Pharmacokinetics of indacaterol, glycopyrronium and mometasone furoate following once-daily inhalation as a fixed-dose combination in healthy subjects

PA2540

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Introduction

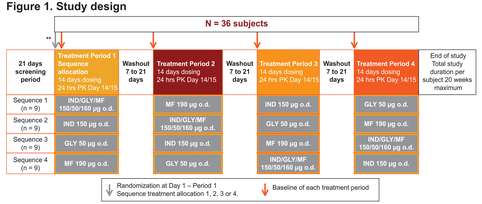
- Asthma is a chronic inflammatory disease of the airways characterised by respiratory symptoms and variable expiratory airflow limitation[1]
- There is increasing evidence that in patients poorly controlled on medium- and high-dose inhaled corticosteroid (ICS)/long-acting β_2-agonists (LABA), a combination of LABA, long-acting muscarinic antagonist (LAMA) and ICS can provide additional benefits[2,3]
- IND/GLY/MF is a combination of indacaterol acetate (IND, a LABA), glycopyrronium bromide (GLY, a LAMA), and mometasone furoate (MF, an ICS) being developed as once-daily maintenance treatment for asthma, to be delivered via the Breezhaler® device
- Here, we present the results from a Phase I study, in which we evaluated potential pharmacokinetic (PK) drug-drug interactions between the active components in the IND/GLY/MF combination by comparing the steady-state plasma PK of individual components after inhalation as a combination versus inhalation of monotherapies alone to be delivered once-daily via the the Breezhaler® inhalation device

Methods

Study design

- This was a randomised, open label, four-sequence, four-period, complete crossover study in healthy men and women (**Figure 1**)
- Subjects were randomised to one of the 4 treatment sequences in the ratio of 1:1:1:1

Figure 1. Study design



**Subjects received the four treatments IND/GLY/MF 150/50/160 µg o.d., IND 150 µg o.d., GLY 50 µg o.d., and MF 190 µg o.d.
IND/GLY/MF is a combination of indacaterol acetate 150 µg, glycopyrronium bromide 50 µg and mometasone furoate 80 µg (medium-dose ICS) or 160 µg (high-dose ICS) delivered o.d. via the Breezhaler®
GLY, glycopyrronium bromide; ICS, inhaled corticosteroids; IND, indacaterol acetate; MF, mometasone furoate; o.d., once daily.; PK, pharmacokinetics

Patients

Key inclusion criteria

- Healthy men and women aged 18 to 45 years
- Subjects who weighed ≥50 kg having a body mass index (BMI) within the range of 18–32 kg/m^2

Key exclusion criteria

- A history of clinically significant ECG abnormalities, presence of long QT syndrome and laboratory abnormalities
- Pregnant or nursing (lactating) women and women of child-bearing potential

Objectives

Primary objective

- To evaluate the steady state plasma PK ($C_{max,ss}$ [maximum plasma concentration at steady state] and $AUC_{0-24h,ss}$ [area under the plasma concentration-time curve from 0 to 24 hours at steady state]) of IND, GLY and MF on Day 14

Secondary objective

- To assess the safety and tolerability of multiple inhaled doses of IND, GLY and MF when administered alone or as a combination (IND/GLY/MF)

Statistical analysis

- The safety analysis set included all subjects who received any study drug
- The PK analysis set included all subjects who received any study drug with at least one valid PK measurement
- Systemic exposure ratio of combination IND/GLY/MF versus IND or GLY or MF, was assessed for log-transformed $AUC_{0-24h,ss}$ and $C_{max,ss}$ on Day 14 using mixed effects model

Results

Patients

- In total, 36 healthy subjects were randomised, 33 of whom completed all treatment periods. Baseline demographics are presented in **Table 1**

Table 1. Baseline demographics (safety analysis set)

Characteristic	Total N = 36
Age in years, median (range)	35.5 (19 to 45)
Gender, n (%)	
Men	34 (94.4)
Women	2 (5.6)
Weight (kg)	83.2 ± 10.36
Body mass index (kg/m^2)	25.2 ± 2.60

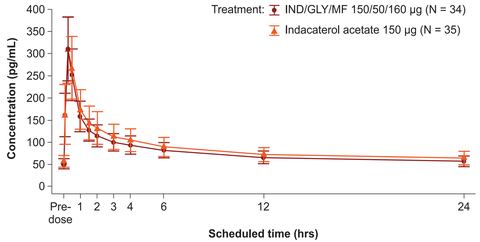
Data presented as mean ± SD, unless otherwise specified

Pharmacokinetics

Plasma concentration-time profiles of IND on Day 14 from IND/GLY/MF combination and IND monotherapy

- The plasma concentration-time profiles for IND when administered as IND/GLY/MF combination and monotherapy were comparable on Day 14 (**Figure 2**)
- Median time to reach maximum concentration ($T_{max,ss}$) for IND was similar from both monotherapy and IND/GLY/MF combination (**Table 2**)
- The trough plasma concentrations of IND were stable from Day 12 to Day 14 when administered as monotherapy and IND/GLY/MF combination, indicating that steady state was attained by Day 12

Figure 2. Plasma concentration-time profiles for IND were comparable on Day 14 when administered as IND/GLY/MF combination or as a monotherapy (PK analysis set)

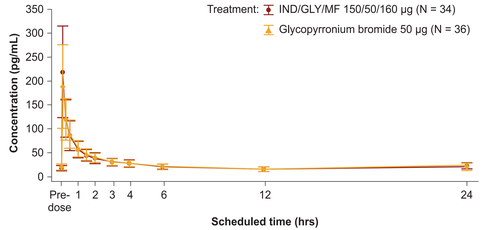


Data presented as mean ± SD
IND/GLY/MF is a combination of indacaterol acetate 150 µg, glycopyrronium bromide 50 µg and mometasone furoate 160 µg delivered o.d. via the Breezhaler®
GLY, glycopyrronium bromide; IND, indacaterol acetate; MF mometasone furoate; o.d., once daily; PK, pharmacokinetics

Plasma concentration-time profiles for GLY on Day 14 from IND/GLY/MF combination and GLY monotherapy

- The plasma concentration-time profiles for GLY when administered as IND/GLY/MF combination and monotherapy were comparable on Day 14 (**Figure 3**)
- Median time to reach maximum concentration ($T_{max,ss}$) for GLY was similar from both monotherapy and IND/GLY/MF combination (**Table 2**)
- Similar to IND, GLY also achieved steady state by Day 12 when administered as both monotherapy and IND/GLY/MF combination

Figure 3. Plasma concentration-time profiles for GLY were comparable on Day 14 when administered as IND/GLY/MF combination or as a monotherapy (PK analysis set)

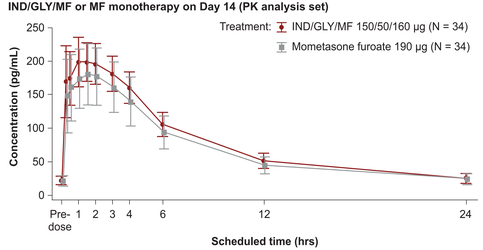


Data presented as mean ± SD
IND/GLY/MF is a combination of indacaterol acetate 150 µg, glycopyrronium bromide 50 µg and mometasone furoate 160 µg delivered o.d. via the Breezhaler®
GLY, glycopyrronium bromide; IND, indacaterol acetate; MF mometasone furoate; o.d., once daily; PK, pharmacokinetics

Plasma concentration-time profiles for MF on Day 14 from IND/GLY/MF combination and MF monotherapy

- The mean plasma concentration of MF administered as monotherapy and IND/GLY/MF combination rose rapidly after inhalation via Breezhaler® and reached a peak at 1.5 hour and 1 hour, respectively post-dose on Day 14 (**Figure 4**)
- The mean plasma concentration of MF observed with IND/GLY/MF combination was slightly higher than the concentration observed following administration of MF monotherapy on Day 14 (**Table 2**)

Figure 4. Plasma concentration-time profiles of MF following administration as IND/GLY/MF or MF monotherapy on Day 14 (PK analysis set)



Data presented as mean ± SD
IND/GLY/MF is a combination of indacaterol acetate 150 µg, glycopyrronium bromide 50 µg and mometasone furoate 160 µg delivered o.d. via the Breezhaler®
GLY, glycopyrronium bromide; IND, indacaterol acetate; MF mometasone furoate; o.d., once daily; PK, pharmacokinetics

Table 2. Summary statistics of plasma PK parameters of IND, GLY, MF on Day 14 following administration as IND/GLY/MF combination and monotherapy (PK analysis set)

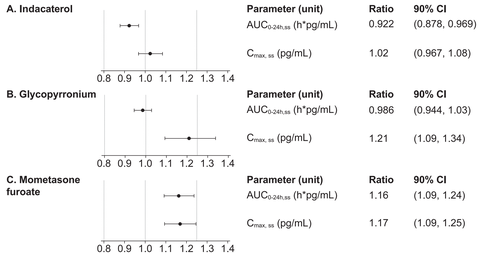
IND		
PK parameters	**IND/GLY/MF 150/50/160 µg o.d. N = 31**	**IND 150 µg o.d. N = 33**
$AUC_{0-24h,ss}$, h*pg/mL	1910 ± 377.0 (19.7)	2110 ± 460.0 (21.8)
$C_{max,ss}$, pg/mL	311 ± 72.9 (23.4)	308 ± 74.4 (24.2)
$T_{max,ss}$, h	0.250 (0.250 to 0.500)	0.250 (0.250 to 0.333)
GLY		
PK parameters	**IND/GLY/MF 150/50/160 µg o.d. N = 31**	**GLY 50 µg o.d. N = 36**
$AUC_{0-24h,ss}$, h*pg/mL	597 ± 148.0 (24.8)	609 ± 147.0 (24.1)
$C_{max,ss}$, pg/mL	220 ± 95.5 (43.5)	189 ± 87.0 (46.0)
$T_{max,ss}$, h	0.0833 (0.083 to 0.117)	0.0833 (0.083 to 0.250)
MF		
PK parameters	**IND/GLY/MF 150/50/160 µg o.d. N = 33**	**MF 190 µg o.d. N = 32**
$AUC_{0-24h,ss}$, h*pg/mL	1910 ± 287.0 (15.0)	1700 ± 421.0 (24.8)
$C_{max,ss}$, pg/mL	215 ± 37.0 (17.2)	192 ± 47.6 (24.8)
$T_{max,ss}$, h	1.00 (0.250 to 3.000)	1.50 (0.250 to 3.000)

For $AUC_{0-24h,ss}$ and $C_{max,ss}$ data is presented as mean ± SD (CV%), whereas for $T_{max,ss}$, median (min-max) values are provided.
IND/GLY/MF is a combination of indacaterol acetate 150 µg, glycopyrronium bromide 50 µg and mometasone furoate 160 µg delivered o.d. via the Breezhaler®
$AUC_{0-24h,ss}$, area under the plasma concentration-time curve from 0 to 24 hours at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; CV, coefficient of variation; GLY, glycopyrronium bromide; IND, indacaterol acetate; MF, mometasone furoate; o.d., once daily; PK, pharmacokinetics

Comparison of $AUC_{0-24h,ss}$ and $C_{max,ss}$ for IND, GLY and MF on Day 14 following administration as IND/GLY/MF combination and monotherapy (geometric mean ratios)

- The comparison expressed in terms of geometric mean ratios (GMRs) and 90% CI for $AUC_{0-24h,ss}$ and $C_{max,ss}$ were both within the bioequivalence limits of 0.80–1.25 for IND and MF (**Figure 5A** and **5C**)
- For GLY, while the GMR and 90% CI for $AUC_{0-24h,ss}$ was within the bioequivalence limits of 0.80 to 1.25, for $C_{max,ss}$ the upper limit of the 90% CI lay marginally outside the bioequivalence limits (**Figure 5B**)

Figure 5. GMR of $AUC_{0-24h,ss}$ and $C_{max,ss}$ for IND/GLY/MF combination versus monotherapy on Day 14



IND/GLY/MF is a combination of indacaterol acetate 150 µg, glycopyrronium bromide 50 µg and mometasone furoate 160 µg delivered o.d. via the Breezhaler®
$AUC_{0-24h,ss}$, area under the plasma concentration-time curve from 0 to 24 hours at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; GLY, glycopyrronium bromide; GMR, geometric mean ratio; IND, indacaterol acetate; MF, mometasone furoate; o.d., once daily; PK, pharmacokinetics

Safety

- In total, 26 (72.2%) subjects reported at least 1 adverse event (AE) (**Table 3**)
- The most common AEs were nasopharyngitis (38.9%), headache (13.9%), oropharyngeal pain (13.9%), cough (5.6%), diarrhoea (5.6), epistaxis (5.6%), influenza like illness (5.6%), nausea and vertigo (5.6%)
- Majority of the AEs were mild or moderate in severity, with only one incidence of severe AE noted as SAE, nephrolithiasis not related to study treatment
- There were no deaths reported during the study

Table 3. Overall incidence of AEs (safety analysis set)

	IND/GLY/MF N = 34	IND N = 35	GLY N = 36	MF N = 34	Total N = 36
Subjects with at least one AE	13 (38.2)	15 (42.9)	6 (16.7)	12 (35.3)	26 (72.2)
AEs suspected to be related to study-drug	8 (23.5)	7 (20.0)	3 (8.3)	9 (26.5)	13 (36.1)
Serious AEs	0 (0.0)	1 (2.9)*	0 (0.0)	0 (0.0)	1 (2.8)
AEs leading to discontinuation of study treatment	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.8)
Study-drug-related AEs leading to discontinuation of study treatment	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.8)

Data presented as n (%)
*Serious adverse event of nephrolithiasis was not suspected to be related to study drug by the investigator
IND/GLY/MF is a combination of indacaterol acetate 150 µg, glycopyrronium bromide 50 µg and mometasone furoate 160 µg delivered o.d. via the Breezhaler®
AEs, adverse events; GLY, glycopyrronium bromide; IND, indacaterol acetate; MF, mometasone furoate; o.d, once daily

Conclusions

- $AUC_{0-24h,ss}$, geometric mean ratios and 90% confidence intervals for the IND/GLY/MF vs. monotherapy comparison fell within the bioequivalence limits (0.80-1.25) for all components, indicating similar systemic exposure
- For $C_{max,ss}$, bioequivalence criteria were met for the IND/GLY/MF vs. monotherapy comparison for indacaterol and mometasone, while for glycopyrronium, the upper limit of the 90% confidence interval fell marginally outside the bio-equivalence limits
- There was no clinically relevant pharmacokinetic interaction between indacaterol acetate, glycopyrronium bromide, and mometasone furoate, when administered as IND/GLY/MF combination
- Multiple inhaled doses of indacaterol acetate, glycopyrronium bromide and mometasone furoate were well tolerated when administered alone or in combination in healthy subjects. No new safety signals were detected

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