Lung function, pharmacokinetics, and tolerability of indacaterol maleate and acetate in asthma patients

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Introduction

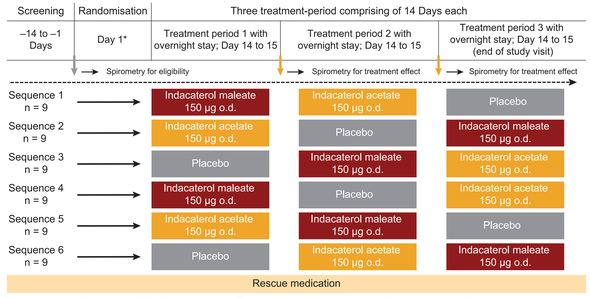
- Asthma is a chronic inflammatory disorder of the airways, associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing[1,2]
- Inhaled corticosteroids (ICS) are the cornerstone in asthma management. For patients who experience persistent symptoms and exacerbations, Global Initiative for Asthma report recommends a higher dose of ICS and/or use of ICS with a long-acting β_2-agonist (ICS/LABA)[3]
- Indacaterol maleate is the LABA used in Onbrez® Breezhaler® and Ultibro® Breezhaler® (in combination with a long-acting muscarinic antagonist (LAMA), glycopyrronium), approved for chronic obstructive pulmonary disease
  - In the development of indacaterol/glycopyrronium/mometasone furoate (a LABA/LAMA/ICS) combination for asthma, the acetate salt of indacaterol was used instead of the maleate salt
- The aim of the study is to compare indacaterol maleate 150 µg once daily (o.d.) and indacaterol acetate 150 µg o.d. in terms of pharmacodynamics (PD), pharmacokinetics (PK) and safety

Methods

Study design

- This was a double-blind, placebo-controlled, three-period complete block, cross-over study in patients with asthma (ClinicalTrials.gov number, NCT03257995)
  - Patients were randomised to one of six treatment sequences across three-treatment periods (14 days each) to receive indacaterol maleate 150 µg o.d., indacaterol acetate 150 µg o.d. and placebo, as described in **Figure 1**

Figure 1. Study design



*Randomisation at Day 1 in one of the 6 treatment arms; Treatment sequences are double-blinded; o.d., once daily

Patients

Key inclusion criteria

- Adult asthma patients receiving a stable ICS dose for at least 4 weeks prior to screening
- Pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥50% and ≤90% of the predicted normal value at screening

Key exclusion criteria

- Current smokers
- Patients who had a severe asthma exacerbation requiring hospitalisation or systemic corticosteroids or emergency room visit, 6 weeks prior to screening
- Patients who had previous intubation for a severe asthma attack/exacerbation

Endpoints

- Trough FEV_1 following indacaterol maleate and acetate inhalation, versus placebo at Day 14 was assessed as the primary endpoint
- Steady state plasma exposure from 0 to 24 hour ($AUC_{0-24h,ss}$) and steady state maximum plasma concentration ($C_{max,ss}$) were determined after 14 days of treatment with indacaterol salts
- Standardised FEV_1 area under the curve from 0 to 4 hour (FEV_1 AUC_{0-4h}) on Day 14 of treatment
- Peak expiratory flow (PEF) rate was evaluated between Days 8 and 14 of each treatment
- Safety profile after 14 days of treatment in each treatment period

Statistical analysis

- The PK and PD analysis sets included all patients who received any study drug and experienced no major protocol deviations with relevant impact on PK and PD data respectively; safety set included all patients who received any study drug
- Trough FEV_1, PEF and FEV_1 AUC_{0-4h} were analysed using analysis of variance with treatment, period and sequence as fixed effects and subjects nested within sequence as random effect
- The log transformed steady state PK parameters ($AUC_{0-24h,ss}$; $C_{max,ss}$) on Day 14 were compared between both salts using a mixed effects model

Results

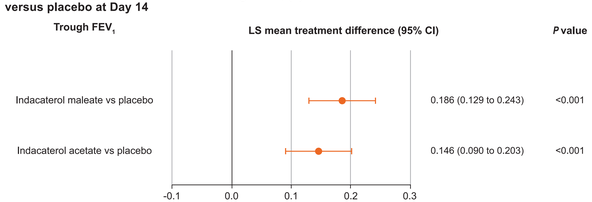
Patients

- Of the 54 patients randomised, 51 patients completed the study
  - One patient discontinued due to a serious adverse event (SAE) and two discontinued due to deviations from study protocol
- Mean age of patients was 47.7 years (range, 26 to 70 years)
- Majority were women (66.7%), with a mean ± SD body mass index of 29.9 ± 5.09 kg/m²

Lung function

- After 14 days of treatment, both indacaterol maleate and indacaterol acetate showed a clinically relevant and statistically significant improvement in trough FEV_1 compared with placebo ($P < 0.001$) (**Figure 2**)

Figure 2. Significant improvement in trough FEV_1 (L) with indacaterol maleate and indacaterol acetate versus placebo at Day 14



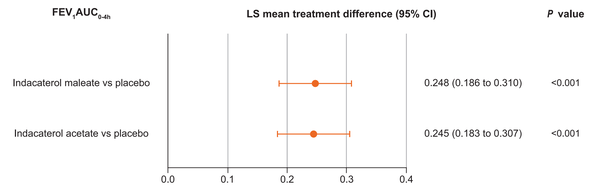
Data are presented as LS mean treatment difference (95% CI)
FEV_1, forced expiratory volume in 1 second; LS, least square

- Improvement was also observed in FEV_1 AUC_{0-4h} with both indacaterol acetate and indacaterol maleate compared with placebo at Day 14 ($P < 0.001$) (**Figure 3**)
- At Day 14, indacaterol maleate and indacaterol acetate showed improvement in PEF, compared with placebo (**Figure 4**)

Systemic pharmacokinetics

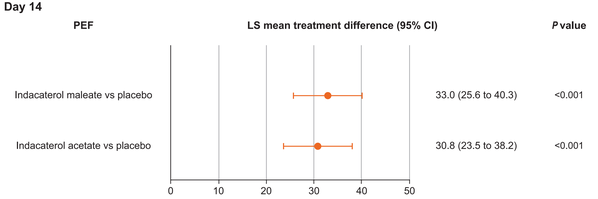
- Indacaterol maleate and indacaterol acetate showed comparable systemic plasma concentration time profiles on Day 14 (**Figure 5**)

Figure 3. Improvement in FEV_1 AUC_{0-4h} (L) with indacaterol maleate and indacaterol acetate versus placebo at Day 14



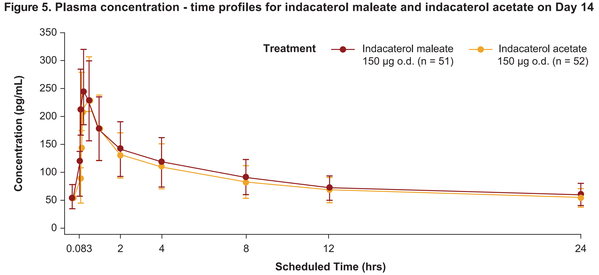
Data are presented as LS mean treatment difference (95% CI)
FEV_1 AUC_{0-4h}, standardised FEV_1 area under the curve from 0 to 4 hour; FEV_1, forced expiratory volume in 1 second; LS, least square

Figure 4. Improvement in PEF (L/min) with indacaterol maleate and indacaterol acetate versus placebo at Day 14



Data are presented as LS mean treatment difference (95% CI)
PEF, peak expiratory flow; LS, least square

Figure 5. Plasma concentration - time profiles for indacaterol maleate and indacaterol acetate on Day 14



Data presented as arithmetic mean ± SD; error bars indicate SD values; o.d., once daily

- There was no relevant difference in exposure ($AUC_{0-24h,ss}$ and $C_{max,ss}$) at steady state between indacaterol acetate and indacaterol maleate (**Table 1**)
- Geometric mean ratios for both $AUC_{0-24h,ss}$ and $C_{max,ss}$ were within the bioequivalence limit (0.80 to 1.25); indicating a comparable exposure from both the indacaterol salts (**Table 2**)

Table 1. Summary statistics of plasma PK parameters for indacaterol salts on Day 14

	Indacaterol maleate 150 µg o.d.	Indacaterol acetate 150 µg o.d.
$AUC_{0-24h,ss}$, h*pg/mL	2300 ± 732 (31.8)	2050 ± 636 (31.0)
$C_{max,ss}$, pg/mL	264 ± 80.2 (30.3)	236 ± 74.0 (31.3)
$T_{max,ss}$, h	0.250 (0.18 to 0.85)	0.467 (0.18 to 1.00)

Data presented as arithmetic mean ± SD (CV%) AUC, area under the curve; C_{max}, maximum plasma concentration; CV%, coefficient of variation; o.d., once daily; PK, pharmacokinetic

Table 2. Comparative analysis of PK between indacaterol maleate and acetate on Day 14

	Indacaterol maleate 150 µg o.d.	Indacaterol acetate 150 µg o.d.	Indacaterol acetate versus indacaterol maleate
	Geometric LSM (90% CI)		Geometric LSM ratio (90% CI)
$AUC_{0-24h,ss}$, h*pg/mL	2180 (2020 to 2350)	1950 (1820 to 2100)	0.897 (0.854 to 0.942)
$C_{max,ss}$, pg/mL	253 (236 to 273)	226 (210 to 243)	0.891 (0.846 to 0.939)

AUC, area under the curve; C_{max}, maximum plasma concentration; LSM, least squares mean; o.d., once daily; PK, pharmacokinetic

Safety

- Safety data for all study treatments is shown in **Table 3**
  - Indacaterol acetate was not associated with post-inhalation cough, whereas 23.5% (n = 12) of patients reported cough with indacaterol maleate

Table 3. Incidence of treatment-emergent AEs by preferred term affecting ≥5% of total patients (safety analysis set)

	Indacaterol maleate 150 µg o.d. n = 51	Indacaterol acetate 150 µg o.d. n = 52	Placebo n = 53	Total N = 54
Patients with at least one AE	14 (27.5)	7 (13.5)	9 (17.0)	24 (44.4)
Cough	12 (23.5)	0 (0.0)	1 (1.9)	13 (24.1)
Upper respiratory tract infection	1 (2.0)	2 (3.8)	2 (3.8)	5 (9.3)

Data presented as n (%)
AE, adverse event; o.d., once-daily

Conclusions

- In patients with asthma, both indacaterol maleate and indacaterol acetate achieved significant improvements in lung function compared with placebo and elicited comparable systemic exposure
- Geometric mean ratios and 90% CIs for both $AUC_{0-24h,ss}$ and $C_{max,ss}$ fell within the bioequivalence limits indicating similar exposure from both indacaterol salts
- Both indacaterol salts demonstrated a good safety profile; no AEs of cough were observed with indacaterol acetate

References

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