

Single- and multiple-dose pharmacokinetics of inhaled indacaterol in healthy Chinese volunteers

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Abstract Indacaterol is an inhaled, ultra-long-acting β_2 -agonist that provides 24-h bronchodilation with once-daily dosing in patients with chronic obstructive pulmonary disorder. This study evaluated the pharmacokinetics, safety, and tolerability of multiple daily inhaled doses of indacaterol 150 or 300 μg once daily in healthy Chinese volunteers. This was a single-center, randomized, double-blind, multiple-dose, parallel-group study, placebo-controlled trial including two doses of indacaterol: 150 and 300 μg . Serum indacaterol was quantified using high-performance liquid chromatography-mass spectrometry with a lower limit of quantification of 0.01 ng/mL. The pharmacokinetic parameters were analyzed using non-compartmental analysis and included C_{\max} , T_{\max} , and $\text{AUC}_{0-24\text{h}}$ on Day 1 and $\text{AUC}_{0-24\text{h,ss}}$, $C_{\max,ss}$, $C_{\min,ss}$, $C_{\text{av,ss}}$, $T_{\max,ss}$, $T_{1/2}$, $T_{1/2,\text{acc}}$, CL/F , V_z/F , and R_{acc} on Day 14 (after repeated once-daily doses). Safety analyses were recorded using physical examination, biochemical tests, and ECG. Indacaterol steady state was achieved after 12–14 days of

daily dosing. The mean effective half-life of indacaterol (based on drug accumulation at steady state) was 33.9 and 35.8 h for 150 and 300 μg , respectively. Systemic exposure to indacaterol increased 1.27 and 1.34-fold between the 150- and 300- μg doses on Day 1 (first dose) and Day 14 (repeated dose), respectively. Indacaterol 150 and 300 μg were safe and well tolerated in these volunteers. The pharmacokinetics of multiple inhaled doses of indacaterol 150 and 300 μg (for 14 days) were consistent with moderate systemic accumulation at steady state after repeated once-daily inhalation in healthy Chinese volunteers.

Keywords Indacaterol · Pharmacokinetics · Chinese population · Healthy volunteers

1 Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world and is estimated to rank fifth by 2020 in burden of disease worldwide (GOLD 2013). It is also an increasing public health concern in China (Fang et al. 2011). In a nationwide cross-sectional survey, the prevalence of COPD in China was found to be 8.2 % in people aged 40 years or older (Zhong et al. 2007).

Inhaled bronchodilators are central to the treatment of stable COPD (GOLD 2013). Short-acting bronchodilators, such as salbutamol (a β_2 -adrenoceptor agonist) and ipratropium (an anticholinergic), are recommended for use, as needed, by patients with mild COPD. Regular use of long-acting bronchodilators is recommended for moderate and more severe COPD. These include the long-acting β_2 -adrenoceptor agonists (LABAs) salmeterol and formoterol, which require twice-daily administration, and the

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muscarinic antagonist tiotropium, which is taken once daily (Fang et al. 2011).

Indacaterol maleate is a novel, inhaled ultra-LABA that provides 24-h bronchodilation with a fast onset of action from the first dose and once-daily dosing in patients with COPD (Cazzola et al. 2005; Kinoshita et al. 2012; Dahl et al. 2010; Kornmann et al. 2011). Once-daily treatment with indacaterol provided a significantly greater bronchodilator effect than currently marketed LABAs such as formoterol (Foradil[®]) and salmeterol (Serevent[®]) and was at least as effective in improving symptoms and health status (Dahl et al. 2010; Kornmann et al. 2011). Indacaterol is formulated as inhalation powder hard capsules for pulmonary administration and delivered using a single-dose dry-powder inhaler (SDDPI), the Breezhaler[®] (EU), Neohaler[®] (US) (Onbrez[®] and Arcapta[®], respectively). This device has a low air-flow resistance to ensure that patients with severe lung conditions are able to use the device effectively (Pavkov et al. 2010; Feldman et al. 2010). Breezhaler[®] has been shown to deliver a consistent dose irrespective of disease severity and age, with no reported device failures in clinical trials (Feldman et al. 2010).

Indacaterol has been approved for use in the maintenance treatment of patients with COPD at doses ranging from 75 to 300 μg once daily in 85 countries worldwide, including China, Japan, the United States of America, and the European Union. The pharmacokinetics of indacaterol have been comprehensively characterized in Caucasian and Japanese patients with COPD and healthy volunteers (Hosoe et al. 2011; EU SMPC).

This is the first study that has been designed to determine the pharmacokinetics, safety, and tolerability of multiple daily inhaled doses of indacaterol in healthy Chinese volunteers.

The primary objective of the present study was to characterize the serum pharmacokinetics (PK) of indacaterol in healthy Chinese volunteers following single and repeated once daily inhaled administration of indacaterol 150 and 300 μg delivered via an SDDPI. Further objectives of the study included safety, tolerability and efficacy assessments.

2 Methods

2.1 Study design

This was a single center, randomized, double-blind, multiple-dose, parallel group study, using a placebo control and two doses of indacaterol 150 and 300 μg . The study protocol and all amendments of the study were reviewed and approved by the Independent Ethics Committee of Peking Union Medical College Hospital, Beijing, China.

The study was conducted according to the ethical principles of the Declaration of Helsinki. Written and signed informed consent was obtained from each subject before any study-specific screening procedures were performed.

2.2 Study population and randomization

Healthy male and female Chinese subjects aged between 18 and 45 years (incl.) and weighing at least 50 kg with a body mass index within the range of 18–27 kg/m^2 were included in the study. Subjects were defined as Chinese if they had both parents and grandparents of Chinese descent. Exclusion criteria included any use of prescription drugs, herbal supplements within 4 weeks prior to initial dosing and/or over-the-counter medication or dietary supplements (including vitamins) within 2 weeks prior to initial dosing; pregnant or lactating women; and smokers who reported cigarette use of more than 10 cigarettes per day. The study randomized 32 subjects; 12 each into the two active treatment groups, indacaterol 150 μg and indacaterol 300 μg , and eight to placebo for comparative safety assessment. The designated randomization ratio was chosen to maximize the number of subjects on each active dose within the recommended 8–12 subjects per treatment group requirement in China's State Food and Drug Administration (SFDA) guidelines (SFDA 2005).

A single inhaled dose of indacaterol (150 or 300 μg) or matching placebo was administered daily as single gelatinous capsules for 14 consecutive days in the morning, using the Breezhaler[®] device.

2.3 Bioanalytics

Pharmacokinetic venous blood samples were collected on Days 1 and 14, at pre-dose, and at 0.08, 0.25, 0.5, 1, 2, 4, 8, 12, and 24 h post dose. Additional samples were collected at 36, 48, 120, and 168 h post dose on Day 14. Trough pharmacokinetic blood samples were collected on Days 7, 10, and 12 before dosing. All blood samples were collected into silica-coated polypropylene collection tubes and left to clot at room temperature for 20 min. The samples were then centrifuged at 2,500g for 10 min to separate the serum. Serum samples were then stored at less than $-20\text{ }^{\circ}\text{C}$ in polypropylene tubes until analyzed.

Indacaterol concentrations in serum were determined by high-performance liquid chromatography-mass spectrometry with lower limit of quantification (LLOQ) of 0.01 ng/mL using 100 μL of human serum.

2.4 Pharmacokinetic analysis

All subjects who provided at least one evaluable determination of C_{max} and/or $\text{AUC}_{0-24\text{h}}$ on Day 1 and/or Day 14

along with actual dose and sampling time information were included in the pharmacokinetic data analysis.

The following pharmacokinetic parameters were determined for indacaterol: C_{\max} (maximum serum drug concentration), T_{\max} (time to reach C_{\max}), and AUC_{0-24h} (area under the serum drug concentration–time curve from time 0 to 24 h post dose) on Day 1; $AUC_{0-24h,ss}$ (the AUC during a dosing interval ($\tau = 24$ h) at steady-state), $C_{\max,ss}$ (maximum steady-state serum drug concentration), $C_{\min,ss}$ (minimum steady-state serum drug concentration), $C_{av,ss}$ (average steady-state serum drug concentration), $T_{\max,ss}$ (time to reach C_{\max} at steady state), $T_{1/2}$ (elimination half-life associated with the terminal slope of a semi logarithmic concentration time curve), $T_{1/2,acc}$ (effective half-life determined according to Boxenbaum and Battle (1995), based on drug accumulation at steady state), CL/F (the total body clearance), $V_{Z/F}$ (the apparent volume of distribution), and R_{acc} (accumulation ratio) after repeated once-daily doses on Day 14.

C_{\max} , T_{\max} , AUC_{0-24h} were determined on Day 1 while on Day 14, $AUC_{0-24h,ss}$, $C_{\max,ss}$, $C_{\min,ss}$, $C_{av,ss}$, $T_{\max,ss}$, $T_{1/2}$, $T_{1/2,acc}$, CL/F , $V_{Z/F}$, R_{acc} were measured.

All parameters except R_{acc} and $T_{1/2,acc}$ were calculated using WinNonlin Professional (Version 5.2, Pharsight Corp., Mountain View, California). R_{acc} and $T_{1/2,acc}$ were determined using SAS Professional, version 8.2. R_{acc} was calculated using AUC values obtained from a dosing interval according to the following equation:

$$(AUC_{0-24h, \text{Day 14}})/(AUC_{0-24h, \text{Day 1}})$$

Effective half-life ($T_{1/2,acc}$) was determined based on drug accumulation at steady state and calculated according to the following equation (Boxenbaum and Battle 1995):

$$T_{1/2,acc} = \ln 2 \cdot \tau / \ln[R_{acc}/(R_{acc} - 1)],$$

where τ is the dosing interval and R_{acc} is the AUC accumulation ratio at steady state.

2.5 Safety and tolerability analysis

Safety and tolerability assessments included recording all adverse events (AEs) and serious AEs. Additional safety assessments included monitoring of vital signs, electrocardiogram (ECG) recordings, and study of blood chemistry, urinalysis, and hematology. AE data, laboratory data for hematology, blood biochemistry, urinalysis, ECG results, and measurements of vital signs were summarized descriptively by treatment group.

2.6 Statistical analysis

The dose-normalized geometric mean ratio (300:150) for all PK parameters was estimated by back transforming the

values of the estimated mean difference and 90 % confidence interval of the 300- and 150- μ g doses (that were calculated using analysis of variance). Change from baseline (0-h measurement on Day 1) in heart rate, QTcF, serum potassium, and blood glucose were compared between each dose of indacaterol and placebo at each post-dose time point using an analysis of covariance model with baseline as covariate. Geometric mean concentrations at any given time point were only calculated if all individual concentrations were \geq LLOQ. Summary statistics were provided for all safety and tolerability data.

3 Results

3.1 Study population

A total of 32 volunteers were enrolled into the study, with 27 males (84.4 %) and 5 females (15.6 %). The demographic characteristics of the patients are shown in Table 1 and were well balanced across dosing groups. All 32 subjects completed the study. There were no significant protocol deviations during the conduct of the study.

3.2 Pharmacokinetic results

Following the single or multiple dose inhaled administration of indacaterol 150 and 300 μ g for 14 days, indacaterol was absorbed rapidly following inhalation, with a median time to reach peak serum concentrations of 15 min post-dose (Table 2). A summary of the mean pharmacokinetic parameters of indacaterol at each dose level and sampling day is given in Tables 2 and 3, respectively.

Arithmetic mean serum concentration time profiles of indacaterol for each dose level (i.e. 150 and 300 μ g) and sampling day (first dose, Day 1 and repeated dose, Day 14) are shown in Figs. 1 and 2.

For Day 14, the geometric mean [% coefficient of variation (CV)] of $C_{\max,ss}$ was 0.28 (44.6) ng/mL for the 150- μ g dose and 0.68 (23.8) ng/mL for the 300- μ g dose (Table 4). The corresponding values for $AUC_{0-24h,ss}$ were 2.36 (38.7) h ng/mL and 6.33 (25.4) h ng/mL, respectively (Table 4). The mean AUC_{0-24h} accumulation ratio (Day 14–Day 1) was calculated as 2.6 and 2.7 for the 150- and 300- μ g doses, respectively (Table 3).

The trough concentrations increased up to Day 12 with the mean (SD) trough values ranging from 0.0574 ng/mL (19.6) on Day 7 to 0.0686 ng/mL (23.8) on Day 12 at 150 μ g, and from 0.164 ng/mL (44.4) on Day 7 to 0.179 ng/mL (51.7) on Day 12 at 300 μ g. However, there was little change between Days 12 and 14, indicating that the steady state was achieved after 12–14 days of daily dosing (Fig. 3). The systemic exposure to indacaterol

Table 1 Summary of patient demographics by treatment group

	Indacaterol 150 µg (n = 12)	Indacaterol 300 µg (n = 12)	Placebo (n = 8)	Total (n = 32)
Age, years	28.3 (4.79)	24.8 (4.09)	26.4 (6.48)	26.5 (5.09)
Male/female (%)	83.3/16.7	83.3/16.7	87.5/12.5	84.4/15.6
Ethnicity (Chinese) (%)	100	100	100	100
Weight (kg)	65.5 (7.79)	61.8 (8.19)	63.0 (8.69)	63.5 (8.06)
Height (cm)	168.0 (7.53)	169.0 (6.30)	166.0 (5.60)	168.0 (6.51)
BMI (kg/m ²)	23.3 (1.85)	21.6 (2.42)	22.8 (2.70)	22.5 (2.34)

Data are mean (SD), except male/female and ethnicity which are %
BMI body mass index, *SD* standard deviation

Table 2 Pharmacokinetic parameters of indacaterol following a single dose of inhaled administration of indacaterol 150 and 300 µg on Day 1 in healthy Chinese subjects

Pharmacokinetic variable	Indacaterol	
	150 µg (n = 12)	300 µg (n = 12)
<i>C</i> _{max} (ng/mL)	0.206 (0.0568)	0.518 (0.0780)
<i>T</i> _{max} (h)	0.25 (0.25–1.00)	0.25 (0.25–0.25)
<i>AUC</i> _{0–24h} (h ng/mL)	0.974 (0.252)	2.43 (0.408)

Data are expressed as mean (SD), except for *T*_{max} which are expressed as median (min–max)

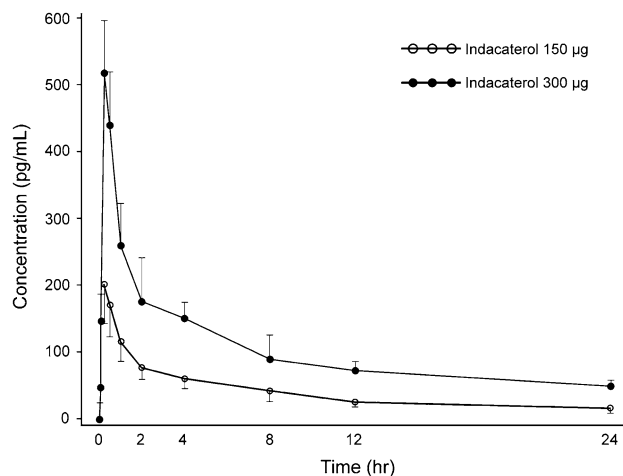
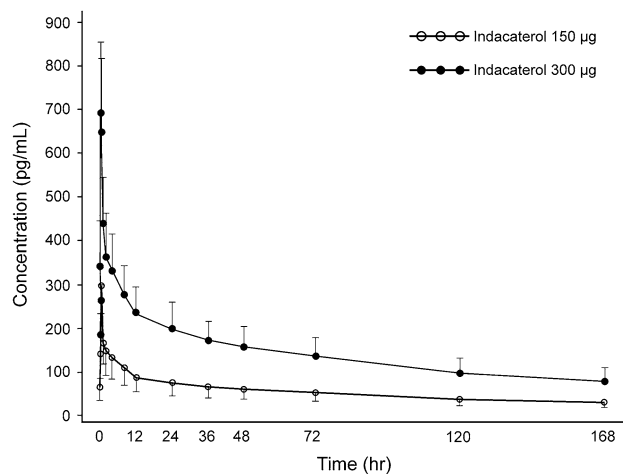
*AUC*_{0–24h,ss} area under curve during a dosing interval ($\tau = 24$ h) at steady-state, *C*_{max} maximum serum drug concentration, *T*_{max} time to reach *C*_{max}

Table 3 Pharmacokinetic parameters of indacaterol following multiple doses of inhaled administration of indacaterol 150 and 300 µg for 14 days in healthy Chinese subjects

Pharmacokinetic variable	Indacaterol	
	150 µg (n = 12)	300 µg (n = 12)
<i>C</i> _{max,ss} (ng/mL)	0.299 (0.116)	0.697 (0.168)
<i>C</i> _{min,ss} (ng/mL)	0.0645 (0.0311)	0.182 (0.0503)
<i>C</i> _{av,ss} (ng/mL)	0.105 (0.0381)	0.272 (0.0685)
<i>T</i> _{max,ss} (h)	0.25 (0.25–0.50)	0.25 (0.25–0.50)
<i>AUC</i> _{0–24h,ss} (h ng/mL)	2.51 (0.914)	6.52 (1.64)
<i>R</i> _{acc}	2.59 (0.636)	2.69 (0.534)
<i>T</i> _{1/2acc} (h)	33.9 (11.0)	35.8 (9.06)
<i>C</i> _{L/F} (L/h)	67.9 (25.6)	48.7 (12.0)
<i>V</i> _{Z/F} (L)	11050 (3506)	8153 (3023)
<i>T</i> _{1/2} (h)	116 (19.3)	118 (38.9)

Data are mean (SD) except for *T*_{max} which are median (min–max)

*AUC*_{0–24h,ss} area under curve during a dosing interval ($\tau = 24$ h) at steady-state, *C*_{max,ss} maximum steady-state serum drug concentration, *C*_{min,ss} minimum steady-state serum drug concentration, *C*_{av,ss} average steady-state serum drug concentration, *T*_{max,ss} time to reach *C*_{max} at steady state, *T*_{1/2} elimination half-life, *T*_{1/2,acc} effective half-life based on drug accumulation at steady state, *C*_{L/F}, the total body clearance, *V*_{Z/F} the apparent volume of distribution, *R*_{acc} accumulation ratio

**Fig. 1** Arithmetic mean (SD) serum concentration–time profile following single dose inhaled administration of indacaterol 150 and 300 µg on Day 1 in healthy Chinese subjects**Fig. 2** Arithmetic mean (SD) serum concentration–time profile following multiple doses inhaled administration of indacaterol 150 and 300 µg for 14 days in healthy Chinese subjects

increased between 1.27- and 1.34-fold for the 150- and 300-µg doses (Table 4).

Based on the observed indacaterol *AUC* accumulation ratio for each subject, the effective half-life (*T*_{1/2,acc}) of

Table 4 Summary statistics for dose-proportionality evaluation of indacaterol 150 and 300 µg for Days 1 and 14

Day	Pharmacokinetic variable	Unit	Geometric mean (%CV)		Ratio of dose normalized geometric means (300 µg:150 µg)		
			150 µg	300 µg	Estimate	Lower 90 % CL	Upper 90 % CL
1	AUC _{0–24h}	h ng/mL	0.94 (28.0)	2.39 (17.2)	1.27	1.08	1.49
	C _{max}	ng/mL	0.20 (28.8)	0.51 (15.8)	1.29	1.10	1.51
14	AUC _{0–24h,ss}	h ng/mL	2.36 (38.7)	6.33 (25.4)	1.34	1.07	1.68
	C _{max,ss}	ng/mL	0.28 (44.6)	0.68 (23.8)	1.23	0.96	1.56

AUC_{0–24h} area under curve during a dosing interval ($\tau = 24$ h) at steady-state, C_{max} maximum steady-state serum drug concentration, ss steady state

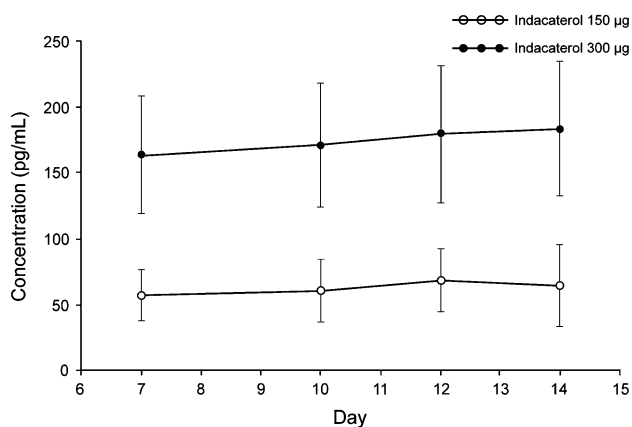


Fig. 3 Arithmetic mean (SD) serum trough concentrations after multiple doses inhaled administration of indacaterol 150 and 300 µg in healthy Chinese subjects

indacaterol was determined for the 150- and 300-µg doses. The mean (SD) of $T_{1/2,acc}$ was 33.9 (11.0) and 35.8 (9.06) hours, respectively. After 14 days of once-daily dosing, the mean terminal elimination half-lives were 116 and 118 h, respectively.

3.3 Safety results

There were no meaningful differences between screening, baseline, and end-of-study vital signs. Individual values were almost entirely within the ranges specified for inclusion in the study and there were no deviations that were of clinical significance.

The overall incidence of AEs by preferred term is presented in Table 4. Most AEs were transient and mild in severity. The most frequently reported AE was cough [56 (98.2 %) subjects; 150 µg ($n = 6$), 300 µg ($n = 8$), placebo ($n = 1$)]. This event was suspected to be dose related although it also occurred in one patient receiving placebo. One volunteer from the indacaterol 300 µg treatment arm reported epistaxis as an AE. No deaths or serious adverse events were reported. There were no clinically meaningful differences in least squares (LS) mean serum potassium or serum glucose all post-dose time-points for all treatments

compared to placebo on Days 1 and 14. There were dose-dependent increases in heart rate and QTcF interval which were consistent with the known effects of Indacaterol and not considered to be clinically meaningful.

4 Discussion

While the pharmacokinetics of indacaterol have been previously extensively studied in Caucasian and Japanese patients (Hosoe et al. 2011; EU SMPC) and healthy volunteers (Khindri et al. 2011), this is the first study to evaluate the pharmacokinetics of indacaterol following administration of single and repeated once-daily doses of 150 and 300 µg in healthy Chinese volunteers. Following single (Day 1) and repeated (Day 14) inhalation, indacaterol was rapidly absorbed into the systemic circulation with the median time to maximum serum concentrations (T_{max}) occurring 15 min post inhalation for both doses. The early serum concentration peak is likely to reflect absorption via the lung indicating that a significant portion of the orally inhaled drug is delivered to and systemically absorbed via the target organ for topical COPD therapy. The systemic exposure to indacaterol, as characterized by AUC_{0–24h} and C_{max}, increased in a dose-proportional manner with moderate accumulation upon repeated once-daily dosing as shown by the estimated AUC accumulation ratios of 2.6 and 2.7 for the 150- and 300-µg dose groups which was within the range seen for indacaterol in other studies (Hosoe et al. 2011).

The disposition kinetics of indacaterol is multiphasic as shown by the mean concentration–time profiles in Fig. 1. Systemic concentrations decreased rapidly within the first 4–8 h after inhalation, and more slowly thereafter. The concept of an effective half-life ($T_{1/2,acc}$) of drug accumulation as proposed by Boxenbaum and Battle (1995), was applied to the data. In principle the effective half-life reflects the actual observed drug accumulation, as opposed to one or more aspects of exponential drug disposition, and is calculated from the AUC accumulation ratio and the dosing interval. The mean (SD) $T_{1/2,acc}$ values determined for the 150- and 300-µg doses on Day 14 were 33.9 (10.9)

and 35.8 (9.1) hours, respectively. The mean (SD) terminal elimination half-life ($T_{1/2}$) values were 116 (19.3) and 118 (39.0) hours for 150 and 300 μg , respectively, on Day 14.

In this study, the indacaterol steady state was achieved between 12 and 14 days of daily dosing. Indacaterol was detectable in serum immediately after inhalation. The ratio (300–150 μg) of the dose-normalized geometric means for C_{max} and $\text{AUC}_{0-24\text{h}}$ on Days 1 and 14 was above 1.0 and ranged from 1.23 to 1.34, indicating that exposure to indacaterol increased more than twofold between the 150- and 300- μg doses. Given the fact that this study was not powered to assess dose proportionality, the observed small deviations from dose-proportionality appeared not to be clinically meaningful.

The finding that systemic concentrations of indacaterol rapidly decline to very low levels may be advantageous for the drug's safety profile, since there is little risk of sustained high systemic concentrations and/or significant drug accumulation during chronic dosing. The dissociation between the short residence time in the systemic circulation and the long duration of action of indacaterol (Hosoe et al. 2011; Khindri et al. 2011; Moen 2010) might be related to the fact that local drug load in the lung is required for maintenance of bronchodilation effect in the lung whilst systemic drug concentrations have little or no relevant contribution to the bronchodilator effect.

Multiple, daily inhaled doses of indacaterol in healthy Chinese subjects were well tolerated and had an acceptable safety profile. There were no serious or unexpected AEs. Cough was the most commonly observed treatment-related adverse event, consistent with previous clinical studies (Kinoshita et al. 2012; Dahl et al. 2010; Kornmann et al. 2011) as well as observations in healthy subjects from other Asian ethnic populations (Khindri et al. 2011).

5 Conclusions

In conclusion, the once-daily dosing of inhaled indacaterol in healthy Chinese volunteers produced a consistent and predictable pharmacokinetic profile. Indacaterol was systemically available shortly after inhalation. Systemic exposure to indacaterol increased in a dose-proportional manner from 150 to 300 μg doses, with moderate accumulation upon repeated once-daily dosing. Multiple inhaled doses of indacaterol 150 and 300 μg (for 14 days) were also found to be safe and well tolerated in healthy Chinese volunteers.

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Conflict of interests All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf

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