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Indacaterol, a novel inhaled β_2-agonist, provides sustained 24-h bronchodilation in asthma

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ABSTRACT: The present study examined the bronchodilator and safety profiles of single-dose indacaterol in intermittent or persistent asthma.

In the present double-blind crossover study, 42 patients were randomised to receive single doses of indacaterol (50, 100, 200 and 400 μg) or placebo *via* a hydrofluoroalkane pressurised metered-dose inhaler. The primary efficacy comparisons were the per cent changes in forced expiratory volume in one second (FEV_1) between indacaterol and placebo 30 min and 21 h post-dose.

All doses resulted in prolonged bronchodilation, with indacaterol 200 and 400 μg meeting pre-specified efficacy criteria. The mean percentage increases in FEV_1 from placebo with indacaterol 200 and 400 μg were 7.6 and 14.9%, respectively, at 30 min, and 7.5 and 10.4%, respectively, at 21 h post-dose. At these doses, changes in mean FEV_1 relative to placebo were statistically significant from 5 min to 25 h, inclusive. At 5 min, the geometric least squares mean values for FEV_1 were 3.08 and 3.22 L for the 200 and 400 μg doses, respectively, compared with 2.99 L for placebo. At 24 h after dosing, the baseline-adjusted geometric least square mean FEV_1 was 3.13, 3.11, 3.24 and 3.30 L for indacaterol 50, 100, 200 and 400 μg, respectively, and 2.98 L for placebo. All treatments were well tolerated.

Once-daily indacaterol at doses of 200 and 400 μg provided sustained 24-h bronchodilation, with a rapid onset and a good tolerability and safety profile.

KEYWORDS: Asthma, bronchodilators, forced expiratory volume in one second, indacaterol, long-acting β_2-agonist, once-daily

Inhaled β_2-adrenoceptor agonists are the most effective bronchodilators for the management of asthma [1]. The Global Initiative for Asthma guidelines recognise the role of long-acting β_2-agonists (LABAs) for the optimal treatment of moderate-to-severe persistent asthma [1]. Currently available inhaled LABAs have durations of action of ~12 h at recommended doses, necessitating twice-daily dosing to provide optimal clinical efficacy [2–5]. The availability of a once-daily β_2-agonist could be expected to improve the treatment of asthma by providing patients with greater convenience and sustained bronchodilation.

Indacaterol is a β_2-agonist bronchodilator in development for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Pharmacologically, indacaterol is a nearly full β_2-agonist with a high intrinsic efficacy and, unlike partial agonists, it does not exhibit antagonistic behaviour in the presence of isoprenaline [6]. Multiple-dose, dose-ranging studies [7, 8] in patients with asthma have shown that indacaterol provides effective bronchodilation with fast onset of action (within 5 min), which is sustained for ⩾24 h on once-daily dosing. Pharmacokinetic data taken during a multiple-dose study of indacaterol 400 or 800 μg once daily for 14 days [9] demonstrated rapid absorption and a mean elimination half-life of >30 h. Likewise, in a single-dose study [10], doses 600–2,000 μg were rapidly absorbed, with maximum serum concentrations reached within 15 min. All doses were well tolerated with a good safety profile and were not associated with consistent or clinically relevant effects on systemic β-agonist mediated events [7–10].

The aim of the current study was to examine the bronchodilator profile of a range of indacaterol doses in patients with intermittent or persistent asthma.

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METHODS

Design

The present study was a multicentre, randomised, double-blind, placebo-controlled, crossover, dose-ranging study. Patients were randomised to one of five crossover treatment sequences (Latin square design) to inhale a single dose of indacaterol 50, 100, 200 or 400 μg or placebo from a hydrofluoroalkane (HFA) pressurised metered-dose inhaler (pMDI), with a 5–14 day washout between treatment periods. At all treatment visits, patients were under continuous medical supervision from the first pre-dose evaluation until 26 h after administration of the study medication. Study medication was administered between 17:00 and 19:00 h and patients were allowed to sleep for 7 h, approximately between 00:00–07:00 h.

The study received institutional review board approval and all patients gave informed written consent prior to the start of the study. The study was conducted according to Good Clinical Practice guidelines and in accordance with the Declaration of Helsinki (1964 and subsequent revisions).

Inclusion and exclusion criteria

Inclusion criteria were: 1) males and females aged 18–65 yrs; 2) a diagnosis of intermittent or persistent asthma [11]; 3) use of daily treatment with an inhaled β_2-agonist, with or without an inhaled corticosteroid (ICS; $\leqslant$1,600 μg of beclometasone dipropionate or equivalent); 4) a stable regimen for $\geqslant$1 month prior to screening; 5) a forced expiratory volume in one second (FEV_1) at screening 60–85% of the predicted normal value [12] in the absence of short-acting β_2-agonist (SABA) and LABA use for $\geqslant$6 and $\geqslant$48 h prior, respectively; and 6) FEV_1 reversibility $\geqslant$15% over their baseline value within 30 min after inhalation of 400 μg (four inhalations) of salbutamol in the afternoon or evening of the screening visit.

Exclusion criteria were: 1) the presence of relevant pulmonary disease; 2) use of tobacco products within 6 months before screening or a smoking history of >10 pack-yrs; 3) hospitalisation or emergency room treatment for acute asthma in the 3 months prior to screening or between screening and the start of the treatment period; 4) a respiratory tract infection within 1 month prior to screening; 5) abnormal blood glucose levels; and 6) corrected QT (QTc) interval at screening >430 or 450 ms for males and females, respectively, or a history of prolonged QTc interval.

Study treatment

Patients received a single dose of indacaterol 50, 100, 200 or 400 μg or placebo on each of five separate visits. The range of doses was chosen on the basis of results from an earlier study [10]. The study drug was administered by one inhalation from each of two HFA pMDIs (delivering indacaterol 50 or 200 μg or placebo).

Inhaled salbutamol was only permitted as rescue medication and was not to be taken within 6 h prior to the start of a treatment period. If rescue salbutamol was needed during this period, the visit was rescheduled. Patients taking ICS ($\leqslant$1,600 μg of beclometasone dipropionate or equivalent) continued to do so throughout the study. Inhaled LABAs were allowed between treatment periods at recommended daily doses, providing the dose remained fixed throughout the study, but had to be discontinued 48 h prior to screening or study drug administration.

Treatments not permitted included fixed combinations of β_2-agonists and ICS, parenteral or oral corticosteroids, theophylline or other xanthines, leukotriene antagonists, and oral or inhaled anticholinergics.

Assessments

Spirometry was conducted according to American Thoracic Society standards [13] at all visits: pre-dose and 5, 10, 20, 30 and 60 min post-dose; hourly from 2–6 h post-dose; every 2 h from 13–19 h post-dose; and hourly from 20–26 h post-dose. The primary efficacy comparisons were the per cent changes in FEV_1 between indacaterol and placebo at 30 min and at 21 h post-dose.

Secondary efficacy comparisons with placebo (both per cent and absolute change) included the standardised areas under the curve (AUC) for FEV_1 0–6 h, 13–24 h and 0–24 h post-dose. A summary table for FEV_1 at all time-points is also provided together with ANCOVAs assessing treatment ratios in FEV_1 at each post-dose time-point.

Safety was assessed by monitoring and recording all adverse events, serious adverse events, haematology, blood chemistry, urinalysis, vital signs, ECGs, spirometry and physical examination.

Statistical analyses

All efficacy variables were analysed for the intention-to-treat population, which included all randomised patients. All safety variables were analysed for the safety population, which included all randomised patients who received at least one dose of study medication.

The primary comparisons were performed using an ANCOVA model for log(FEV_1), with patient as a random effect, period and treatment as fixed effects and log(baseline FEV_1) as covariate. If patients took rescue medication prior to the 30-min post-dose evaluation, this value was excluded from the analysis. If a patient took rescue medication or withdrew 13–21 h post-dose, the 21-h value was derived using last observation carried forward. However, the 21-h measurement was used in the analysis if it was lower than the last pre-rescue measurement. If a patient withdrew from the study prior to the 13-h post-dose evaluation, the 21-h value was not derived. For either time-point, data missing for any other reason were imputed using linear interpolation.

ANCOVAs, similar to those used for the primary comparisons, were used for each of the AUC comparisons with no adjustment for multiplicity.

Sample size calculation

An improvement of 12% in FEV_1 compared with placebo was defined as clinically relevant [13]. Assuming a within-patient variance of 0.011 for log(FEV_1), a sample size of 35 was required to detect an increase of 12% in FEV_1. This sample size would provide an overall one-sided error rate of 2.1% and an overall power of 95.5%. It was expected that ~43 patients should be recruited in order for 35 to complete the study.

TABLE 1 Baseline demographics and disease characteristics

Variable	Total
Age yrs	40.5 (24–64)
Sex	
Male	36 (85.7)
Female	6 (14.3)
Caucasian	42 (100.0)
Height cm	179.3 (164–200)
Duration of asthma yrs	21.31 (3.8–53.0)
FEV1 L	
Mean±SD	3.010±0.596
Range	1.78–4.32
FEV1 % pred	
Mean±SD	75.62±7.11
Range	59.6–85.6
FEV1 reversibility %#	
Mean±SD	25.20±11.12
Range	14.6–62.6
FVC L	
Mean±SD	4.485±1.001
Range	2.49–6.71
Vital signs at screening	
SBP mmHg	
Mean±SD	124.9±9.1
Range	100–145
DBP mmHg	
Mean±SD	80.6±6.9
Range	60–95
Cardiac frequency bpm	
Mean±SD	74.0±9.6
Range	50–96
ECG findings	
Normal	35 (83.3)
Clinically insignificant abnormality	7 (16.7)
Clinically significant abnormality	0
At least one concomitant disease	23 (54.8)

Data are presented as mean (range) or n (%), unless otherwise stated. FEV1: forced expiratory flow in one second; % pred: % predicted; FVC: forced vital capacity; SBP: systolic blood pressure; DBP: diastolic blood pressure; bpm: beats·min^{-1}. #: % increase in FEV1 within 30 min after inhalation of salbutamol.

Establishing optimal dose

The optimal dose was identified using three pre-specified criteria. First, at both 30 min and 21 h post-dose, an effective dose was defined as a dose that was superior to placebo for FEV1 at the 2.5% one-sided significance level, with an upper limit of the 95% confidence interval (CI) for the treatment/placebo ratio of >1.12, which corresponds to a clinically relevant increase of 12% improvement over placebo. Secondly, efficacy was to be determined from an estimation of the treatment difference between each pair of active doses. Thirdly, the safety of each dose would be considered.

RESULTS

Patients

The present study was carried out at three locations. A total of 50 patients were screened and 42 were randomised, all receiving at least one dose of study medication. Their demographics are shown in table 1. More than half of the patients had at least one concomitant disease at the start of the study, most frequently related to allergic rhinoconjunctivitis, and 24 (57%) were using ICS.

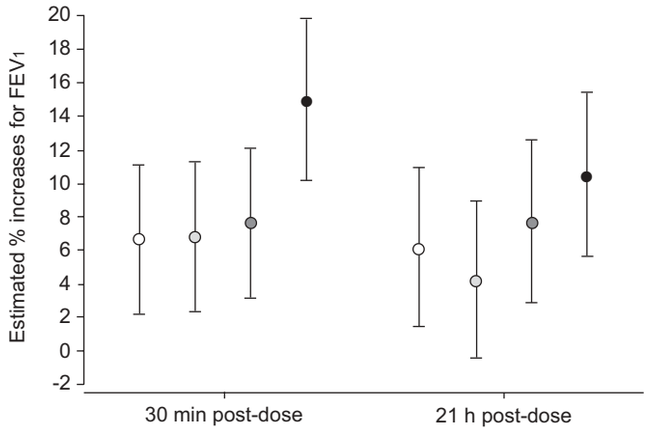

FIGURE 1. Estimates of per cent increases for forced expiratory volume in one second (FEV1) of treatment groups compared with placebo and associated 95% confidence intervals at 30 min and 21 h post-dose. ○: 50 μg *versus* placebo; ●: 100 μg *versus* placebo; ●: 200 μg *versus* placebo; ●: 400 μg *versus* placebo. p-Values were 0.003, 0.003, <0.001 and <0.001 for 50, 100, 200 and 400 μg, respectively, at 30 min post-dose and 0.011, 0.080, 0.002 and <0.001 for 50, 100, 200 and 400 μg, respectively, at 21 h post-dose.

In total, 40 (95%) patients completed all five treatments in the study. One patient discontinued due to protocol violation (out of range FEV1 at pre-dose spirometry), and one, who later reported a previous history of a minor abnormality in a liver function test, due to mildly elevated bilirubin levels (suspected Gilbert's syndrome).

Efficacy

Indacaterol 50, 200 and 400 μg were superior to placebo for FEV1 at both 30 min and 21 h post-dose; indacaterol 100 μg was superior to placebo at 30 min, but not at 21 h post-dose (fig. 1). Indacaterol 400 μg was the most effective dose, although the difference from the other indacaterol doses was not always statistically superior. The upper boundary of the 95% CI for the ratio with placebo exceeded 1.12 (corresponding to an increase of 12% over placebo) for indacaterol 200 and 400 μg at both time-points (fig. 1). Therefore, both the 200 and 400 μg doses met the first set of pre-specified criteria for clinical efficacy.

FEV1 at each post-dose time-point is shown both as a summary table (table 2) and with ANCOVAs assessing treatment ratios (table 3). All indacaterol doses demonstrated higher mean FEV1 values over the 26-h assessment period compared with placebo (fig. 2, table 3). At the (first) 5-min time-point, significant improvements relative to placebo ($p<0.05$) were obtained for indacaterol 200 and 400 μg (table 3), and these were sustained at each subsequent time-point up to and including 25 h (200 μg) and 26 h (400 μg). Indacaterol 400 μg was statistically superior ($p<0.05$) to the other indacaterol

TABLE 2 Summary statistics of mean values for forced expiratory volume in one second (FEV_1) at selected time-points[#]

Variable	Time-point	Placebo	Indacaterol			
			50 μg	100 μg	200 μg	400 μg
Subjects n		40	41	41	41	41
Mean FEV_1 L	Pre-dose	3.00	3.03	3.07	3.07	3.03
	5 min	3.04	3.13	3.19	3.18	3.31
	10 min	3.05	3.17	3.23	3.23	3.38
	20 min	3.03	3.15	3.25	3.25	3.42
	30 min	3.01	3.18	3.25	3.27	3.45
	21 h	3.09	3.24	3.24	3.33	3.39
	22 h	3.10	3.27	3.29	3.36	3.42
	23 h	3.10	3.27	3.29	3.36	3.41
	24 h	3.07	3.21	3.23	3.35	3.39
	25 h	3.06	3.23	3.23	3.31	3.39
	26 h	3.12	3.20	3.23	3.29	3.40

[#]: intention-to-treat population.

TABLE 3 Comparison of geometric least squares mean values[#] for forced expiratory volume in one second (FEV_1) at selected time-points[¶]

Variable	Time-point	Placebo	Indacaterol			
			50 μg	100 μg	200 μg	400 μg
Subjects n		40	41	41	41	41
FEV_1 L	5 min	2.99	3.07	3.07	3.08*	3.22*, +
	10 min	3.00	3.11*	3.12*	3.12*	3.30*, +
	20 min	2.98	3.10*	3.14*	3.14*	3.34*, +
	30 min	2.93	3.13*	3.13*	3.16*	3.37*, +
	21 h	2.99	3.17*	3.11	3.22*	3.30*, §
	22 h	3.02	3.20*	3.17*	3.25*	3.32*, §
	23 h	3.01	3.20*	3.16*	3.25*	3.32*, §
	24 h	2.98	3.13*	3.11	3.24*	3.30*, +, ƒ
	25 h	2.96	3.16*	3.11	3.20*	3.30*, §
	26 h	3.04	3.14	3.12	3.17	3.31*, +

Data are presented as geometric least squares mean values. [#]: Analysed using the ANCOVA model log(FEV_1)= patient+period+treatment+log[baseline (FEV_1)]. [¶]: Intention-to-treat population; *: $p<0.05$ *versus* placebo; [+]: $p<0.05$ *versus* indacaterol 50, 100 and 200 μg; [§]: $p<0.05$ *versus* indacaterol 100 μg; [ƒ]: $p<0.05$ *versus* indacaterol 50 μg.

doses at most time-points (fig. 2). The highest mean differences in FEV_1 from placebo were reached at 2–3 h post-dose.

Analysis of standardised AUC for FEV_1 at 0–6, 13–24 and 0–24 h (table 4) demonstrated that all doses of indacaterol were superior to placebo ($p<0.05$), with the exception of the 100 μg dose at 13–24 h. FEV_1 AUC for indacaterol 400 μg was statistically superior to all other doses ($p<0.05$) at 0–6 h and 0–24 h, and was superior to indacaterol 100 μg at 13–24 h ($p<0.05$).

Safety and tolerability

All doses of indacaterol were well tolerated, with no serious adverse events experienced in any treatment sequence. The overall number of adverse events appeared to be dose-related (table 5). The most common adverse events were headache and cough, all episodes of which were mild to moderate apart from one severe headache with indacaterol 400 μg. There were no asthma-related adverse events.

Haematological and biochemical measurements fell within the normal ranges and, with one exception, there were no clinically significant differences between treatments. One patient who had abnormally high values of creatinine kinase at the screening visit also had marked increases 6 h post-dose whilst receiving indacaterol 100 μg, although the values returned to normal 13–26 h post-dose. The incidence of newly occurring biochemical abnormalities was low, with no clinically meaningful differences across treatments. There were minimal changes in mean potassium and glucose levels 6 h post-dose, with no statistically significant or clinically meaningful differences between treatments (table 6).

There were no clinically significant differences in vital signs, including cardiac frequency and blood pressure, or ECG abnormalities between treatments. For all treatments, the QTc interval decreased from pre-dose to 15 min post-dose, with only minor changes at 6 and 24 h post-dose. There were no clinically meaningful or statistically significant differences in mean QTc interval between indacaterol and placebo. No QTc interval increases >60 ms from pre- to post-dose were observed.

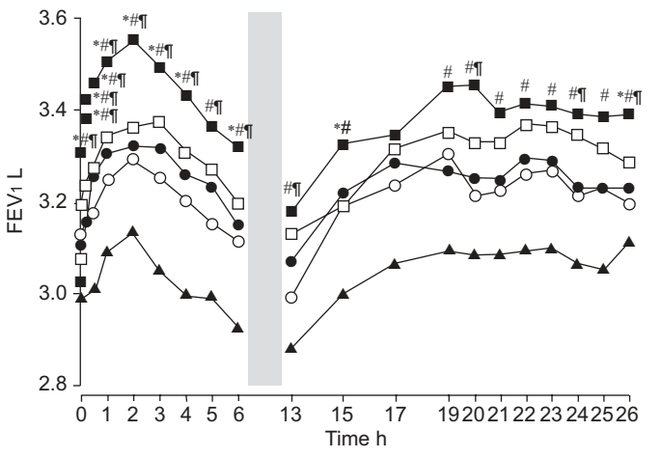

FIGURE 2. The 26-h profile of mean forced expiratory volume in one second (FEV_1). Indacaterol 400 μg was superior to placebo ($p<0.05$) at all post-dose time-points; 200 μg superior to placebo ($p<0.05$) from 5 min to 25 h post-dose (inclusive); 100 μg superior to placebo ($p<0.05$) from 10 min to 6 h, 15–19 h and 22–23 h post-dose (inclusive); 50 μg superior to placebo ($p<0.05$) from 10 min to 6 h and 15–25 h post-dose (inclusive). ■: Sleep; ■: indacaterol 400 μg (n=41); □: indacaterol 200 μg (n=41); ●: indacaterol 100 μg (n=41); ○: indacaterol 50 μg (n=41); ▲: placebo (n=40). *: $p<0.05$ *versus* indacaterol 200 μg; [#]: $p<0.05$ *versus* indacaterol 100 μg; [¶]: $p<0.05$ *versus* indacaterol 50 μg.

TABLE 4 Standardised area under curve[#] (AUC) for forced expiratory volume in one second (FEV_1) for the intention-to-treat population

Variable	Time interval post-dose h	Placebo	Indacaterol			
			50 μg	100 μg	200 μg	400 μg
Subjects n		40	41	41	41	41
FEV_1 L	0–6	2.9908	3.1469*	3.1409*	3.1967*	3.3602*, ¶
	13–24	2.8018	3.1176*	3.0027	3.1852*	3.2965*, +
	0–24	2.9661	3.1098*	3.0982*	3.1605*	3.2725*, ¶

Data are presented as adjusted geometric means. [#]: Analysed using the ANCOVA model log(standardised AUC for FEV_1)=patient+period+treatment+log[baseline (FEV_1)]. *: $p<0.05$ *versus* placebo; ¶: $p<0.05$ *versus* indacaterol 50, 100 and 200 μg; +: $p<0.05$ *versus* indacaterol 100 μg.

DISCUSSION

The present study demonstrates that indacaterol provides sustained 24-h bronchodilation when taken once daily. During the current study, indacaterol was administered in the late afternoon (17:00–19:00 h), at a time when the upswing of diurnal variation in FEV_1 would have already occurred. Despite this, a rapid and sustained increase in FEV_1 was observed, with the rapid onset of action of indacaterol (within 5 min of dosing) comparable to that of the SABA salbutamol (~2–3 min) [14]. In the present study, the first time-point (30 min post-dose) for one of the primary efficacy comparisons (% change in FEV_1 from placebo) was selected on the basis of the characteristics of salmeterol, which has a relatively slow onset of action, achieving a clinically meaningful effect at ~30 min post-dose [14]. Therefore, the 30-min time-point was used to assess whether indacaterol was at least as fast in onset as salmeterol. The second time-point for comparison (21 h post-dose) was selected as this was considered to be the minimum requirement for a single dose of a drug that was to be given once a day.

All doses and placebo displayed a similar overnight decrease in FEV_1, as can be seen from the 6 and 13 h measurements in figure 2, consistent with circadian variation of lung function. Patients were allowed to sleep for ~7 h during the test period (from 00:00–07:00 h) and thus preserving the circadian variation in pulmonary function. Accentuation of the circadian variation of lung function is a recognised feature of asthma and an expression of bronchial hyperreactivity. It is influenced by diurnal changes in adrenaline, adenosine monophosphate, histamine and other inflammatory mediators, cortisol, vagal tone, body temperature and lower airway secretions [15, 16]. Other occurrences during sleep, such as the supine posture, sleep-associated reductions in lung volume, intrapulmonary pooling of blood and sleep-associated upper airway narrowing, may also have influenced the early morning measurement [17]. Similar data have been shown in patients with mild asthma, in whom single doses of formoterol and salbutamol administered in the morning significantly improved FEV_1 for $\geqslant$12 h and moved the pattern of circadian variation in lung function to a higher FEV_1 level through the subsequent night, without actually influencing either the phase or amplitude of the variation over the 24-h observation period [18].

The lung function data in the present study demonstrate that there is a dose-dependent upward shift of the circadian pattern over the entire 26-h period in which FEV_1 was measured. Despite the preservation of the circadian pattern, indacaterol doses provided trough FEV_1 values (*i.e.* 21–24 h post-dose) that were superior to placebo. This confirms the sustained 24-h bronchodilator efficacy of indacaterol, although only the 200 and 400 μg doses were statistically superior to placebo at all time-points from 5-min to 24-h post-dose. Since FEV_1 for all doses of indacaterol was greater than placebo at all time-points, this provides evidence that the duration of action of indacaterol is dose-independent across the range tested and it may possibly be due to an intrinsic property of the molecule at the receptor level.

Besides indacaterol, other once-daily LABAs are being developed [19]. The convenience of once-daily dosing, together with sustained bronchodilation, will allow for better compliance, thus increasing the likelihood of medication adherence and asthma control. Improved clinical outcomes associated with prolonged bronchodilation have previously been shown when comparing twice-daily LABAs with regular SABA therapy [20, 21]. In COPD, once-daily tiotropium is clearly superior to regular short-acting anticholinergic therapy for all relevant clinical outcomes [22].

Alongside the potential advantages of a once-daily LABA, one also needs to consider that the regular use of LABAs has been linked with the potential development of tolerance to bronchoprotective and bronchodilator effects. The pharmacological profile may favour indacaterol in this respect. In preclinical studies (relative to isoprenaline) indacaterol (73%) has more of a full agonist profile than the partial agonist salmeterol (38%) [23, 24] and, therefore, might be expected to incur fewer problems of cross-tolerance to SABA rescue medication. Clinical studies to investigate these interactions, as well as the potential for receptor down-regulation in humans, have still to be carried out.

The regular use of the LABA salmeterol without concomitant anti-inflammatory treatment has been associated with an increased risk of asthma death [25]. The combination of LABA and ICS is currently considered as the gold standard for patients with moderate-to-severe persistent asthma [1].

TABLE 5 Patients with most frequent adverse events[#] in the safety population

	Placebo	Indacaterol			
		50 μg	100 μg	200 μg	400 μg
Patients studied	40 (100)	41 (100)	41 (100)	41 (100)	41 (100)
Patients with an adverse event	6 (15.0)	8 (19.5)	11 (26.8)	14 (34.1)	15 (36.6)
Nervous system disorders					
Headache	1 (2.5)	3 (7.3)	5 (12.2)	5 (12.2)	7 (17.1)
Respiratory, thoracic and mediastinal disorders					
Cough	0	3 (7.3)	5 (12.2)	6 (14.6)	5 (12.2)

Data are presented as n (%). Patients may be counted more than once if they had more than one occurrence of an adverse event within different treatment periods. [#]: >5% for any group.

Thus, it is anticipated that a once-daily LABA will be recommended to be combined with a once-daily ICS, *e.g.* ciclesonide or mometasone, either in free or fixed combination. A rapid onset of action of the bronchodilator component (as shown for indacaterol) in such combinations might be beneficial since it would also allow for use in acute situations, a strategy that has been successfully developed for fixed combinations of budesonide/formoterol [26, 27]. Experiments using indacaterol in isolated human bronchus have demonstrated an onset of effect very similar to those of formoterol and salbutamol, the classic rescue bronchodilator, in contrast to a more than two-fold slower onset for salmeterol [24]. Finally, another possible future use would be to combine treatment with a once-daily LABA with once-daily tiotropium (or other once-daily anticholinergic) in COPD. With distinct but complementary pharmacological modes of action [28], such a combination would be likely to provide additional therapeutic benefits in this indication [29].

TABLE 6 Adjusted mean serum potassium, blood glucose and cardiac frequency at selected time-points in the safety population

Time post-dose	Placebo	Indacaterol			
		50 μg	100 μg	200 μg	400 μg
Subjects n	40	41	41	41	41
Serum potassium mmol·L^{-1}					
15 min	4.31	4.27	4.29	4.33	4.33
6 h	4.08	4.07	4.12	4.12	4.09
13 h	4.29	4.33	4.29	4.28	4.27
24 h	4.30	4.34	4.22	4.30	4.36
Blood glucose mmol·L^{-1}					
15 min	4.61	4.47	4.56	4.63	4.51
6 h	5.03	5.21	5.10	5.22	5.07
13 h	4.90	4.88	4.85	5.01	4.89
24 h	5.04	4.93	4.94	5.02	5.15
Cardiac frequency bpm					
15 min	73.2	74.5	75.9	73.2	74.0
1 h	72.4	73.1	73.2	72.4	73.8
3 h	74.7	75.3	76.5	74.9	76.9
5 h	73.0	72.8	75.6	73.7	73.8
13 h	71.2	69.7	69.9	70.4	70.4
19 h	73.5	73.2	74.0	72.5	74.5
24 h	69.9	70.5	71.7	71.2	70.2

bpm: beats·min^{-1}.

Since the present study was limited to several single-dose exposures separated by $\geqslant$5 days, few conclusions can be drawn on the long-term safety of indacaterol. However, these results are consistent with those of a longer study, in which patients received indacaterol $\leqslant$600 μg daily for 28 days [30]. A preliminary report of the systemic effects of indacaterol 1,000 μg as a single dose (more than twice the upper dose used in the present study) showed that the prolonged bronchodilation was not accompanied by a similar prolongation in the predictable β_2-adrenoceptor-mediated systemic effects. Plasma glucose, potassium, QTc and cardiac frequency showed initial changes but all remained within normal levels. All of these values matched placebo levels sooner for indacaterol than the active comparator, salmeterol, administered at a dose of 250 μg [31].

In conclusion, single 200 and 400 μg doses of indacaterol provided effective and sustained 24-h bronchodilator control with a rapid onset of action (<5 min) and a good tolerability and safety profile. The convenience of once-daily dosing could lead to better compliance and may help to treat both daytime and nocturnal symptoms of asthma.

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