800/320 MF doses in the two different inhalers [13]. Comparable improvements from baseline in lung function (trough forced expiratory volume in 1 second [FEV_1]) were observed for the corresponding ICS doses, respectively administered via the Breezhaler® versus the Twisthaler® (**Table 1**), both for the low- and the high-dose of ICS comparison.

The safety and tolerability were also comparable at the corresponding doses between Breezhaler® and Twisthaler®, as was the systemic exposure (PK) (Table 2).

2.4. Pharmaceutical component interaction and PK evaluation of MF/IND

After the dose determination of MF mono-component in the Breezhaler®, the next work package was to evaluate for potential PK/biopharmaceutical interactions between IND and MF when combined for delivery via the Breezhaler®. A randomized, open-label, 4-way crossover, Phase I study assessed PK profiles in healthy adults (N = 64) treated with MF/IND (320/150 μg) (free or FDC), IND or MF (each mono-component), all delivered via the Breezhaler® [14]. The MF/IND FDC treatment showed comparable systemic exposure to the free combination and monotherapy treatments in terms of area under the plasma concentration curve ($AUC_{0\text{-}24h,ss}$) and maximum peak plasma concentration ($C_{max,ss}$) for both IND and MF, indicating an absence of clinically relevant PK or biopharmaceutical interactions [14]. These data supported further development of MF/IND without dose adjustment for either of the mono-components.

2.5. Pharmaceutical component interaction and PK evaluation of MF/IND/GLY

In the MF/IND/GLY co-formulation, an increase in the MF fine particle mass was observed compared to the corresponding nominal MF doses in MF/IND due to pharmaceutical interaction with GLY. A dose adjustment was carried out to reduce the nominal doses of MF to 80 μg o.d. and 160 μg o.d. in the lactose blend co-formulation of MF/IND/GLY delivered via the Breezhaler® device with magnesium stearate as the force control agent. The fine particle mass of MF in the 80 μg o.d. and

Table 1
Improvements in trough FEV_1 with mometasone furoate at Week 4 in patients with asthma [13].

Dose	LS mean difference (95 % CI)[a]
MF 80 μg (Breezhaler®) versus MF 200 μg (Twisthaler®)	27.0 mL (−34.0–89.0 mL)
MF 320 μg (Breezhaler®) versus MF 800 μg (Twisthaler®)	0.0 mL (−60.0–61.0 mL)

MF low-dose (Breezhaler®), 80 μg o.d.; MF high-dose (Breezhaler®), 320 μg o.d.; MF low-dose (Twisthaler®), 200 μg o.d.; MF low-dose (Twisthaler®), 800 μg (400 μg x 2 inhalations) o.d.
FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LS, least squares; MF, mometasone furoate; o.d., once daily; CI, confidence interval.
The data was adapted from Buhl et al. Pulm Pharmacol Ther. 2020; 62:101919.
[a] Based on model including ICS sensitivity.

Table 2
Summary statistics of MF PK parameters by treatment & profile day (24-hr PK subset).

Profile Day	PK parameter (unit)	Statistics	Treatment			
			Low Dose		High Dose	
			MF Twisthaler® 200 μg	MF Breezhaler® 80 μg	MF Twisthaler® 800 μg	MF Breezhaler® 320 μg
Day 28/29	AUC_{last} (hr*pg/mL)	Mean (CV%)	672 (48.6)	493 (94.7)	1490 (48.1)	1230 (37.7)
		n	23	26	25	23
	C_{max} (pg/mL)	Mean (CV%)	63.4 (43.1)	54.7 (96.5)	132 (43.8)	133 (38.8)
		n	23	26	25	23
	T_{max} (hr)	Median	1.02	0.983	1.00	0.967
		[Min; Max]	[0.367; 4.05]	[0.467; 12.0]	[0.433; 12.1]	[0.483; 4.08]
		n	23	26	25	23

N values vary due to missing values.
AUC, area under the plasma concentration curve; C_{max}, maximum peak plasma concentration; MF, mometasone furoate; PD, pharmacodynamics; PK, pharmacokinetics; T_{max}, maximum concentration after drug administration.

160 μg o.d. in MF/IND/GLY was comparable with the nominal MF doses in MF/IND 160 μg o.d. and 320 μg o.d. combinations, respectively (Table 3). The comparable fine particle mass had been expected to result in equivalent delivery of MF to the lung and equivalent systemic exposure between the corresponding doses of MF/IND/GLY and MF/IND.

2.6. Pharmaceutical component interaction and PK evaluation of MF/IND/GLY

The next phase of the development program involved assessment of PK characteristics and biopharmaceutical interactions of the inhaled combination of MF/IND/GLY delivered via the Breezhaler® device. Steady-state PK was evaluated over a 14-day treatment period in a randomized, open-label, 4-way crossover study including 36 healthy subjects who received MF/IND/GLY (MF160 μg) and the components of MF/IND/GLY separately o.d. via the Breezhaler® device. The PK was characterized in plasma on Day 14 up to 24 h post dose [16].

The MF/IND/GLY FDC treatment showed comparable systemic exposure to the monotherapy treatments in terms of $AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$ for all three components (IND, GLY and MF), indicating an absence of clinically relevant PK or biopharmaceutical interactions [17]. These data supported the further development of MF/IND/GLY without further dose adjustment for either of the mono-components.

2.7. Pharmacokinetic assessments in phase III of MF/IND/GLY versus MF/IND

A population PK analysis of the Phase III PK data was conducted, which also assessed the systemic exposure (C_{max}, C_{trough}) of the different MF doses in the combination therapies of MF/IND and MF/IND/GLY delivered via the Breezhaler® device in patients with asthma. The analysis included 279 patients [18]. Graphical and tabulated presentation of data allows for a comparison of degree of similarity in distributions. Since no null hypothesis is associated with this approach to understand the data, hypothesis tests to compare summary statistics of the distributions were not performed.

At Day 86, the median MF C_{max} and C_{trough} were comparable between the two high-dose FDCs, MF/IND (MF 320 μg) and MF/IND/GLY (160 μg), and between the two medium-dose FDCs, MF/IND (160 μg) and MF/IND/GLY (80 μg), respectively (Fig. 1; Table 4). This finding confirms that systemic MF exposure between the corresponding dose strengths of MF/IND and MF/IND/GLY is comparable (data on file). The exposure of IND and GLY was also assessed and was comparable between the formulations (Supplementary Appendix).

Table 3
Nominal doses of MF.

ICS dose level	MF (Twisthaler®)	MF[a] (Breezhaler®)	MF/IND (Breezhaler®)	MF/IND/GLY (Breezhaler®)
Low	200 μg	80 μg	80 μg	Not investigated
Medium	400 μg	160 μg[†]	160 μg	80 μg
High	800 μg (400 μg b.i.d.)	320 μg	320 μg	160 μg

b.i.d, twice daily; GLY, glycopyrronium bromide; ICS, inhaled corticosteroid; IND, indacaterol acetate; MF/IND, mometasone furoate/indacaterol acetate; MF/IND/GLY, mometasone furoate/indacaterol acetate/glycopyrronium bromide; MF, mometasone furoate.
[a] Mometasone furoate (Breezhaler®) is not a commercialized product;[†] Mometasone furoate at 160 μg not investigated in clinical trial as monotherapy.

3. Discussion

This manuscript presents the studies performed to determine the MF doses delivered by the Breezhaler® inhaler and used in the clinical development program of MF/IND and MF/IND/GLY. Three dose strengths of MF (80, 160 and 320 μg; low-, medium-, and high-dose level) were investigated in the MF/IND formulation and their correspondence to the MF doses delivered by Twisthaler® was determined. Two dose strengths of MF (80 μg and 160 μg; medium and high dose level) were investigated in the MF/IND/GLY formulation. Due to pharmaceutical interaction in the MF/IND/GLY formulation, the nominal MF doses differ between the MF/IND and the MF/IND/GLY formulation, but deliver a comparable ICS dose to the lung. These doses were then used in the Phase III clinical trials of MF/IND and MF/IND/GLY and PK data from these trials confirm that the MF doses at the corresponding dose levels provide similar exposure [16,17]. It is coincidental that the nominal doses of MF in the MF/IND/GLY formulation are exactly half of those in the MF/IND formulation at the same dose level. This approach is unique to the MF/IND and MF/IND/GLY clinical development program. The difference of nominal ICS dose at the same dose level between the ICS/LABA and ICS/LABA/LAMA combinations has not been described for other ICS/LABA/LAMA combinations primarily due to the different delivery systems used. The mechanism of the apparent boost in performance of compounds such as MF in the presence of small amounts of GLY has not been exhaustively described in literature until now. However, a very similar phenomenon has been reported previously for the FDC drug product Ultibro® Breezhaler® (110/50 μg IND/GLY) [9], which delivers an equivalent lung dose of IND (as maleate salt) compared to the respective mono product Onbrez® Breezhaler® (150 μg IND) [15]. Despite of the presence of GLY, dose adjustment of IND in MF/IND/GLY had not been required, which may be attributed to slightly different formulation interactions observed with the IND acetate salt compared to the maleate salt used in Ultibro® Breezhaler® and Onbrez® Breezhaler®.

A twice-daily FDC of beclomethasone dipropionate (BDP)/formoterol fumarate (FOR)/glycopyrronium bromide (GLY) is available in a solution-based pressurised metered-dose inhaler (pMDI) with all three

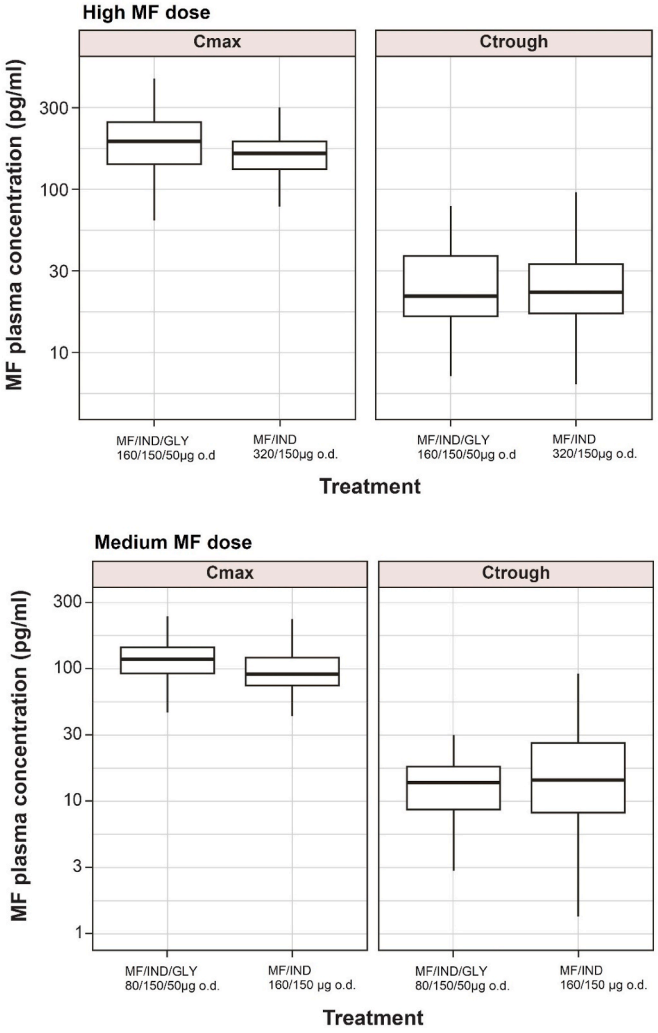

Fig. 1. C_{max} and C_{trough} concentrations of MF in high- and medium-dose MF/IND and MF/IND/GLY combinations. Data are presented as median with quartiles. MF/IND/GLY high-dose, 160/150/50 µg o.d.; MF/IND/GLY medium-dose, 80/150/50 µg o.d.; IND/MF high-dose, 320/150 µg o.d.; IND/MF medium-dose, 160/150 µg o.d. C $_{max}$, maximum plasma concentration; C_{trough}, trough plasma concentration; MF/IND/GLY, mometasone furoate/indacaterol acetate/glycopyrronium bromide; o.d., once daily.

active pharmaceutical ingredients (BDP/FOR/GLY) dissolved in the propellant formulation. The aerodynamic particle size distribution (APSD) of active pharmaceutical ingredients (APIs) for this product depends on propellant and the composition of solvents/co-solvents as well as on the pMDI components, i.e. API dose alone is not the only key factor for such a formulation when considering APSD [19,21]. A once-daily FDC of fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) is delivered by the Ellipta® device, which contains two separate blister strips. Each blister in one strip contains FF, each blister in the other strip contains UMEC and VI; both blisters are opened in parallel to allow inhalation of powder from two separate cavities, in this way generating an aerosol with the three APIs with the inhalation. There is no pharmaceutical interaction of the FF with other API's which could modify its pharmaceutical performance [20]. We observed a complex interplay among the three APIs and excipients in the capsule-based Breezhaler® inhaler that uses a simple, reliable mechanism of delivery. The once-daily FDC formulation of MF/IND/GLY was developed following the approach of maintaining the doses of two of the three APIs consistent with those of already approved mono components (IND and GLY) and adjusting the dose of one API (MF) to match the approved mono component dose.

Table 4
Summary statistics of PK parameters for MF in FDCs.

Treatment arm	Day 30		Day 86	
	C_{max} (pg/mL)	C_{trough} (pg/mL)	C_{max} (pg/mL)	C_{trough} (pg/mL)
MF/IND/GLY 160/150/50 µg o.d	192 (91.3–310.7)	24.1 (11.1–89.3)	187.5 (78.1–288.9)	22.0 (3.6–75.8)
MF/IND 320/150 µg o.d.	161 (75.8–261.4)	23.7 (1.3–119.0)	159.0 (82.4–232.2)	23.1 (6.2–116.6)
MF/IND/GLY 80/150/50 µg o.d.	116 (63.7–183.6)	13.3 (2.7–63.0)	113 (57.1–174.9)	13.5 (3.4–70.3)
MF/IND 160/150 µg o.d.	94.2 (51.7–173.2)	16.0 (2.4–84.7)	86.4 (48.0–163.3)	14.0 (2.7–82.7)

Data are presented as percentiles of the distributions: 5, 50 and 95 percentiles. C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration. MF/IND, mometasone furoate/indacaterol acetate; MF/IND/GLY, mometasone furoate/indacaterol acetate/glycopyrronium bromide; o.d., once daily.

While several published review articles have looked at interparticulate forces between carrier surface and API in adhesive mixtures for inhalation dry powder blends [22–26], to date little is known in the literature about the impact on cohesive/adhesive balance, on blend microstructure, and on powder dispersion properties when a second or a third API is added to an inhalation powder blend. The extent of improvement of lung delivery of MF observed with the MF/IND/GLY formulation when compared to MF/IND indicates the need for future research to understand and quantify the corresponding carrier to API to API formulation interactions.

4. Conclusions

The PK/PD data summarized above confirm that MF 80 µg o.d. (medium-dose strength) and 160 µg o.d. (high-dose strength) in MF/IND/GLY formulation provide matching ICS systemic exposure to MF 160 µg o.d. (medium-dose strength) and 320 µg o.d. (high-dose strength) in the MF/IND formulation, respectively. The main reason for the observed increase in fine particle mass of MF in MF/IND/GLY, necessitating the lower MF dose, is related to a physicochemical interaction through the presence of GLY powder blend. In order to maintain comparability, the nominal dose of MF in MF/IND/GLY was adjusted from 320 µg (in MF/IND) to 160 µg (in MF/IND/GLY), and from 160 µg (in MF/IND) to 80 µg (in MF/IND/GLY). *In vitro* fine particle mass data and data from the Phase II studies supported the use of these doses in the PLATINUM Phase III clinical development program that investigated the efficacy and safety of MF/IND and MF/IND/GLY combinations in patients with asthma and established that 160 µg and 80 µg of MF in MF/IND/GLY and 320 µg and 160 µg in MF/IND are appropriate and corresponding high and medium dose strengths of MF in the respective FDCs [17,18]. Consequently, the once-daily FDCs of MF/IND and MF/IND/GLY, both delivered via the Breezhaler® device, have been approved for the maintenance treatment of asthma based on the clinical evidence generated from the PLATINUM program.

5. Data sharing statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. Result

summaries have been posted on the Novartis clinical trial database and other online public databases. More information on Novartis' position on access to clinical trial results and patient-level data is available at: https://www.novartis.com/our-science/clinical-trials/clinical-trial-information-disclosure.

Author contribution statement

All authors contributed to the interpretation of data. All authors provided intellectual input into the content of the manuscript, drafting and revising the article, and approved the final version for publication; all agree to be accountable for all aspects of the work.

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Declaration of interest

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Appendix A. Supplementary data

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