CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022383Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology
Pharmacometrics review amendment

NDA Number: 22383
Generic name: Indacaterol
Sponsor: Novartis
Pharmacometrics Reviewer: Yaning Wang, Ph.D.
Secondary Pharmacometrics Reviewer: Joo-Yeon Lee, Ph.D.

Reference ID: 2961422

EXECUTIVE SUMMARY

Additional patient-level analyses showed that the model based claim of additional benefit of 150 mcg over 75 mcg for more severe patients is not supported by the data. Inappropriate covariate model structures for Emax and ED50 contributed to this inconsistency. The inappropriate Emax assumption identified from the study-level analysis may also play a role.

The study-level meta-analysis overestimates the incremental difference between two adjacent doses, especially for 150 mcg versus 75 mcg, 75 mcg versus 37.5 mcg. Two factors contributed to this observation: the inappropriate Emax model assumption and the unbalanced dose distribution across studies.

_____
Yaning Wang, Ph.D.
Division of Pharmacometrics, Office of Clinical Pharmacology

_____
Joo-Yeon Lee, Ph.D.
Division of Pharmacometrics, Office of Clinical Pharmacology

Reference ID: 2961422

Introduction

FDA's sensitivity analyses for the patient level analysis were communicated to the sponsor to facilitate the discussion about the modeling method applied in this NDA. The sponsor submitted new information to comment on FDA's analyses. The aim of this amendment is to address the specific comments raised in the sponsor's new submission and demonstrate the flaws of the model based on more analyses.

Brief Description of Sponsor's comments on FDA's sensitivity analyses

By showing the observed FEV1 response data stratified by the quartiles of baseline FEV1 (Figure 1), the sponsor tried to substantiate the simulated curves (Figure 2) that support the claim of additional benefit of 150 mcg over 75 mcg for more severe COPD patients. Despite the apparent inconsistency between the observed data (flatter profile for more severe patients) and the simulated curves (flatter profile for less severe patients), the sponsor concluded that "it is apparent that higher doses are required to achieve (the significantly lower) maximal bronchodilation in severe patients".

After repeating FDA's sensitivity analyses based on day 15 data alone, the sponsor modified the initials of parameters and obtained a new set of parameter estimates, which led to a lower value of -2 log-likelihood function (Table 1). The new set of parameter estimates is consistent with the sponsor's original modeling results while FDA's sensitivity analyses resulted in an opposite conclusion (Figure 3), suggesting 150 mcg provides less additional benefit in more severe patients compared to less severe patients. The sponsor explained the FDA's finding as unstable estimates due to low information in the data to underwrite the model after the exclusion of uncontrolled day 14 data. The sponsor added more data from other visits and studies to increase the number of observations from 3454 to 34615 and the number of patients included from 1835 to 5558. With this larger dataset, the sponsor applied a similar model and obtained similar results (Table 2). However, the initial had to be set at a value close to the final parameter. Even with a much larger dataset, the information is still not sufficient to stabilize the parameter estimate.

Figure 1. Observed Data from Study B2335 and Study B2356 Combined

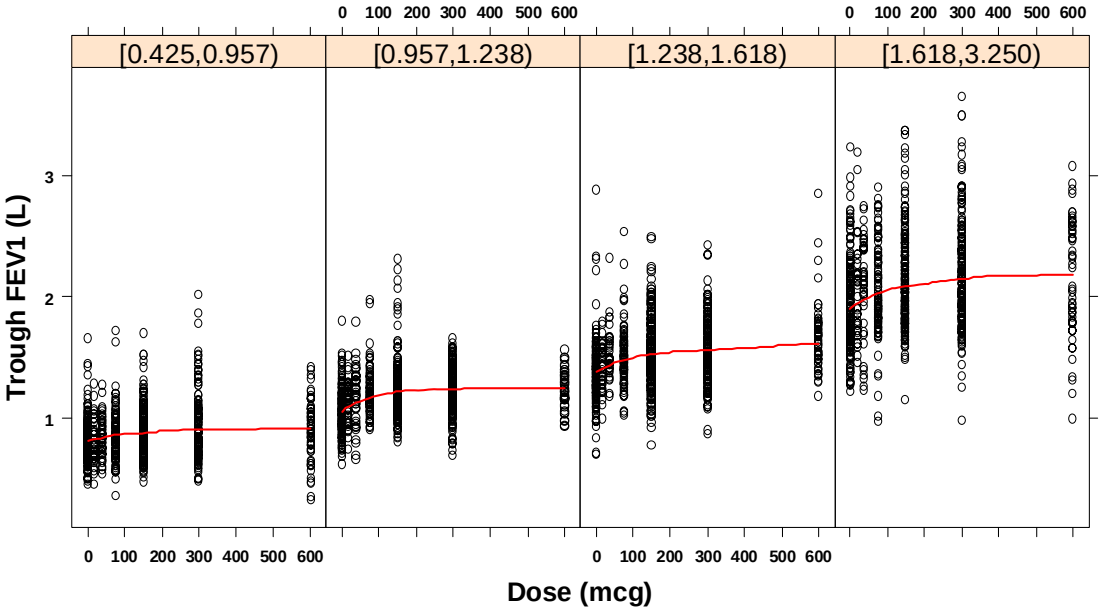


Figure 2. Prediction of the indacaterol dose response for moderate and severe patients as defined by GOLD criteria based on the patient-level analysis

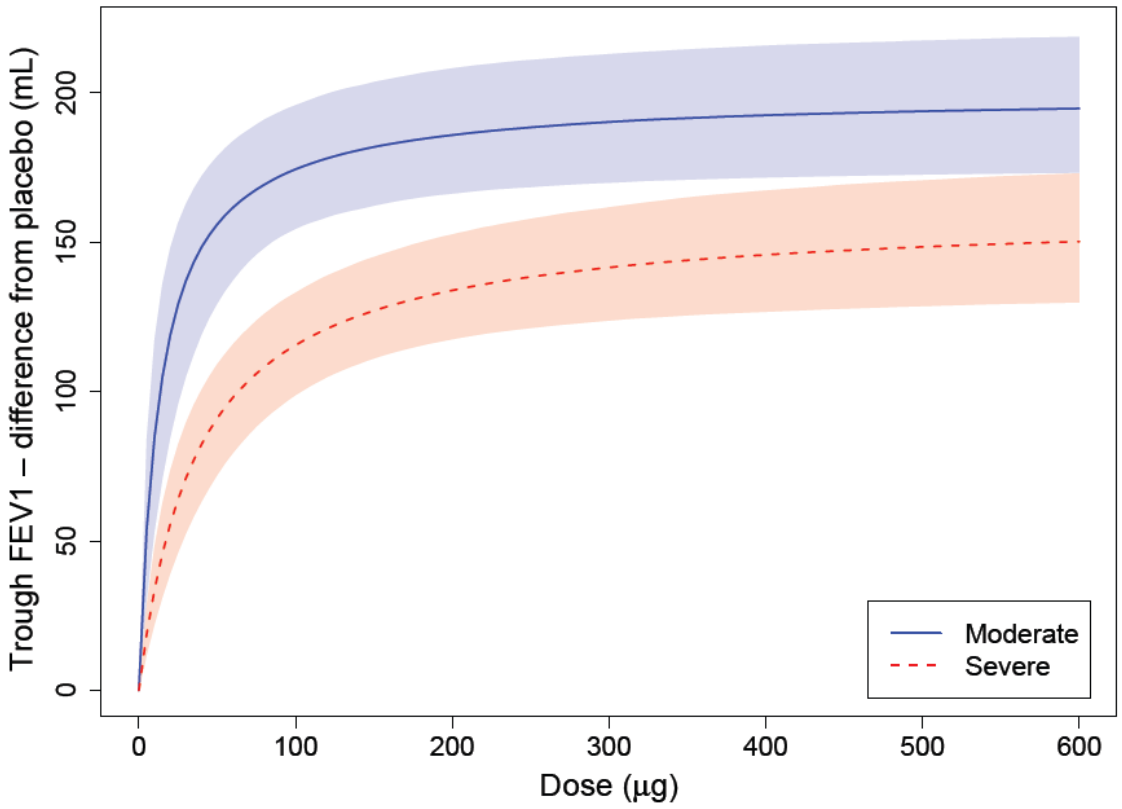


Figure 3. Prediction of the indacaterol dose response for moderate and severe patients as defined by GOLD criteria based on the patient-level analysis (FDA sensitivity analysis based on day 15 data alone)

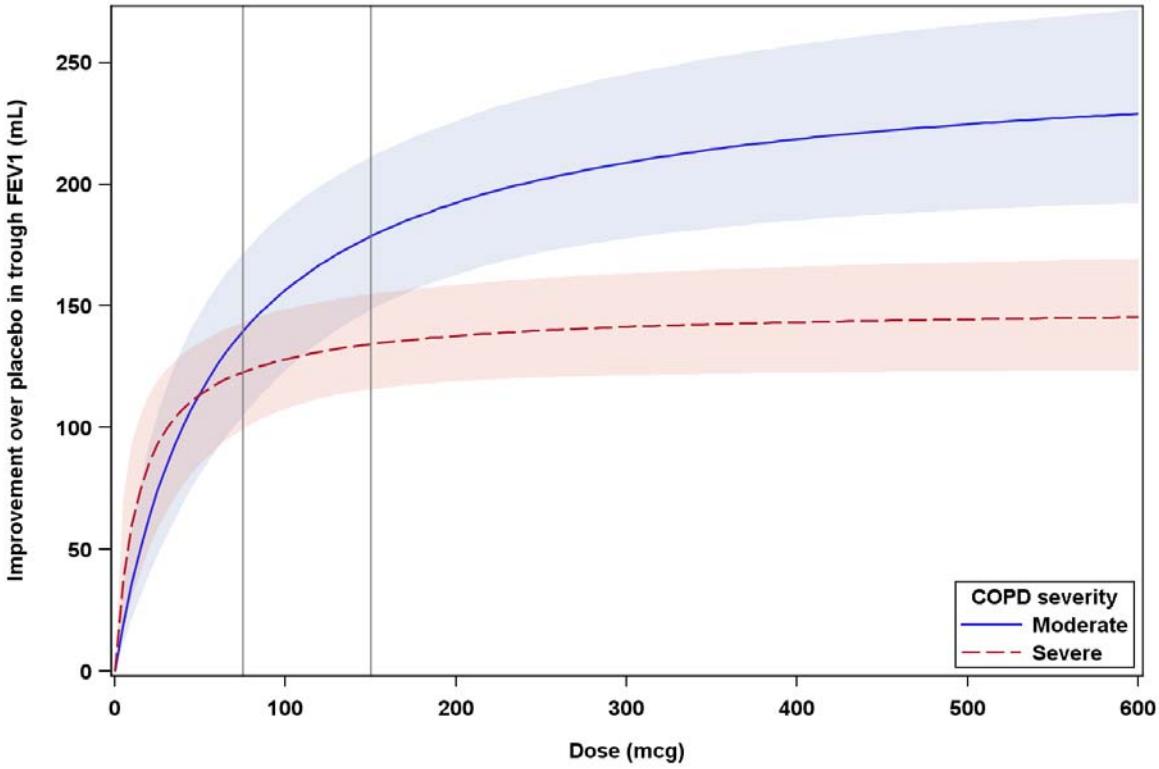


Table 1. Estimates of baseline FEV1 effect on ED50 for different initial values in dose-response model based on day 15 data alone

Initial value	Estimated value (SE)	-2 log likelihood	Note
1	3.09 (1.12)	-1798	FDA's sensitivity Analysis
0	-1.92 (0.80)	-1800	Sponsor's new estimate

Table 2. Estimates of baseline FEV1 effect on ED50 for different initial values in dose-response model based on different datasets

Data	Number of Patients	Number of Observations	Initial value	Estimated value (SE)	-2 log likelihood
B2335 and B2356 (day 14 and 15)	1834	3454	1	-2.27 (0.60)	-4881
			0	-2.27 (0.60)	-4881
			-1	ONC	ONC
B2335 and B2356 (day 15)	1789	1789	1	3.09 (1.12)	-1798
			0	-1.92 (0.80)	-1800
			-1	ONC	ONC

Reference ID: 2961422

Larger dataset (9 studies)	5558	34615	-1.5	-1.58 (0.71)	-49777
			0	-0.03 (NA)	-49775
			1	0.93 (1.39)	-49775

ONC: Optimization not completed; NA: not available

Additional analyses on patient-level model

Given the visual inconsistency between the observed data (Figure 1) and the simulated curves (Figure 2), additional analyses were conducted to demonstrate the magnitude of inconsistency for the difference in FEV1 response between 150 mcg and 75 mcg and explore the reason for the inconsistency. Figure 4 shows the summarized data (mean and 95% CI) for the two studies included in Figure 1. As a contrast, Figure 5 shows the model predicted FEV1 response at the median baseline FEV1 within each quartile. Even though the model is predicting the largest difference between 150 mcg and 75 mcg for the most severe patients (with median baseline FEV1 of 0.805L), the observed data are showing the opposite, the least difference between the two doses for the most severe patients. Since the focus is the additional benefit of 150 mcg over 75 mcg for more severe patients, all the following discussion is related to the difference between these two dose levels. Two different methods were used to summarize the difference between the two doses to create a more direct comparison between the observed data and the model prediction. The first method is the difference between the two doses without any covariate adjustment and the second method is the least square (LS) mean difference between the two doses after adjusting for two baseline covariates, baseline FEV1 and reversibility, the same covariates used in the sponsor's model. Both methods were applied in each quartile. Since two visits from two studies were included in the dataset, a weighted average of the two estimates from the two visits was calculated for each study followed by either a random-effect meta-analysis or fixed-effect meta-analysis to combine the results from the two studies into one overall estimate. This overall estimate is reported as the final estimate of the difference between the two doses within each quartile. The weight for each difference estimate is the reciprocal of the estimation variance for the difference at each visit from each study. Table 3 lists the comparison between the summaries of observed data and the model predictions. Little difference was observed between random-effect and fixed-effect meta-analyses. Figure 5 clearly shows the point estimates for the observed means or the LS means do not support the model predicted trend even though the confidence intervals for LS means are wide within each baseline FEV1 quartile. Figure 6 shows the similar comparison when only day 15 data were used with the additional prediction based on the FDA's sensitivity analysis. Even though neither the Novartis' original model nor the model based on FDA's sensitivity analysis can describe the full spectrum of data sufficiently well, the observed data based on baseline FEV1 quartiles and a pre-specified subgroup analysis in study B2356 (Table 4) support the finding from FDA's sensitivity analysis for the more severe patients.

Reference ID: 2961422

Table 3. Comparison between summaries of observed data and the model predictions for the additional FEV1 improvement (mL) of 150 mcg over 75 mcg within four quartiles based on baseline FEV1

Meta-Analysis	Method	Quartile 1 [0.425,0.957)	Quartile 2 [0.957,1.238)	Quartile 3 [1.238,1.618)	Quartile 4 [1.618,3.250)
Random-effect	Observed mean (95% CI)	0(-54,54)	28(-22,77)	40(-24,103)	65(-29,159)
	LS mean (95% CI)	5(-34,43)	9(-34,53)	45(-5,94)	1(-58,60)
Fixed-effect	Observed mean (95% CI)	2(-41,45)	28(-22,77)	40(-24,103)	65(-29,159)
	LS mean (95% CI)	5(-28,37)	9(-34,53)	45(-5,94)	1(-58,60)
	Model prediction*	24	19	14	10

*: predicted at the median baseline FEV1 within each quartile

Figure 4. Summary of trough FEV1 improvement over placebo indacaterol dose response for moderate and severe patients as defined by GOLD criteria based on the patient-level analysis (FDA sensitivity analysis based on day 15 data alone)

Reference ID: 2961422

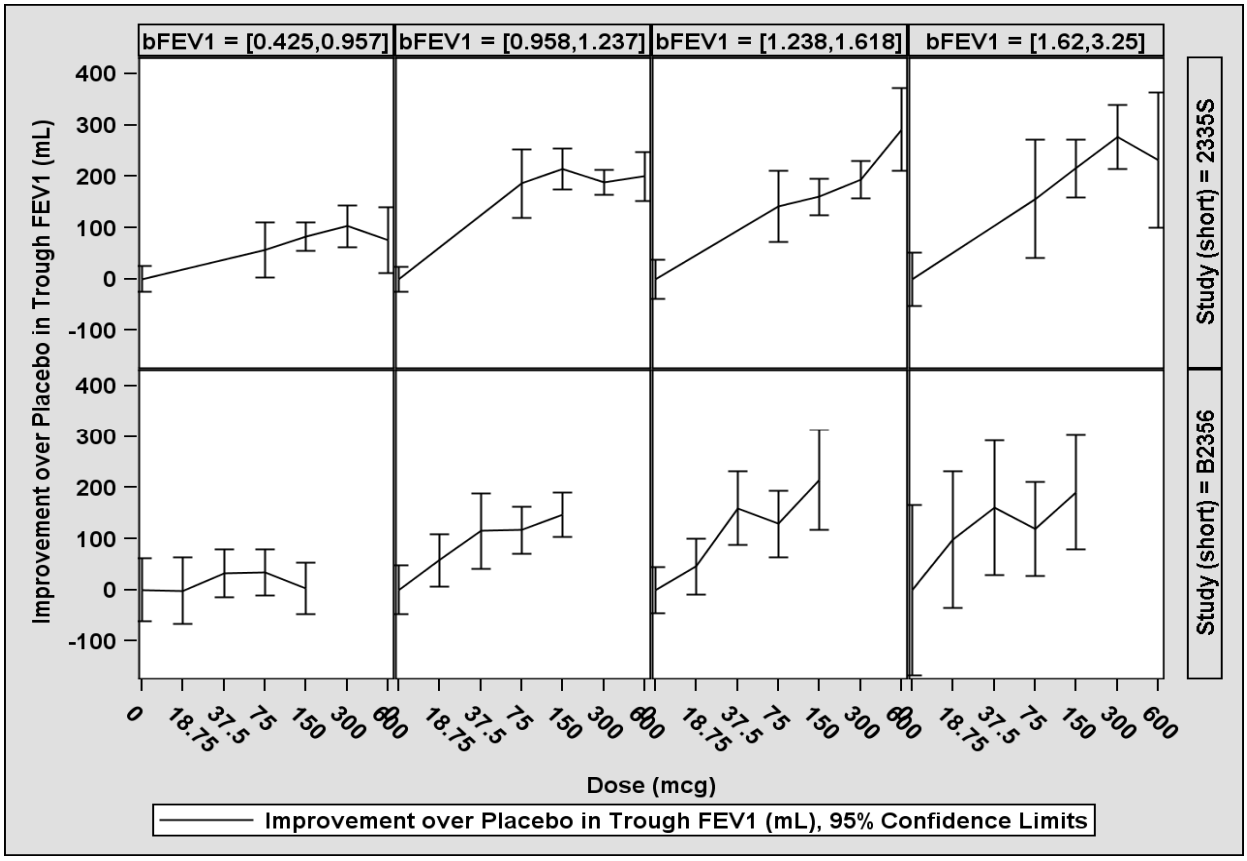


Figure 5. Model predictions versus actual data for FEV1 improvement of 150 mcg dose over 75 mcg dose by baseline FEV1 quartiles (patient-level analysis)

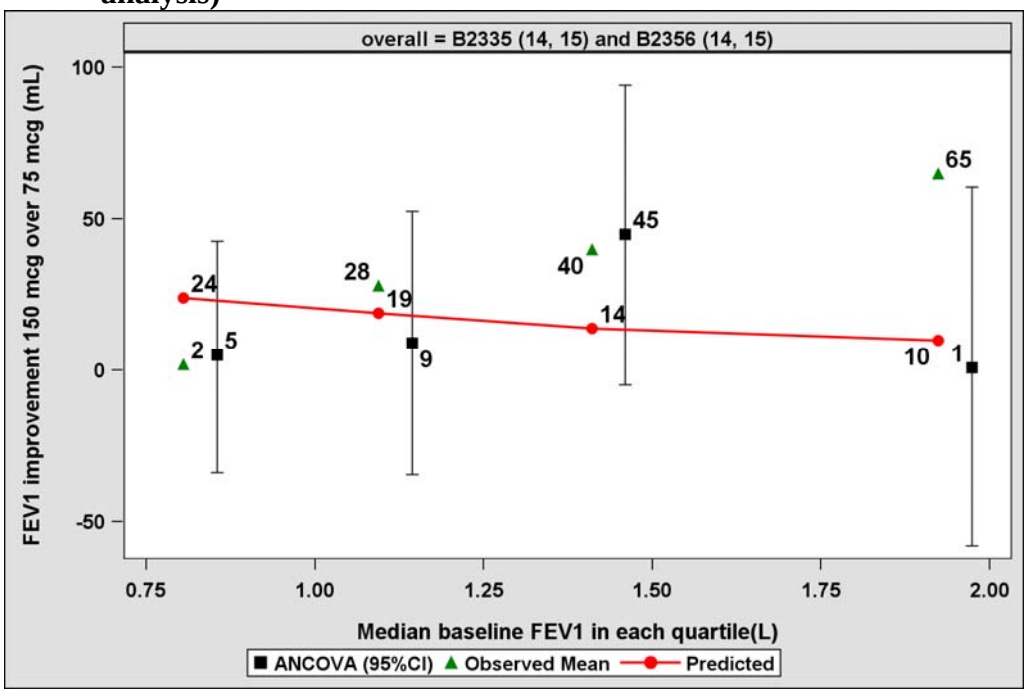


Figure 6. Model predictions versus actual data for FEV1 improvement of 150 mcg dose over 75 mcg dose by baseline FEV1 quartiles (patient-level analysis, PredFDA is based on FDA's sensitivity anlaysis, PredNOV is based on sponsor's model)

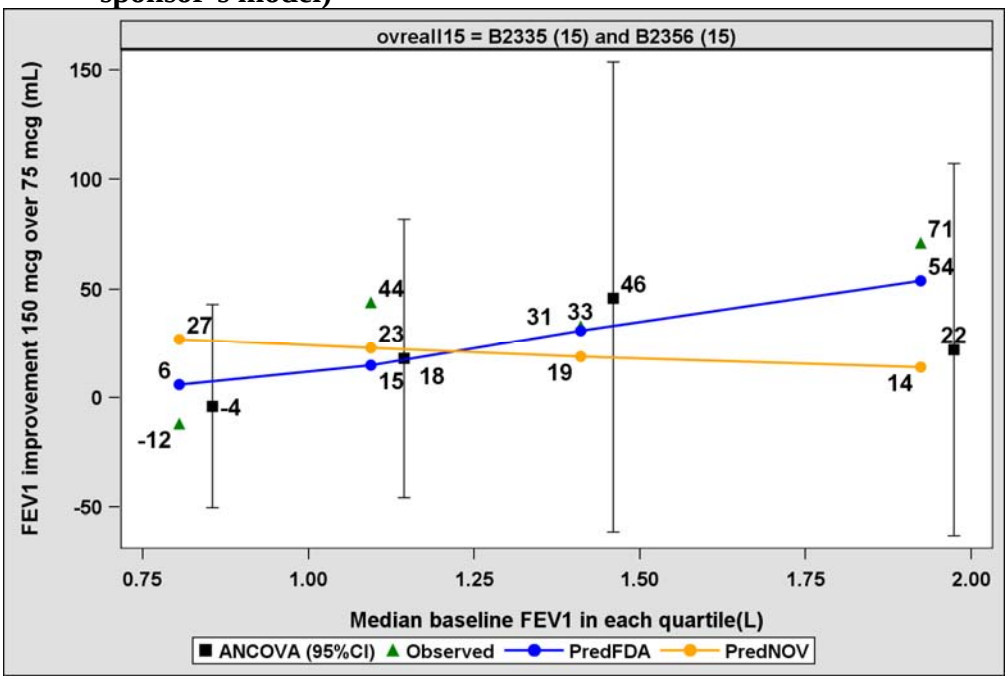


Table 4: Least squares mean of trough FEV1 (L) at Day 15 (imputed with LOCF), by subgroup (Full analysis set)*

	75 mcg		150 mcg	
Subgroup	N	LSM (SE)	N	LSM (SE)
Moderate or less	51	1.35 (0.026)	44	1.40 (0.027)
Severe or worse	36	1.41 (0.030)	46	1.40 (0.027)

*: Extracted from table 11-6 in sponsor's report for study B2356

To explore the reasons for the inconsistency between the model predictions and the observed data, additional model diagnostic analyses were conducted. Due to the lack of individual dose-response data, it is impossible to identify the appropriate structure for the covariate models assumed for placebo response (E0), Emax and ED50 based on individual parameter estimates. The sponsor assumed the covariate models for E0 and Emax based on physiological principles and started the model building with the following base model:

$$y_{ij} = \left[\begin{array}{l} E_0 + E_{0i} + \beta_1 \times base_i \\ + \dfrac{[E_{\max} \times (base_i / mean_{FEV1})^{\beta_2} \times \exp(E_{mi}) + \beta_3 \times (revers_i - mean_{REV})] \times dose_i}{ED_{50} + dose_i} \end{array} \right] \times \varepsilon_{ij}$$

Equation 1

where:

Reference ID: 2961422

· y_{ij} represents trough FEV_1 measured on patient i at day j.

· E_0 is the intercept fixed effect, and the E_{max} and ED_{50} fixed effects are defined as the maximum response and the dose to reach 50% of the maximum response.

· *base* represents baseline FEV_1 taken as the average of four FEV_1 measurements available before treatment with indacaterol, that is, two measurements obtained prior to treatment in the reversibility testing sessions and two measurements taken pre-dose on Day 1. Baseline FEV_1 acts on E_0 (additive effect) and E_{max} (multiplicative effect) in the base model.

· $mean_{FEV1}$ denotes the mean value of baseline FEV_1 over the dataset.

· *revers* represents SABA reversibity, that is, the ratio of the difference between post and pre-test FEV_1 values to the pre-test value. SABA reversibility acts on E_{max} (additive effect) in the base model.

· $mean_{REV}$ denotes the mean value of SABA reversibility over the dataset.

· E_{0i} and E_{mi} are random effects to account for inter-patient variation in response, assumed to be independently normally distributed with mean 0 and standard deviation σ_b and σ_m, respectively. Inter-patient variability is additive on E_0 and multiplicative (through a log normal distribution) on E_{max}. Note that correlation between E_{0i} and E_{mi} could not be estimated.

· ε_{ij} denotes the within-patient multiplicative errors, assumed to be independently distributed as log-normal (0, σ) variables.

Since most subjects had 2 observations (day 14 and day 15), it is possible to estimate the between subject variability on placebo response (E_{0i}). However, it is impossible to estimate the between subject variability on Emax unless no between subject variability is assumed for ED50 because the studies were following parallel design and each patient was under one treatment. It is unlikely such an assumption can be valid. To evaluate whether the assumed covariate model structures for E0, Emax and ED50 in the following final model (Equation 2) are appropriate, the data are divided into 5 subgroups based on baseline FEV1 (approximately 20% data in each subgroup) to visualize the trend for E0, Emax and ED50 in 5 increasing range of baseline FEV1.

$$\boldsymbol{y_{ij}} = \left[\begin{array}{l} \boldsymbol{E}_0 + \boldsymbol{E}_{0i} + \boldsymbol{\beta}_1 \times \boldsymbol{base}_i + \boldsymbol{\beta}_4 \times \boldsymbol{Day}14 \\ + \dfrac{[\boldsymbol{E}_{\max} \times (\boldsymbol{base}_i / \boldsymbol{mean}_{\boldsymbol{FEV1}})^{\boldsymbol{\beta}_2} \times \exp(\boldsymbol{E}_{mi}) + \boldsymbol{\beta}_3 \times (\boldsymbol{revers}_i - \boldsymbol{mean}_{\boldsymbol{REV}})] \times \boldsymbol{dose}_i}{\boldsymbol{ED}_{50} \times (\boldsymbol{base}_i / \boldsymbol{mean}_{\boldsymbol{FEV1}})^{\boldsymbol{\beta}_5} + \boldsymbol{dose}_i} \end{array} \right] \times \boldsymbol{\varepsilon}_{ij}$$

Equation 2

where Day14 is an indicator for day 14 observation or not and all other parameters are defined the same as in the base model.

A simple Emax model (Equation 3) without any covariate was applied to each subgroup to estimate the average E0, Emax and ED50 within each subgroup.

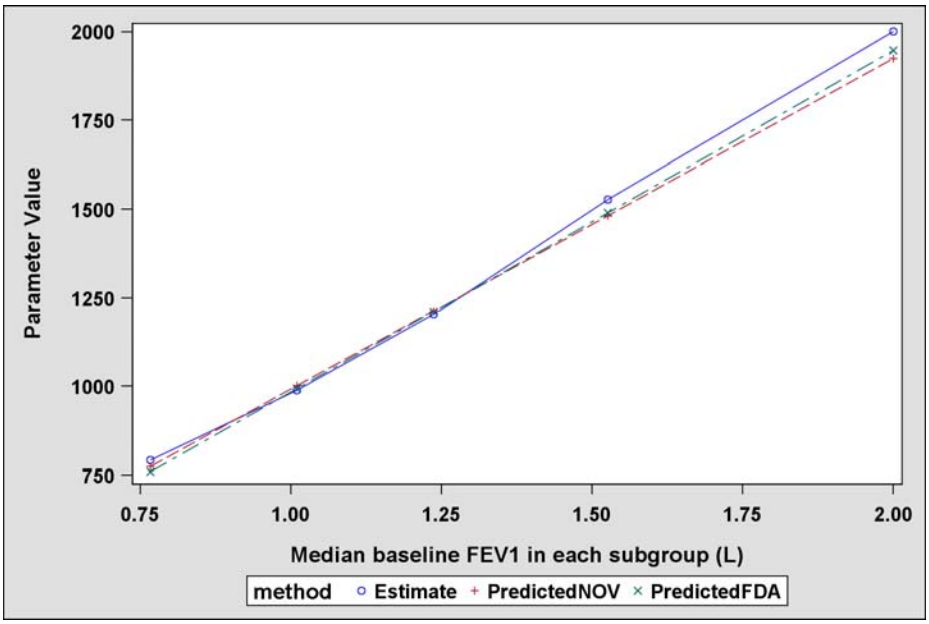
$$\boldsymbol{y_{ij}} = \left[\boldsymbol{E}_0 + \frac{\boldsymbol{E}_{\max} \times \boldsymbol{dose}_i}{\boldsymbol{ED}_{50} + \boldsymbol{dose}_i} \right] \times \boldsymbol{\varepsilon}_{ij} \qquad \text{Equation 3}$$

Reference ID: 2961422

Figures 7 shows the comparison between the parameter estimates from simple Emax model from 5 subgroups and the model predicted parameters based on the sponsor's model and the FDA's sensitivity analysis at the median baseline FEV1 in each subgroup. While the covariate model structure for E0 is consistent with the diagnostic analysis, both Emax and ED50 show considerable model misspecification. Even though Emax is following the expected trend based on the physiology principles (the larger the baseline FEV1, the larger the Emax), the magnitude of Emax change over FEV1 is significantly underestimated by the sponsor's covariate model for Emax while the FDA's sensitivity analysis is more consistent with the diagnostic analysis result. If the underlying Emax model is valid, the data are suggesting that ED50 is changing with baseline FEV1 in a U-shape pattern. However, the covariate model structure assumed by the sponsor only allows ED50 to change with FEV1 in a monotone pattern, which is why the sponsor's model predicted a downward trend while FDA's sensitivity analysis predicted an upward trend with neither model capturing the full spectrum correctly. This also explains the unstable parameter estimates when only day 15 data were used. It is the inconsistency between the data and the assumed model structure that led to the unstable parameter estimates. Simulation was conducted to show that if data are simulated under the assumed Emax model with the associated covariate models, the parameter estimates are quite stable even if only day 15 data are fitted. The diagnostic analysis did not evaluate the validity of the assumed Emax model structure. This assumption was assessed in the study-level analysis.

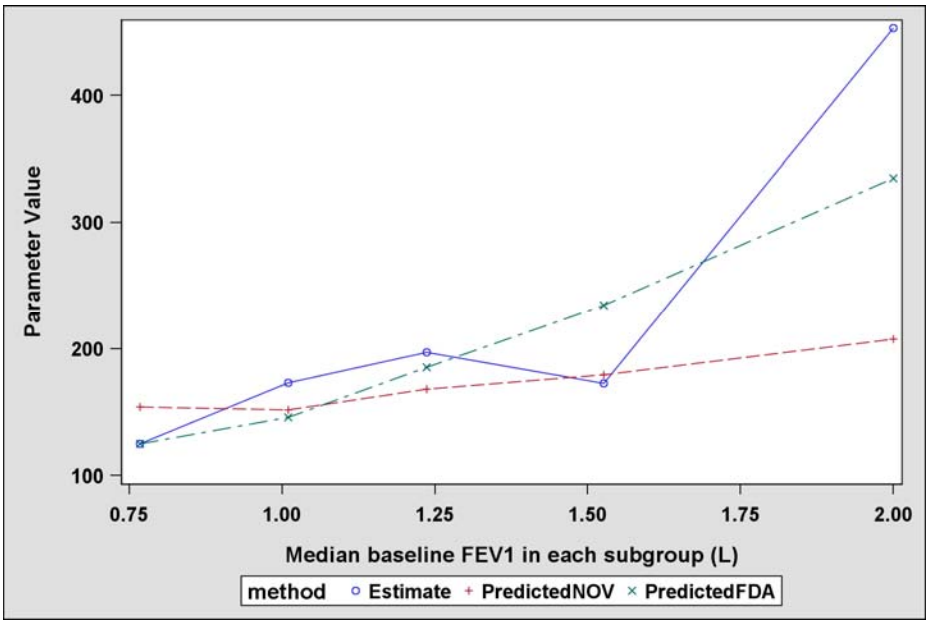
Figure 7. Model predictions versus estimates from simple Emax model in 5 baseline FEV1 subgroups for E0, Emax and ED (patient-level analysis, PredictedFDA is based on FDA's sensitivity analysis, PredictedNOV is based on sponsor's model)

E0

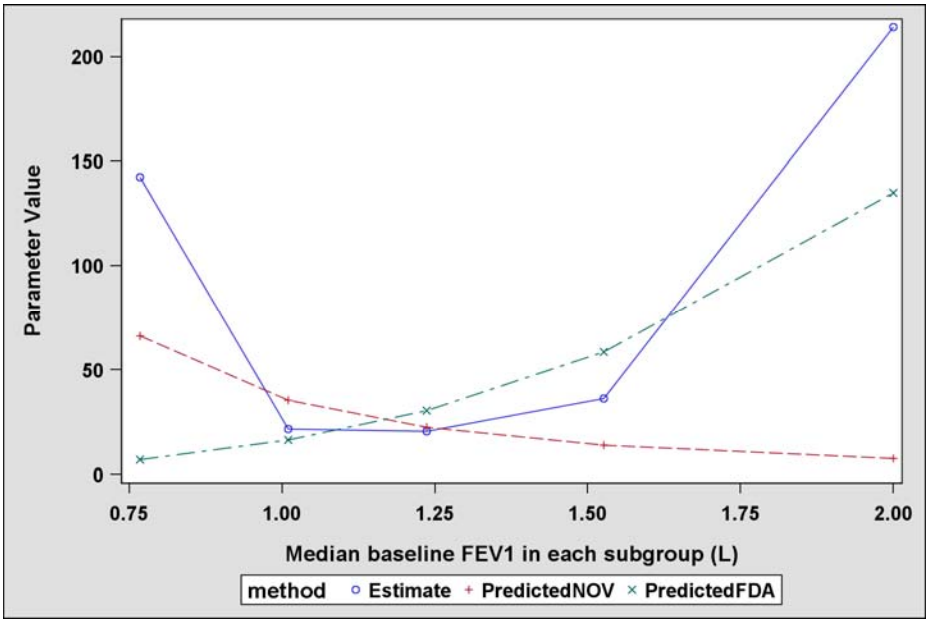


Emax

Reference ID: 2961422



ED50



Additional analyses on study-level model

As pointed out by the sponsor in the report, "If the assumption of an E_{max} model is valid and adequate data is available to support it, this approach will provide a robust estimate of the average dose response based on the totality of the study-level data". Therefore, the validity of Emax model structure is the foundation of the study-level meta-analysis. The sponsor combined estimates from multiple visits in 12 studies and Figure 8 shows the distribution of estimates and doses studied in each study. In this Bayesian meta-analysis, the sponsor assumed between study variability on Emax and estimated ED50 as a common parameter for all studies. Even though 12 studies were included in the analysis,

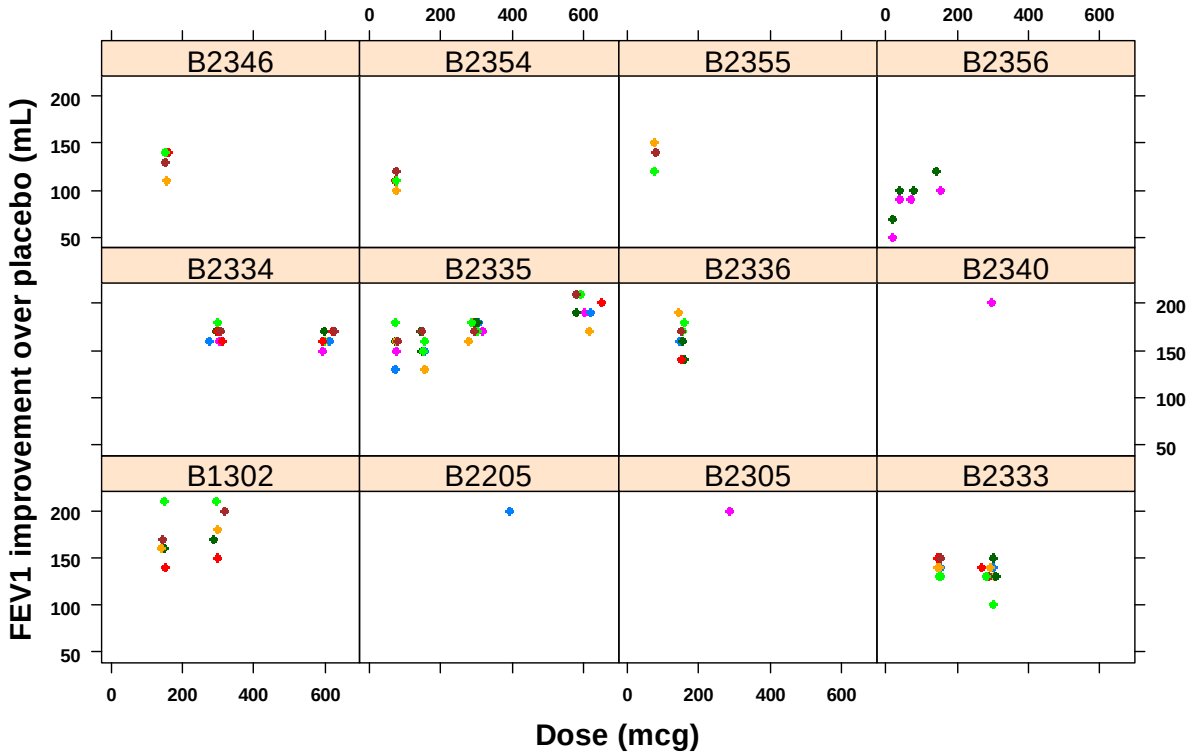
only two studies (B2356 and B2335) included more than 2 dose levels that can allow the assessment of Emax model assumption. Under Emax model assumption, the relationship between transformed variables (1/LSM and 1/dose where LSM is the least square mean difference between a dose and placebo) is assumed to be linear (Equation 4) with the intercept being 1/Emax and the slope being ED50/Emax.

$$\frac{1}{\boldsymbol{LSM}} = \frac{1}{\boldsymbol{E}_{\max}} + \frac{\boldsymbol{ED}_{50}}{\boldsymbol{E}_{\max}} \times \frac{1}{\boldsymbol{dose}} \qquad \text{Equation 4}$$

where LSM is the LS mean of FEV1 improvement over placebo for a dose.

Figure 9 shows the linear assumption for the transformed variables is not supported by the data in either study. This inappropriate assumption led to the overestimation of incremental difference between two adjacent doses, especially for 150 mcg versus 75 mcg and 75 mcg versus 37.5 mcg, as shown in Figure 10. The meta-summary in Figure 10 was calculated the same way as described for the total estimate of LS mean for the patient-level analysis. As an example, the calculation for 150 mcg versus 75 is shown in Figure 11.

Figure 8. LS estimates of FEV1 improvement over placebo from multiple visits (different colors)



Reference ID: 2961422

Figure 9. Assumed model structure versus observed data trend (study level meta-analysis)

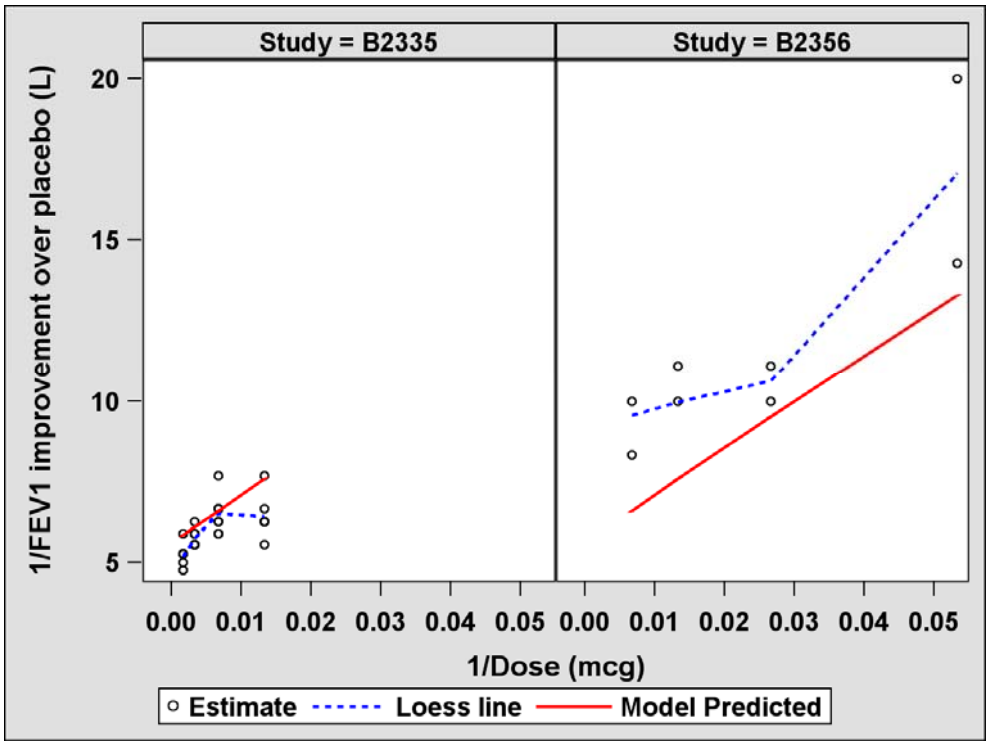
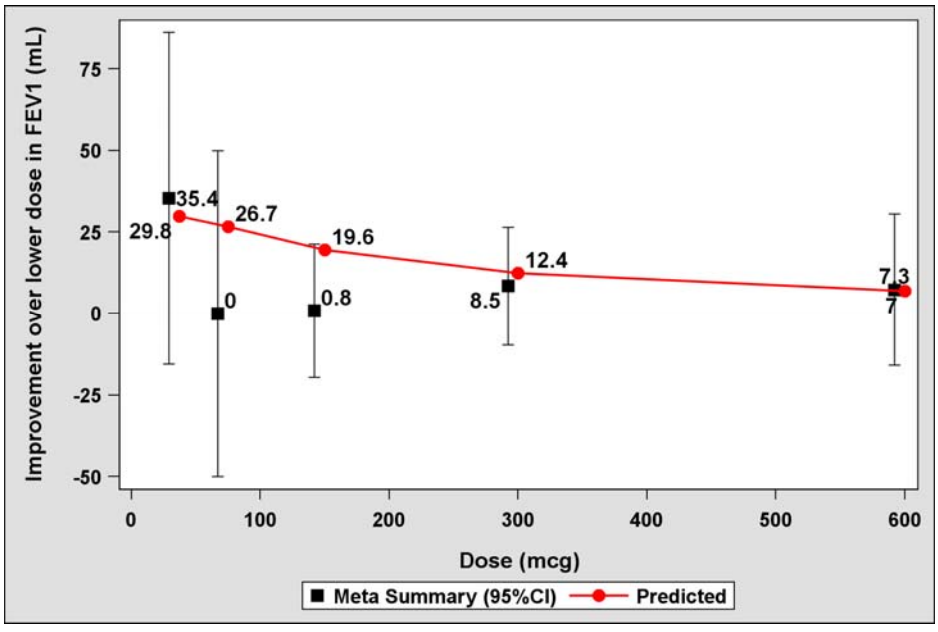
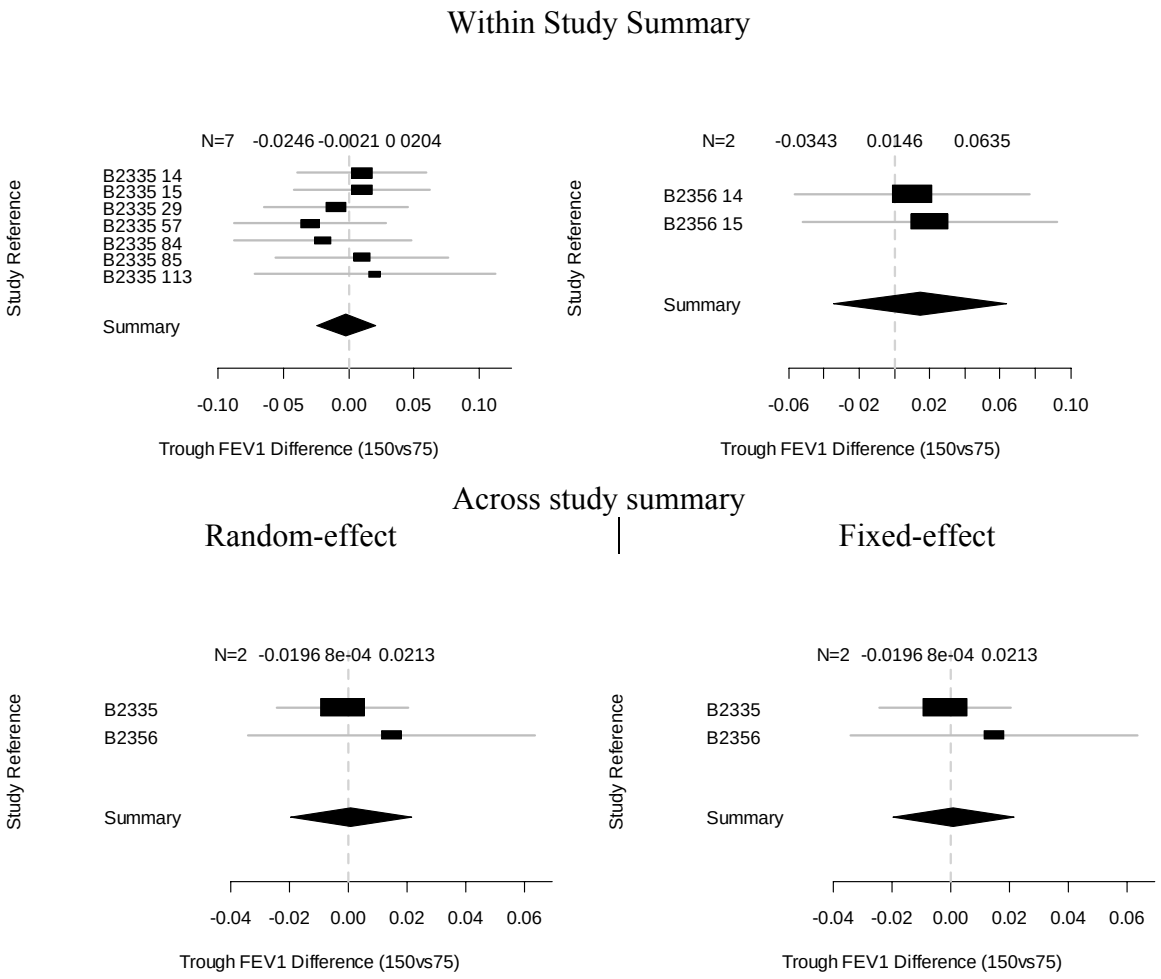


Figure 10. Model prediction versus observed data for incremental difference between doses (study level meta-analysis)



Reference ID: 2961422

Figure 11. Meta-analysis for the treatment difference (L) between 150 mcg and 75 mcg (study level meta-analysis)



The impact of unbalanced distribution of doses across the 12 studies was evaluated via simulation under a true Emax model. The purpose of simulation under a true Emax model is to remove the impact of model misspecification on the overestimation of incremental difference between two adjacent doses and explore whether the unbalanced dose distribution across studies also contributes to the overestimation. One noticeable unbalance is that the data from lower doses (37.5 mcg and 18.75 mcg) happened to be in a study that had the lowest response for 75 mcg and 150 mcg across all studies as shown in Figure 12. Full dataset was simulated for each study to include the full dose range from 18.75 mcg to 600 mcg with 9 visits (the maximum number of visits observed in the data) at each dose level. The simulated data were summarized at each dose for each study and the summarized data were ranked to approximately mimic the ranking order of the observed data across the 12 studies (B2356<B2354<=B2346<B2355<= B2333<B2334<B2335< B1302<B2205<B2336<=B2305<=B2340). Then the full simulated dataset was reduced to the unbalanced distribution of doses and visits to match the observed pattern in the 12 studies. For example, the lowest ranked study will only maintain 2 visits at 18.75 mcg, 37.5 mcg, 75 mcg and 150 mcg to represent study B2356.

Reference ID: 2961422

The highest ranked study will only maintain 1 visit at 300 mcg to represent study B2340. Figure 13 shows the comparison of full dataset and reduced dataset under one simulation scenario. Various scenarios were simulated and overestimation of incremental difference between two adjacent doses was observed under all simulated scenarios, ranging from 5% to 31% (Table 5). The simulation results demonstrate that even if the Emax model is the true underlying mode, the dose range and unbalanced distribution observed in the 12 studies will still lead to overestimation of incremental difference between two adjacent doses. The lower the true ED50 is, the larger the overestimation will be.

Figure 12. Prediction of dose response for trough FEV1 at steady state in COPD patients for indacaterol and comparators (circled data are from study B2356, study-level meta-analysis)

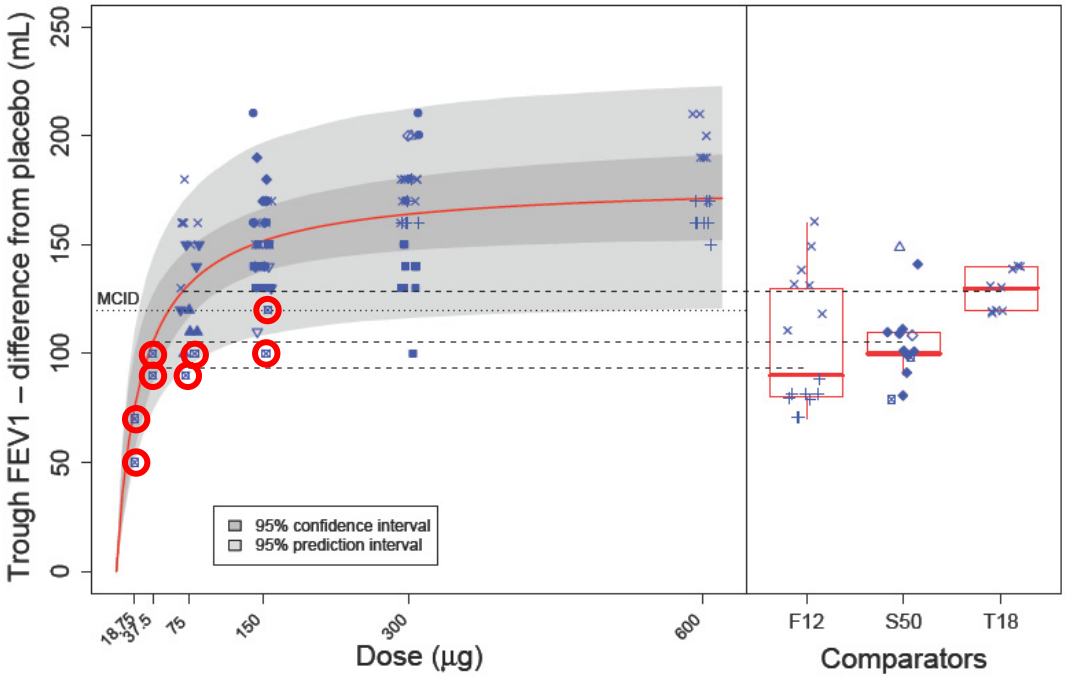
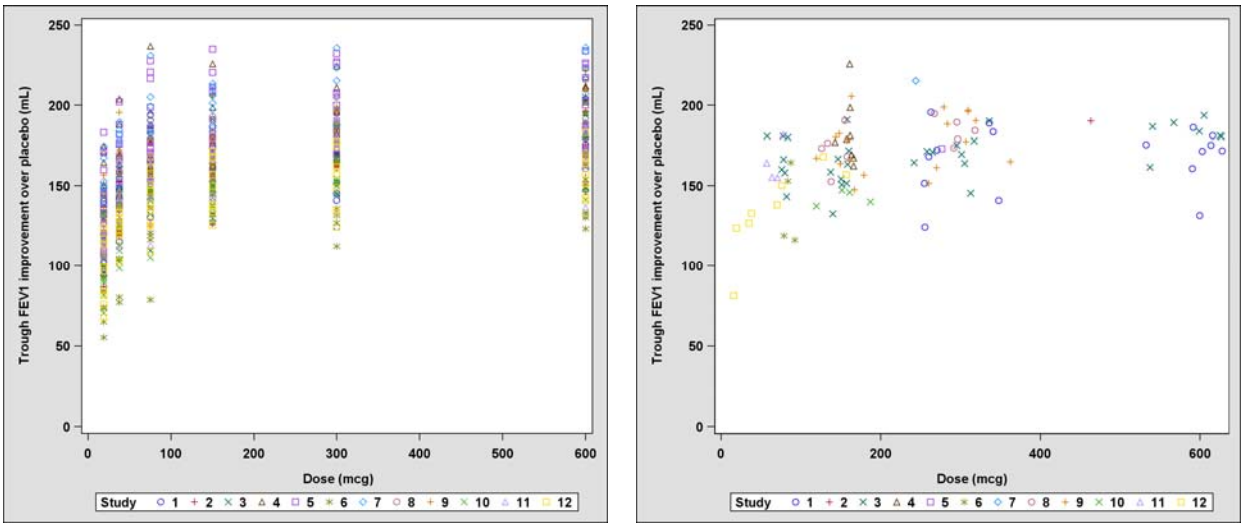


Figure 13. Comparison of simulated full dataset and reduced dataset under scenario 1

Full dataset Reduced dataset*

Reference ID: 2961422



*: doses were jittered around the nominal doses to have better visual effect and avoid overlapping symbols

Table 5. Percent of overestimation for incremental difference between two adjacent doses under various simulation scenarios*

Scenario	ED50	600-300	300-150	150-75	75-37.5	37.5-18.75
1	10	31	29	26	21	14
2	20	29	26	22	16	9
3	30	29	25	20	13	6
4	40	28	24	18	11	5

*: Emax was assumed to be 0.18 L; between-study standard deviation for response was assumed to be 0.02; between-visit standard deviation for response was assumed to be 0.014; within-visit standard deviation for response was assumed to be 0.014.

Conclusion

Additional patient-level analyses showed that the model based claim of additional benefit of 150 mcg over 75 mcg for more severe patients is not supported by the data. Inappropriate covariate model structures for Emax and ED50 contributed to this inconsistency. The inappropriate Emax assumption identified from the study-level analysis may also play a role.

The study-level meta-analysis overestimates the incremental difference between two adjacent doses, especially for 150 mcg versus 75 mcg, 75 mcg versus 37.5 mcg. Two factors contributed to this observation: the inappropriate Emax model assumption and the unbalanced dose distribution across studies.

Reference ID: 2961422

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YANING WANG
06/15/2011

JOO YEON LEE
06/15/2011

CLINICAL PHARMACOLOGY REVIEW

NDA:	22-383
Proprietary Drug Name:	ARCAPTA NEOHALER
Generic Name:	Indacaterol Maleate Inhalation Powder
Indication:	Treatment of Chronic Obstructive Pulmonary Disease
Dosage Form:	Dry Powder Inhaler
Strength:	75μg, 150 μg
Route of Administration:	Oral Inhalation
Applicant:	Novartis
Clinical Division:	DPARP
Submission Dates:	September 28, 2010
Clinical Pharmacology Reviewers:	Ying Fan, Ph.D.
Team Leader (Acting):	Yun Xu, Ph.D.
Pharmacometric Reviewer:	Joo Yeon Lee, Ph.D.
Pharmacometrics Team Leader:	Yaning Wang, Ph.D.
Pharmacogenomics Reviewer:	Hobart Rogers, Pharm.D., Ph.D.
Pharmacogenomics Team Leader:	Mike Pacanowski, Pharm.D., M.P.H.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology II (OCP / DCPII) has reviewed NDA 22-383 resubmitted on September 28, 2010 and found it acceptable. However, based on our analysis, the sponsor has not adequately characterized the dosing regimen for Arcapta Neohaler for the treatment of obstructive pulmonary disease (COPD). The minimum effective dose has not been identified and the sponsor's claim of additional benefit with 150 μg over 75 μg for more severe patients can not be supported. The dose selection topic will be further discussed in the March 8, 2011 Advisory Committee meeting.

We have the following comments to the medical officer regarding dose selection. Based on the observation of dose-response profile after two weeks (steady-state),

- The sponsor's dose-response modeling analysis does not fully address minimum effective dose issue
- The sponsor's claim with additional benefit with 150 μg over 75 μg for severe COPD patients is not considered as a robust finding
- A better alternative regimen of a loading dose of 150 μg for 2 weeks followed by the long-term maintenance dose of 37.5 μg is recommended.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceuticals Findings

Arcapta Neohaler (Inhalation Powder) contains (R)-indacaterol maleate, a selective $beta_2$-adrenergic bronchodilator. Arcapta is proposed for a long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Arcapta is proposed in two strengths: 75 μg or 150 μg of indacaterol inhalation powder hard capsules. The proposed dosage of Arcapta is 75 or 150 μg once daily.

The clinical pharmacology studies submitted by the sponsor Novartis, originally was submitted on December 15, 2008, included 36 clinical studies that contain pharmacokinetic (PK) information collected from healthy volunteers (14 studies), patients with COPD (10 studies), and asthma patients (12 studies). For the detail of the original submission, please see the Clinical Pharmacology review by Dr. Sandra Suarez on August 25, 2009. The Complete response letter was given on October 16, 2009. In the current submission, the clinical pharmacology studies include 3 *in vitro* drug-drug interaction studies, 1 bioavailability study, 1 intrinsic factor PK study in healthy Chinese

subjects, and 1 extrinsic factor PK study assessing the PK interaction of indacaterol with ritonavir in healthy adult subjects.

Based on the current re-submission, the pharmacokinetic results can be summarized as follows: The absolute bioavailability of indacaterol after an inhaled dose was on average 45%. Systemic exposure results from a composite of pulmonary and intestinal absorption. Based on the *in vitro* investigations of enzyme and transporter induction indicated that indacaterol has negligible potential to act as an inducer at clinically relevant serum levels. *In vitro* investigation indicated that, indacaterol is unlikely to significantly inhibit transporter proteins such as P-glycoprotein (P-gp), multidrug resistance-associated protein 2 (MRP2), human breast cancer resistance protein (BCRP), the human organic cationic transporters hOCT1 and hOCT2, and the human multidrug and toxin extrusion transporters hMATE1 and hMATE2K, and that indacaterol has negligible potential to induce P-gp or MRP2. Concomitant administration of indacaterol 300 μg with ritonavir 300 mcg b.i.d for 7.5 days resulted in a 1.6-fold to 1.8-fold increase in indacaterol AUC whereas indacaterol Cmax was unaffected. The magnitude of exposure increases does not raise safety concerns because the safety experience of treatment with Arcapta Neohaler in clinical trials was up to one year at doses up to 600 mcg.

2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What is the regulatory background of Indacaterol?

The sponsor Novartis is resubmitting the New Drug Application (NDA 22-383) for Arcapta Neohaler (Indacaterol maleate inhalation powder) for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The original submission was dated on December 18, 2008 and the Complete Response letter was given on October 16, 2009. The reason for issuing the Complete Response letter is as follows:

1. The submitted data did not provide substantial evidence of safety to support the use of Arcapta Neohaler at the proposed doses of 150 mcg and 300 mcg once daily in patients with chronic obstructive pulmonary disease (COPD). At the proposed doses, there were unacceptable higher frequencies of cardiovascular and cerebrovascular serious adverse events compared to placebo and to formoterol in patients with COPD, and possible asthma related deaths compared to salmeterol in patients with asthma.

2. The submitted studies did not show a clinically meaningful efficacy difference between the 75 mcg once daily dose compared to the 150 mcg or 300 mcg once daily doses or the 150 mcg dose compared to the 300 mcg dose.

3. An appropriate dosing frequency has not been explored in clinical studies.

4. The submitted data did not provide substantial evidence to support use of two different doses in patients with COPD. The data submitted did not show a clinically meaningful advantage of 300 mcg dose over 150 mcg dose, especially in regards to potential safety disadvantages associated with the administration of a higher dose.

The Agency also gave the recommendation to the sponsor that: a.) in order to support approval of indacaterol in COPD patients, the sponsor will need to conduct clinical studies to explore efficacy and establish the safety of doses lower than the proposed 150 mcg dose and to study various dosing frequencies to support your proposed dosing frequency; b) in order to support approval of two doses of indacaterol in COPD patients, the sponsor will need to provide replicate data showing clinically meaningful advantage of a higher dose compared to a lower dose, and balancing safety data to show no unacceptable safety disadvantage with the higher dose.

In response to the Complete Response letter, the sponsor resubmitted the application on October 16, 2009. In the current submission, the clinical pharmacology studies include 3 *in vitro* drug-drug interaction studies, 1 bioavailability study, 1 intrinsic factor PK study in healthy Chinese subjects, and 1 extrinsic factor PK study assessing the PK interaction of indacaterol with ritonavir in healthy adult subjects.

The Planning meeting for this submission was held on November 1, 2010.

2.1.2. What are the proposed dosage(s) and route(s) of administration?

Originally, the proposed dosages were 150 mcg and 300 mcg for oral inhalation. In the current submission, the proposed dosages are 75 mcg and 150 mcg for oral inhalation.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology program?

In the original submission, there are 36 clinical studies that contain pharmacokinetic information collected from: Healthy volunteers (14 studies), Patients with COPD (10 studies) and Asthma patients (12 studies).

In the current submission, it includes following clinical pharmacology studies:
Pharmacokinetics (PK) Drug-drug interaction (DDI) study:
Evaluation of QAB149 as an inducer of drug metabolizing enzymes and transporters in primary human hepatocytes (DMPK R0900287)
Assessment of QAB149 as an inhibitor of human BCRP, P-gp and MRP2 (DMPK R0900394)
Assessment of QAB149 as an inhibitor of human OCT1, OCT2, MATE1 and MATE2K (DMPK R0900759)

Bioavailability (BA) study:
Randomized, open-label, single dose, 3-period crossover study to determine the relative and absolute BA of orally inhaled indacaterol maleate (delivered by inhalation via Concept1) in healthy volunteers (QAB149B2106)

Intrinsic factor PK study:
A Randomized, double-blinded, placebo-controlled, parallel-group study to evaluate the PK of multiple daily doses of indacaterol (150 μg and 300 μg) delivered by oral inhalation via the Concept1 device in healthy Chinese subjects (QAB149B2101)

Extrinsic factor PK study:
An open-label, single-dose, 2-period, single sequence study to assess the PK interaction of indacaterol (300 μg via oral inhalation) with ritonavir (300mg b.i.d.) in healthy adult subjects (QAB149B2107)

2.2.2 What is the absolute inhaled bioavailability of indacaterol?

Originally, the absolute bioavailability was determined in Study CQAB149B2103 where the inhaled bioavailability was on average 43.2% that was determined in Study CQAB149A2106 (see Clinical Pharmacology review by Dr. Sandra Suarez on August 25,

2009). In the current submission, the relative and absolute bioavailability with 300 mcg indacaterol was determined in a randomized, open-label, single-dose, three-period crossover study of inhaled indacaterol (300 mcg) versus an intravenous infusion of 200 mcg indacaterol via constant rate infusion over 120 minutes, and the relative bioavailability of a 600 mcg inhaled indacaterol dose given with charcoal compared to a 300 mcg indacaterol dose inhaled without charcoal. The results of the pharmacokinetics analysis indicated that the absolute bioavailability of oral inhaled indacaterol was 45%.

2.2.3 Are the sponsor's newly proposed doses (75 μg and 150μg QD) acceptable?

No. For COPD patients, there appeared to be clear dose-response relationship for trough FEV1 response after the first dose and 150 μg has a faster onset of action compared to 75 μg or lower doses. However, after two weeks of treatment, there was no obvious difference among 37.5 μg, 75 μg and 150 μg. Since indacaterol is targeting for the long-term maintenance effect and the safety concern for long-acting beta-against (LABA) is associated with higher doses, it is desirable to select the minimum maintenance dose with acceptable effectiveness to avoid potential safety concerns related to unnecessarily high doses. The sponsor's analyses at steady-state did not fully justify 75μg QD as a minimum effective dose and the sponsor's claim of additional benefit with 150 μg over 75 μg for more severe patients is not considered a robust finding. See details in Pharmacometrics Review (Appendix 4.2).

2.2.4 Do ADRB2 polymorphisms play a significant role in indacaterol response variability?

The sponsor included a single report containing a summary of published literature and a pharmacogenetic substudy report based on a pooled analysis of indacaterol-treated subjects in trials CQAB149B2335S (150 mcg indacaterol qd, 300 mcg indacaterol qd, 18 mcg tiotropium qd, placebo qd) and CQAB149B2336 (150 mcg indacaterol qd, 50 mcg salmeterol bid, placebo bid). Overall, it appears as if the *ADRB2* polymorphisms do not play a significant role in indacaterol response variability. The sponsor's response to the previous recommendations is satisfactory from the perspective of the Genomics Group and no additional action is indicated. See details in Pharmacogenomics Review (Appendix 4.3).

2.3 Intrinsic Factors

2.3.1 Is there any significant covariate which affects Indacaterol PK?

Yes. Weight, age, gender and ethnicity were found to be significant factors on indacaterol PK. However, it is not necessary to adjust dose based on these covariates. In the previous submission, weight, age and gender were the significant covariates on indacaterol PK, but dose adjustment was not recommended as these covariates showed relatively small effects. The sponsor updated population PK report by adding new studies. The effects of

weight, age and gender remained similar to the previous report; peak concentration (Cmax) increases with age, by 35% over the range of 49-78 years; Cmax in COPD patients decreases with body weight, by 28% over the range of 49-105kg; Cmax is an average of 7.6% greater in female COPD patients than in male patients. In addition, there were some observation of higher exposure in Asian subpopulations in the updated analysis; Cmax on average 17% and 25% higher in Korean and Japanese patients compared to the typical COPD patient. However, it is not conclusive whether there were true ethnic differences or whether the results were caused by inter-study variability in the population PK analyses. See Pharmacometrics Review in Appendix 4.2.

2.3.2 What are the PK characteristics of indacaterol in the Chinese population?

The PK characteristics of indacaterol were evaluated in Study CQAB149B2101. It was a single center, double-blind, randomized, multiple-dose, placebo-controlled, parallel group trial, using a placebo control and 2 doses of indacterol, 150 μg and 300 μg. The primary objective was to characterize the pharmacokinetics following multiple, daily inhaled administrations of indacaterol (150 μg and 300 μg dose) delivered via the single-dose dry powder inhaler device in healthy Chinese subjects.

Serum concentrations of indacaterol increased rapidly following drug inhalation and reached a maximal level approximately 15 minutes. At Day 1, following 150 mcg dose, the systemic exposures are 0.974 ng.hr/mL for AUC0-24 h, and 0.206 ng/mL for Cmax, respectively. The systemic exposures are 2.43 ng.hr/mL for AUC0-24 h, and 0.518 ng/mL for Cmax following 300 mcg dose (Table 1). Systemic exposure to indacaterol increased more than 2-fold between the 150 μg and 300 μg doses.

Table 1 Pharmacokinetic parameters of indacaterol following multiple dose inhaled administration of 150 mcg indacaterol for 14 days in healthy Chinese subjects (Study CQAB149B2101) in Day 1

Dose(mcg)	Tmax (h)	Cmax (pg/mL)	AUC0-24 (pg.h/mL)
150	0.25	206	974
300	0.25	518	2430

Table 2 Pharmacokinetic parameters of indacaterol following multiple dose inhaled administration of 150 mcg indacaterol for 14 days in healthy Chinese subjects (Study CQAB149B2101) in Day 14

Dose (mcg)	Tmax (h)	Cmax ss (pg/mL)	AUC0-24 ss (pg.h/mL)	T1/2 (h)
150	0.25	299	2510	33.9
300	0.25	697	6520	35.8

Following the multiple dose inhaled administration for 14 days, peak serum oncentrations of 150 µg and 300 µg indacaterol were reached at median Tmax of 15 minutes. The mean effective half-lives of 33.9 and 35.8 hours, respectively (Table 2).

2.4 Extrinsic Factors

2.4.1 Drug-Drug Interactions (DDI)

2.4.1.1 Does indacaterol has potential to act as an inducer of enzyme and transporter?

Based on the in vitro investigations of enzyme and transporter induction indicated that indacaterol has negligible potential to act as an inducer at clinically relevant serum levels (Study R0900287).

2.4.1.2 Can indacaterol inhibit transporter proteins such as P-gp, MRP2, BCRP, the cationic substrate transporters hOCT1 and hOCT2, and the human multidrug and toxin extrusion transporters hMATE1 and hMATE2K?

In vitro study indicated that, indacaterol is unlikely to significantly inhibit transporter proteins such as P-gp, MRP2, BCRP, the cationic substrate transporters hOCT1, hOCT2, and the human multidrug and toxin extrusion transporters hMATE1 and hMATE2K (Study R0900759 and Study R0900394).

2.4.1.3 Does indacaterol has potential drug-drug interaction with ritonavir?

Concomitant treatment of indacaterol 300 mcg with dual inhibitor of CYP3A4 and P-gp, ritonavir 300 mcg b.i.d for 7.5 days, resulted in a 1.6-fold to 1.8-fold increase in AUC of indacaterol, whereas Cmax of indacaterol was virtually unaffected. Since the safety data (Study CQAB149B2339) and of the pivotal studies (which both confirmed safe use of a 600 mcg dosage regimen up to one year), the magnitude of exposure increases due to drug-interactions do not raise major safety concerns for therapeutic doses of 75 mcg or 150 mcg.

3. LABELING COMMENTS

Presented below are preliminary labeling comments from the Clinical Pharmacology perspective. The ***blue bolded italic*** words indicate the addition text, and the ~~**bold strike through**~~ words indicate the deletion.

7 DRUG INTERACTIONS

(b) (4)

[redacted]

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Absorption
The median time to reach peak serum concentrations of indacaterol was approximately 15 minutes after single or repeated inhaled doses. Systemic exposure to indacaterol increased with increasing dose (150 mcg to 600 mcg) in a dose proportional manner, and was about dose-proportional in the dose range of 75 mcg to 150 mcg. Absolute bioavailability of indacaterol after an inhaled dose was on average ***43***-45%. Systemic exposure results from a composite of pulmonary and intestinal absorption.

Drug-drug Interaction
Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e., ketoconazole, erythromycin, verapamil and ritonavir). The

(b) (4)

[redacted]

Verapamil: Co-administration of indacaterol 300 μg (single dose) with verapamil (80 μg t.i.d for 4 days) showed 2-fold increase in indacaterol AUC0-24, and 1.5-fold increase in indacaterol Cmax.

Erythromycin: Co-administration of indacaterol inhalation powder 300 μg (single dose) with erythromycin (400 μg q.i.d for 7 days) showed an 1.4-fold increase in indacaterol AUC0-24 , and 1.2-fold increase in indacaterol Cmax.

Ketoconazole: Co-administration of indacaterol inhalation powder 300 μg (single dose) with ketoconazole (200 μg b.i.d for 7 days) caused a 1.9-fold increase in indacaterol AUC0-24, and 1.3-fold increase in indacaterol Cmax.

Ritonavir: Co-administration of indacaterol 300 μg (single dose) with ritonavir (300 mcg b.i.d for 7.5 days) resulted in a 1.7-fold increase in indacaterol AUC0-24 whereas indacaterol Cmax was unaffected.

Appendix:
4.1 Individual Study Reports

"A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the pharmacokinetics of multiple, daily doses of indacaterol (150 µg and 300 µg) delivered by oral inhalation via the Concept1 device in healthy Chinese subjects"

Study No. CQAB149B2101 **Development phase of study**: Phase 1

Objective:
The primary objective was to characterize the pharmacokinetics following multiple, daily inhaled administrations of indacaterol (150 µg and 300 µg dose) delivered via the single-dose dry powder inhaler (SDDPI, Concept1) device in healthy Chinese subjects.

Methodology:
This was a single center, double-blind, randomized, multiple-dose, placebo-controlled, parallel group trial, using a placebo control and 2 doses of indacterol, 150 µg and 300 µg.

Number of patients (planned and analyzed):
Thirty-two (32) subjects were planned to be enrolled. Thirty-two (32) healthy Chinese subjects were enrolled and completed the study. Twelve (12) subjects each received doses of 150 µg and 300 µg, respectively, and 8 subjects received placebo.

Diagnosis and main criteria for inclusion:
Subjects were non-smoking or light smoking healthy Chinese male or female subjects aged between 18 and 45 years (inclusive).

Duration of treatment:
A single inhaled dose of indacaterol (150 µg or 300 µg) or matching placebo was administered daily, for 14 consecutive days in the morning, using the Concept1 inhaler device.

Pharmacokinetic:
PK blood samples were collected on Day 1 (24hr profile), pre-dose on Days 7, 10, and 12, and on Day 14 (24 hr profile, and additionally up to 168 h after dosing). Serum indacaterol was determined by a HPLC-MS/MS method with a LLOQ of 10 pg/mL.

Pharmacokinetic results:
Pharmacokinetic parameter of indacaterol following single and multiple, daily inhaled administrations of indacaterol (150 µg and 300 µg dose) delivered via the single-dose dry powder inhaler (Concept1) device in healthy Chinese subjects are shown in Table 1 and Table 2.

Table 1 Summary of pharmacokinetic parameters of indacaterol following a single inhaled dose of indacaterol in healthy Chinese subjects (Day 1)

	Cmax ng/mL	Tmax hr	AUC0-24h hr·ng/mL
Dose: 150 µg (N=12 subjects)			
Mean	0.206	0.25 [1)]	0.974
SD	0.0568	0.25 - 1.00 [2)]	0.252
Dose: 300 µg (N=12 subjects)			
Mean	0.518	0.25 [1)]	2.43
SD	0.0780	0.25-0.25 [2)]	0.408

[1)] median; [2)] range [min-max]

Serum concentrations of indacaterol increased rapidly following drug inhalation and reached a maximal level approximately 15 minutes. At Day 1, following 150 mcg dose, the systemic exposures are 0.974 ng.hr/mL for AUC0-24 h, and 0.206 ng/mL for Cmax, respectively. The systemic exposures are 2.43 ng.hr/mL for AUC0-24 h, and 0.518 ng/mL for Cmax following 300 mcg dose (Table 1). Systemic exposure to indacaterol increased more than 2-fold between the 150 µg and 300 µg doses.

Table 2 Summary of pharmacokinetic parameters of indacaterol following repeated once-daily inhaled doses of indacaterol in 12 healthy Chinese subjects (Day 14)

	Cmax,ss ng/mL	Cmin,ss ng/mL	Cav,ss ng/mL	Tmax,ss hr	AUC0-24h,ss hr·ng/mL	Racc	T1/2,acc hr
Daily dose: 150 µg (N=12 subjects)							
Mean	0.299	0.0645	0.105	0.25 [1)]	2.51	2.59	33.9
SD	0.116	0.0311	0.0381	0.25-0.50 [2)]	0.914	0.636	11.0
Daily dose: 300 µg (N=12 subjects)							
Mean	0.697	0.182	0.272	0.25 [1)]	6.52	2.69	35.8
SD	0.168	0.0503	0.0685	0.25–0.50 [2)]	1.64	0.534	9.06

[1)] median; [2)] range [min-max]

Following the multiple dose inhaled administration for 14 days, peak serum oncentrations of 150 µg and 300 µg indacaterol were reached at median Tmax of 15 minutes. The mean accumulation ratio, i.e. the AUC0-24h ratio Day 14 to Day1, was 2.6 and 2.7 for 150 µg and 300 µg, respectively, which resulted in the mean effective half-lives of 33.9 and 35.8 hours, respectively (Table 2).

The trough concentrations increased up to Day 12, but there was little change between Day 12 and Day 14, indicating that the steady state was achieved within the treatment duration of the present study (Figure 1).

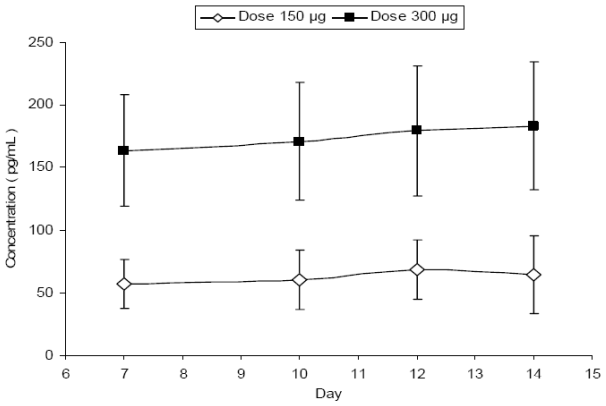


Figure 1 Arithmetic mean (SD) serum trough concentrations after multiple doses inhaled administration of 150 µg and 300 µg indacaterol in healthy Chinese subjects

Conclusions:

1. Steady state of indacaterol was achieved after 12 to 14 days of daily dosing. The mean AUC0-24h accumulation ratio (Day 14 to Day 1) was 2.6 and 2.7 for the 150 µg and 300 µg dose, respectively.

2. The mean effective half life for accumulation of indacaterol was 33.9 and 35.8 hours for 150 µg and 300 µg, respectively.

3. Systemic exposure to indacaterol increased more than 2-fold between the 150 µg and 300 µg doses.

"A randomized, open-label, single-dose, three-period crossover study to determine the relative and absolute bioavailability of orally inhaled indacaterol maleate (delivered by inhalation via Concept1) in healthy volunteers"

Study No. CQAB149B2106 **Development phase of study**:

Objective
1. To determine the absolute bioavailability of a single 300 μg dose of inhaled indacaterol.
2. To determine the relative bioavailability of a single 600 μg dose of inhaled indacaterol given together with oral activated charcoal relative to a single 300 μg dose of inhaled indacaterol given without oral activated charcoal.

Methodology:
This was a two-part, open-label, randomized, single dose crossover study in healthy volunteers, conducted at a single center.

Number of subjects (planned and analyzed):
Twelve (12) healthy volunteers were randomized into the study: eight (8) to Treatment Part 1 and four (4) to Treatment Part 2. All 12 subjects completed all assigned treatments.

Treatment A - indacaterol 300μg inhaled via Concept1® device
Treatment B - indacaterol solution 200μg IV via controlled infusion
Treatment C - indacaterol 600μg inhaled via Concept1® device + oral activated charcoal
Treatment D oral indacaterol 600μg + oral activated charcoal

Pharmacokinetic blood sampling and bioanalytics:
Serum samples were collected pre-dose and following each treatment as described in the protocol. Indacaterol concentrations (expressed as the free base) in serum were determined by a validated LC/MS/MS method with LLOQ of 0.01 ng/mL (10 pg/mL).

Pharmacokinetic results:
Following intravenous infusion of indacaterol at a dose of 200 μg, arithmetic mean dose normalized AUClast and AUCinf were 45.6 and 55.4 (h*pg /mL)/μg, respectively (Table 1). The mean systemic serum clearance was 18.8 L/h, the mean Vss and Vz was 1362 and 2361 L respectively, and the mean apparent terminal half-life (T1/2) was 92.5 h (Table 1).

Following inhalation of 300 μg indacaterol, arithmetic mean dose normalized AUClast and AUCinf were 21.1 and 27.1 (h*pg /mL)/μg, respectively. The mean apparent terminal half-life (T1/2) was 91.8 h (Table 1).

Table 1 Arithmetic mean [CV%] serum pharmacokinetic parameters of indacaterol after single IV infusion of 200 mcg and inhalation of 300 mcg indacaterol

Parameter (Unit)	IV Infusion (N=8)	Inhalation (N=7)
Dose (µg)	200	300
Cmax (pg/mL)	1650 [7.6]	637 [29.2]
Cmax/Dose ((pg/mL)/µg)	8.25 [7.6]	2.13 [29.2]
AUClast (h*pg/mL)	9110 [14.6]	6327 [28.4]
AUClast /Dose ((h*pg/mL)/µg)	45.6 [14.6]	21.1 [28.4]
AUCinf (h*pg/mL)	11090 [19.3]	8114 [24.7] [a)]
AUCinf /Dose ((h*pg/mL)/µg)	55.4 [19.3]	27.1 [24.7] [a)]
T1/2 (h)	92.5 [34.1]	91.8 [23.1] [a)]
CL (L/h)	18.8 [23.4]	39.4 [29.8] [a),b)]
Vz (L)	2361 [18.0]	5242 [36.9] [a),c)]
Vss (L)	1362 [28.9]	-
Fabs, based on individual AUClast/Dose values (n=7)		0.47 [22.5]
Fabs, based on individual AUCinf/Dose values (n=6)		0.51 [23.3]

a) Calculated based on N=6 subjects.
b) CL/F; c) Vz/F.

Table 2 Ratio of geometric means (inhaled/intravenous) and 90% confidence intervals for dose normalized PK variables after single IV infusion of 200 mcg and inhalation of 300 mcg indacaterol

	Adjusted geo-mean*		Ratio of geo-means*		
Parameter (Unit)	Inhaled	Intravenous	Estimate	Lower 90% CL	Upper 90% CL
AUClast/Dose ((h*pg/mL)/ug)	20.27	45.05	0.45	0.37	0.55
AUCinf/Dose ((h*pg/mL)/ug)	26.54	54.43	0.49	0.40	0.60

* back-transformed from log scale; geo-mean=geometric mean.

Absolute bioavailability (Fabs) was calculated based on individual dose normalized AUClast and AUCinf parameters for subjects that received indacaterol by both routes. Based on dose normalized AUC_{last} parameters, the point estimate for the absolute bioavailability of inhaled indacaterol (compared to the intravenous dose) was 0.45 with a 90% confidence interval of (0.37, 0.55) (Table 2).

Table 3 Arithmetic mean [CV%] serum pharmacokinetic parameters of indacaterol after inhalations of indacaterol (300 mcg alone and 600 mcg with charcoal)

	Inhalation alone (N=7)	Inhalation + charcoal (N=8)
Dose (µg)	300	600
Tmax (h)	0.25 [0.25; 0.25] [a)]	0.25 [0.25; 0.25][a)]
Cmax (pg/mL)	637 [29.2]	1043 [23.3]
Cmax/Dose ((pg/mL)/µg)	2.13 [29.2]	1.74 [23.3]
AUClast (h*pg/mL)	6327 [28.4]	9276 [20.5]
AUClast /Dose ((h*pg/mL)/µg)	21.1 [28.4]	15.5 [20.5]
AUCinf (h*pg/mL)	8114 [24.7]	12140 [20.6]
AUCinf /Dose ((h*pg/mL)/µg)	27.1 [24.7] [b)]	20.2 [20.6]
T1/2 (h)	91.8 [23.1] [b)]	95.6 [25.3]
Frel, based on individual AUClast/Dose values (n=7)		0.74 [12.8]
Frel (%), based on individual AUCinf/Dose values (n=6)		0.76 [9.5]

a) Median [Min; Max]
b) Calculated based on N=6 subjects.

Following oral inhalation of indacaterol both without charcoal and with charcoal, absorption of indacaterol was rapid with maximal systemic levels (Cmax) being reached 15 minutes post dose in all subjects (Table 3). Following inhalation of a 300 µg dose, mean dose normalized AUClast and AUCinf were 21.1 and 27.1 (h*pg/mL)/µg, respectively (Table 3). The mean dose normalized serum Cmax was 2.13 (pg/mL)/µg and the mean apparent terminal half-life (T1/2) was 91.8 h (Table 3). Following inhalation of a 600 µg dose together with oral activated charcoal, mean dose normalized AUClast and AUCinf were 15.5 and 20.2 (h*pg/mL)/µg, respectively. The mean dose normalized serum Cmax was 1.74 (pg/mL)/µg and the mean apparent terminal half-life (T1/2) was 95.6 h (Table 3).

Table 4 Ratio of geometric means (inhaled + charcoal/inhaled) and 90% confidence intervals for dose normalized PK variables after inhalation of indacaterol (300 mcg alone and 600 mcg with charcoal)

	Adjusted geo-mean*		Ratio of geo-mean ratio*		
Parameter (Unit)	Inhaled + charcoal	Inhaled	Estimate	Lower 90% CL	Upper 90% CL
AUClast/Dose ((h*pg/mL)/ug)	15.15	20.49	0.74	0.67	0.81
AUCinf/Dose ((h*pg/mL)/ug)	19.82	26.26	0.75	0.70	0.82

* back-transformed from log scale; geo-mean=geometric mean.

Relative bioavailability (Frel) was calculated based on individual dose normalized AUClast and AUCinf parameters for subjects that received indacaterol by inhalation with and without charcoal. Based on dose normalized AUC_{last}, the point estimate for the relative bioavailability of inhalation with charcoal to inhalation without charcoal, was 0.74 with a 90% confidence interval of (0.67, 0.81) (Table 4). Therefore, almost 75% of systemic exposure following oral inhalation of indacaterol via Concept1® is due to lung absorption, and 25% is due to gastrointestinal (GI) absorption.

Conclusions:

1. Following inhalation, lung absorption of indacaterol was rapid and the absolute bioavailability was 45% of the nominal dose.

2. The relative bioavailability of indacaterol inhaled in the presence of oral charcoal was 74%, compared with inhalation without charcoal.

3. Approximately 75% of systemic exposure following oral inhalation of indacaterol via Concept1 was due to lung absorption, and 25% was due to gastrointestinal (GI) absorption.

"An open-label, single-dose, two-period, single sequence study to assess the pharmacokinetic interaction of indacaterol (300 µg via oral inhalation) with ritonavir (300mg b.i.d.) in healthy adult subjects"

Study No. CQAB149B2107 **Development phase of study**: Phase 1

Objective:

To compare the pharmacokinetics of a single 300 µg dose of indacaterol administered alone and in the presence of ritonavir at a dose producing maximal CYP3A4 and P-gp inhibition in healthy adult subjects.

Methodology:

The study employed an open-label, single dose, two-period, single sequence design. Eighteen (18) healthy male or female subjects were enrolled. Each subject participated in a screening period (Day -14 to Day -2), two baseline periods (Day -1 of each period), two treatment periods, a Washout period of at least fifteen days between the two treatment periods and a study completion evaluation. Subjects received both treatments. Pharmacokinetic samples for the determination of indacaterol in serum were taken after each dose of indacaterol as specified in the protocol.

Treatment period 1:
Indacterol 300 µg capsule as a single dose for oral inhalation administered using the Concept1 device under fasted conditions.
Treatment period 2:
Ritonavir 300 mg was administered orally b.i.d dosing for 7.5 days. On Day 2 of ritonavir treatment a single dose of Indacterol 300 µg capsule for oral inhalation was administered using the Concept1 device under fasted conditions.

Results/Conclusions:

1. There was a modest increase in the median time to maximum serum concentration (T_{max}) being 0.25 and 0.53 hours for indacaterol alone and when coadministered with ritonavir; respectively (Table 1).

2. Co-administration of a single inhaled dose of indacaterol with ritonavir resulted in an increase of total systemic exposure to indacaterol, as compared with a single inhaled dose of indacaterol given alone; AUC_{0-24} increased by 67%, AUC_{last} by 77% and AUC_{inf} by 58% (Table 2). Peak exposure (C_{max}) of indacaterol was similar between treatments.

Table 1 Summary statistics for serum PK parameters of indacaterol after administration alone (reference) and together with ritonavir (test)

Treatment	Statistic	Cmax (pg/mL)	AUC0-24 (hr*pg/mL)	AUClast (hr*pg/mL)	AUCinf (hr*pg/mL)	Tmax* (hr)	T1/2 (hr)
Reference	N	18	18	18	17	18	17
	Mean (SD)	491.2 (84.130)	2183 (472.75)	4259 (1338.2)	5556 (1602.8)	0.2500 [0.250;0.483]	70.48 (21.148)
	CV%	17.13	21.66	31.42	28.85		30.01
Test	N	16	16	15	15	16	15
	Mean (SD)	531.3 (119.68)	3624 (853.34)	7141 (1590.0)	8249 (1489.4)	0.5330 [0.283;1.48]	64.01 (8.5269)
	CV%	22.52	23.55	22.27	18.06		13.32

*Tmax – median and range [min;max]
Reference: single 300 µg orally inhaled dose of indacaterol administered alone.
Test: indacaterol (300 µg via oral inhalation) with ritonavir (300mg b.i.d.).

Table 2 Ratios of geometric means (test/reference) and 90% confidence intervals for PK variables of indacaterol

	Adjusted geometric mean		Ratio of geometric means		
Parameter (Unit)	Test	Reference	Estimate	Lower 90% CL	Upper 90% CL
Cmax (pg/mL)	522.5	484.1	1.08	0.99	1.18
AUC0-24 (hr*pg/mL)	3567	2133	1.67	1.55	1.80
AUClast (hr*pg/mL)	7157	4034	1.77	1.60	1.97
AUCinf (hr*pg/mL)	8308	5275	1.58	1.43	1.74

Reference: single 300 µg orally inhaled dose of indacaterol administered alone.
Test: indacaterol (300 µg via oral inhalation) with ritonavir (300 mg b.i.d.).

"Evaluation of QAB149 as an inducer of drug metabolizing enzymes and transporters in primary human hepatocytes"

Study No. DMPK R0900287 **Development phase of study**:

Objective:

The objective of this study was to examine the *in vitro* induction potential of QAB149 on select drug metabolizing enzymes and drug transporters in primary human hepatocytes of three individual donors.

Methods:

QAB149 was examined for its potential to induce cytochrome P450 (CYP) enzymes and UDP-glucuronosyltransferase (UGT) UGT1A1 mRNA and activities, as well as mRNAs of Pglycoprotein (P-gp, ABCB1) and the multidrug resistance-associated protein-2 (MRP2, ABCC2) transporters in primary human hepatocytes of three individual donors after 48 h of treatment. Induction of mRNA, relative to the vehicle control, was determined by real-time PCR and evaluation of changes in enzyme activities were assessed after the induction period by quantitative LC/MS/MS analysis of enzyme-selective probe substrate metabolism. Human hepatocytes were treated with QAB149 at a concentration range of 0.0005-0.05 μM. The 0.05 μM dose is >10-fold above the mean highest serum concentration of QAB149 observed in the clinic at the highest administered dose. Rifampicin (RIF) and phenobarbital (PB) were used as positive controls for induction of the majority of these genes. β-napthoflavone (BNF) was included as positive control for CYP1A and UGT1A1 induction in human hepatocytes.

Results/Conclusion:

QAB149 (up to 0.05 μM) did not induce the activities or mRNA levels of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, and UGT1A1 in all three livers. QAB149 was also not found to be an *in vitro* inducer of CYP1A1, CYP1B1, CYP2J2, P-gp, or MRP2 mRNAs.

The criteria for classification as a non-inducer were that activity or mRNA levels increased less than 2-fold with respect to the vehicle control and/or were less than 40% of the maximal positive control responses. Thus, QAB149 was not found to be an inducer of CYP enzymes and UGT1A1, as well as P-gp or MRP2 mRNAs *in vitro* at maximum therapeutic circulating concentrations and up to an order of magnitude above this. It is unlikely that QAB149 would cause relevant increases in the clearance of co-administered compounds by an induction mechanism.

"Assessment of QAB149 as an inhibitor of human breast cancer resistance protein (BCRP), P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2)"

Study No. DMPK R0900394 **Development phase of study**:

Objective

The objective of this study was to examine the potential of QAB149 to inhibit BCRP, P-gp and MRP2 transport activity in mammalian cells over expressing the respective transporters (BCRP, T8 cells; P-gp, MDA435 T0.3 cells; MRP2, MDCKII cells).

Method:

The potential for QAB149 to inhibit transport mediated by the human orthologs of BCRP (T8 cells), P-gp (MDA435 T0.3 cells) and MRP2 (MDCKII cells) over-expressed in mammalian cells was examined. Flow cytometry assays were used to assess the potential for QAB149 to inhibit the efflux of fluorescent substrates Bodipy FL prazosin (BDP) and Rhodamine 123 (Rho123) by BCRP and P-gp, respectively. [^{14}C]Valsartan was used as a probe substrate of MRP2.

Results/Conclusion:

BDP efflux from BCRP-expressing T8 cells, Rho123 efflux from P-gp-expressing MDA435 T0.3 cells and [^{14}C]VAL489 efflux from MRP2-expressing MDCKII cells was not inhibited by QAB149 up to a concentration of 50 μM. In contrast, the positive control inhibitors of BCRP (fumitremorgin C), P-gp (cyclosporin A) and MRP2 (MK571) effectively inhibited efflux activity mediated by the respective transport proteins. These data suggest that QAB149 up to a concentration of 50 μM should not inhibit BCRP, P-gp or MRP2.

"Assessment of QAB149 as an inhibitor of human organic cation transporters OCT1, OCT2, MATE1 and MATE2K"

Study No. DMPK R0900759 **Development phase of study**:

Objective:

The objective of this study was to examine whether QAB149 can inhibit transport activity of human organic cation transporter 1(hOCT1), human organic cation transporter 2 (hOCT2), human multidrug and toxin extrusion transporter 1 (hMATE1) and/or human multidrug and toxin extrusion transporter 2K (hMATE2K).

Method:

The potential of QAB149 to inhibit the hOCT1, hOCT2, hMATE1 and hMATE2K was examined in human embryonic kidney (HEK) cells either transiently (hOCT1 and hOCT2) or stably (hMATE1 and hMATE2K) expressing the respective transport proteins.

Results/Conclusion:

QAB149 at concentrations up to 5 μM maximally inhibited hOCT1 and hOCT2 by 26% and 19%, respectively. QAB149 maximally inhibited hMATE1 and hMATE2K transport activity by 99% (at 50 μM) and 83% (at 25 μM), respectively. The IC_{50} values for QAB149 inhibition of hMATE1 and hMATE2K were 1.26 ± 0.20 μM and 26.5 ± 13 μM, respectively. Given its relatively low systemic concentrations in the clinic (0.0042 μM), QAB149 is not expected to inhibit hOCT1, hOCT2, h hMATE1 and hMATE2K *in vivo*.

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there any significant covariate which affects Indacaterol PK?

Yes. Weight, age, gender and ethnicity were found to be significant factors on indacaterol PK. However, it is not necessary to adjust dose based on these covariates.

In the previous submission, weight, age and gender were the significant covariates on indacaterol PK, but dose adjustment was not recommended as these covariates showed relatively small effects. The sponsor updated population PK report by adding new studies. The effects of weight, age and gender remained similar to the previous report; peak concentration (Cmax) increases with age, by 35% over the range of 49-78 years; Cmax in COPD patients decreases with body weight, by 28% over the range of 49-105kg; Cmax is an average of 7.6% greater in female COPD patients than in male patients. In addition, there were some observation of higher exposure in Asian subpopulations in the updated analysis; Cmax on average 17% and 25% higher in Korean and Japanese patients compared to the typical COPD patient. However, it is not conclusive whether there were true ethnic differences or whether the results were caused by inter-study variability in the population PK analyses.

1.1.2 Are the sponsor's newly proposed doses (75 μg and 150μg QD) acceptable?

No. For COPD patients, there appeared to be clear dose-response relationship for trough FEV1 response after the first dose and 150 μg has a faster onset of action compared to 75 μg or lower doses. However, after two weeks of treatment, there was no obvious difference among 37.5 μg, 75 μg and 150 μg. Since indacaterol is targeting for the long-term maintenance effect and the safety concern for long-acting beta-against (LABA) is associated with higher doses, it is desirable to select the minimum maintenance dose with acceptable effectiveness to avoid potential safety concerns related to unnecessarily high doses. The sponsor's analyses at steady-state did not fully justify 75μg QD as a minimum effective dose and the sponsor's claim of additional benefit with 150 μg over 75 μg for more severe patients is not considered a robust finding.

1.1.2.1 Is 75 μg the minimum effective dose as a long-term maintenance regimen ?

Reference ID: 2905780

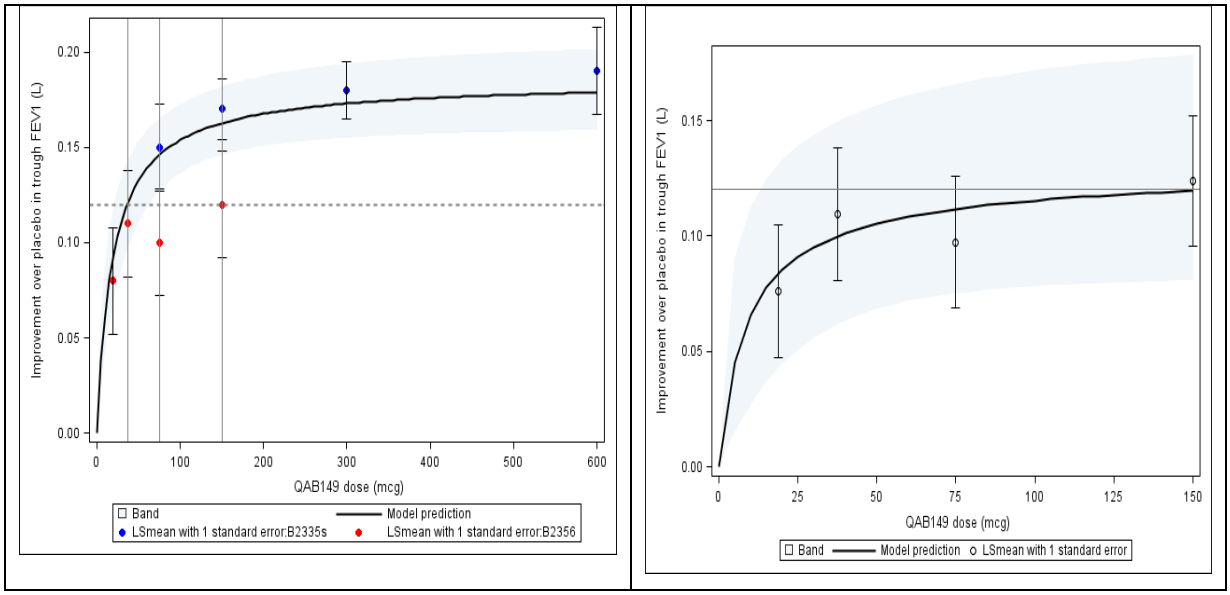
The sponsor updated the previous dose-response modeling by adding new studies and submitted a report titled 'Update of the bronchodilatory dose-response analysis of indacaterl in COPD' to justify their proposed doses. The analyses methods are similar to the previous report but two lower doses (18.75 μg and 37.5 μg) from new studies are added in the analyses, which resulted in better characterization of dose-response relationship. Two separate model-based methods were applied using Emax model; Bayesian meta-analysis and a non-linear mixed effect modeling (hereafter NLME). Lsmean contrasts to placebo with standard error for three different endpoints (trough FEV1, observed peak, peak average response (AUC0-4)) at each visit up to 26 weeks from 13 studies were collected and used in the Bayesian meta-analysis. For NLME analysis trough FEV1 on day 14 and 15 from two dose-ranging studies (CQAB149B2335S, CQAB149B2356; hereafter B2335S and B2356) were pooled and analyzed. Both analyses produced similar results.

The sponsor's model predicted that 75 μg just exceeds MCID of 0.12 L and 150 μg is located mid-way between the MCID and the maximum response whereas 37.5 μg is inferior to the MCID of 0.12 L. In addition to the dose-response analysis at steady-state, the sponsor assessed the relationship between dose and rate of onset by comparing trough FEV1 after the first dose and at steady state using meta analysis. The results (Figure 5, **Figure 6**) showed the clear dose-response relationship and that 150 μg has a fast onset of action, attaining about 75% of its steady-state trough FEV1 on the first dose whereas 75 μg has about 50%. Hence, the sponsor claimed that 75 μg provides clinically meaningful bronchodilation based on these all observation.

However, as shown in Figure 1(left panel), there is little difference in LSM between 37.5 μg (0.11 L) and 75 μg (0.10 L) within study B2356 (please notice that B2356 is the only study which includes 18.75 μg and 37.5 μg in COPD patients). Noticeable differences were observed between the two dose-ranging studies for the common doses studied (75 μg and 150 μg). More importantly, the sponsor's prediction was mainly driven by study B2335S and the covariates identified in the model could not explain the difference between the two studies. Hence, the reviewer reanalyzed the dose-response relationship with study B2356 only, and the result is shown in Figure 1(right panel). The reviewer's reassessment predicted that none of the doses (including 75 μg and 150 μg) in study B2356 could achieve FEV1 response above MCID of 0.12 L. Moreover, % maximum effect at both 37.5 μg and 75 μg are more than 80%, which are different from the sponsor's prediction (37.5 μg: 66%, 75 μg: 79%) based on the pooled analysis. The reviewer's analyses suggested that 37.5 μg achieved comparable FEV1 response as 75 μg within the same study. If 37.5 μg were included in other studies where 75 μg had larger effect size than that in study B2356, 37.5 μg would be expected to have larger effect size too. Since week 2 FEV1 responses were consistent with long term FEV1 responses (week 12) based on the original review of study 2335s, 37.5 μg appears to be the minimum effective dose for long-term maintenance treatment. To compensate for the slow onset of 37.5 μg, a higher loading dose, such as 150 μg, can be used for the initial 2 weeks. The combination of a high loading dose with a low maintenance dose will achieve the optimal effectiveness (fast onset and acceptable long-term effect) with the minimum chronic drug exposure to the patients.

Reference ID: 2905780

Figure 1. Model-predicted dose-response (trough FEV1) relationship. Left panel: the sponsor's analysis using pooled two studies with lsmean with standard error for each study. Right panel: the reviewer's analysis using the study of B2356 only.



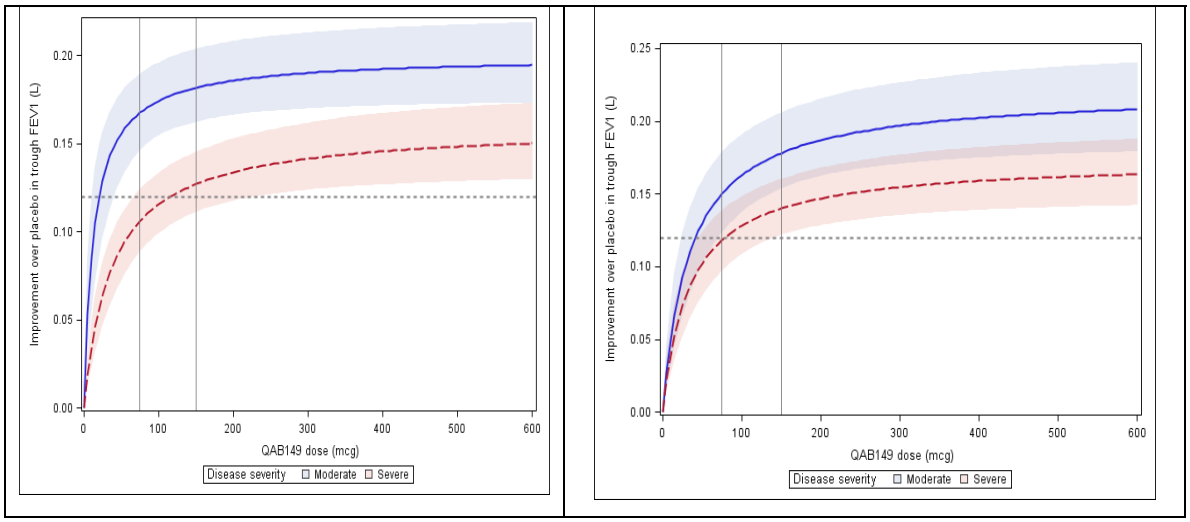
1.1.2.2 Is the sponsor's claim of additional benefit with 150 μg over 75 μg for more severe patients appropriate?

One of the sponsor's findings from NLME analysis is that baseline FEV1 was found to be a significant covariate for the maximum response and the dose that is required to achieve 50% of the maximum response. Figure 2 (left panel) shows the different predicted dose-response relationships between moderate and severe COPD patients from the sponsor's NLME analysis. The sponsor claimed that if 0.12 L is considered the MCID, 150 μg is necessary to exceed this threshold in severe patients, and therefore 150 μg provides additional benefit over 75 μg in more severe patients.

However, the reviewer observed that there is clear difference in observed dose-response profile between day 14 and 15. Since data from day 14 were not obtained under controlled condition, the reviewer excluded data on day 14 and fitted the same model as the sponsor's to the day 15 data only as a sensitivity analysis. Based on analysis using day 15 data only, baseline FEV1 was not found to be a significant covariate on ED50, which resulted in slightly different predicted lines by disease severity (Figure 2, right), and the dose of 75 μg appears to meet the MCID criteria (0.12 L) for severe patients also. Hence, the sponsor's claim of additional benefit with 150 μg for severe patients based on MCID of 0.12L is sensitive to the data used for analysis. It is not considered a robust finding by the reviewer.

Reference ID: 2905780

Figure 2. Predicted dose-response relationship for trough FEV1 at steady state for typical patient by COPD severity.



1.2 Recommendations

The Office of Clinical Pharmacology has reviewed the submission (NDA 22383) and has the following recommendation:

- Based on the observation of dose-response profile after two weeks (steady-state),
    - The sponsor's dose-response modeling analysis does not fully address minimum effective dose issue
    - The sponsor's claim with additional benefit with 150 µg over 75 µg for severe COPD patients is not considered as a robust finding
    - A better alternative regimen is a loading dose of 150 µg for 2 weeks followed by the long-term maintenance dose of 37.5 µg.

Reference ID: 2905780

2 PERTINENT REGULATORY BACKGROUND

This is the re-sbumission for NDA 22383. The doses proposed in the previous submission were 150 μg and 300 μg once daily (QD). FDA issued the complete response as the sponsor failed to identify the minimum effective dose and optimal dosing regimen. In this re-submission the sponsor is seeking the approval for indacaterol 75 μg and 150 μg QD for the treatment in patients with chronic obstructive pulmonary disease (COPD).

3 RESULTS OF SPONSOR'S ANALYSIS

The sponsor conducted population PK analysis to address the effects of covariates on indacaterol PK. Also the sponsor submitted an updated dose-response analysis to justify the proposed doses (75 μg and 150μg QD).

PK analysis

The updated population PK analyses included nine clinical studies by addition four additional new studies (CQAB149B1202, CQAB149B1302, CQAB149B2335SE, CQAB149B2331) to the previous five clinical studies (CQAB149A2228, CQAB149B2212, CQAB149B2334, CQAB149B2335S, CQAB149B2338).

Due to the limited data to support characterization of indacaterol absorption in the full nonlinear mixed effects modeling, an alternative linear mixed effects approach was used to investigate covariate effects on peak concentration (Cmax) and trough concentration (Cmin).

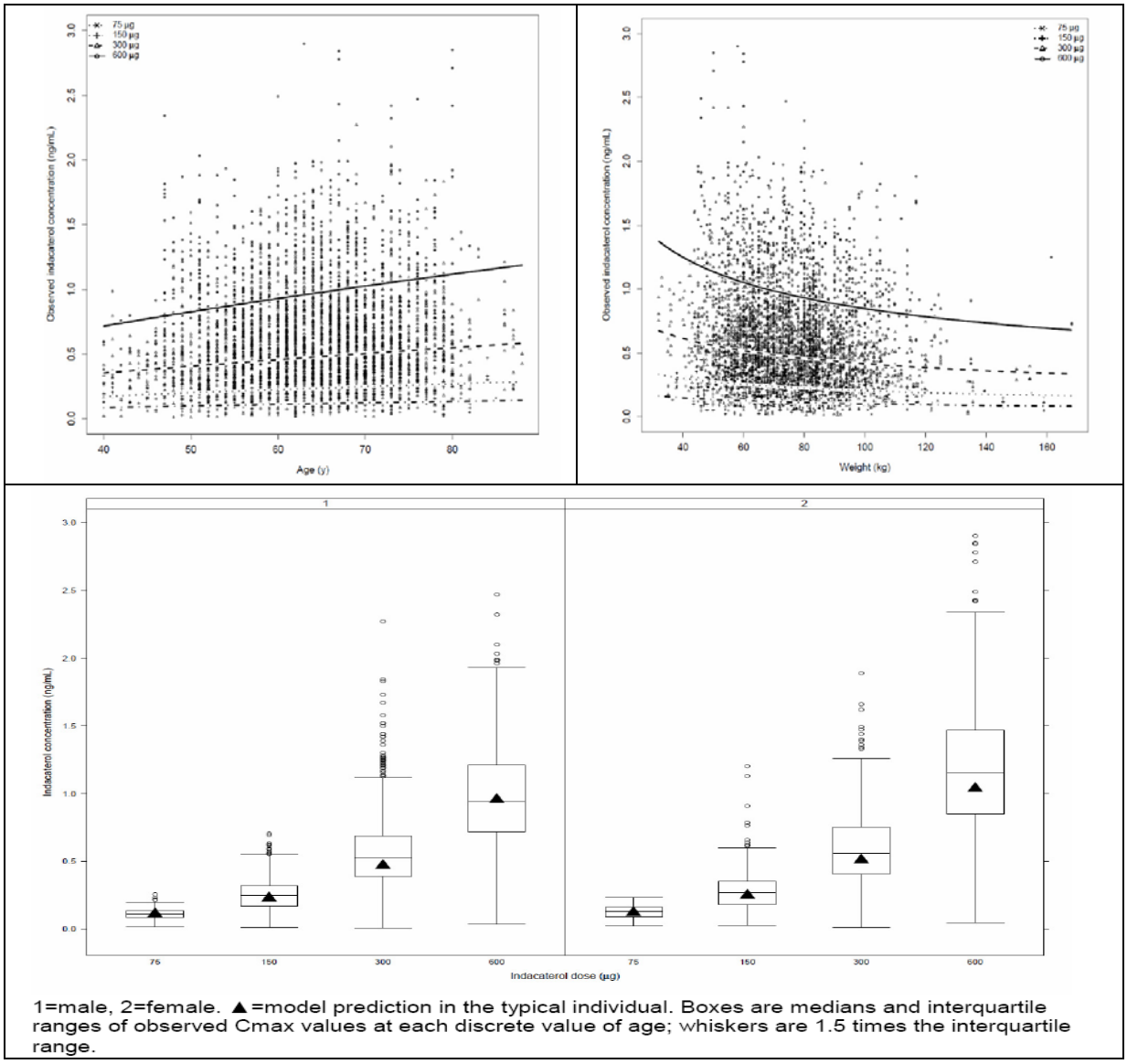
Figure 3 presents the effects of covariates at each dose level. The population PK analysis (linear mixed effects modeling) confirmed the previous findings of significant effects of weight, age and gender; Cmax increases with age, by 35% over the range of 49-78 years; Cmax in COPD patients decreases with body weight, by 28% over the range of 49-105kg; Cmax is an average of 7.6% greater in female COPD patients than in male patients. In addition to this, Cmax on average 17% and 25% higher in Korean and Japanese patients compared to the typical COPD patient. However, dose adjustment is not warranted based on these covariates as these covariates showed relatively small effects.

Figure 3. The effect of covariates(age, body weight, sex and ethnicity) on Cmax of indacaterol after 14 days of continuous dosing, by dose. The solid line represents the final

Reference ID: 2905780

Best Available Copy

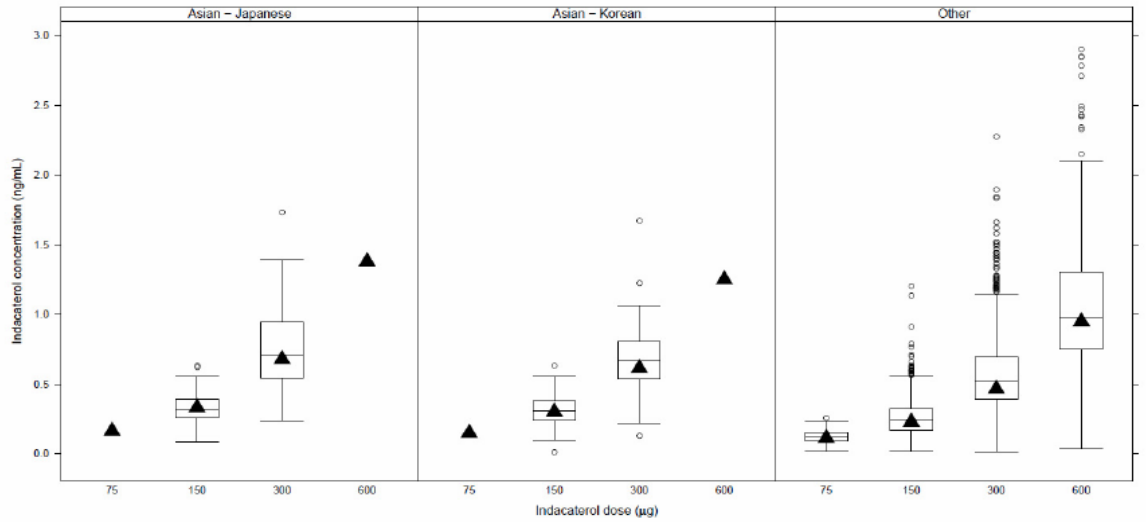
linear mixed effects model predicted peak concentration of indacaterol at steady state for each dose level with respect to age (top left) and body weight (top right).



1=male, 2=female. ▲=model prediction in the typical individual. Boxes are medians and interquartile ranges of observed Cmax values at each discrete value of age; whiskers are 1.5 times the interquartile range.

Reference ID: 2905780

Best Available Copy



▲=model prediction in the typical individual. Boxes are medians and interquartile ranges of observed Cmax values at each discrete value of age; whiskers are 1.5 times the interquartile range.

The "Other" panel represents the peak concentration of indacaterol by dose in non-Japanese, non-Korean COPD patients.

Source: the sponsor's report, page 35-38.

Reviewer's comments:
Sponsor's population PK analysis is acceptable.

Reference ID: 2905780

Dose-response analyses

The sponsor updated the previous dose-response modeling by adding new studies and submitted a report titled 'Update of the bronchodilatory dose-response analysis of indacaterl in COPD' to justify their proposed doses. The analyses methods are similar to the previous report but two lower doses from new studies are added in the analyses, which resulted in better characterization of dose-response relationship.

Two separate model-based methods were applied using Emax model; Bayesian meta-analysis and a non-linear mixed effect modeling (hereafter NLME).

The Bayesian meta-analysis included data from 13 studies in COPD patients; studies from previous analyses; CQAB149B2205, CQAB149B2212, CQAB149B2305, CQAB149B2334, CQAB149B2335S, CQAB149B2340 and CQAB149B2346; new studies; CQAB149B1302, CQAB149B2333, CQAB149B2336, CQAB149B2354, CAQB149B2344 and CQAB149B2356. LSmean contrasts to placebo with standard error at each visit up to 26 weeks were collected.

In terms of endpoint, three different endpoints were used for meta-analysis; trough FEV_1 (defined as the average of the FEV_1 measurements typically obtained around 23.25 h and 23.75 h post-dose), observed peak FEV_1 (0-4h, determined as the maximum FEV_1 value measured within the first 4 hours post-dose), peak average response (AUC0-4) which is AUC taken between 5min and 4 hour post-dose, standardized by dividing by 4 hour.

For NLME analysis, trough FEV1 on day 14 and 15 from two dose ranging studies (CQABB2335S, CQABB2356) were evaluated.

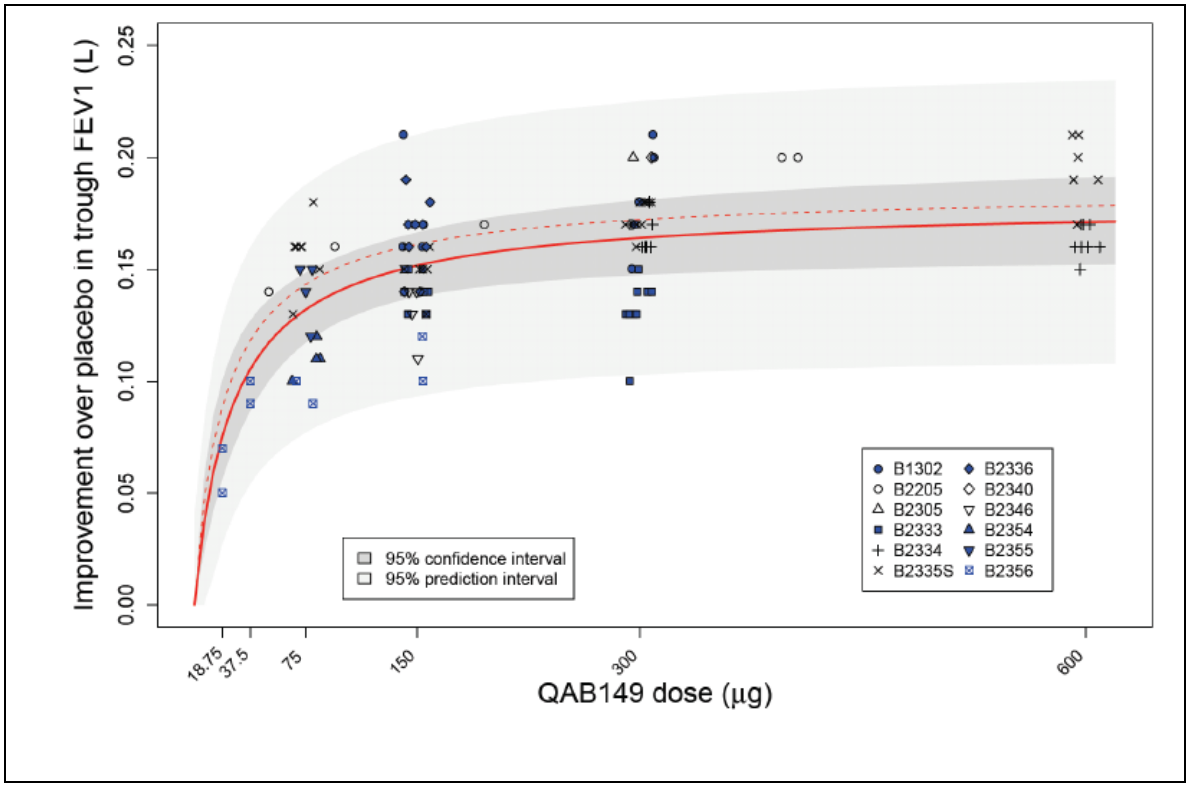
Table 1 summarized the parameter estimates from both meta-analysis and NLME analysis. Both analyses produced similar estimates; 75 μg corresponds to the ED74 and ED79 from meta-analysis and NLME analysis, respectively.
Figure 4 displays predicted dose-response relationship from both meta-analysis and NLME analysis with lsmean from the 13 studies. Model predicted that 75 μg just exceeds MCID of 0.12 L and 150 μg is located mid-way between the MCID and the maximum response whereas 37.5 μg is inferior to the MCID of 0.12 L.

Reference ID: 2905780

Table 1. The parameter estimates from meta-analysis and NLME analysis. The numbers in parenthesis indicate 95% CI.

	Meta-analysis			NLME analysis
	Trough FEV1	Peak average (AUC0-4)	Observed Peak FEV1	Trough FEV1
Emax	0.18 (0.16-0.20)	0.25 (0.21-0.30)	0.25 (0.20-0.30)	0.19 (0.16-0.21)
ED50	27 (12-46)	27 (11-49)	37 (13-70)	19 (10-36)
%max effect at 18.75µg	43 (29-60)	43 (28-63)	36 (21-60)	49 (34-65)
%max effect at 37.5µg	59 (45-75)	59 (43-78)	52 (35-75)	66 (51-79)
%max effect at 75µg	74 (62-86)	74 (60-87)	68 (52-86)	79 (67-88)
%max effect at 150µg	85 (77-92)	85 (75-93)	81 (68-92)	89 (80-94)
%max effect at 300µg	92 (87-96)	92 (86-97)	89 (81-96)	94 (89-97)
%max effect at 600µg	96 (93-98)	96 (92-98)	94 (90-98)	97 (94-98)

Figure 4. Prediction of dose response for trough FEV1 at steady state. The data points represent the least-squares means as determined for each visit and treatment arm of the respective study. The solid line and the inner and outer shaded areas represent the mean dose response curve, its 95% confidence interval and 95% prediction interval from meta-analysis, respectively. Also red dotted line is from NLME analysis.

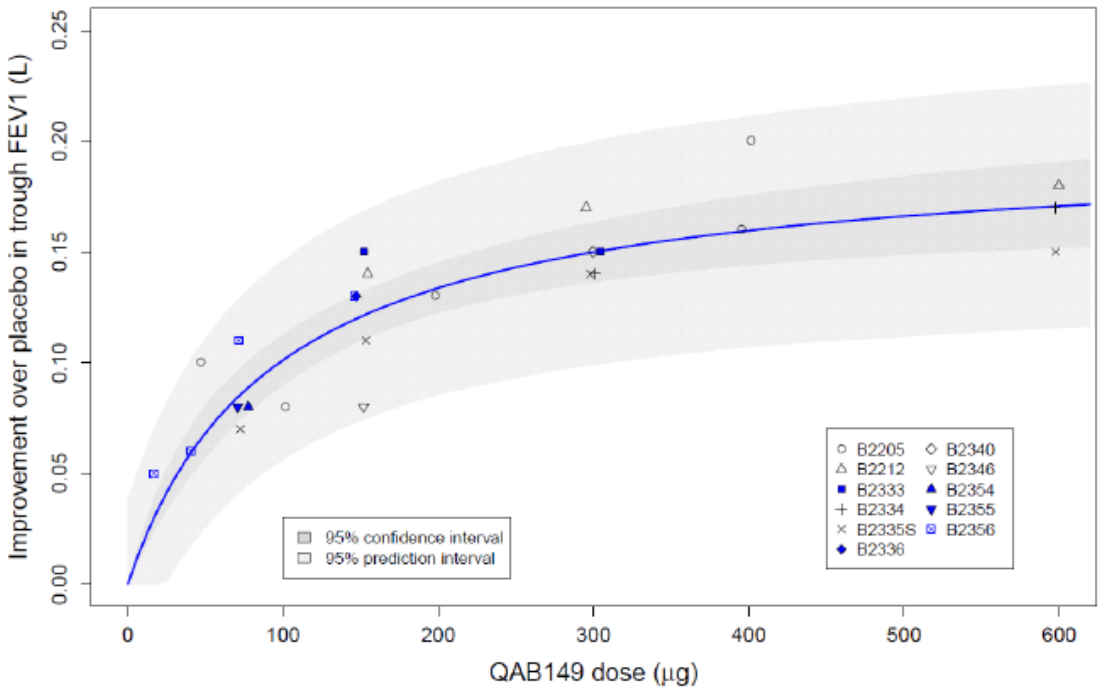


Source: the sponsor's report. Page 26

In addition to the dose-response analysis at steady state (after week 2), the dose-response (trough FEV1) profile after the first dose of indacaterol (day 2) was examined using the meta analysis. Figure 5 shows clear dose-response relationship even within the study of B2356. The sponsor assessed the rate of onset by comparing it with dose-response profile at steady state and the result is shown in **Figure 6**. The sponsor's analysis showed that 150 µg has a fast onset of action, attaining about 75% of its steady-state trough FEV1 on the first dose whereas 75 µg has about 50%.

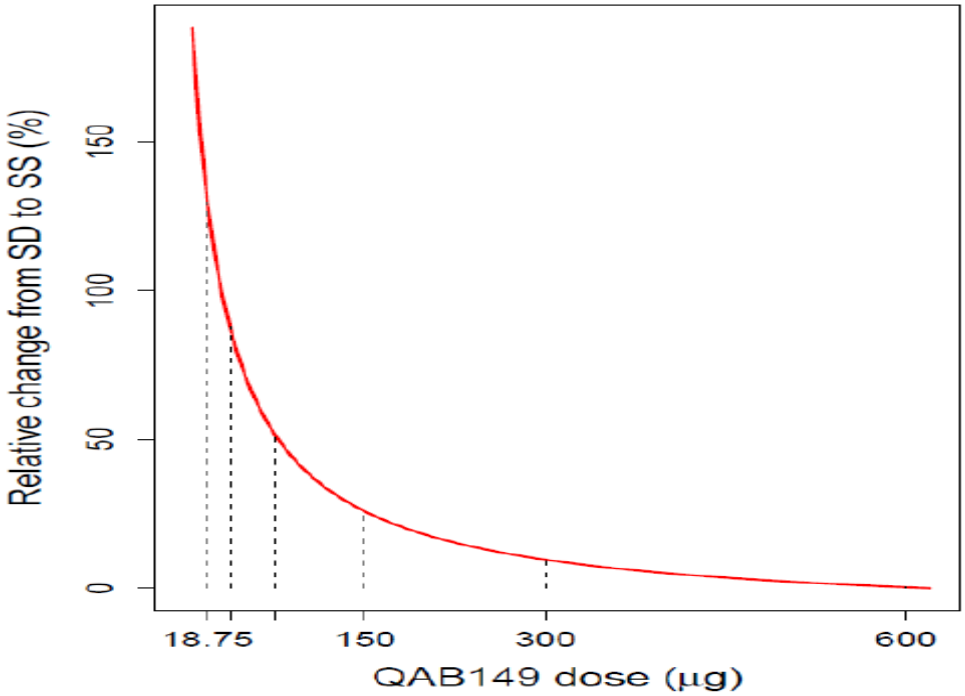
Figure 5. Predicted dose-response for trough FEV1 after first dose from the sponsor's meta analysis

Reference ID: 2905780



Source: the sponsor's report, page 28

Figure 6. Comparison of predicted dose-response for trough FEV1 after the first dose (SD) and at steady-state (SS) from meta-analysis.

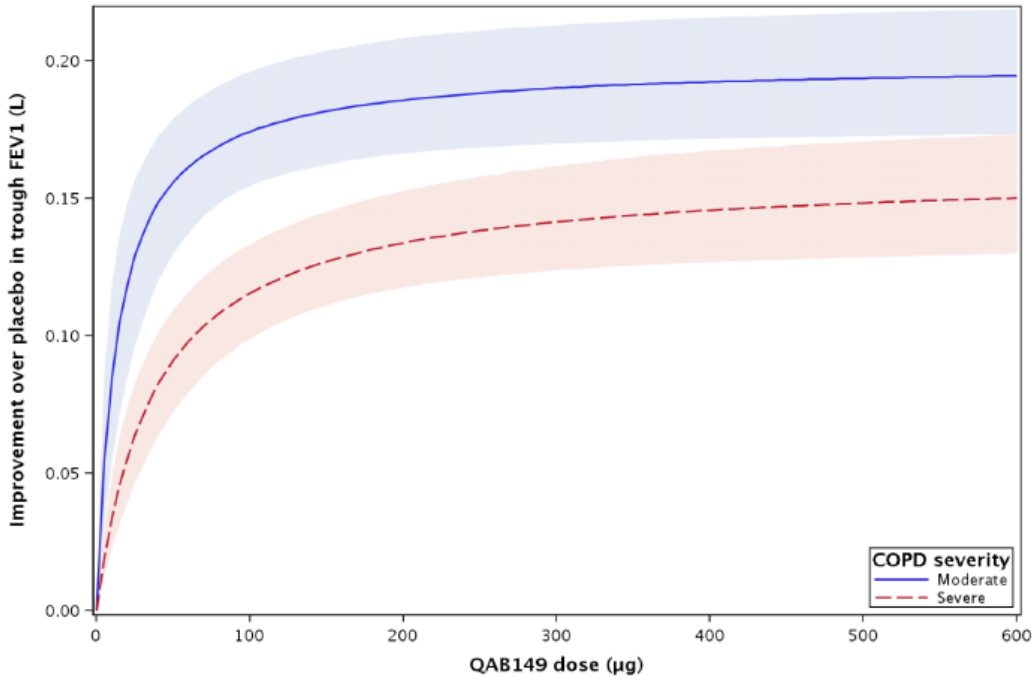


Source: the sponsor's report, page 29.

Reference ID: 2905780

One of the sponsor's findings from NLME analysis is that baseline FEV1 was found to be a significant covariate on ED50 as well as Emax, meaning that as baseline FEV1 increases, not only is the maximum response increased, but the dose required to attain it decreases. Figure 7 shows a clear separation in predicted dose-response relationship between moderate and severe COPD patients from the sponsor's NLME analysis. The sponsor claims that if 0.12 L is considered the MCID, 150 µg is necessary to exceed this threshold in severe patients, and therefore 150 µg provides additional benefit over 75 µg in more severe patients.

Figure 7. Predicted dose-response relationship for trough FEV1 at steady state for typical patient by COPD severity.



Source: the sponsor's report. Page 36

Reviewer's comments:

- *Based on the observation of dose-response profile after the first dose (day 2),*
  - *The reviewer agreed with the sponsor's claim of faster onset of action of 150* µg compared to 75 µg.
  - *The reviewer also observed clear dose-response relationship.*
- *Based on the observation of dose-response profile after two weeks,*
  - *The sponsor does not fully address the justification of 75*µg *as a minimum effective dose.*

Reference ID: 2905780

- *Within the study of B2356 there appears to be flat dose-response relationship 37.5* μg through 150 μg and none of doses in study B2356 could achieve FEV1 response above MCID of 0.12L

- *The sponsor's claim of additional benefit with 150* μg *over 75*μg for more severe patients is not considered as a robust finding

4 REVIEWER'S ANALYSES

4.1 Introduction

The sponsor' modeling results provided two important findings; 1) 75 μg is the lowest dose which provides clinically relevant bronchodilation (Bayesian meta-analysis, NLME analysis) 2) 150 μg may provide an additional benefit over 75 μg to severe COPD patients (NLME analysis). The sponsor's NLME analysis included data on day 14 as well as day 15 from pooled two dose –ranging studies (B2335S and B2356). However, the reviewer observed apparent difference in dose-trough FEV1 profile between two dose-ranging studies. More importantly, trough FEV1 on day 14 could have uncontrolled measurements, meaning that dosing on the previous day was not ensured to take place at the clinic as the sponsor also reported. Hence, the reviewer performed a sensitivity analysis whether the sponsor's claim can be supported without data on day 14. Also dose-response relationship was re-evaluated for the study of B2356 only to see whether 75 μg is a minimum effective dose or not because of a clear difference in FEV1 responses observed between the two studies.

4.2 Objectives

To re-analyze the data to see whether the sponsor's claims could be supported.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 2.

Table 2. Analysis Data Sets

Study Number	Name	Link to EDR
QABB2335s, QABB2356	Spider.xpt	

Reference ID: 2905780

4.3.2 Software

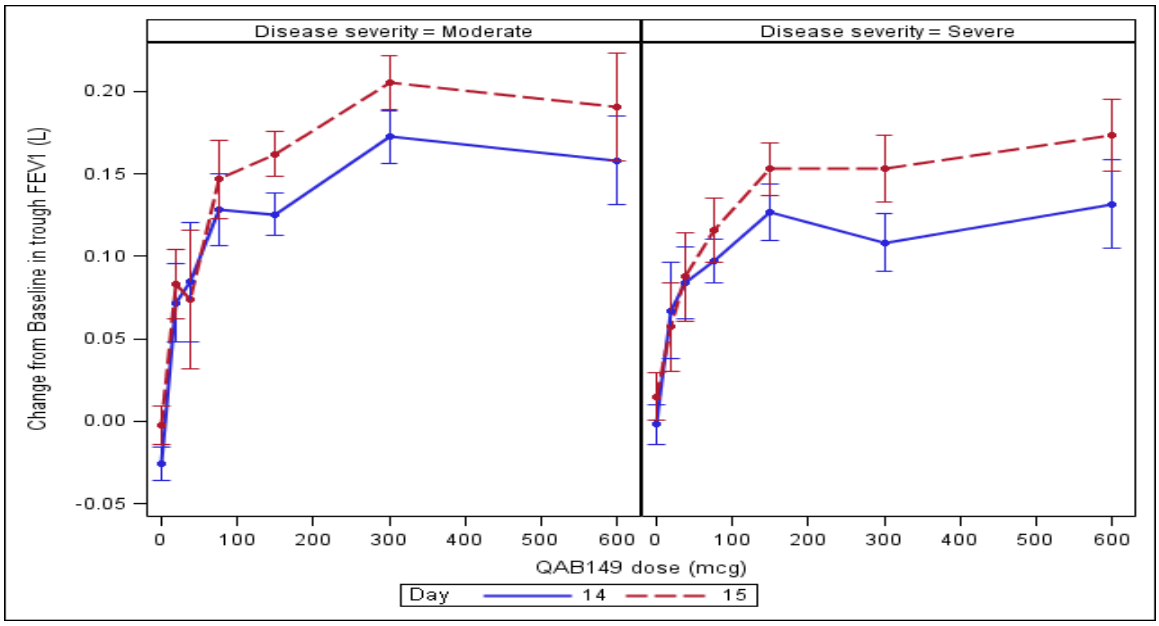
SAS 9.2 was used for the analysis.

4.3.3 Model Results

First, **Figure 8** presents the change from baseline in trough FEV1 from the observed data by disease severity at day 14 and 15, which clearly shows the difference in dose-response profile between day 14 and day 15. Since data from day 14 were not obtained under controlled condition, the reviewer excluded data on day 14 and fitted the same model as the sponsor's as a sensitivity analysis. Based on reanalysis using only day 15, baseline FEV1 was not found to be a significant covariate on ED50, which resulted in slight different predicted lines by disease severity (**Figure 9**), and the dose of 75 μg appears to meet the sponsor's MCID criteria (0.12 L) for severe patients also. Hence, the sponsor's claim of additional benefit with 150 μg for severe patients based on MCID of 0.12L is sensitive to the data used for analysis. It is not considered a robust finding by the reviewer.

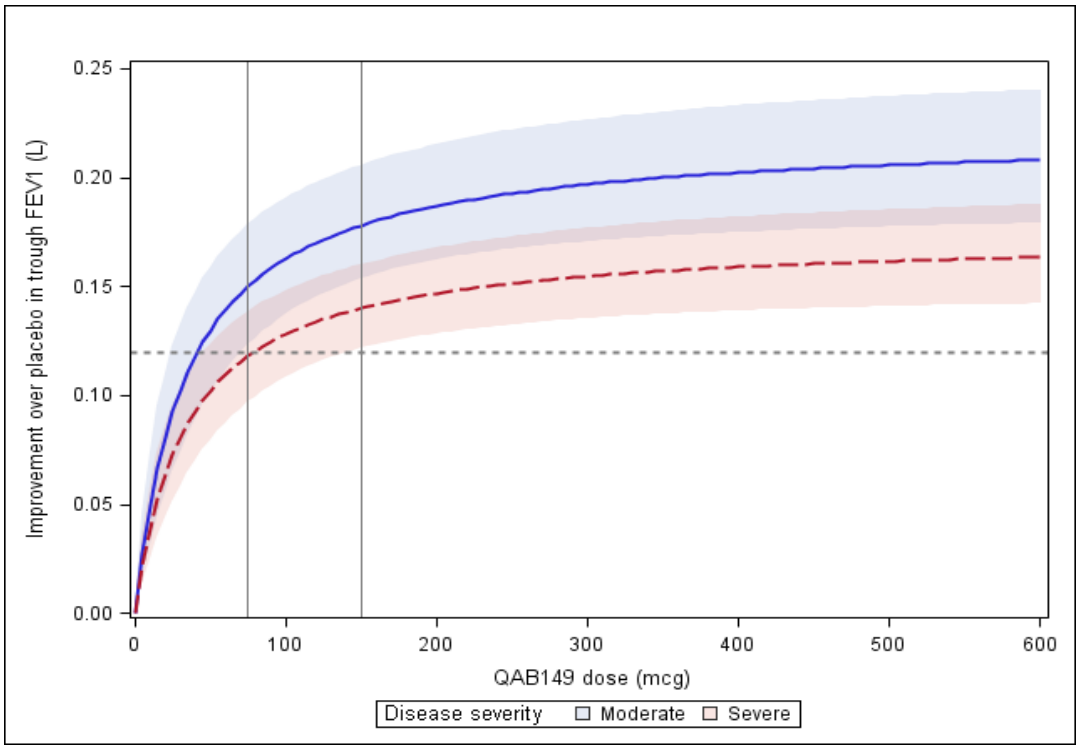
Reference ID: 2905780

Figure 8. Change from baseline in trough FEV1 from observed data by disease severity at each day 14 and 15.



Reference ID: 2905780

Figure 9. Model-predicted dose-response relationship from the reviewer's analysis using day 15 only.

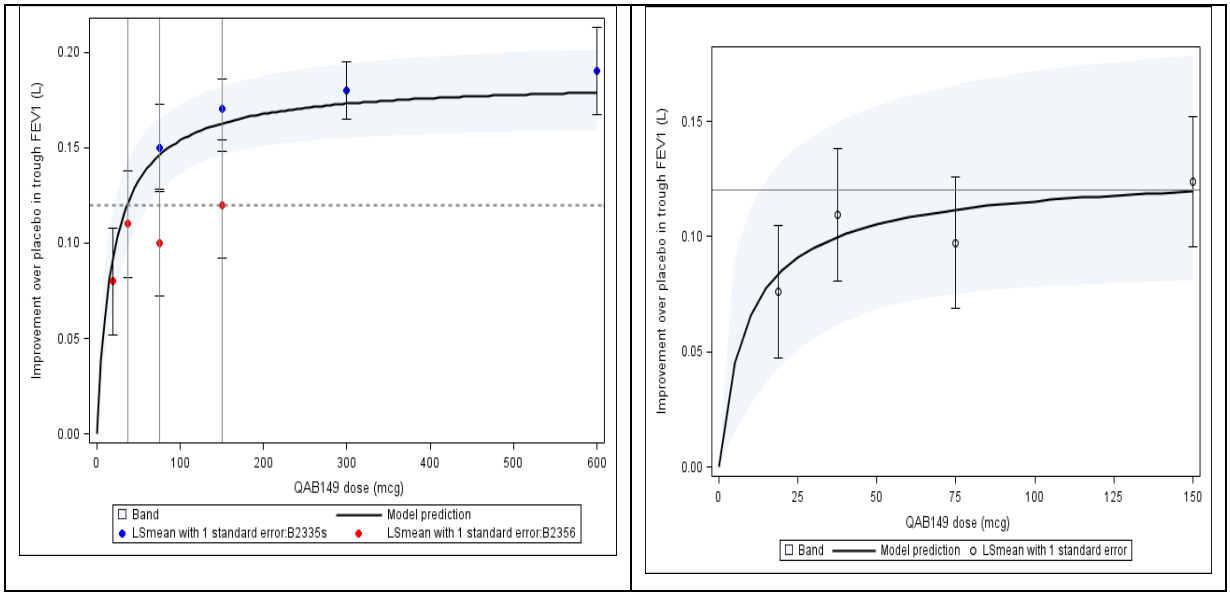


In order to evaluate whether the dose of 75 µg is a minimum effective dose as a next step, lsmeans from the studies of B2335S and B2356 were examined (Notice that the study of B2356 was the only study for COPD patients which includes lower dose than 75 µg). As shown in **Figure 10** (left panel), there is little difference in LSM between 37.5 µg (0.11 L) and 75 µg (0.10 L) within study B2356 (please notice that B2356 is the only study which includes 18.75 µg and 37.5 µg in COPD patients). Noticeable differences were observed between the two dose-ranging studies for the common doses studied (75 µg and 150 µg). More importantly, the sponsor's prediction was mainly driven by study B2335S and the covariates identified in the model could not explain the difference between the two studies. Hence, the reviewer reanalyzed the dose-response relationship with study B2356 only, and the result is shown in **Figure 10** (right panel). The reviewer's reassessment predicted that none of the doses (including 75 µg and 150 µg) in study B2356 could achieve FEV1 response above MCID of 0.12 L. Moreover, % maximum effect at both 37.5 µg and 75 µg are more than 80%, which are different from the sponsor's prediction (37.5 µg: 66%, 75 µg: 79%) based on the pooled analysis. The reviewer's analyses suggested that 37.5 µg achieved comparable FEV1 response as 75 µg within the same study. If 37.5 µg were included in other studies where 75 µg had larger effect size than that in study B2356, 37.5 µg would be expected to have larger effect size too. Since week 2 FEV1 responses were consistent with long term FEV1 responses (week 12) based on the original review of study 2335s, 37.5 µg appears to be the minimum effective dose for long-term maintenance treatment. To compensate for the slow onset of

Reference ID: 2905780

37.5 µg, a higher loading dose, such as 150 µg, can be used for the initial 2 weeks. The combination of a high loading dose with a low maintenance dose will achieve the optimal effectiveness (fast onset and acceptable long-term effect) with the minimum chronic drug exposure to the patients

Figure 10. Model-predicted dose-response (trough FEV1) relationship. Left panel: the sponsor's analysis using pooled two studies with lsmean with standard error for each study. Right panel: the reviewer's analysis using the study of B2356 only.



5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
NLME.SAS NLME_B2356.SAS	Reviewer's analyses modified from the sponsor's	

Reference ID: 2905780

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA Number	22,383
Submission Date	10/1/10
Applicant Name	Novartis
Generic Name	Indacaterol
Proposed Indication	Maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema
Primary Reviewer	Hobart Rogers, Pharm.D., Ph.D.
Secondary Reviewer	Mike Pacanowski, Pharm.D., Ph.D.

1 Background

Variable indacaterol exposure and response were noted during review of the original NDA. Potential sources of pharmacodynamic or pharmacokinetic variability include genetic variants of the drug target and drug metabolism enzyme(s), in addition to other patient-related factors. Indacaterol is metabolized by CYP3A, and the gene encoding *CYP3A5* has common polymorphisms that affect substrate metabolism. Additionally, the gene encoding the drug target, *ADRB2*, is known to have functional polymorphisms influence β_2-agonist responses in asthma, albeit inconsistently. Few studies have evaluated *ADRB2* pharmacogenetics in COPD patients. To the extent that genotype data could inform the dose- or exposure-response characteristics of indacaterol, the following recommendations were specified in the Complete Response letter sent to the sponsor on 10/16/2009:

1. Evaluate the ADRB2 polymorphisms as a possible source of underlying heterogeneity in response to indacaterol.
2. Evaluate the CYP3A5 polymorphism as a possible source of underlying pharmacokinetic variability of indacaterol.

2 Submission Contents Related to Genomics

The sponsor included a single report containing a summary of published literature and a pharmacogenetic substudy report based on a pooled analysis of indacaterol-treated subjects in trials CQAB149B2335S (150 mcg indacaterol qd, 300 mcg indacaterol qd, 18 mcg tiotropium qd, placebo qd) and CQAB149B2336 (150 mcg indacaterol qd, 50 mcg salmeterol bid, placebo bid).

3 Summary of Findings

3.1 ADRB2 Pharmacogenetics

Published literature

Published literature review conducted by the sponsor and reviewer identified three single-dose SABA response studies and one multiple-dose LABA response study. The key findings were as follows:

- 389 Caucasians (Boston) with severe COPD were given 2 puffs of inhaled albuterol and change in FEV1 was assessed. No effect of *ADRB2* genetic variation was seen. (Kim, et al 2009)
- 107 Caucasians (Slovakia) hospitalized for acute exacerbation of COPD were assessed for change FEV, PEF, FVC after salbutamol inhalation. No effect of *ADRB2* variation on response was seen. (Morky, et al 2008)
- 274 Japanese patients with COPD were assessed for change in FEV1 after salbutamol inhalation. *ADRB2* Arg16 homozygotes had worse improvement in FEV1 (with borderline significant p-values ~$0.005<p<0.05$ in the several models evaluated); the effect was inconsistent with that observed in the asthma field. (Hizawa, et al 2007)
- FEV changes were assessed following 12 weeks of salmeterol+steroid in 104 Korean patients with COPD. No impact of *ADRB2* genetic variation was observed.

Indacaterol Clinical Database: Pharmacogenetic Methods and Results

To assess whether key common *ADRB2* genetic variants are associated with differential response to daily indacaterol treatment in COPD patients at weeks 12 (and 26), the applicant conducted a pooled analysis of indacaterol-treated subjects (n=626 for primary endpoint analysis) for the pivotal trials CQAB149B2335S and CQAB149B2336. Both trials were 26 weeks in length and evaluated trough FEV1 at week 12 as their primary endpoints. The following SNPs were assayed: Arg16Gly, Gln27Glu, Thr164Ile, -47bp 5' C>T using Taq-Man allelic discrimination or sequencing. These SNPs were evaluated for association with 24-hour post-dose FEV1 at 12 weeks (primary trial endpoint) and 26 weeks, COPD exacerbations over 26 weeks, change in morning PEF over 26 weeks, and TDI score after 26 weeks. The primary analysis assumed an additive genetic model; Gly16Arg was tested using dominant and recessive models. Subgroup testing was performed based on smoking-status, prior β-agonist use, corticosteroid use, airflow limitation reversibility. Analyses adjusted for clinical- and protocol-related factors (e.g., race, country, dose, trial, baseline value of tested endpoint, center, SABA and anticholinergic reversibility). The Bonferroni-corrected p-value for statistical significance assuming 216 tests was set at 0.0002.

Genotype data were available for >97% of the assayed samples. Gln27Glu and -47bp 5' C>T were not in Hardy-Weinberg equilibrium (unclear if performed by race/ethnicity). Gln27Glu and -47bp 5' C>T were in linkage disequilibrium ($r^2=0.99$). DNA study participants were reported to be clinically similar to patients not providing DNA. No nominally significant ($p<0.05$) pharmacogenetic relationships were observed for any of the endpoints in the overall population. No significant or consistent effects across any of the SNPs, endpoints, or subgroups were identified. The primary analysis results for trough FEV1 at 12 weeks are shown in the table below.

	SNP model					
	SNP156 minor allele dose	SNP156 minor allele recessive	SNP156 minor allele dominant	SNP27 minor allele dose	SNP155 minor allele dose	SNP2946 minor allele dose
Patient subset						
All QAB recipients	0.89	0.78	0.99	0.35	0.87	0.40
Ex-smokers	0.26	0.37	0.36	0.75	0.70	0.75
Current smokers	0.29	0.52	0.30	**0.04**	0.93	0.06
Prior regular-BA users	0.73	0.77	0.49	0.48	0.44	0.69
No regular BA use	0.95	0.45	0.62	0.82	0.61	0.84
Inhaled corticosteroid recipients	0.97	0.83	0.93	0.59	0.74	0.79
No inhaled corticosteroids	0.96	0.99	0.93	0.77	0.98	0.60
Reversible airflow limitation	0.37	0.69	0.13	0.93	0.98	0.91
Non-reversible limitation	0.85	0.16	0.20	0.80	0.81	0.74

Nominally significant relationships (P<0.05) were as follows: FEV1 at 12 weeks and Gln27Glu in current smokers (P=0.04); COPD exacerbation and Thr164Ile in non-reversible airflow limitation (P=0.004); morning PEF and Gly16Arg (dominant) in reversible airflow limitation (P=0.02). Several trends were noted for *ADRB2* genotype relationships and TDI, as shown in the following table.

Table 9-4 PG Results (p-values) for TDI at 26 weeks

	SNP model					
	SNP156 minor allele dose	SNP156 minor allele recessive	SNP156 minor allele dominant	SNP27 minor allele dose	SNP155 minor allele dose	SNP2946 minor allele dose
Patient subset						
All QAB recipients	0.06	0.08	0.18	0.02	0.53	0.05
Ex-smokers	0.07	0.32	0.08	0.01	0.17	0.03
Current smokers	0.50	0.31	0.86	0.40	0.94	0.47
Prior regular-BA users	0.15	0.25	0.21	0.12	0.10	0.29
No regular BA use	0.31	0.47	0.37	0.25	0.38	0.28
Inhaled corticosteroid recipients	0.01	0.0012	0.15	0.01	0.73	0.02
No inhaled corticosteroids	0.95	0.54	0.58	0.45	0.75	0.49
Reversible airflow limitation	**0.0007**	0.03	0.0013	0.0013	0.99	0.0036
Non-reversible limitation	0.33	0.54	0.35	0.84	0.18	0.97

3.2 CYP3A5 Pharmacogenetics

The sponsor did not conduct pharmacogenomic studies to investigate *CYP3A5* genotype effects on indacaterol pharmacokinetics. Rather, the sponsor cited previously conducted *in vitro* and DDI studies. *In vitro* studies with recombinant CYP3A4 and CYP3A5 preparations indicated that CYP3A4 was far more effective in metabolizing indacaterol compared to CYP3A5. Furthermore, ketoconazole (strong CYP3A4 inhibitor) resulted in a doubling of indacaterol AUC

levels, thus they concluded that the sole contribution of *CYP3A5* variants were likely to be of minimal significance.

4 Conclusions

- *ADRB2* genotype was not associated with the primary trial endpoint in the overall population. Additionally, no robust and consistent associations were detected across the secondary endpoints, SNPs or subgroups. The sponsor's justification for the minor role of *CYP3A5* is reasonable.
- Subject-level data were not available for analysis. Descriptive statistics were not provided by the sponsor for the genotypic subgroups. However, screening for associations based on the reported p-values is sufficient to make a determination on the relevance of *ADRB2* variants on indacaterol response.
- *ADRB2* haplotype analysis was not conducted. However, a large and robust pharmacogenetic interaction would likely be evident in testing individual SNP associations.
- Considering the potential relatedness of the endpoints and linkage disequilibrium between SNPs, a less conservative multiplicity correction may be more appropriate. Even at a P-value of 0.0125 (i.e., testing of 4 endpoints) no robust associations were apparent in the overall population.
- Subgroup testing of genotype effects increases the potential for spurious findings because of multiplicity. Trends toward significance were noted for changes in TDI at 26 weeks in inhaled corticosteroid recipients and those with reversible airflow limitation. The associations were consistent across the SNPs suggesting that the association is plausible.
- Placebo data were not analyzed, limiting the ability to draw conclusions regarding treatment x genotype interactions (e.g., if genotype modulates disease progression in untreated patients, or treatment masks genetic effects).

5 Recommendations

The Genomics Group has reviewed the NDA resubmission for indacaterol in the treatment of COPD. Overall, it appears as if the *ADRB2* polymorphisms do not play a significant role in indacaterol response variability. The sponsor's response to the previous recommendations is satisfactory from the perspective of the Genomics Group and no additional action is indicated.

5.1 Post-marketing studies

None.

5.2 Label Recommendations

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YING FAN
02/15/2011

JOO YEON LEE
02/15/2011

HOBART ROGERS
02/15/2011

YANING WANG
02/15/2011

MICHAEL A PACANOWSKI
02/15/2011
Concur

YUN XU
02/15/2011

SECONDARY REVIEWER MEMORANDUM

NDA:	22-383
Proprietary Drug Name:	ARCAPTA NEOHALER
Generic Name:	Indacaterol Maleate Inhalation Powder
Indication:	Treatment of Chronic Obstructive Pulmonary Disease
Dosage Form:	Dry Powder Inhaler
Strength:	150 μg, 300 μg
Route of Administration:	Oral Inhalation
Applicant:	Novartis
Clinical Division:	DPAP (HFD-570)
Submission Dates:	December 15, 2008; April 2, 2008
Clinical Pharmacology Reviewers:	Sandra S. Sharp Ph.D., Ying Fan, Ph.D.
Team Leader (Acting):	Dakshina Chilukuri, Ph.D.
Pharmacometric Reviewer:	Joo Yeon Lee, Ph.D.
Pharmacometrics Team Leader:	Yaning Wang, Ph.D.
Pharmacogenomics Reviewer:	Mike Pacanowski, Pharm.D., M.P.H.
Pharmacogenomics Team Leader:	Issam Zineh, Pharm.D., M.P.H

1. EXECUTIVE SUMMARY

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCPII) has reviewed NDA 22-383 submitted on December 15, 2008. The primary review for the NDA was performed by Dr. Sandra S. Sharp and her review dated 08/24/09 can be located in DAARTS. This secondary reviewer memo is to provide clarification on "Section 1.1 Recommendation". Dr. Sharp mentioned on her review the following under Section 1.1:

"The Office of Clinical Pharmacology/ Division of Clinical Pharmacology II (OCP / DCPII) has reviewed NDA 22-383 submitted on December 15, 2008. We found this NDA submission NOT acceptable from a CPB standpoint. The sponsor has not adequately characterized the dosing regimen for Arcapta Neohaler for the treatment of COPD. Lower doses of Arcapta showed similar efficacy profiles than that for the proposed dosing regimen of 150 μg QD. Given the local safety concerns (loss of bronchoconstriction/disease exacerbation) linked to this class of drugs (LABA) the evaluation of lower doses is needed to ensure the safety of the drug. Labeling revisions will not be entertained in this review cycle since this submission will receive a complete response action by DPAP."

A clarification to the above paragraph is provided below.

The sponsor has submitted several clinical pharmacology studies in support of their application. Upon review of the information provided by the sponsor, the review team agreed that the sponsor

has adequately characterized the clinical pharmacology of Arcapta (indacaterol). No additional clinical pharmacology studies are being requested from the sponsor during this review cycle. However, as noted by Dr. Sharp, the sponsor has not adequately characterized the dosing regimen for Arcapta Neohaler for the treatment of COPD. Lower doses of Arcapta Neohaler were found to show similar efficacy profiles compared to the proposed dosing regimen of 150 µg QD.

Final version signed by Dakshina Chilukuri, Team leader (acting)

cc

OCP	Sahajwalla, Dodappaneni, Chilukuri, Sharp
HFD-570:	Chowdhury, Durmowicz, Wu, Hill, Chilukuri, Sharp

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	INDACATEROL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAKSHINA M CHILUKURI
09/09/2009

YANING WANG
09/09/2009

CLINICAL PHARMACOLOGY REVIEW

NDA:	22-383
Proprietary Drug Name:	ARCAPTA NEOHALER
Generic Name:	Indacaterol Maleate Inhalation Powder
Indication:	Treatment of Chronic Obstructive Pulmonary Disease
Dosage Form:	Dry Powder Inhaler
Strength:	150 µg, 300 µg
Route of Administration:	Oral Inhalation
Applicant:	Novartis
Clinical Division:	DPAP (HFD-570)
Submission Dates:	December 15, 2008; April 2, 2008
Clinical Pharmacology Reviewers:	Sandra S. Sharp Ph.D., Ying Fan, Ph.D.
Team Leader (Acting):	Dakshina Chilukuri, Ph.D.
Pharmacometric Reviewer:	Joo Yeon Lee, Ph.D.
Pharmacometrics Team Leader:	Yaning Wang, Ph.D.
Pharmacogenomics Reviewer:	Mike Pacanowski, Pharm.D., M.P.H.
Pharmacogenomics Team Leader:	Issam Zineh, Pharm.D., M.P.H

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology II (OCP / DCPII) has reviewed NDA 22-383 submitted on December 15, 2008. We found this NDA submission NOT acceptable from a CPB standpoint. The sponsor has not adequately characterized the dosing regimen for Arcapta Neohaler for the treatment of COPD. Lower doses of Arcapta Neohaler showed similar efficacy profiles compared to the proposed dosing regimen of 150 μg QD. Given the safety concerns (loss of bronchoconstriction/disease exacerbation) linked to this class of drugs (Locally Acting beta-Agonists, LABA), evaluation of lower doses of indacaterol is needed to ensure the safety of the drug. Labeling revisions will not be provided in this review cycle since this submission will receive a Complete Response action by the DPAP.

1.2 Phase IV Commitments

None

1.3 Comments to be conveyed to the sponsor

- You have not adequately characterized the dosing regimen for Arcapta Neohaler for the treatment of COPD. Lower doses of Arcapta showed similar efficacy profile compared to the proposed dosing regimen of 150 μg QD. Given the local safety concerns linked to this class of drugs, evaluation of lower doses is needed to improve the benefit/risk ratio of the drug.

- The drug target gene, *ADRB2*, has functional polymorphisms that affect β_2-agonist responses. In addition, indacaterol may be metabolized by CYP3A5, which is also genetically polymorphic. You should explore exposure and response according to *ADRB2* and *CYP3A5* genotype using previously collected DNA samples to assess their contribution to response variability.

1.4 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Arcapta Neohaler (Inhalation Powder) contains (R)-indacaterol maleate, a selective beta$_2$-adrenergic bronchodilator. Arcapta is proposed for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Arcapta is available in two strengths: 150 μg or 300 μg of indacaterol (equivalent to 194 μg or 389 μg of indacaterol maleate, respectively) with approximately 25 mg of lactose monohydrate as the carrier. The proposed dosage of Arcapta is once-daily inhalation of the content of one 150 μg Arcapta capsule using the inhalation device. The maximum dose is 300 μg once-daily. The doses evaluated on clinical pharmacology studies ranged from 50 μg to 2000 μg (single dose) and 75 μg to 600 μg (multiple dosing).

The efficacy and safety of Arcapta Neohaler in patients with COPD was primarily assessed in one seamless, adaptive design, phase 2/3 trial and in two phase 3 clinical trials enrolling a total of about 2000 patients and ranging in duration from 12 to 52 weeks. The primary efficacy endpoint was 24h post-dose (trough) FEV1 (forced expiratory volume in one second) after 12 weeks treatment. The doses evaluated in these trials were 75, 150, 300, and 600 μg QD.

In support of this submission, the sponsor included the results from 36 clinical studies that contain pharmacokinetic information collected from healthy volunteers (14 studies), patients with COPD (10 studies), and asthma patients (12 studies). In these studies indacaterol was administered via the inhaled route using either single dose dry powder inhaler (SDDPI) devices, a pressurized metered dose inhaler (pMDI) device, or a multi dose dry powder inhaler (MDDPI) device. The development of the pMDI and

the MDDPI was discontinued and the device used in the to-be marketed formulation is an SDDPI variant called Concept1.

Pharmacokinetic data after inhalation of indacaterol via Concept1 was collected in studies in healthy subjects and patients with COPD and in studies in asthmatic patients. The studies conducted in asthma patients (12 studies) were not reviewed as part of this submission because of their lack of relevance on the approval of this NDA for COPD. There were four studies conducted in healthy volunteers to assess drug-drug interactions (DDI), Study A2311 (ketoconazole Study), Study B2216 (verapamil Study), Study B2220 (erythromycin Study), and Study (mometasone study). Special populations were investigated in Study A2307 which studied hepatic impairment and Study A2221 which investigated UGT1A1 genotype. Ethnic differences between Japanese and Caucasian subjects were addressed in healthy subjects (Study A2215). Information about the effect of covariates (such as age, gender, body weight, body mass index and race) on the PK of indacaterol were investigated using a population PK modeling approach with pooled pharmacokinetic data from Studies B2212, A2228, B2334, B2335S, and B2338. Dose-response was evaluated in three single/multiple dose studies (Studies B1212, B2205, and B2335S). The characterization of the effects of indacaterol on the QT-interval (thorough QT-Study B2339) was conducted in 404 healthy subjects. According to the sponsor, because renal clearance plays a very minor role in elimination of indacaterol a study in renally impaired subjects was not conducted. Information regarding protein binding, metabolism and inhibition of CYP enzymes was also reviewed. A summary of the clinical pharmacology findings is presented below.

Pharmacokinetics in Healthy Volunteers

Single Dose

Following inhalation of indacaterol 150 µg using the Concept1 device (to be-marketed formulation), Cmax values of indacaterol were generally observed within 0.25 hours post-dose. Mean Cmax and $AUC_{0-24hrs}$ values were 253 ± 120 pg/mL and 1202 ±554 pg*hr/mL, respectively. The absolute bioavailability of indacaterol following inhalation was about 43%. Oral bioavailability of indacaterol was about 46% of that after inhalation. Dose proportionality over the entire dose range of 150 µg to 600 µg was demonstrated for peak exposure (Cmax). AUC values were nearly proportional to the dose in the range of 150 µg to 600 µg.

Repeat Dose

Mean trough concentrations increased from 20.2 pg/mL to 105.1 pg/mL in the 150 µg dose group, from 45.3 to 216.9 pg/mL in the 300 µg dose group, and from 84.9 to 399.0 pg/mL in the 600 µg dose group, between Day 2 and Day 14 following multiple dose administration of indacaterol via Concept 1. In all treatment groups, the trough concentrations were similar on Day 12 and Day 14 and the Day14/Day12 mean ratios were close to unity (between 1.03 and 1.09) indicating that steady-state was achieved by Day 12. Cmax increased 1.85-, 1.79- and 1.65-fold and $AUC_{0-24hrs}$ increased 3.48-, 3.22-, and 2.93-fold in the 150 µg, 300 µg and 600 µg dose groups, respectively. Dose proportionality over the entire dose range of 150 µg to 600 µg was demonstrated for Cmax and $AUC_{0-24hrs}$

The Cmax and $AUC_{0-24hrs}$ of the major metabolites QAZ033 (metabolites P26.9 + P30.3) was approximately 7% and 11% of those for indacaterol.

Distribution

Following inhalation of indacaterol in COPD patients and healthy subjects, measurable plasma concentrations of indacaterol were observed in the systemic circulation within 5 minutes post-dose. After intravenous infusion the volume of distribution (V_z) of indacaterol was 2,557 L. *In vitro* blood distribution and plasma protein binding of indacaterol were independent of concentration over the tested

concentration range of 1-2000 ng/mL. The fraction of indacaterol distributed to red blood cells ranged from 0.499-0.584 in humans. The plasma protein binding of the compound in humans, determined by ultracentrifugation, ranged from 95.1-96.2. The *ex vivo* serum protein binding of indacaterol in healthy subjects was similar to that observed *in vitro* as well as in hepatically impaired subjects.

Elimination

The CL/F and half-life of indacaterol 150 μg following multiple dose administration via Concept1 inhalation device averaged 45.1 (24.2) L/h and 49.1 h (17.3), respectively. In a radiolabeled mass-balance study, the overall mean total recovery of radioactivity in feces and urine was 85.3 % (± 7.6%) and 9.7 % (± 3.7%) of the dose, respectively. The majority of the dose in the feces was recovered as unmodified indacaterol (54.4 ± 20.9%) with a significant portion also being recovered in the form of the oxidative metabolites P26.9 and P30.3 (23.8 ± 11.4%). The portion of the dose recovered in the urine was distributed between multiple metabolites and unchanged parent drug. In serum, the largest contributor to the exposure ($AUC_{0\text{-}24hrs}$) was indacaterol (32.5%). Metabolites contributing to the serum exposure included P19 (5.8%, P26.9 (12.4%) and P37 (4.2%) P37.7, P38.2, and P39 co-eluted in the serum radiochromatogram but together contributed 12.9% to the $AUC_{0\text{-}24hrs}$.

In vitro studies with indacaterol using recombinant human cytocrome P450 enzymes and recombinant human UGT enzymes showed that the key enzymes responsible for metabolic clearance of indacaterol are UGT1A1 and CYP3A4. Indacaterol was primarily metabolized in human liver microsomes to the inactive metabolite phenolic o-glucuronide (P37), followed by formation of minor monooxygenation products, P26.9 and P30.3. In addition, indacaterol did not inhibit the major CYP450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. Indacaterol is a low affinity (Km>150 μM) substrate for the efflux pump P-gp. The potential of indacaterol/major metabolites to induce drug metabolizing enzymes is considered negligible based on the low indacaterol serum concentrations (2.2 nM) observed in humans compared to the EC50 levels that are known for typical enzyme inducers.

Pharmacokinetics in COPD Patients

Indacaterol AUC values across doses in COPD patients were about 16% to 20% lower than that observed in healthy volunteers.

Pharmacokinetics in Special Populations

Based on population PK analysis, weight, age, and gender were found to be significant factors for CL/F (% change was less than 50% across covariates). Dose adjustment on the basis of these covariates may not necessary given that safety has been demonstrated in doses of up to 600 μg QD and that dose-response (efficacy) relationship is shallow. Based on a dedicated single dose study, the systemic exposure (AUC) in healthy Japanese was about 15% lower than that observed in healthy Caucasians.

Nonsignificant trends toward higher C_{max} and $AUC_{0\text{-}24hrs}$ (19% and 20%, respectively) were noted in patients with the (TA)7 genotype.

Renal Impairment

The effect of renal impairment on the PK of indacaterol and its metabolites was not evaluated. Renal clearance of serum indacaterol was on average between 0.5 and 1.2 L/h in healthy subjects and COPD patients. After inhaled administration of indacaterol, generally less than 2% of the inhaled dose was excreted into urine.

Hepatic Impairment
Following single dose administration of indacaterol 600 µg via the Concept1 device to mild, moderate hepatic impairment patients and matching controls, the ratio of geometric means (90% CI) for mild impairment/control were 1.012 (0.72-1.42) and 0.978 (0.67-1.43) for $AUC_{0\text{-}24hrs}$ and Cmax, respectively. The ratio of geometric means (90% CI) for moderate impairment/control were 0.948 (0.67-1.33) and 0.772 (0.53-1.13) for $AUC_{0\text{-}24hrs}$ and Cmax, respectively. Dose adjustment is not necessary due to the relative small changes observed in PK. The effect of severe hepatic impairment on the PK of the drug and its major metabolites was not evaluated.

Drug/Drug Interactions (DDI)
Concomitant administration of Arcapta with ketoconazole, verapamil or erythromycin increased the systemic exposure of indacaterol by less than 2-fold. Concomitant administration with mometasone increased the systemic exposure of indacaterol by 41%. Indacaterol did not alter the PK of mometasone. Dose adjustment of the basis of concomitant administration with these drugs is not necessary.

Dose-Response Relationships
The results of 3 dose-ranging studies showed a numeric trend for the higher doses tested to produce a bigger response in through FEV1; however a clear dose-ordering response was not observed following either single dose (150 µg to 600 µg) or multiple dose (50 µg to 600 µg) of once a day administration of indacaterol inhalation powder. Based on the results of the pivotal dose-finding study, the mean differences with respect to placebo in trough FEV1 were 0.15 L, 0.18 L, 0.21 L and 0.20 L for indacaterol 75, 150, 300, and 600 µg, respectively. Since the dose selection guideline was based on the values of the adjusted mean contrasts given by these analyses but did not use the associated p-values, there were no p-values presented. However, looking into the means for treatment differences and 95% intervals it is apparent that statistical significance was not achieved between adjacent treatment (e.g. 75 µg vs. 150 µg: LS means difference = 0.03 95% CI=-0.05 to 0.06).

The majority of systemic adverse events reported appeared not to be related to indacaterol dose given once a day in the range of 50 µg to 600 µg. Data from one dose-finding study showed that cough occurred at a higher frequency in the active drug treatment groups compared to placebo (2.9-12.4% vs. 0.9%) with evidence that this was a dose related response. In addition, a numerical trend for dose-response relationship for serum glucose was observed. The 400 µg indacaterol group blood glucose was significantly higher compared to the 200 µg and 50 µg indacaterol groups. Heart rate also increased by 1.77 bpm, 1.98 bpm, 2.9 bpm and 13.3 bpm for indacaterol doses of 400, 600, 800 and 3000 µg, respectively. The rate of other adverse events was low and there were no meaningful differences between treatment groups. No significant QT prolongation effect of indacaterol (150 µg, 300 µg and 600 µg) was detected in a TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between indacaterol (150 µg, 300 µg and 600 µg) and placebo were below 10 ms.

The dose-response analysis performed for the justification of the proposed dose (150µg) and peak-to-trough ratio analysis for the justification of dosing interval (QD) did not fully justify 150µg QD as an optimal dosing regimen. Indacaterol 75 µg QD clearly showed effectiveness compared to placebo even though the lower bound of 95% confidence interval is lower than 0.12L. Therefore, given the safety (local) concern with LABA treatment (lack of bronchoprotection/disease exacerbation) as raised in the advisory committee for LABA products in December 2008, it is recommended that the sponsor should evaluate indacaterol doses lower than 75 µg QD for the treatment of COPD. Improvement of local safety profile for indacaterol through the exploration of twice a day administration may not be accomplished due to the inherent activity of beta adrenergic drugs to produce lack of bronchoprotection through development of tolerance/receptor down regulation.

Reviewers

Sandra Suarez Sharp, Ph.D.
Division of Clinical Pharmacology 2
Office of Clinical Pharmacology

Ying Fan, Ph.D.
Division of Clinical Pharmacology 2
Office of Clinical Pharmacology

Joo Yeon Lee, Ph.D.
Pharmacometrics Reviewer
Office of Clinical Pharmacology

Yaning Wang, Ph.D.
Pharmacometrics Team Leader
Office of Clinical Pharmacology

Mike Pacanowski, Pharm.D., M.P.H.
Pharmacogenomics Reviewer
Office of Clinical Pharmacology

Issam Zineh, Pharm.D., M.P.H
Pharmacogenomics Director
Office of Clinical Pharmacology

Final version signed by:
Dakshina Chilukuri, Team leader (acting)
Division of Clinical Pharmacology 2
Office of Clinical Pharmacology

cc

OCP	Sahajwalla, Dodappaneni, Chilikuri, Fan, Lee, Wang, Pacanowski, Zinah, Sharp
HFD-570:	Chowdhury, Durmowicz, Wu, Hill, Chilukuri, Fan, Sharp

2. QUESTION BASED REVIEW

2.1 General Attributes

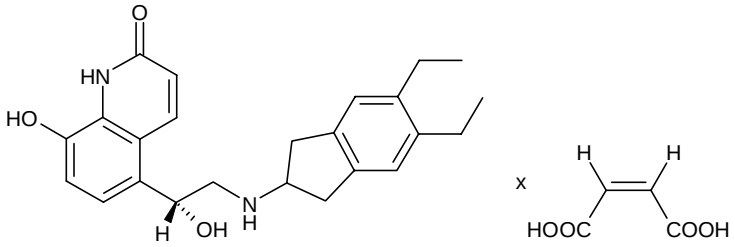
2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

The active component of Arcapta Neohaler is indacaterol maleate (R-enantiomer), a selective beta$_2$-adrenergic bronchodilator.

Chemical name:

The chemical name for indacaterol is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate; its structural formula is.

Structural formula:



Molecular formula: $C_{24}H_{28}N_2O_3 \bullet C_4H_4O_4$

Molecular weight: 508.56

The molecular weight of indacaterol free base is 392.49. To convert from pg/mL to nmol/L divide by 392.49.

Solubility: Indacaterol maleate is freely soluble in N-methylpyrrolidone and dimethylformamide, slightly soluble in methanol, ethanol, propylene glycol and polyethylene glycol 400, very slightly soluble in water, isopropyl alcohol and practically insoluble in 0.9% sodium chloride in water, ethyl acetate and n-octanol.

FORMULATION

Arcapta Neohaler consists of a capsule dosage form containing a dry powder formulation of indacaterol maleate for oral inhalation only with the Neohaler device. Each clear, hard gelatin capsule contains a dry powder blend of either (b) (4) with approximately 25 mg of lactose monohydrate as the carrier. The Neohaler is a plastic device used for inhaling Arcapta. Under standardized *in vitro* testing at a fixed flow rate of 60 L/min for 2 seconds, the Neohaler delivered (b) (4)) from the mouthpiece.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

Indacaterol is a long-acting beta$_2$-adrenergic agonist being proposed for once-daily administration. The pharmacological effects of beta$_2$-adrenoceptor agonist drugs, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic monophosphate).

Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. According to the sponsor, i*n vitro* studies have shown that indacaterol has more than 24-fold greater agonist activity at $beta_2$-receptors compared to $beta_1$-receptors and 20-fold greater agonist activity compared to $beta_3$-receptors.

INDICATION (as per proposed label)
Arcapta Neohaler is indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

2.1.3 What are the proposed dosage(s) and route(s) of administration?
Arcapta should be administered once daily every day by the orally inhaled route only.

DOSAGE AND ADMINISTRATION (as per proposed label)

(b) (4)

2.2 General Clinical Pharmacology
2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data?
Arcapta Neohaler for the treatment of COPD was evaluated in the following 3 pivotal clinical trials:

- **Study B2335S**: This was a placebo- and active-controlled (using open-label tiotropium) seamless, adaptive design Phase II/III study (26 weeks duration) conducted to provide guidance for dose selection and the pivotal efficacy and safety data for the 150 µg QD and 300 µg QD doses in about 1945 patients. The primary efficacy endpoint was 24h post-dose (trough) FEV1 (forced expiratory volume in one second) after 12 weeks treatment.

- **Study B2334:** This was a placebo- and active-controlled (using blinded formoterol) Phase III study (12 weeks duration) providing evidence of long-term efficacy and safety with the 300 µg QD dose in about 290 patients. The primary efficacy endpoint was 24h post-dose (trough) FEV1 after 12 weeks treatment.

- **Study B2346:** This was a placebo-controlled Phase III study (52 weeks duration) providing replicate evidence of efficacy and safety for the 150 µg QD dose in about 1716 patients. The primary efficacy endpoint was 24h post-dose (trough) FEV1 after 12 weeks treatment.

Although FEV_1 is a well established and validated clinical endpoint of efficacy in COPD, it does not, by itself, fully describes the level of overall COPD control. Apart from 24 h post-dose FEV1, other related spirometry outcomes were measured. These included the AUC for FEV1 at various study-specific timepoints and Peak FEV1. In addition to these lung function endpoints, a wide range of symptom-related outcomes, covering many aspects of COPD and its effects, were assessed to evaluate the effectiveness of indacaterol in the treatment of COPD. These included the St. Georges' Respiratory Questionnaire (SGRQ), the transitional dyspnea index (TDI), COPD exacerbations, use of rescue medication, days of poor control (DOPC) and daytime and nighttime symptoms.

The assessment of safety included the review of the frequency and incidence of adverse events, 12-lead ECG and vital signs and other laboratory analysis (such as heart rate, glucose and potassium levels). The effect of indacaterol on the QT interval prolongation was studied in one pivotal placebo- and active controlled control cardiac repolarization studies in 388 healthy volunteers given indacaterol inhalation aerosol 150 µg, 300 µg and 600 µg once daily for 14 days.

Since systemic absorption of inhaled drugs is the result of pulmonary and gastrointestinal absorption, and because there is uncertainty about the site of absorption along the respiratory tract/airways, currently plasma concentrations cannot be correlated to efficacy (FEV_1).

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?
As indicated above, the primary endpoint in these three studies was trough FEV1. This was defined as the average of two FEV1 measurements taken in the clinic after 23 h 10 min and 23 h 45 min post dose measured using spirometry. Spirometry equipment and performance of spirometric testing was in accordance with ATS standards.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?
Yes. QAB149 (indacaterol free base) was analyzed in serum and urine using a specific HPLC-MS/MS method with a lower limit of quantification (LLOQ) of 10 pg/mL using 200 µL serum (100 µL with online SPE) and of 50 pg/mL using 100 µL urine, respectively. In early phases of development indacaterol was analyzed with bioanalytical methods that were less sensitive (e.g. 250 pg/mL, 70 pg/mL and 50 pg/mL in serum).

2.2.4 Exposure Response
2.2.4.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?
Systemic absorption of inhaled drugs is the result of pulmonary and gastrointestinal absorption, therefore, unless there is enough evidence of the contribution of pulmonary absorption to systemic exposure and enough information on site of deposition and absorption from the lungs, plasma concentrations cannot be correlated to efficacy (trough FEV1).

In the case of dose-response relationship for efficacy, there was a numeric trend for the higher doses tested to produce a bigger response in through FEV1; however a clear dose-ordering response was not observed following either single dose (150 µg to 600 µg) or multiple dose (50 µg to 600 µg) of once a day administration of indacaterol inhalation powder.

Three dose-response studies were included in the present submission as follows:
Study B2212 was a single dose study in 60 (12 per arm) patients with COPD. Patients received a single dose of either indacaterol 150 µg, 300 µg and 600 µg, formoterol 12 µg or placebo via SDDPI. The mean difference to placebo in through FEV1 increased from 0.14 to 0.18 L for the 150 µg and 600 µg, respectively. However, the treatment contrast between indacaterol doses showed no statistically significant difference between indacaterol 600 µg vs. 300 µg and indacaterol 300 µg vs. 150 µg ($p>0.57$). (Table 2.2.4.1.1)

Table 2.2.4.1.1. Analysis of covariance of 24 h post-dose (trough) FEV1 (L) (modified ITT population) (Data from Study B2212)

	n	LSMean	SE	95% CI*	p-value*	SS 95% CI**	SD p-value (2-sided)**
Treatment Effect							
Indacaterol 600 µg	50	1.46	0.014	(1.43, 1.49)			
Indacaterol 300 µg	49	1.45	0.015	(1.42, 1.48)			
Indacaterol 150 µg	47	1.42	0.015	(1.39, 1.45)			
Formoterol 12 µg	50	1.41	0.014	(1.38, 1.43)			
Placebo	48	1.28	0.015	(1.25, 1.31)			
Treatment Contrast (Primary Analysis)							
Indacaterol 600 µg-Placebo		0.18	0.021	(0.14, 0.22)	<0.001	(0.13, 0.23)	<0.001
Indacaterol 300 µg-Placebo		0.17	0.020	(0.13, 0.21)	<0.001	(0.12, 0.22)	<0.001
Indacaterol 150 µg-Placebo		0.14	0.020	(0.10, 0.18)	<0.001	(0.09, 0.19)	<0.001
Treatment Contrast (Secondary / Exploratory Analysis)							
Indacaterol 600 µg-300 µg		0.01	0.020	(-0.03, 0.05)	0.5690		
Indacaterol 600 µg-150 µg		0.04	0.020	(0.00, 0.08)	0.0428		
Indacaterol 600 µg-Formoterol 12 µg		0.05	0.020	(0.01, 0.09)	0.0089		
Indacaterol 300 µg-150 µg		0.03	0.020	(-0.01, 0.07)	0.1382		
Indacaterol 300 µg-Formoterol 12 µg		0.04	0.020	(0.00, 0.08)	0.0426		
Indacaterol 150 µg-Formoterol 12 µg		0.01	0.020	(-0.03, 0.05)	0.5925		
Formoterol 12 µg-Placebo		0.13	0.020	(0.09, 0.17)	<0.001		

*95% CIs and p-values are calculated without multiplicity adjustment
** SS 95% CIs are based on a single step Dunnett procedure implemented using % SimIntervals SAS macro. The SD p-values are based on stepdown Dunnett procedure implemented using % SimTests SAS macro

Study B2205 was a placebo-controlled, parallel group, multiple dose study in 660 patients (110 per arm) with COPD. Patients were randomized to one of six treatments arms indacaterol 50 µg, 100 µg, 200 µg, or 400 µg via the MDDPI, indacaterol 400 µg via the SDDPI or placebo for 7 days. There was a numerical trend for dose-response relationship in the range of indacaterol doses tested following either single (Table 2.2.4.1.2) or multiple (Figure 2.2.4.1.1) dose administration of the treatments. The mean difference to placebo in trough FEV1 increased from 0.14 to 0.21 L for the 50 µg and 400 µg, respectively at Day 7. However, only the differences between the 400 µg dose and the 100 µg dose, and between the 400 µg dose and the 50 µg dose were statistically significant (P<0.007).

It should be noted that this study was conducted using a different inhalation device (MDDPI) than that intended for marketing (SDDDI). It should also be noted that this study also evaluated the efficacy of indacaterol 400 µg delivered via SDDPI (to-be marketed formulation) whose effect on trough FEV1 in this study was not different than that shown for indacaterol 400 µg delivered via MDDPI (Table 2.2.4.1.2).

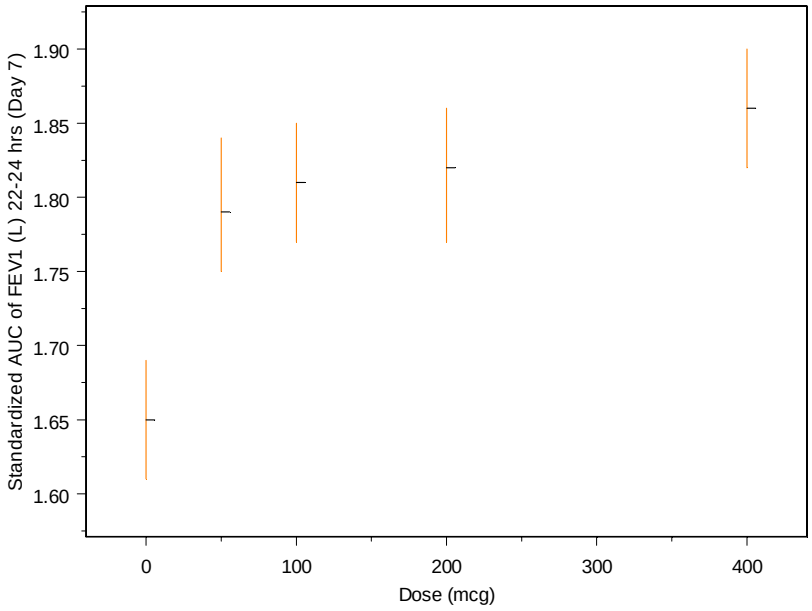


Figure 2.2.4.1.1. Standardized AUC of FEV1 (L) 22-24 h post-dose at Day 7 following multiple dose administration (QD) of the treatments (0=PLB) (Data from Study B2205).

Table 2.2.4.1.2. Analysis of covariance of 24 h post-dose (trough) FEV1 (L) (modified ITT population) (Day 7) (Data taken from Study B2205)

	LSM	**SE**	**95% CI**	**P value 2-sided**
Treatment effect				
QAB149 400 µg MDDPI	1.83	0.020	(1.79, 1.87)	
QAB149 200 µg MDDPI	1.79	0.020	(1.75, 1.83)	
QAB149 100 µg MDDPI	1.74	0.021	(1.70, 1.78)	
QAB149 50 µg MDDPI	1.76	0.020	(1.71, 1.80)	
QAB149 400 µg SDDPI	1.87	0.021	(1.83, 1.91)	
Placebo	1.65	0.020	(1.62, 1.69)	
QAB149 Treatment contrast (Primary analysis)				
400 µg MDDPI -Placebo	0.17	0.027	(0.12, 0.23)	<0.0001
200 µg MDDPI -Placebo	0.13	0.027	(0.08, 0.19)	<0.0001
100 µg MDDPI -Placebo	0.08	0.027	(0.03, 0.14)	0.0023
50 µg MDDPI -Placebo	0.10	0.027	(0.05, 0.15)	0.0002
QAB149 Treatment contrast (Secondary analysis)				
400 µg MDDPI -200 µg MDDPI	0.04	0.027	(-0.01, 0.09)	0.1524
400 µg MDDPI -100 µg MDDPI	0.09	0.027	(0.04, 0.14)	0.0009
400 µg MDDPI -50 µg MDDPI	0.07	0.027	(0.02, 0.13)	0.0070
400 µg MDDPI -400 µg SDDPI	-0.05	0.027	(-0.10, 0.01)	0.0929

200 µg MDDPI -100 µg MDDPI	0.05	0.027	(0.00, 0.10)	0.0587
200 µg MDDPI -50 µg MDDPI	0.03	0.027	(-0.02, 0.09)	0.2079
200 µg MDDPI -400 µg SDDPI	-0.08	0.027	(-0.14, -0.03)	0.0023
100 µg MDDPI -50 µg MDDPI	-0.02	0.027	(-0.07, 0.04)	0.5262
100 µg MDDPI -400 µg SDDPI	-0.14	0.027	(-0.19, -0.08)	<0.0001
50 µg MDDPI - 400 µg SDDPI	-0.12	0.027	(-0.17, -0.06)	<0.0001
400 µg SDDPI - Placebo	0.22	0.027	(0.16, 0.27)	<0.0001

Study B2335S was a placebo-controlled, adaptive, seamless, parallel group, efficacy and safety study in about 770 (115 per arm) patients with COPD. Patients were randomized to one of seven treatments arms with indacaterol 75 µg, 150 µg, 300 µg, or 600 µg given once a day via the SDDPI, formoterol 12 µg BID, tiotropium 18 µg QD or placebo for 2 weeks (Stage 1). Following 2 weeks of treatment, an interim analysis of the efficacy and safety results from Stage 1 was conducted to determine the doses to be evaluated on Stage 2. Dose selection was based on pre-defined criteria comparing the efficacy of indacaterol with placebo and the active controls, as well as safety data. Based on the results of this analysis indacaterol doses of 150 µg QD and 300 µg QD were continued into Stage 2 together with the tiotropium and placebo arms in about 805 patients.

A graphical analysis of the dose-response relationship considering the data from Stage 1 indicate a trend for dose-response relationship in the range of indacaterol doses tested following ((Figure 2.2.4.1.2). The mean differences with respect to placebo in trough FEV1 were 0.15 L, 0.18 L, 0.21 L and 0.20 L for indacaterol 75, 150, 300, and 600 µg, respectively (Table 2.2.4.1.3). Since the dose selection guideline was based on the values of the adjusted mean contrasts given by these analyses but did not use the associated p-values, there were no p-values presented. However, looking into the means for treatment differences and 95% intervals it is apparent that statistical significance was not achieved between adjacent treatment (e.g. 75 µg vs. 150 µg: LS means difference = 0.03 95% CI=-0.05 to 0.06).

Table 2.2.4.1.3. Key interim analysis results at Day 15 (imputed with LOCF): treatment comparisons (interim ITT population) (Data from Study 2235S)

Treatment	**n**	**LS Mean**	**SE**	**Comparison**	**LS mean**	**SE**	**95% CI**
Trough FEV1 (L)							
Comparison with Placebo							
Ind 75 µg	104	1.46	0.024	Ind 75 µg - Pbo	0.15	0.029	(0.09, 0.20)
Ind 150 µg	105	1.49	0.024	Ind 150 µg - Pbo	0.18	0.029	(0.12, 0.24)
Ind 300 µg	110	1.52	0.024	Ind 300 µg - Pbo	0.21	0.029	(0.15, 0.27)
Ind 600 µg	108	1.51	0.024	Ind 600 µg - Pbo	0.20	0.029	(0.14, 0.25)
For	105	1.42	0.024	For - Pbo	0.11	0.029	(0.06, 0.17)
Tio	112	1.45	0.023	Tio - Pbo	**0.14**	0.028	(0.08, 0.19)
Pbo	104	1.31	0.024				

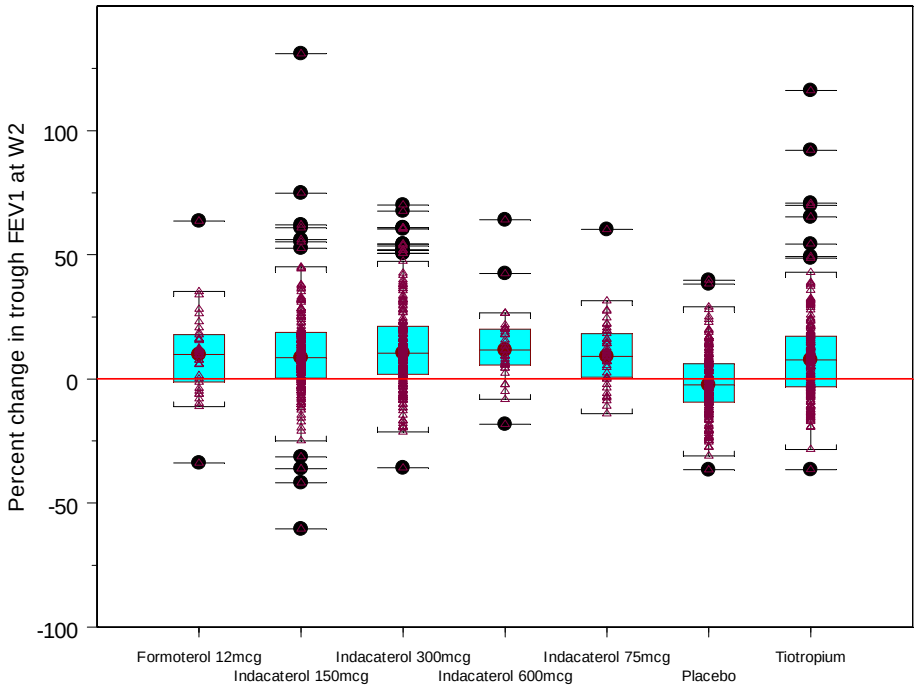


Figure 2.2.4.1.2. Percentage change from baseline in trough FEV1 at week 2 following administration of the treatments (data from study B2235s) (N=376-393).

2.2.4.2 What are the characteristics of the dose-systemic exposure relationships for safety?

In general, based on the results of the 3 dose-finding studies above mentioned, the majority of systemic adverse events reported appeared not to be related to indacaterol dose given once a day as inhalation powder in the range of 50 µg to 600 µg. However, data from Study B2205 above mentioned showed that cough occurred at a higher frequency in the active drug treatment groups compared to placebo (2.9-12.4% vs 0.9%) with evidence that this was a dose related response (Figure 2.2.4.2.1). In addition, a numerical trend for dose-response relationship for serum glucose was observed in Study B2205. The 400 µg indacaterol group blood glucose was significantly higher compared to the 200 µg and 50 µg indacaterol groups. Heart rate increased by 1.77 bpm, 1.98 bpm, 2.9 bpm and 13.3 bpm for indacaterol doses of 400, 600, 800 and 3000 µg, respectively. The rate of other adverse events was low and there were no meaningful differences between treatment groups (Figure 2.2.4.2.2).

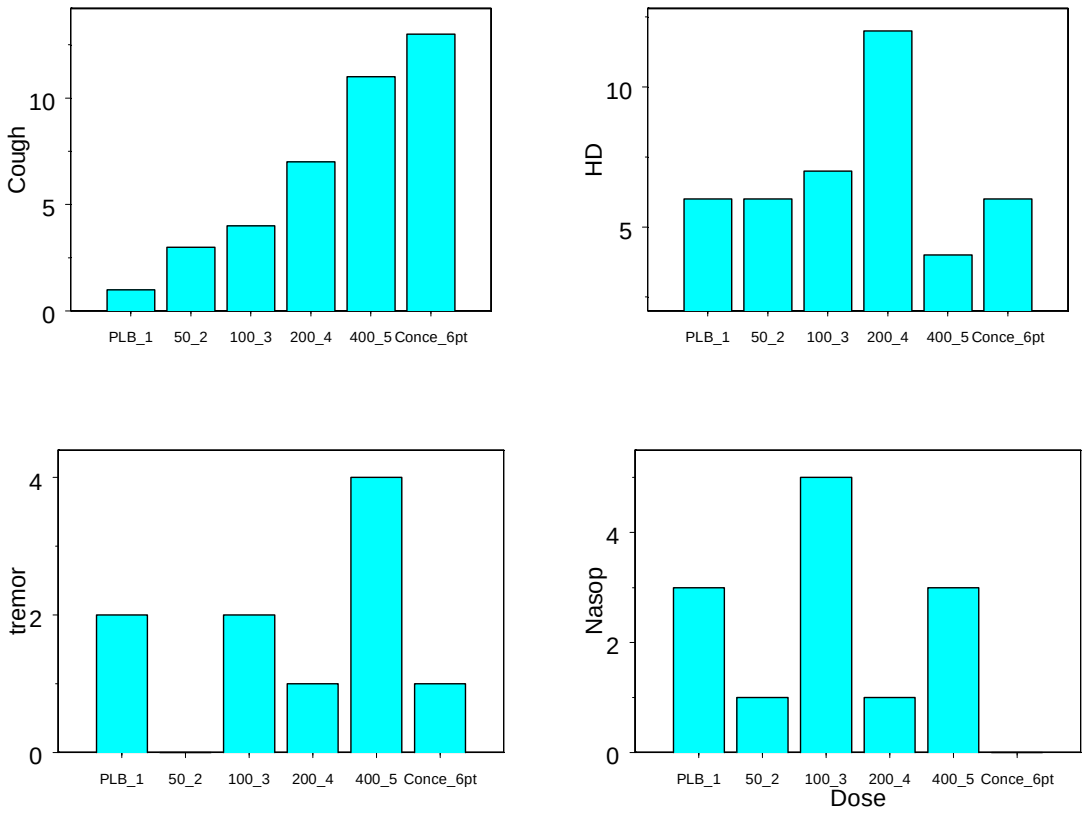


Figure 2.2.4.2.1. Number (%) of patients with most frequent AEs (> 1 patient for any group) (Safety population) (HD=headache, Nasop=nasopharyngitis) (data from study B2205).

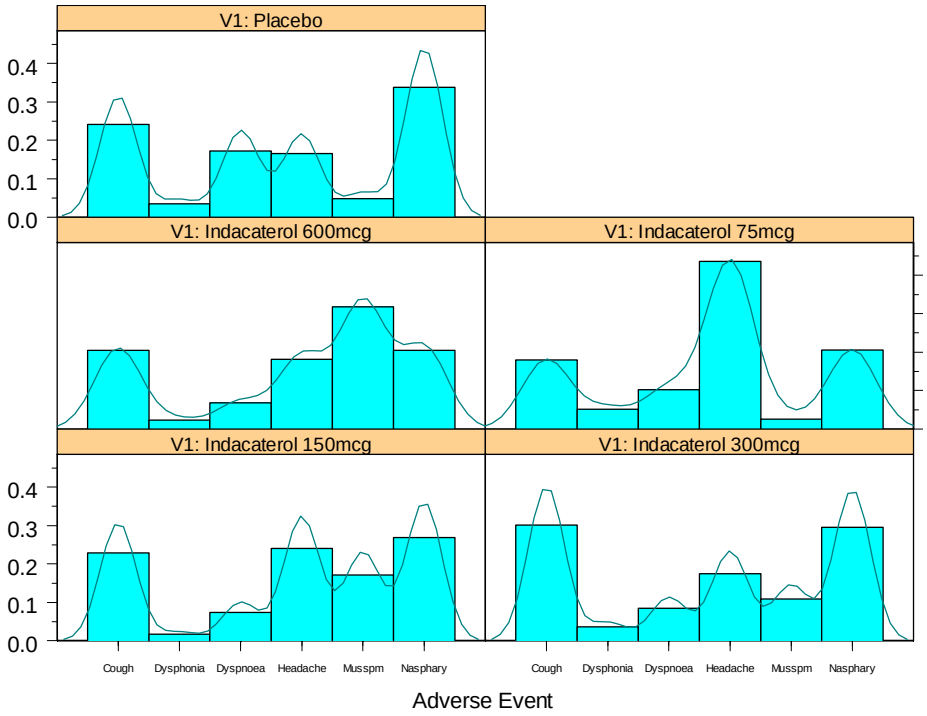


Figure 2.2.4.2.2. Density chart of most frequent adverse event frequency following 2 weeks of treatment (Data from (Study 2235S).

2.2.4.3 Does this drug prolong the QT or QTc interval?

No significant QT prolongation effect of indacaterol (150 mcg, 300 mcg and 600 mcg) was detected in a TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between indacaterol (150 mcg, 300 mcg and 600 mcg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time was adequately demonstrated, indicating that assay sensitivity was established. In this randomized, blinded, five-arm parallel group study, 404 healthy subjects received indacaterol 150 mcg, indacaterol 300 mcg, indacaterol 600 mcg placebo, and a single oral dose of moxifloxacin 400 mg (refer to IRTQt review for more detailed information).

Table 2.2.4.3.1. The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for indacaterol (150 mcg, 300 mcg and 600 mcg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Indacaterol 150 mcg	2	2.7	(0.7, 4.6)
Indacaterol 300 mcg	2	2.9	(0.9. 4.9)
Indacaterol 600 mcg	6	2.7	(0.4, 5.1)
Moxifloxacin 400 mg*	2	14.0	(10.9, 17.0)

Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 9.8 ms.

2.2.4.4 Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

As mentioned previously, the systemic absorption of inhaled drugs is the result of pulmonary and gastrointestinal absorption, and therefore plasma concentrations may not be correlated to efficacy. Thus, the appropriate dose and dosing regimen need to be based on dose-response relationships rather than exposure-response relationships. The proposed dose of indacaterol inhalation powder in COPD patients is 150 μg once a day not to exceed 300 μg QD. As stated above, there was a trend for higher doses to produce a bigger response in trough FEV1; however a clear dose-ordering was not observed for doses ranging from 50 μg to 600 μg given once daily. In addition, the 75 μg dose evaluated as part of the adaptive dose-finding study appears to have similar efficacy than the 150 μg dose given QD. Therefore, during the NDA review, the sponsor was informed that the appropriate dose (s) and dose regimen has not been identified for indacaterol inhalation powder for the treatment of COPD.

In order to address the Agency's concerns, the sponsor submitted a separate report assessing the dose-response and frequency of dosing for indacaterol to justify their originally proposed dosing regimen. The report includes dose-response analysis for the justification of the proposed dose (150μg) and peak-to-trough ratio analysis for the justification of dosing interval (QD). The sponsor's analyses did not fully justify 150μg QD as an optimal dosing regimen as described below.

Based on the sponsor's dose-response analysis (meta-analysis) of trough response, the doses of 75, 150, 300 and 600 μg were predicted to correspond to the ED78, ED88, ED93, and ED97, respectively. The sponsor claimed that indacaterol 75μg, dosed once daily provides less complete bronchodilation in the typical patient compared with 150 μg or 300 μg doses. However, the sponsor's Emax model did not fit the observed data especially well at lower dose due to the lack of data, which made ED50 estimates unreliable due to the large uncertainty (Table 2.2.4.4.1). In addition, the sponsor's minimum clinically

important difference (MCID, 0.12 L) is not justified according to the medical team's opinion. Indacaterol 75 µg QD clearly showed effectiveness compared to placebo even though the lower bound of 95% confidence interval is lower than 0.12L. Furthermore, the paper[1] published by the authors from the sponsor demonstrated that the sponsor's rule for finding the minimum effective dose (MED) based on the lower bound of 95% confidence interval tends to overestimate the target dose.

In order to justify the dosing interval (QD), the sponsor performed the peak-to-trough ratio analysis. As shown in Figure 2.2.4.4.1, peak-to-trough ratio at 12 h for a twice-daily drug such as formoterol or salmeterol should be greater than that for indacaterol. However, it could be argued that the extended duration of effect might be a result of simply increasing the dose to artificially extend the duration of action. To address this question, the sponsor assessed two different metrics of the dose-response: the peak response and the trough response. Similar estimates of the ED50 for the respective metrics would provide evidence that the once daily property of indacaterol is not achieved at the expense of elevating the dose to artificially extend the duration of action. However, the sponsor's claim on dosing interval (once daily) could not be supported by their analysis mainly due to the large uncertainty in ED50 estimates for trough FEV1 and especially peak FEV1.

Therefore, given the safety (local) concern with LABA treatment (disease exacerbations) it is recommended that the sponsor evaluates indacaterol doses lower than 75 µg QD for the treatment of COPD.

Table 2.2.4.4.1. The parameter estimates from meta-analysis and NLME analysis. The numbers in parenthesis indicate 90% CI.

	Meta-analysis			NLME analysis		
	Trough FEV1	Peak average (AUC0-4)	Observed Peak FEV1	Trough FEV1	Peak average (AUC0-4)	Observed Peak FEV1
Emax	0.18 (0.12-0.20)	0.27 (0.23-0.30)	0.26 (0.22-0.30)	0.18 (0.16-0.21)	0.23 (0.19-0.26)	0.22 (0.18-0.25)
ED50	22 (10-35)	25 (11-42)	35 (10-69)	22 (7-68)	14 (3-73)	12 (2-93)
%max effect at 75µg	78 (68-88)	76 (64-87)	70 (52-88)	78 (53-92)	84 (57-95)	86 (53-97)
%max effect at 150µg	88 (81-94)	86 (78-93)	82 (69-94)	87 (69-96)	91 (73-98)	93 (69-99)
%max effect at 300µg	93 (90-97)	92 (88-97)	90 (81-97)	93 (82-98)	95 (84-99)	96 (82-99)
%max effect at 600µg	97 (94-98)	96 (93-98)	95 (90-98)	97 (90-99)	98 (91-99)	98 (90-99)

[1] Combining Multiple Comparisons and Modeling Techniques in Dose-Response Studies, F.Brets, J.C.Pinheiro and M.Branson. Biometrics, 2005,61, p.738-748.

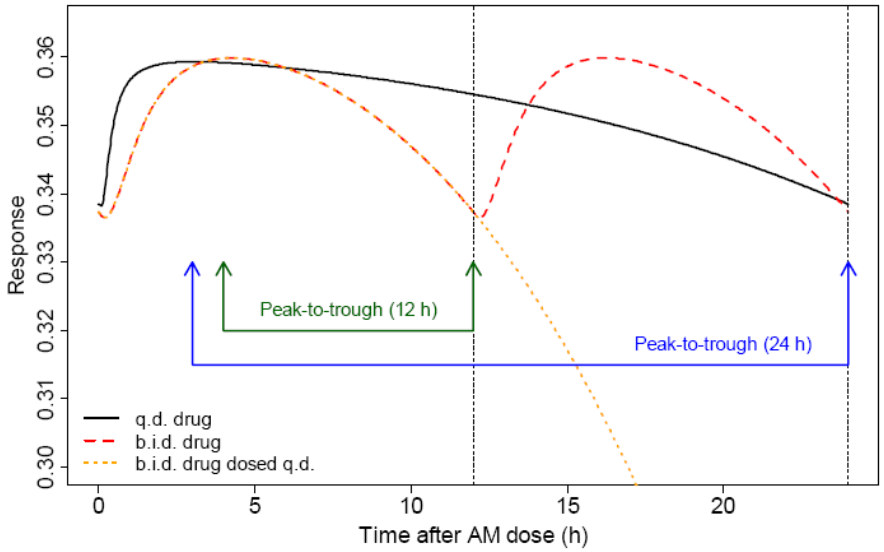


Figure 2.2.4.4.1. The sponsor's schematic presentation of the peak-to-trough concept at steady-state (not based on real data). Source: the sponsor's report, dose-response and regimen modeling report. Page 13.

2.2.4.5 Are individual indacaterol exposures or responses heterogeneous?

Yes. The PK of indacaterol was not excessively variable in densely sampled healthy volunteer studies. However, marked variability was evident in the changes in FEV1 following at least 12 weeks of per-protocol indacaterol treatment in the 3 pivotal studies. Approximately 50% of patients demonstrated less than a 10% improvement in FEV1. Non-response rates were similar or greater for formoterol and tiotropium, indicating the response heterogeneity may be typical of other inhaled agents used in COPD.

A linear regression was performed to identify covariates that predict the absolute change in FEV1 at 3 months. Variables entered into this analysis included age, baseline FEV1, inhaled corticosteroid use, race, baseline COPD severity, sex, and smoking history. Significant covariates are highlighted in Table 2.2.4.5.1. These factors account for a small portion of the overall variability in treatment response (R^2 approximately 4%).

Table 2.2.4.5.1. Linear regression model for absolute change in FEV1 after 12 weeks of indacaterol treatment

	150 µg (n=531)			300 µg (n=720)		
Variable	**Parameter estimate**	**SE**	**P**	**Parameter estimate**	**SE**	**P**
Age	-0.00397	0.00138	0.0042	-0.00502	0.00123	<.0001
Baseline FEV1	-0.15676	0.03091	<.0001	-0.12304	0.02931	<.0001
Inhaled corticosteroid use	-0.02847	0.02311	0.2186	0.02227	0.01994	0.2645
Race	-0.02948	0.01861	0.1137	-0.01852	0.01448	0.2013
COPD Severity (<mod vs. >sev)	-0.08506	0.02755	0.0021	-0.12339	0.02554	<.0001
Sex (F vs. M)	-0.1268	0.02672	<.0001	-0.06909	0.0254	0.0067
Smoking history	0.01264	0.02378	0.5954	-0.04202	0.02087	0.0445
	Adjusted R^2 = 0.0426			*Adjusted R^2 = 0.0457*		
Analysis based on 3-month data from Integrated Summary of Efficacy dataset						

Source Genomics reviewer

2.2.5 What are the PK characteristics of the drug and its major metabolite?
2.2.5.1 What are the single dose and multiple dose PK parameters? What are the characteristics of drug distribution? How do the PK parameters change with time following chronic dosing?

Healthy volunteers
Parent Compound/Single and Multiple Dose PK
The pharmacokinetics of indacaterol inhalation powder 150, 300 and 600 µg were assessed as part of the cardiac safety study (B2339) after single and multiple (QD) dose administration in healthy volunteers using the to be-marketed formulation.

The mean indacaterol concentration time profiles following single and multiple dose administration of the treatment is shown in Figure 2.2.5.1.1. The mean PK parameters resulting are shown in Tables 2.2.5.1.1 and 2.2.5.1.2. In most subjects, the maximum serum concentration of indacaterol was reached 15 min post-dose on Day 1 and Day 14. Mean trough concentrations increased from 20.2 pg/mL to 105.1 pg/mL in the 150 µg dose group, from 45.3 to 216.9 pg/mL in the 300 µg dose group, and from 84.9 to 399.0 pg/mL in the 600 µg dose group, between Day 2 and Day 14. In all dose groups, the trough concentrations were similar on Day 12 and Day 14 and the Day14/Day12 mean ratios were close to unity (between 1.03 and 1.09). These findings indicate that steady-state was achieved by Day 12.

The apparent accumulation of indacaterol in serum of each subject during multiple dosing, i.e. between days 1 and 14, was characterized by the accumulation ratios (=R) of Cmax and $AUC_{0\text{-}24hrs}$. Cmax increased 1.85-, 1.79- and 1.65-fold and $AUC_{0\text{-}24hrs}$ increased 3.48-, 3.22-, and 2.93-fold in the 150 µg, 300 µg and 600 µg dose groups, respectively.

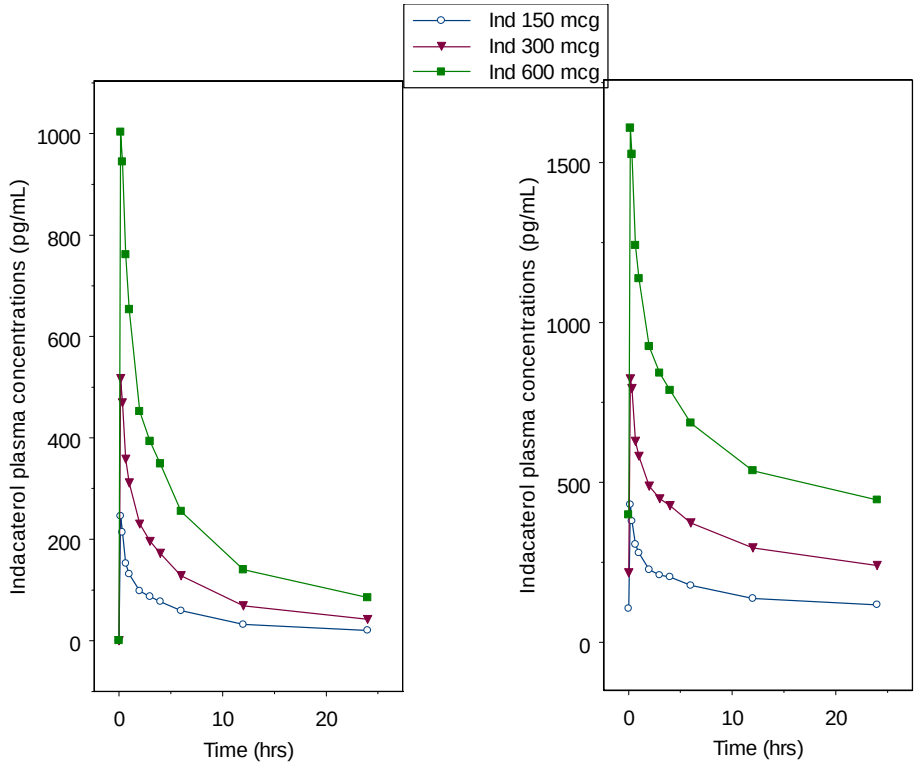


Figure 2.2.5.1.1. Mean serum concentration-time plots for indacaterol following single and multiple dose administration of the treatments (data from Study B2339).

Table 2.2.5.1.1. Summary statistics of indacaterol PK parameters - Day 1 (Data from Study B2339)				
Dose (µg)	**Statistic**	**[1]tmax (h)**	**Cmax (pg/mL)**	**AUC0-24 (pg.h/mL)**
150	N	72	72	72
	Mean/median[1] SD/range[1]	0.25 0.25-0.48	252.9 120.8	1202 554
	CV%	-	47.8	46.1
300	N	73	73	73
	Mean/median[1] SD/range[1]	0.25 0.22-1.08	537.2 224.2	2639 862
	CV%	-	41.7	32.7
600	N	37	37	37
	Mean/median[1] SD/range[1]	0.25 0.25-0.75	1043.8 285.5	5279 1155
	CV%		27.4	21.9

[1]t_{max} – median and range

Table 2.2.5.1.2. Summary statistics of indacaterol PK parameters - Day 14 (data from Study 2339)

Dose (µg)	Statistic	[1]tmax (h)	Cavg (pg/mL)	Cmin (pg/mL)	Cmax (pg/mL)	$AUC_{0-24hrs}$ (pg h/mL)	CLss/F (L/h)	T ½ (hrs)
150	N	70	70	70	70	70	70	69
	Mean/median[1] SD/range[1]	0.25 0.22-3.08	161.7 64.4	104.4 43.8	438.6 196.4	3882 1545	45.1 24.2	49.1 17.3
	CV%	-	39.8	42	44.8	39.8	53.6	
300	N	68	68	68	68	68	68	68
	Mean/median[1] SD/range[1]	0.25 0.17-1.08	339.0 99.5	214.5 68.8	858.6 264.2	8137 2388	40.1 12.0	44.7 12.4
	CV%	-	29.4	32.1	30.8	29.4	29.9	
600	N	37	37	37	37	37	37	37
	Mean/median[1] SD/range[1]	0.25 0.25-0.42	628.5 142.8	396.8 121.4	1656.6 540.8	15085 3428	42.0 10.7	39.8 12.1
	CV%	-	22.7	30.6	32.6	22.7	25.4	

[1]t_{max} – median and range

Healthy volunteers

Metabolites /Multiple Dose PK

Summary of the relevant pharmacokinetic parameters of relevant metabolites (QAZ033= P26.9 and P30.3) is presented in Table 2.2.5.1.3. The median tmax of QAZ033 occurs after that of indacaterol; 2.08 h vs 0.25 h. Serum concentrations of QAZ033 were considerably lower than that observed for indacaterol. The Cmax and $AUC_{0-24hrs}$ of QAZ033 (metabolites P26.9 + P30.3) was approximately 7% and 11% of those for indacaterol.

Table 2.2.5.1.3. Summary statistics of metabolite PK parameters - Day 14 (Data from Study B2339)					
Statistic	[1]t_{max} (h)	C_{max} (pg/mL)	AUC_{0-24} (pg.h/mL)	[2]$R_{met, Cmax}$	[2]$R_{met, AUC0-24}$
N	32	32	32	32	32
Mean/median[1]	2.08	101.3	1661	0.0654	0.1118
SD/range[1]	0.25-12.08	33.3	665	0.0286	0.0499
CV%	-	32.9	40.0	43.7	44.7

[1]tmax – median and range [2]R_{met} = QAZ033/indacaterol (based on mass concentrations)

Single Dose PK in COPD Patients

The PK of indacaterol inhalation powder in COPD patients were examined after single dose administration as part of Study B2212 (dose-ranging study). Table 2.2.5.1.4 summarizes the relevant PK parameters following administration of the treatments. A comparison of PK values from this study and those from Table 2.2.5.1.1 shows that indacaterol Cmax values across doses in COPD patients were about 35% to 43% lower than that observed in healthy volunteers. On the other hand, $AUC_{0-24hrs}$ values were about 7% to 15% higher than that observed in healthy volunteers.

Table 2.2.5.1.4. Mean ± SD (range) Pharmacokinetic Parameters of indacaterol after single dose administration of the treatment (data from Study B2212)

Dose	**Statistic**	**Tmax [h]**	**Cmax [pg/mL]**	**Cmax/Dose [pg/mL/µg]**	$AUC_{0-24hrs}$ **[pg*h/mL]**	**AUC0-24/Dose [pg*h/mL/µg]**
150 µg (N=47)	Mean SD	--	145.4 65.2	0.97 0.434	1284 646	8.56 4.3
300 µg (N=46)	Mean SD Min	0.5	327.9 151.4 35.3	1.093 0.505 0.118	2975 1663 213	9.92 5.54 0.71
600 µg (N=50)	Mean SD Min	0.42	680.5 331.7 213	1.134 0.553 0.355	6017 3161 1162	10.03 5.27 1.94

Multiple Dose PK in COPD Patients

The PK of indacaterol in COPD patients were examined after multiple dose administration as part of population PK analysis. Table 2.2.5.1.5 summarizes the relevant PK parameters following administration of the treatments. A comparison of PK values from this study and those from Table 2.2.5.1.2 shows that indacaterol AUC values across doses in COPD patients were about 16% to 20% lower than that observed in healthy volunteers.

Table 2.2.5.1.5. Mean steady-state AUC values for indacaterol in various population subsets, at COPD population median age (64 y) and weight (75 kg)

Gender		Indication	Race		AUC_{τ} at dose (mean [95% CI of the mean], ng·h·mL^{-1})		
M	F	C OPD	Non Black	black	150 µg	300 µg	600 µg
■		■	■		3.04 [2.95 ; 3.14]	6.09 [5.91 ; 6.27]	12.2 [11.8 ; 12.5]
	■	■	■		3.26 [3.12 ; 3.40]	6.51 [6.25 ; 6.79]	13.0 [12.5 ; 13.6]
■		■		■	2.58 [2.17 ; 2.99]	5.17 [4.37 ; 5.94]	10.3 [8.74 ; 11.9]
	■	■		■	2.76 [2.33 ; 3.20]	5.53 [4.68 ; 6.41]	11.1 [9.36 ; 12.8]

Absolute Bioavailability

The absolute bioavailability of indacaterol was examined in an open label, single-dose, two period crossover study (Study B2103). Healthy subjects were randomized to receive either a single inhaled dose of indacaterol 300 µg or a single intravenous administration of indacaterol 400 µg administered over 45 minutes. Based on the individual dose normalized $AUC_{0\text{-tlast}}$ and $AUC_{0\text{-}\infty}$ values of the four individuals who received indacaterol by both routes, the inhaled bioavailability of indacaterol was 43.2%, and 50.7%, respectively. The fraction of extrapolated AUC in $AUC_{0\text{-}\infty}$ was <20% in all cases, except for one subject where it was 50% after inhalation. Therefore, the results based on $AUC_{0\text{-tlast}}$, which is based on measured concentrations only, are considered as the primary outcome of this part of the study.

Relative Bioavailability

The relative bioavailability of indacaterol was examined in a two period, randomized, open label cross over study (Study 2106). Healthy subjects (4) received single doses of indacaterol via inhaled (800 µg) and oral (800 µg) routes. The relative BA (inhaled/dose= AUC48 inhaled/AUC48hr oral) was 218%. In other words the oral BA of QAB149 was 46% of that after inhalation of the same dose.

Assuming that following inhalation of indacaterol via the Aerolizer™ device, 27% of the dose was deposited in the lung with the remainder deposited in the stomach, it was estimated that 76% of the systemic exposure was attributed to lung absorption and 24% due to oral absorption. The results of this study should be interpreted with caution since the device used in this study (Aerolizer) is different than the device proposed for marketing (Concept 1).

2.2.5.2 Are the PK of indacaterol linear and dose-proportional?

Dose-proportionality following single and multiple dose administration of indacaterol inhalation powder in healthy volunteers was evaluated as part of study B2339. Dose proportionality over the entire dose range of 150 µg to 600 µg was demonstrated for Cmax of indacaterol on Day 1 and Day 14 and for total exposure ($AUC_{0\text{-}24hrs}$) on Day 14. For $AUC_{0\text{-}24hrs}$ on Day 1, the increase can be considered as dose-proportional over a dose multiple of up to 2.9 (Table 2.2.5.2.1)

Table 2.2.5.2.1. Estimate of the slope for the linear regression between log-PK parameter and log-dose (data from Study B2339)						
Profile Day	PK parameter	Slope estimate	Lower 90% confidence limit	Upper 90% confidence limit	Dose proportionality across the whole dose range*	Proportionality dose range**
1	AUC_{0-24}	1.124	1.039	1.209	no	2.9
	C_{max}	1.062	0.965	1.160	yes	
14	AUC_{0-24}	1.024	0.946	1.101	yes	
	C_{max}	0.998	0.908	1.088	yes	

* Dose range = ratio highest to lowest dose = 4.00.

** Maximum dose range within which the increase in the pharmacokinetic parameter can still be considered proportional to the increase in dose.

The critical region for the 90% confidence interval for the slope in order to conclude dose-proportionality across the dose range considered is (0.839, 1.161).

Application of the power model to data from Study B2215 showed that following single dose administration of indacaterol 400, 800, 1200, and 2000 µg via the RS-01 device to healthy volunteers the exposure ($AUC_{0-24hrs}$) increased more than proportional to the dose (slope estimate: 1.3; 90% CI= 1.24-1.35) (Figure 2.2.5.2.1)

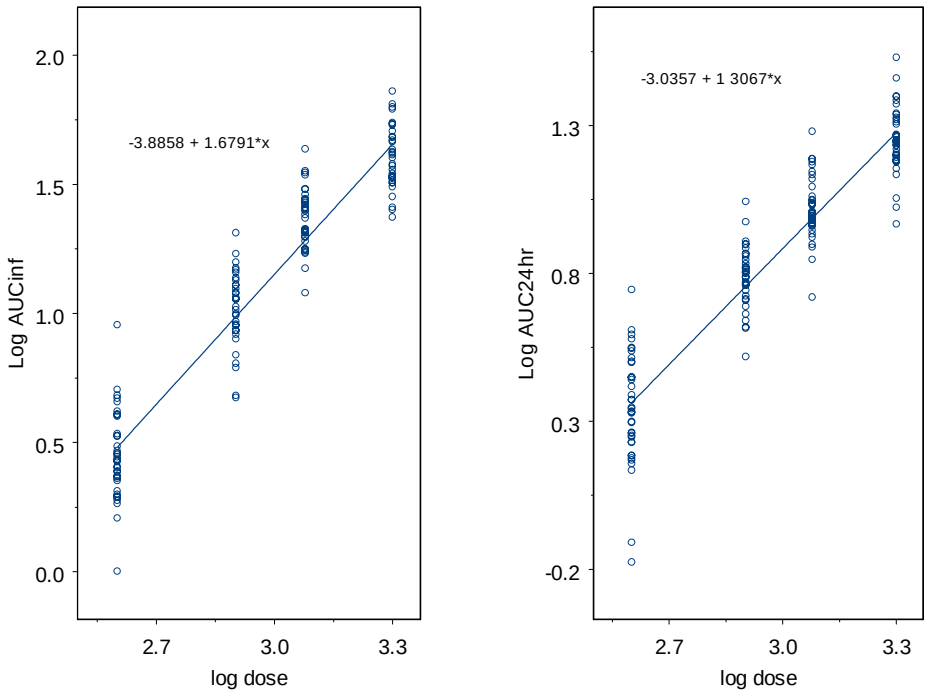


Figure 2.2.5.2.1. Pooled Individual AUCinf (left panel) and $AUC_{0-24hrs}$ (right panel) versus dose. Fitted line from power model : AUCinf = $e^{-3.9} * (strength)^{1.67}$ and AUC24hr = $e^{-3.0} * (strength)^{1.31}$

2.2.5.3 What are the mass balance characteristics of the drug?

Following a single oral (800 μg) administration of ^{14}C-indacaterol (62.5 μCi/mg indacaterol free base) to 4 healthy volunteers, the overall mean total recovery of radioactivity (over the entire 13 days postdose interval) in feces and urine was 85.3 % (± 7.6%) and 9.7 % (± 3.7%) of the dose, respectively. The majority of the dose in the feces was recovered as unmodified indacaterol (54.4 ± 20.9%) with a significant portion also being recovered in the form of the oxidative metabolites P26.9 and P30.3 (23.8 ± 11.4%). The portion of the dose recovered in the urine was distributed between multiple metabolites and unchanged parent drug. The mean (SD) excretion of unchanged indacaterol in urine (0-96 hrs) accounted for 0.34 % (0.37) of the dose.

The major metabolites of indacaterol identified in this study were **P19** (glucuronide conjugate of P26.9), **P26.9** (hydroxylation of the benzyl carbon in the diethyl-indane moiety), **P30.3** (diastereomer of P26.9), **P37** (phenolic O-glucuronide conjugate), **P37.7** (N-glucuronide conjugate of the diethyl-indanylamine nitrogen), **P38.2** (diethylindanylamino- acetic acid metabolite formed from oxidative cleavage), and **P39** (diethylindanylamine metabolite resulting from N-dealkylation).

In serum, the largest contributor to the exposure ($AUC_{0\text{-}24hrs}$) was indacaterol (32.5%). Metabolites contributing to the serum exposure included P19 (5.8%, P26.9 (12.4%) and P37 (4.2%). P37.7, P38.2, and P39 co-eluted in the serum radiochromatogram but together contributed 12.9% to the $AUC_{0\text{-}24hrs}$.

2.2.5.4 What are the characteristics of drug metabolism and excretion?

The key enzymes responsible for metabolic clearance of indacaterol are UGT1A1 and CYP3A4. These conclusions were base on the results of the following in vitro metabolism studies:

- **Metabolism of [3H]QAB149 by human liver or pulmonary microsomes**: QAB149 was primarily metabolized by glucuronidation in human liver microsomes, in the presence of UDPGA. Indacaterol was primarily metabolized in human liver microsomes, in the presence of NADPH and UDPGA, to the phenolic o-glucuronide (P37), followed by formation of minor monooxygenation products, P26.9 and P30.3

- **Metabolism of [3H]QAB149 by human recombinant UGT enzymes:** To examine the roles of specific human UGT enzymes in the metabolism of [3H]QAB149, the following recombinant UGT enzymes were tested for [3H]QAB149 metabolizing activity: UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B15. The phenolic *o*-glucuronide metabolite, P37, was predominately formed in reactions with recombinant human UGT1A1.

- **Metabolism of [3H]QAB149 by specific recombinant human cytochrome P450 enzymes**: [3H]QAB149 (10 μM) was incubated with fourteen different P450s (CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5 or CYP4A11) at a concentration of 250 pmol P450·mL^{-1}. The metabolites P26.9 and P30.3 formed in reactions with human liver microsomes were also found in incubations with recombinant human CYP1A1, CYP2D6, and CYP3A4 (monooxidation products). Kinetic parameters for QAB149 metabolism by CYP3A4 and CYP2D6 were established and CYP3A4 was found to be 2-fold more efficient in formation of total metabolites than CYP2D6 (89 versus 42 mLh^{-1}·nmol P450^{-1}). As determined by relative activity or abundance of these P450s in human liver microsomes, it was predicted that CYP3A4 would contribute 20 to 40-fold more than CYP2D6 in oxidative metabolism of QAB149 in human liver. However, due

to the lack of oxidative metabolism found previously in human liver slices and primary formation of the glucuronidated metabolite in the presence of UDPGA in human liver microsomes, it is predicted that glucuronidation is a major biotransformation pathway of QAB149 in human liver.

Based on the metabolites characterized in human excreta and in serum, a general biotransformation scheme for QAB149 is proposed in Figure 2.2.5.4.1. The primary metabolic reactions observed included:

- Hydroxylation of the benzylic carbon in the diethyl-indanyl moiety. This pathway leads to the formation of the diastereometric metabolites P26.9 and P30.3 which together accounted for 25.3 % of the excreted dose.
- Both N- and O- glucuronidation. This pathway leads to the formation of metabolites P19, P37 and P37.7. Although these metabolites only accounted for 1.35% of the excreted dose, they represented a significant fraction of the drug-related material found circulating in the serum AUC pool (the exact percentage could not be calculated due to the co-elution of P37.7 with P38.2).
- Oxidative cleavage. This leads to the formation of metabolites P38.2 and P39 which together accounted for 2.7% of the excreted dose.

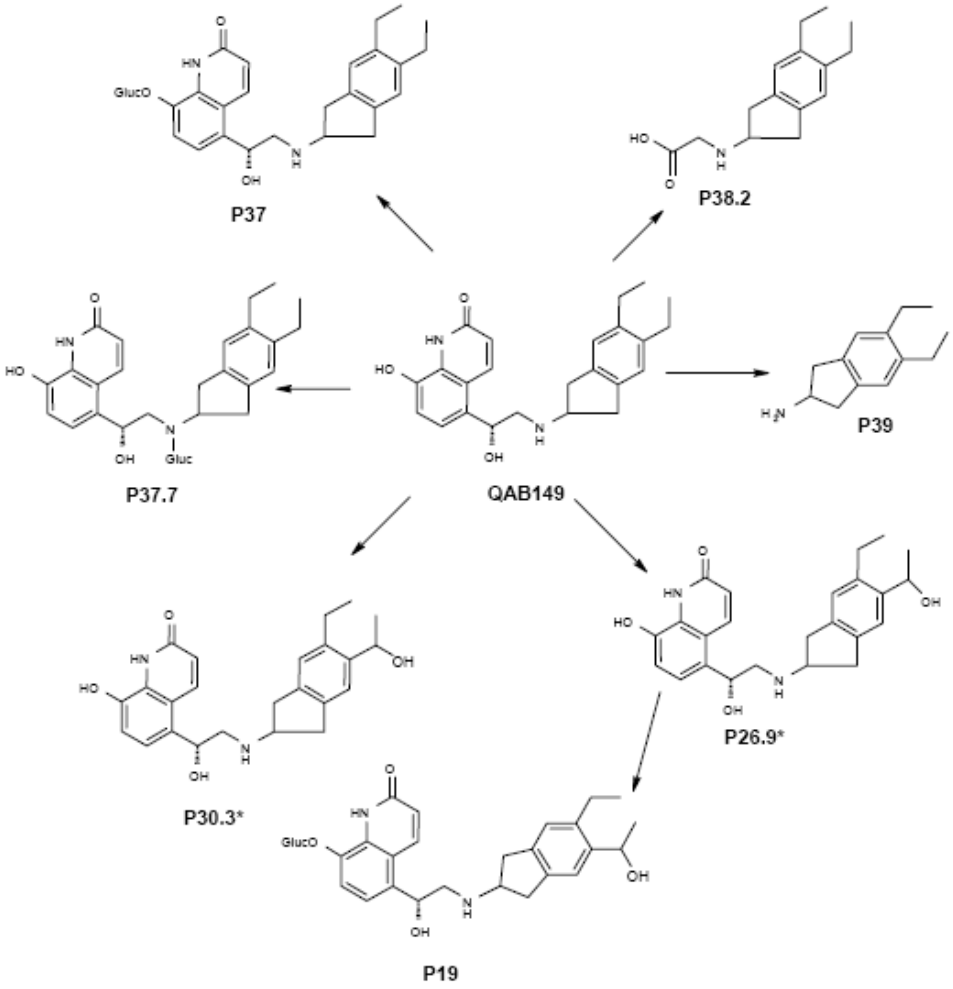


Fig. 2.2.5.4.1. Proposed metabolic pathway of indacaterol in humans.

2.2.5.5. Do UGT1A1 polymorphisms affect the indacaterol PK or responses?

Nonsignificant trends toward higher C_{max} and AUC_{0-24} (19% and 20%, respectively) were noted in patients with the (TA)7 genotype (Study A2221). These findings are consistent with the reduced metabolic function of this form of the enzyme. The magnitude of the difference may be greater at higher doses. However, Cmax and AUC values following the 200 µg dose in (TA)7 subjects did not exceed those of the 300 µg dose in other studies. The alleles assessed in this study were appropriate given that the population was predominantly white. Non-white subjects and their respective variants of UGT1A1 have not been evaluated, although the findings for (TA)6/7 are likely representative.

The impact of UGT1A1 TA6 genotype on indacaterol PK was evaluated in a prospective, open-label, parallel-arm, healthy volunteer study with genotype-based enrollment (A2221). Briefly, subjects who were homozygous for 7 TA repeats ((TA)7) or 6 TA repeats ((TA)6) were enrolled in a balanced fashion and treated with 200 µg of indacaterol daily via Aerolizer for 14 days. Dense PK sampling was performed over the first 24 hours after the initial dose and until 168 hours after the last of 14 daily doses. Trough samples were collected on Day 4, 6, 8, 10 and 13. The study population consisted of 12 subjects in each genotype group. All except 2 subjects with the (TA)7/(TA)7 genotype were white, and all were male except 2 subjects in each genotype group.

2.2.5.6 Does indacaterol undergo steroconverion in vivo?

No, (R)-Indacaterol does not undergo significant stereoconversion *in-vivo*. Analysis of urine samples from Study A2211 showed no evidence of significant stereochemical conversion of indacaterol (the pure R-enantiomer) to the S-enantiomer.

To evaluate the potential for *in-vivo* conversion of indacaterol (R-enantiomer) to its enantiomer, S-enantiomer concentrations were measured in the urine samples from Study A2211. After administration of a single dose of 3000 µg of QAB149 (highest dose), all S-enantiomer concentrations were measured below the LLOQ (0.200 ng/mL). Therefore, no determinations of S-enantiomer were performed in samples from subjects receiving lower doses.

Urine samples were analyzed using by HPLC-MS/MS. The chromatography was performed on a chiral column which allowed the separation of QAB149 and its S-enantiomer.

2.2.5.7 What is the inter- and intra-subject variability in PK parameters in volunteers and patients?

The CV% for the Cmax and AUC of indacaterol in healthy volunteers and COPD patients was less than 50%. Disease state did not change the degree of variability.

Table 2.2.5.7.1. Inter- and intra-subject variability (%CV of geometric mean) and intra-class coefficient of correlation of C_{max} and AUC_{0-24h} for a single inhaled dose of 300 µg indacaterol via Concept1 in cross-over studies (sponsor's analysis)

		Inter-subject CV% 1)		Intra-subject CV%		Intra-class coefficient of correlation 2)	
	n	C_{max}	AUC_{0-24h}		AUC_{0-24h}	C_{max}	AUC_{0-24h}
[Study CQAB149B2313]	20	28.6	30.2	21.0	14.4	0.645	0.809
[Study CQAB149B2216]	12	18.7	22.6	18.0	14.0	0.520	0.719
[Study CQAB149B2220]	12	35.4	22.9	18.0	17.9	0.788	0.620
[Study CQAB149B2212]	46	42.1	47.5	28.1	28.0	0.682	0.730

1) Geometric CV%: $100*\sqrt{(\exp(s_2)-1)}$, where s_2 is the variance component of the log transformed pharmacokinetic parameter.

2) Intra-class coefficient of correlation: $s_{B2}/(s_{B2} + s_{W2})$ where s_{B2} is the between subject variance component estimate and s_{W2} is the corresponding within subject variance component estimate from the PROC MIXED outputs.

2.3 Intrinsic Factors

2.3.1 Do race, gender, age, and disease status affect the PK and PD of the drug? What dosage regimen adjustments are recommended for each of these subgroups?

Yes. Based on population PK analysis, weight, age and gender were found to be significant factors for CL/F. However, dose adjustment on the basis of age/ weight /gender may not be necessary given that safety has been demonstrated in doses of up to 600 μg QD and dose-response (efficacy) relationship is shallow.

The population PK model developed for indacaterol used data generated with the Concept1 SDDPI device in COPD and asthma patients. Indacaterol-containing arms of five Phase II and Phase III clinical studies (CQAB149A2228, CQAB149B2212, CQAB149B2334, CQAB149B2335S, CQAB149B2338) were pooled to develop the model. In total, 20097 concentration-time observations from 2409 COPD and asthma patients dosed with 75 μg, 150 μg, 300 μg, and 600 μg QD were included. A summary of covariate effects estimates is as follows:

- Age
  - Cmax increase by 41% in patients between 48 (38%) to 78 (53%) years in COPD patients and 21% between 16 -69 years in asthma patients
  - AUC increase by 23% between 48-78 years
- Body weight
  - Cmax decrease by 25% between 50-107kg in COPD patients and 27% between 52 -110kg in asthma patients
  - AUC decrease by 21% between 50-107kg
- Gender
  - Cmax is 11% greater in female in COPD patients
  - AUC is 7% greater than in female
- AUC is 17% greater in asthma patients than in COPD patients
- Age and body weight were not correlated.

A numeric trend of lower systemic exposure in Japanese population was observed following single dose administration of indacaterol inhalation powder (400 to 2000 μg). The AUC was about 15% lower across doses tested. However, there was not significant difference in the systemic exposure between Caucasians and Japanese population (Study B2215).

2.3.1.2. Does renal impairment affect the PK of the drug and its major metabolite? Is dosage regimen adjustment recommended?

The effect of renal impairment on the PK of indacaterol and its metabolites was not evaluated. Renal clearance of serum indacaterol was on average between 0.5 and 1.2 L/h in healthy subjects and COPD patients. After inhaled administration of indacaterol, generally less than 2% of the inhaled dose was excreted into urine. In a human ADME study the majority of the orally administered radioactive dose was excreted into feces and only a minor fraction was found in the urine.

2.3.1.3 Does liver impairment affect the PK of the drug? Is dosage adjustment recommended?

Yes, mild and moderate hepatic impairment (classified based on Child-Pugh System) affected the PK of indacaterol. Following single dose administration of indacaterol 600 μg inhalation powder via the Concept 1 device to mild, moderate hepatic impairment patients and matching controls, the ratio of geometric means (90% CI) for mild impairment/control were 1.012 (0.72-1.42) and 0.978 (0.67-1.43) for $AUC_{0\text{-}24hrs}$ and Cmax, respectively. The ratio of geometric means (90% CI) for moderate impairment/control were 0.948 (0.67-1.33) and 0.772 (0.53-1.13) for $AUC_{0\text{-}24hrs}$ and Cmax, respectively (Table 2.3.1.3.1). However, dose adjustment it is not necessary due to the relative small changes

observed in PK.

The hepatic impairment study (Study A2307) was a single center, open-label, parallel group, single-dose design in subjects with stable chronic liver disease and demographically-matched healthy controls. All subjects received a single dose of 600 µg indacaterol via. A total of 32 subjects were planned to be included in the study consisting of 16 healthy subjects, 8 mild hepatic impaired and 8 moderate hepatic impaired subjects.

Table 2.3.1.3.1. Comparison of impaired groups to control groups for AUC_{0-24}, $AUC_{0-\infty}$, C_{max} and Ae_{0-24}

		Ratio to	90% Confidence
PK Parameter	Group Comparison	control (1)	Interval (2)
AUC_{0-24} (pg.h/mL)	Impaired (mild)/Control (mild)	1.012	(0.72,1.42)
	Impaired (moderate)/ Control (moderate)	0.948	(0.67,1.33)
$AUC_{0-\infty}$ (pg.h/mL)	Impaired (mild)/Control (mild)	0.866	(0.59,1.28)
	Impaired (moderate)/ Control (moderate)	1.120	(0.76,1.65)
C_{max} (pg/mL)	Impaired (mild)/Control (mild)	0.978	(0.67,1.43)
	Impaired (moderate)/ Control (moderate)	0.772	(0.53,1.13)
Ae_{0-24} (µg)	Impaired (mild)/Control (mild)	0.984	(0.62,1.57)
	Impaired (moderate)/ Control (moderate)	0.954	(0.58,1.57)

The effect of hepatic impairment on the PK of major metabolites was not reported in this submission.

The mean serum protein binding of indacaterol determined by ultracentrifugation was 92.9% (SD=1.6%, n=9) in the patients with mild hepatic impairment and 91.5% (SD=2.2%, n=8) in their healthy control group. Binding was 92.6% (SD=1.6%, n=8) in the patients with moderate hepatic impairment and 90.5% (SD=1.9%, n=9) in their control group. No significant difference was observed among the time-points in either the hepatically impaired or the healthy subjects. These data were consistent with that determined previously (95.1-96.2%) *in vitro* in human serum by ultracentrifugation. Serum protein binding was similar to plasma protein binding. Samples protein binding assay were prepared by adding a radiolabeled stock solution to each serum sample. Radioactivity in serum and supernantant was measured by radioactivity counting.

2.3.1.4 What pregnancy and lactation use information is there in the application?

As per proposed labeling, based on lactating rodent studies, indacaterol is excreted into breast milk. Clinical data from nursing women exposed to indacaterol are not available. There are no adequate and well-controlled studies with indacaterol inhalation powder in pregnant women. Indacaterol inhalation powder should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics? What other biomarkers may predict response to indacaterol?

The effects of herbal products, diet, smoking and alcohol used on the PK of indacaterol have not been evaluated.

2.4.2 Drug-Drug Interactions (DDI)

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. Data from the in-vitro metabolism showed that the key enzymes responsible for metabolic clearance of indacaterol are UGT1A1 and CYP3A. Therefore, it is likely that substrates, inhibitors or inducers of these enzymes may affect the PK of indacaterol and its metabolites. Also, indacaterol did not affect the activity of the major CYPP450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 (see 2.4.2.3). Therefore, no major effects of indacaterol should be expected on the PK of other drugs.

2.4.2.2 Is the drug a substrate of CYP enzymes?

Yes. Based on in vitro metabolism studies CYP3A4 appear to be the major CYP enzyme involved in the metabolism of indacaterol with a minor contribution to the overall elimination. The sponsor did not evaluate whether indacaterol is also metabolized by CYP3A5. Substrates for CYP3A4 and CYP3A5 often overlap, and CYP3A5 is polymorphic.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

No. Indacaterol showed no significant inhibition of the P450 enzymes: CYP2C9, CYP2E1 and CYP3A4/5, when tested at concentrations of up to 100 μM. Relatively weak inhibition of the P450 enzymes: CYP1A2 (IC50 ≈ 10 μM), CYP2C8 (IC50 ≈ 25 μM), CYP2C19 (IC50 ≈ 25-50 μM), and CYP2D6 (IC50 ≈ 5-10 μM), was observed. Based on the maximum indacaterol serum concentrations observed at a therapeutically relevant dose of 300 μg (850 pg/mL=2.17 nM/L) ([i]/ki=0.00217/10<<<<20), it is unlikely that indacaterol could inhibit significantly (clinically) the metabolism of drugs metabolized by any of the major cytochrome P450 enzyme.

Due to the high *K*m value for glucuronidation of indacaterol by UGT1A1 and expected low indacaterol systemic concentrations, it is unlikely that indacaterol would have an effect on endogenous bilirubin metabolism.

The potential for indacaterol or its metabolites to act as an inducer of CYP enzymes was not evaluated. However, the potential of indacaterol/major metabolites to induce drug metabolizing enzymes is considered negligible based on the much lower indacaterol serum concentrations (2.2nM which is 115-fold lower than the lowest reported EC50 value (0.25 μM) for rifampicin) observed in humans compared to the EC50 levels that are known for typical enzyme inducers.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Indacaterol is a low affinity (Km>150 μM) substrate for the efflux pump P-gp. *In-vitro* investigations in Caco-2 monolayer systems characterized indacaterol as a medium to high permeability drug substance that is also a low affinity substrate for P-gp mediated efflux.

Table 2.4.2.4.1. In vitro permeability (Papp) of indacaterol across Caco-2 cells monolayers in the presence and absence of transport protein inhibitors, pH 7.4[a] (Data from study R0500761)

Nominal concentration (μM)	Inhibitor[b]	Papp (x 10^{-5} cm/min) Apical to Basolateral	Papp (x 10^{-5} cm/min) Basolateral to Apical	Efflux ratio[c]
2.0	None	3.3 ± 1	58 ± 4	17 ± 5
	MK571	1.2 ± 0.3	66 ± 1.7	55 ± 14
	LY335979	16 ± 1	15 ± 2	0.9 ± 0.1
12	None	1.5 ± 0.3	65 ± 4	43 ± 8
	MK571	1.4 ± 0.5	89 ± 2	63 ± 20
	LY335979	13 ± 2	18 ± 1	1.3 ± 0.2

a Cell monolayer integrity was determined prior to the experiment by measuring the transepithelial electrical resistance (TEER); average TEER ranged between 425-490 Ωcm2.
b Final concentrations of LY335979 and MK571 were 1 and 10 μM, respectively.
c Efflux ratio = P_{app} (Basolateral to Apical) / P_{app} (Apical to Basolateral)

2.4.2.6 What is the effect of indacaterol on the PK of other drugs? What is the effect of other drugs on the PK of indacaterol?

DDI with Ketoconazole

Concomintant administration of indacaterol inhalation powder 300 μg with ketoconazole 200 μg BID resulted in a 2-fold increase in the AUC and a 31% increase in Cmax (Table 2.4.2.6.1). However, dose adjustment on the basis of concomitant administration with ketoconazole may not be necessary given that safety has been demonstrated for multiple doses of indacaterol up to 600 μg QD.

Table 2.4.2.6.1. Statistical results for PK parameters of indacaterol

PK parameter (unit)	Treatment group	N	Geometric mean[1]	Ratio[2]	90% CI	P value
Cmax [ng/mL]	Indacaterol	18	0.63			
	Indacaterol + Ketoconazole	18	0.82	1.31	1.16, 1.48	0.001
AUC0-24 [ng.h/mL]	Indacaterol	18	2.85			
	Indacaterol + Ketoconazole	18	5.35	1.88	1.73, 2.04	<0.001
AUC0-tlast [ng.h/mL]	Indacaterol	18	5.19			
	Indacaterol + Ketoconazole	18	10.12	1.95	1.78, 2.13	<0.001
AUC0-∞ [ng.h/mL]	Indacaterol	18	6.78			
	Indacaterol + Ketoconazole	18	12.99	1.92	1.76, 2.09	<0.001

(1) Obtained from analysis of variance of logarithmically transformed values.
(2) Ratio = indacaterol+ketoconazole/indacaterol.

It is noted that this study used the 200 µg BID regimen for ketoconazole rather than the 400 µg QD as recommended in the FDA Guidance. Given that the half-life of indacaterol is about 50 hours, the administration of ketoconazole twice a day may be more appropriate than the 400 µg QD dosing regimen for the evaluation of maximum degree of interaction.

DDI with Verapamil

Concomitant administration of indacaterol 300 µg with verapamil 80 µg t.i.d for 4 days showed an increase in the AUC and Cmax of indacaterol of 200% and 50%, respectively (Table 2.4.2.6.2). However, dose adjustment of indacaterol inhalation powder may not be necessary.

Table 2.4.2.6.2. Statistical results for PK parameters of indacaterol – ratios of geometric means and 90% confidence intervals

Pharmacokinetic parameter					
C_{max}		AUC_{0-24}	AUC_{0-48}	$AUC_{0-tlast}$	$AUC_{0-\infty}$
Ratio [1]	1.53	2.00	1.90	1.47	1.35
90 % CI	1.34, 1.76	1.80, 2.23	1.71, 2.11	1.32, 1.64	1.20, 1.52

1) Ratio = indacaterol+verapamil/indacaterol alone (using geometric means), back transformed from log scale

DDI with Erythromycin

Concomitant administration of indacaterol inhalation powder 300 µg (single dose) with erythromycin 400 µg q.i.d for 7 days showed an increase in the indacaterol AUC and Cmax of 60% and 15%, respectively (Study B2220). Dose adjustment on the basis of concomitant administration with erythromycin is not necessary.

DDI with Mometasone

The indacaterol Cmax and AUC increased by 12% and 41%, respectively following single dose administration of indacaterol 250 µg via Twisthaler + mometasone furoate 200 µg dry powder inhaler formulation administered via Twisthaler™ compared to that after indacaterol 250 µg alone via Twisthaler. Indacaterol did not alter the systemic exposure of mometasone (Study A2206). Dose adjustment for concomitant administration with mometasone is not necessary.

2.4.2.7 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

Indacaterol is mainly metabolized by UGT1A1. The effect of inhibitors/inducers of UGT1A1 on the systemic exposure of indacaterol is unknown.

Indacaterol may be metabolized by CYP3A5 and this should be explored as a potential source of PK variability. The drug target, ADRB2, is known to have functional polymorphisms that have demonstrated effects on β_2-agonist responses in asthma. The sponsor should assess responses according to ADRB2 polymorphisms in the pivotal studies and subsequent efficacy studies to assess their contribution to response variability.

2.5 General Biopharmaceutics

2.5.1 What is the BCS Class classification for indacaterol?

This information was not provided by the sponsor. Also, this information may not be relevant since this is not a solid dosage form.

2.5.2 Was the to-be-marketed formulation used in the PK/clinical trials?
Phase III clinical development of indacaterol was completed using the Concept1 SDDPI device. Other devices used in earlier clinical pharmacology studies were the single-dose dry powder inhalation (SDDPI) devices, RS01 and Aerolizer™ and a multiple-dose dry powder inhalation (MDDPI) device, Certihaler™. A pressurized-metered dose inhaler (pMDI) was also used in a number of studies. The majority of the pivotal clinical pharmacology studies were conducted with the to-be marketed formulation/ device (Concept 1 SDDPI). Table 2.5.2.1 summarizes doses evaluated within each device.

Table 2.5.2.1. Inhalation devices used in development of indacaterol

Device	Type	Indacaterol doses tested (μg)
Concept1	SDDPI	150, 300, 600
Aerolizer ™	SDDPI	25, 100, 200, 300, 400, 800, 1200, 2000
RS01	SDDPI	400, 1000, 2000, 3000
Certihaler ™	MDDPI	50, 100, 200, 300, 400, 600, 1200, 2000
pMDI	HFA	200, 400, 600, 800

2.5.3 Are the method and dissolution specifications supported by the data provided by the sponsor?
This does not apply for orally inhaled drugs.

2.5.4 What is the effect of food on the BA of the drug?
This was not assessed. Generally, the effect of food on the PK of orally inhaled drugs is not evaluated since the effect of these drugs is local. However, food may increase the systemic exposure of these drugs which may change its safety profile.

2.6 Analytical Section
2.6.1 Was the suitability of the analytical method supported by the submitted information?
Bioanalytical methods for indacaterol and its metabolites
QAB149 (indacaterol free base) was analyzed in serum and urine using a specific HPLC-MS/MS method with a lower limit of quantification (LLOQ) of 10 pg/mL using 200 μL serum (100 μL with online SPE) and of 50 pg/mL using 100 μL urine, respectively. The assays met all validation acceptance criteria with regard to precision, accuracy and specificity, except for one study which %CV was higher than 20%. This study was not considered a pivotal study.

In early phases of development indacaterol was analyzed with bioanalytical methods that were less sensitive (e.g. 250 pg/mL, 70 pg/mL and 50 pg/mL in serum). Methods for the analysis of indacaterol glucuronide in serum and urine were based on the determinations of "total indacaterol (i.e. the sum of parent and conjugated indacaterol) after sample treatment with glucuronidase followed by subtraction of the concentration of indacaterol measured in untreated samples. For the determination of potential enantiomeric conversion of indacaterol, in-vivo using urine samples from [Study CQAB149A2211], an enantio-selective bioanalytical method for the determination of the S-enantiomer was developed that allowed chromatographic separation of the S- and R-enantiomers. A specific bioanalytical method for analysis of oxidative metabolites (P26.9 and P30.3) in serum samples of [Study CQAB149B2339] was developed as well. All pivotal trials and the majority of PK studies used the most sensitive method with

an LLOQ of 10 pg/mL. The table below shows a summary of analytical methods used in the analysis of indacaterol and its metabolites in this NDA submission.

A summary of the relevant methods is as follows:
Method A for indacaterol in serum with LLOQ of 10 pg/mL: The linearity of the analytical method for analysis of indacaterol in serum was validated (linear regression) in the range 10 pg/mL to 2000 pg/mL. The method is specific in human serum (maximum interference 5.1 % of signal at LLOQ). The inter-day accuracy and precision of the method was evaluated as the mean bias and precision of quality control samples analyzed during 3 validations days: bias at LLOQ was 4.2 %, and precision was 10.9 %. Above LLOQ, the biases were within the range -0.8 % to 1.8 % and the precisions were within the range 2.2 % to 9.9 %.

Method G for hydroxy-indacaterol in serum with LLOQ of 46 pg/mL: The linearity of the analytical method for analysis of hydroxy-indacaterol in serum was validated (linear regression) in the range 46 pg/mL to 460 pg/mL. The method quantified the sum of four enantiomers potentially resulting from hydroxylation at the ethyl-indan moiety of indacaterol. Out of the four enantiomers a pair of two diastereomers were observed in feces samples from the human ADME (i.e. P26.9 and P30.3 at a ratio of 1/3; see CTD section 4.2.2).The method is specific in human serum (maximum interference 5.0 % of signal at LLOQ). The inter-day accuracy and precision of the method was evaluated as the mean bias and precision of quality control samples analyzed during 3 validations days: bias at LLOQ was 13.9 %, and precision was 7.1 %. Above LLOQ, the biases were within the range 4.1 % to 6.5 % and the precisions were within the range 6.8 % to 10.2 %.

Method H for indacaterol in urine with LLOQ of 100 pg/mL: The linearity of the analytical method in urine without glucuronidase/sulfatase sample treatment was validated (quadratic regression) in the range 0.1 ng/mL to 100 ng/mL. The method is specific in human urine (maximum interference 6.7 % of signal at LLOQ). The inter-day accuracy and precision of the method was evaluated as the mean bias and precision of quality control samples analyzed during one validation day: bias at LLOQ was -1.3 %, and precision was 10.3 %. Above LLOQ, the biases were within the range -12.5 % to 3.0 % and the precisions were within the range 1.3 % to 3.8 %.

Method J for S-enantiomer to indacaterol in urine with LLOQ of 200 pg/mL: The linearity of the analytical method in urine was validated (quadratic regression) in the range 0.2 ng/mL to 20 ng/mL. The method is specific in human urine (maximum interference 0.4 % of signal at LLOQ). The inter-day accuracy and precision of the method was evaluated as the mean bias and precision of quality control samples analyzed during 2 validation days: bias at LLOQ was -2.5 %, and precision was 8.2 %. Above LLOQ, the biases were within the range - 4.0 % to 5.5 % and the precisions were within the range 2.2 % to 4.4 %.

3. LABELING COMMENTS

There are no labeling comments to the sponsor at this time since this NDA will not be approved in this review cycle.

Appendix:
4.1 Individual Study Reports

"An open-label study in adult healthy male subjects to assess the absorption, distribution, metabolism and excretion of a single oral dose of 800 µg [^{14}C]QAB149"

Study No. A2223 **Development phase of study**: phase IIb

Objective

Primary objectives
• To determine mass balance
• To identify and quantify QAB149 and its metabolites in serum, urine and feces
• To identify the biotransformation pathways of QAB149
• To determine the rate and routes of excretion of QAB149 and its metabolites
• To determine the kinetics of total radioactivity in blood and serum

Secondary objective
• To determine the kinetics of QAB149

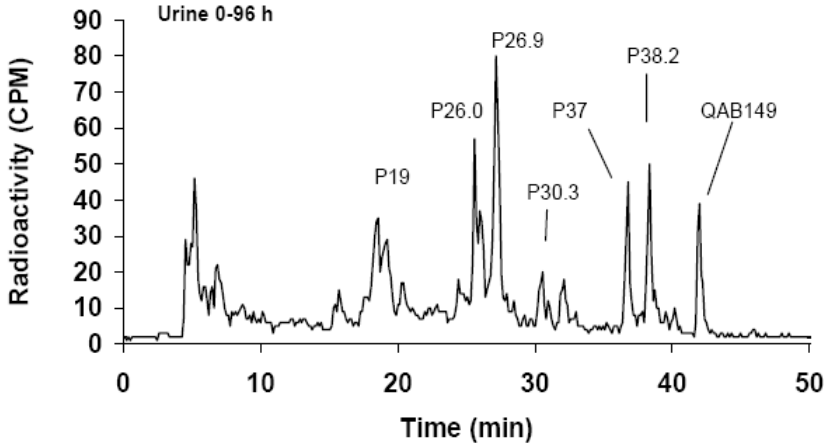
Study Design and Methods
This study was an open-label, single-dose study in healthy male subjects to assess the absorption, distribution, metabolism and excretion of a single oral dose of 800 µg [^{14}C]QAB149. Four Subjects (Healthy, non-smoking, male subjects, between 21 and 55 years of age and in good health as determined by past medical history, physical examination, electrocardiogram, laboratory tests and urinalysis) received a single oral dose of 800 µg [^{14}C]QAB149. The actual administered radioactive dose and radiochemical purity was determined by liquid scintillation counting by the investigator prior to dosing. Specific radioactivity of the free base was 62.5 µCi/mg. If the recovery of radioactivity in the total excreta indicated incomplete recovery at 168 h, it was planned that a single oral dose of 800 µg cold QAB149 would be administered on the morning of Day 8 and Day 9.

Blood was collected from each of the four subjects at the study center at fixed time points post dose (0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168 h). A portion of the blood was processed to obtain serum. The radioactivity of the serum at each time point was measured by liquid scintillation counting (LSC). The measurements were performed by the DMPK-ADME section at Novartis. Pharmacokinetic parameters for serum based on these radioactivity values were calculated by the DMPK-ADME section at Novartis. All urine and feces samples produced by the subjects from 0 to a maximum of 312 h post dose were collected at the study center. The radioactivity associated with each urine and feces sample was measured at the study center using liquid scintillation counting (LSC). These radioactivity values were used by the study center to calculate the percentage of dose excreted. Subjects were not released until it had been confirmed

that greater than 85% of the radioactivity administered in the dose had been excreted. A portion of the serum collected by the study center was sent to the Bioanalytical section at Novartis where it was assayed for QAB149 concentrations using a validated liquid chromatography-mass spectrometry (LC-MS) method. Pharmacokinetic parameters for QAB149 based on these concentration values were calculated by the DMPK-ADME section at Novartis. A portion of the serum, urine, and feces collected by the study center was sent to the DMPKADME section at Novartis where metabolite patterns were determined by liquid chromatography (LC) with radiometric detection. Metabolite structural elucidation was performed using mass spectrometry.

Results:

Representative HPLC profiles of the radiolabeled components in pooled urine (0-312 h) and feces (0-312 h) from subject 5104 are shown in Figure 1. The amounts of each component are listed in Table 1. The major metabolites of QAB149 identified in this study were **P19** (glucuronide conjugate of P26.9), **P26.9** (hydroxylation of one of the benzyl carbons in the diethyl-indane moiety), **P30.3** (diastereomer of P26.9), **P37** (phenolic O-glucuronide conjugate), **P38.2** (diethyl-indanylamino-acetic acid metabolite formed from oxidative cleavage), and **P39** (diethyl-indanylamine metabolite resulting from N-dealkylation).



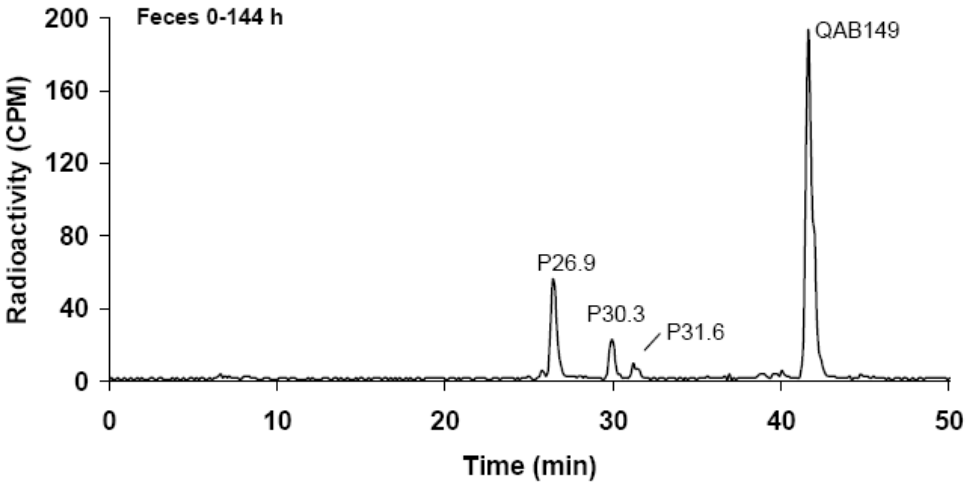


Figure 1 Metabolite profiles in the excreta of human subject 5104 following a single oral dose of 800 micrograms [^{14}C] QAB149

Table 1 Amounts of QAB149 and its metabolites (expressed as % of dose) in urine (0-96 h) and feces (0-144 h) of four human subjects following a single oral dose of 800 micrograms [^{14}C]QAB149

Metabolites	Subject 5101		Subject 5102		Subject 5103		Subject 5104		Total in excreta	
	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Mean	SD
P19	1.15	0.00	0.39	0.00	0.78	0.00	1.01	0.00	0.83	0.33
P26.0*	0.94	0.00	0.73	0.00	1.12	0.00	1.58	0.00	1.09	0.36
P26.9	1.34	29.86	0.53	9.56	0.98	16.20	2.11	14.15	18.68	8.92
P30.3	0.42	10.04	0.12	3.51	0.31	6.31	0.40	5.44	6.64	2.85
P31.6*	0.00	4.57	0.00	1.98	0.00	2.54	0.00	2.20	2.82	1.19
P37	0.77	0.00	0.21	0.00	0.31	0.00	0.81	0.00	0.52	0.31
P38.2	1.22	0.00	0.66	0.00	0.92	0.00	1.07	0.00	0.97	0.24
P39	0.00	1.85	0.00	2.59	0.00	2.35	0.00	0.00	1.70	1.17
P42 (QAB149)	0.60	25.48	0.04	74.19	0.00	63.84	0.72	54.17	54.76	20.69
Sum	6.45	71.80	2.68	91.83	4.41	91.24	7.70	75.97	88.02	8.46

* not identified

The majority of the dose in the feces was recovered as unmodified QAB149 (54.76 ± 20.69%) with a significant portion also being recovered in the form of the oxidative metabolites P26.9 and P30.3 (23.8 ± 11.4%). The portion of the dose recovered in the urine was distributed between multiple metabolites and unchanged parent drug.

The majority of the dose (85.3 ± 7.6%) was excreted in the feces within 312 h while urinary excretion accounted for 9.7 ± 3.7% of the dose (Table 2). Mass balance was achieved in this study with ≥ 90% of the administered radioactivity being recovered in the excreta after 13 days.

Table 2. Excretion of radioactivity in urine and feces for 13 days (% of dose)

Subject	5101	5102	5103	5104	(mean ±SD)
Urine (0-312 h)	10.3	4.8	10.1	13.7	9.7±3.7
Feces (0-312 h)	82.1	91.8	91.2	76.0	85.3±7.6
Dose recovery (%)	92.4	96.6	101.3	89.7	95.0±5.1

[a]Subjects 5101 and 5104 exited the study at 264 hours post-dose while subjects 5102 and 5103 exited the study at 312 hours post-dose

Concentrations of total radioactivity in serum were measured by liquid scintillation counting (LSC). The serum total radioactivity concentration-time profiles are shown in Figure 2. The key pharmacokinetic variables are summarized in table 3

Figure 2 Individual subject total radioactivity in serum concentration-time profiles

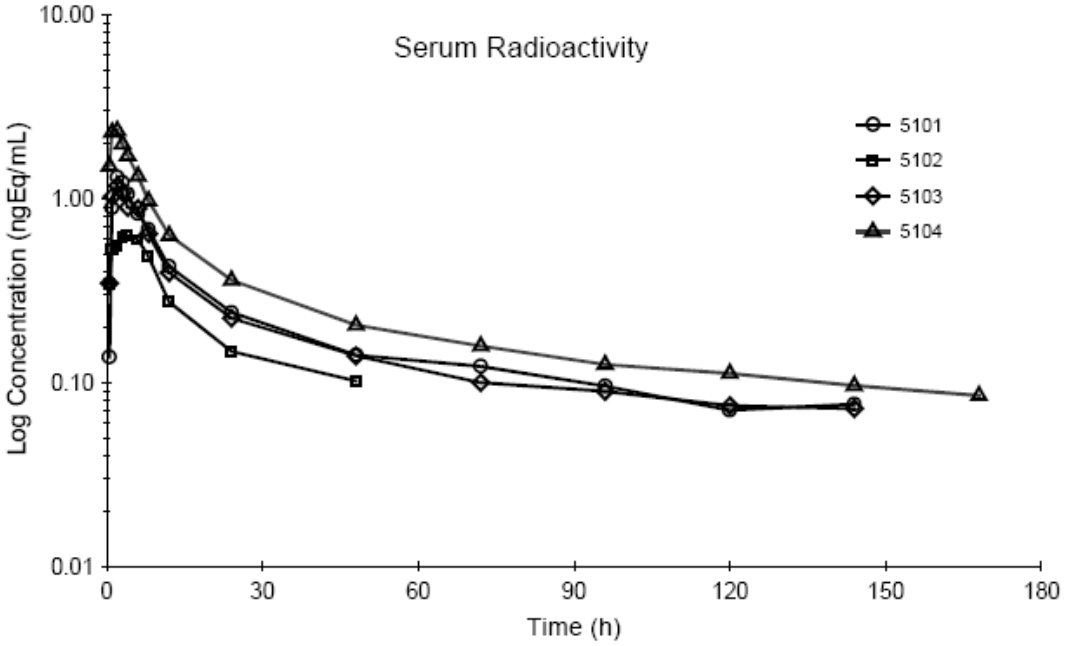


Table 3 Pharmacokinetic parameters for total radioactivity in serum following a single oral dose of 800 micrograms [14C]QAB149

Subject	C_{max} ngEq/mL	t_{max} h	$t_{1/2}$ h	AUC_{0-24} ngEq.h/mL	AUC_{0-last} ngEq.h/mL[a]	AUC_{0-inf} ngEq.h/mL
5101	1.3	2	96.4	13.4	27.5	37.0
5102	0.6	4	-----[d]	8.4	11.3	-----[d]
5103	1.2	2	143.5	12.7	25.9	40.4
5104	2.3	2	110.6	22.0	44.0	57.2
Mean (median)[b]	1.4	2.0	116.8	14.1	27.2	44.9
SD (range)[c]	0.70	2 - 4	24.2	5.7	13.3	10.8
CV%	52.8	40.0	20.7	40.3	49.1	24.1

[a]The last time point included in the calculation of AUC's was 48 h for subject 5102, 144 h for subjects 5101 and 5103, and 168 h for subject 5104
[b]Values are median for tmax and mean for t1/2, Cmax and AUC's
[c]Values are range for tmax and SD for t1/2, Cmax and AUC's
[d]For subject 5102 there were insufficient later time points in the concentration versus time profile to allow for a determination of t1/2 and AUC_{0-inf}

Following the single oral dose, mean peak radioactivity concentrations of 1.4 ± 0.70 ngEq/mL in the serum were attained at about 2 h. The mean AUC_{0-24h} for radioactivity was 14.1 ± 5.7 ngEq•h/mL in the serum. The mean AUC_{0-last} for radioactivity was 27.2 ± 13.3 ngEq•h/mL in the serum. The mean AUC_{0-inf} for radioactivity (estimated from subjects 5101, 5103, and 5104) was 44.9 ± 10.8 ngEq•h/mL in the serum. The mean terminal half-life of radioactivity in serum (estimated from subjects 5101, 5103, and
5104) was calculated to be 116.8 ± 24.2 h. In serum, the largest contributor to the exposure was QAB149 (32.5% of $AUC_{0-24hrs}$). Metabolites contributing to the serum exposure included P19 (5.8% of $AUC_{0-24hrs}$), P26.9 (12.4% of $AUC_{0-24hrs}$) and P37 (4.2% of $AUC_{0-24hrs}$). P37.7, P38.2, and P39 co-eluted in the serum radio chromatogram but together contributed 12.9% to the $AUC_{0-24hrs}$.

The serum PK parameters for QAB149 are listed in Table 4. The QAB149 peak serum concentrations were in the range of 0.30 – 0.79 ng/mL (mean 0.47 ng/mL) for the four subjects. These levels were reached between 1 and 3 h (median 1.5 h). The serum exposure to QAB149 (AUC_{0-last}) ranged from 0.77 to 3.87 ng•h/mL (mean 1.81 ng•h/mL). There were an insufficient number of later time points to allow a mean terminal half-life ($t_{1/2}$) to be estimated which also prevented the calculations of the mean apparent plasma clearance (CL/f) and the mean apparent volume of distribution (Vz/f).

Table 4 PK parameters of QAB149 in serum following a single oral dose of 800 micrograms [14C]QAB149

Subject	5101	5102	5103	5104	mean (median)[a]	SD (range)[b]
C_{max}, ng/ml	0.43	0.30	0.35	0.79	0.47	0.22
t_{max}, h	1	3	2	1	1.50	1 - 3
$AUC_{0\text{-}last}$[c], ng.h/mL	0.77	1.50	1.10	3.87	1.81	1.41

[a]Values are mean for C_{max} and $AUC_{0\text{-}last}$ and median for t_{max}

[b]Values are SD for C_{max} and $AUC_{0\text{-}last}$ and range for t_{max}

[c]The last time point included in the calculation of AUC was 3 h for subject 5101, 8 h for subject 5102, 6 h for subject 5103, and 12 h for subject 5104

Table 5 PK parameters of QAB149 and its metabolites in serum from four healthy volunteers following a single oral dose of 800 micrograms [14C]QAB149

		P19	P26.9	P37	P37.7/ P38.2/P39	QAB149
2 h pool	ngEq/mL	0.12	0.18	0.10	0.16	0.42
	% of total radioactivity in pool	9.31	13.2	7.42	11.7	31.4
$AUC_{0\text{-}24h}$ pool	ngEq.h/mL	0.82	1.8	0.60	1.82	4.58
	% of total radioactivity in pool	5.78	12.4	4.22	12.9	32.5

The pharmacokinetics parameters of QAB149 and its metabolites in serum from four healthy volunteers following a single oral dose of 800 micrograms [14C]QAB149 was shown in Table 5.

In serum, the largest contributor to the exposure was QAB149 (32.5% of $AUC_{0\text{-}24hrs}$ Metabolites contributing to the serum exposure included P19 (5.78% of $AUC_{0\text{-}24hrs}$), P26.9 (12.4% of AUC0-24h) and P37 (4.22% of $AUC_{0\text{-}24hrs}$). P37.7, P38.2, and P39 co-eluted in the serum radiochromatogram but together contributed 12.9% to the $AUC_{0\text{-}24hrs}$.

The total radioactivity in the serum achieved its maximum levels (Cmax) within 2-4 hours. The terminal half life of elimination (t1/2) for serum radioactivity was 116.8 ± 24.2 hours. QAB149 achieved its maximum levels (Cmax) within 1 -3 hours (Table 6).

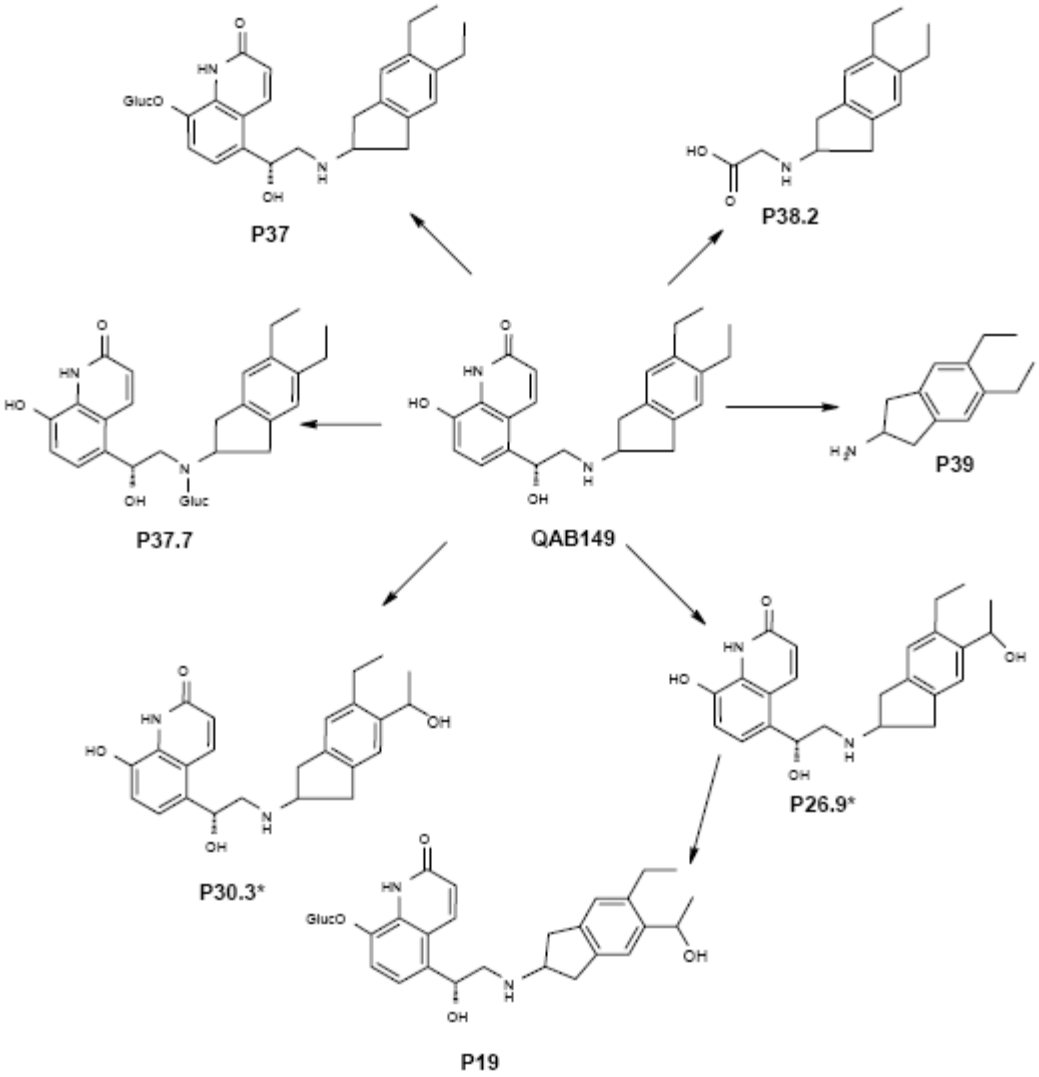
Table 6. Summary of PK metabolism and excretion results:

Subjects	four healthy adult males	
Route of administration	oral	
Dosage form	capsules	
Dosage	800 µg [^{14}C] QAB149, 50 µCi	
QAB149 in serum	C_{max}, ng/mL	0.47 ± 0.22
	t_{max}, h	1.50 (1-3)
	AUC $_{0\text{-last}}$, h.ng/mL	1.81 ± 1.41
Total radioactivity in serum	C_{max}, ngEq/mL	1.4 ±0.70
	t_{max}, h	2 (2-4)
	AUC $_{0\text{-last}}$, h.ngEq/mL	27.2 ± 13.3
Excretion of radioactivity in urine (0-312 h)	% of dose	9.7 ± 3.7
Excretion of unchanged QAB149 in urine (0-96 h)	% of dose	0.34 ± 0.37
Excretion of radioactivity in feces (0-312 h)	% of dose	85.3 ± 7.6
Excretion of unchanged QAB149 in feces (0-144 h)	% of dose	54.4 ± 21.0
Total radioactivity recovery in excreta (0-312 h)	% of dose	95.0 ± 5.1

Unmodified parent drug was mainly excreted in the feces where it accounted for an average of 54.4% of the administered dose. In urine, unmodified parent drug accounted for an average of only 0.34% of the dose. Based on the metabolites characterized in human excreta and in serum, a general biotransformation scheme for QAB149 is proposed in Figure 3. The primary metabolic reactions observed included:

1. Hydroxylation of the benzylic carbon in the diethyl-indanyl moiety. This pathway leads to the formation of the diastereometric metabolites P26.9 and P30.3 which together accounted for 25.3 % of the excreted dose.
2. Both N- and O- glucuronidation. This pathway leads to the formation of metabolites P19, P37 and P37.7. Although these metabolites only accounted for 1.35% of the excreted dose, they represented a significant fraction of the drug-related material found circulating in the serum AUC pool (the exact percentage could not be calculated due to the co-elution of P37.7 with P38.2).
3. Oxidative cleavage. This leads to the formation of metabolites P38.2 and P39 which together accounted for 2.7% of the excreted dose.

Figure 3 Biotransformation scheme of QAB149 in man



Conclusion:

• Mass balance was achieved in this study with ≥ 90% of the administered radioactivity being recovered in the excreta after 13 days.

• The majority of the dose was recovered in the feces (85.3 ± 7.6%) with a minor fraction being recovered in the urine (9.7 ± 3.7%).

• The major metabolites of QAB149 identified in this study were **P19** (glucuronide conjugate of P26.9), **P26.9** (hydroxylation of the benzyl carbon in the diethyl-indane moiety), **P30.3** (diastereomer of P26.9), **P37** (phenolic O-glucuronide conjugate), **P37.7** (N-glucuronide conjugate of the diethyl-indanylamine nitrogen), **P38.2** (diethylindanylamino-acetic acid metabolite formed from oxidative cleavage), and **P39** (diethylindanylamine metabolite resulting from N-dealkylation).

• The majority of the dose in the feces was recovered as unmodified QAB149 (54.4 ± 20.9%) with a significant portion also being recovered in the form of the oxidative metabolites P26.9 and P30.3 (23.8 ± 11.4%). The portion of the dose recovered in the urine was distributed between multiple metabolites and unchanged parent drug.

• In serum, the largest contributor to the exposure was QAB149 (32.5% of $AUC_{0\text{-}24h}$).

Metabolites contributing to the serum exposure included P19 (5.8% of $AUC_{0\text{-}24h}$), P26.9 (12.4% of $AUC_{0\text{-}24h}$) and P37 (4.2% of $AUC_{0\text{-}24h}$). P37.7, P38.2, and P39 co-eluted in the serum radiochromatogram but together contributed 12.9% to the $AUC_{0\text{-}24h}$.

• The total radioactivity in the serum achieved its maximum levels (C_{max}) within 2-4 hours. The terminal half life of elimination ($t_{1/2}$) for serum radioactivity was 116.8 ± 24.2 hours. QAB149 achieved its maximum levels (C_{max}) within 1 -3 hours.

"[^{3}H] QAB149 Metabolic profile in human liver microsomes and potential to inhibit the cytochrome P450-mediated reactions"

Study No. R01994

Objective

To examine the biotransformation pathways of QAB149 in human liver microsomes to confirm the predominant metabolism by glucuronidation found in the liver slice cultures

To examine the roles of specific human UDPglucuronosyl transferases and cytochrome P450s in the metabolism of QAB149 and to investigate the potential of QAB149 to function as an *in vitro* inhibitor of cytochrome P450-mediated reactions

To determine if QAB149 could be metabolized in human lung by examination of QAB149 biotransformation in human pulmonary microsomes

Material:
Unlabeled QAB149-HCl (MW 428.7) was obtained from Isotope Laboratory, Novartis Pharma, East Hanover, New Jersey, USA. Pooled human liver microsomes (n=16 donors) were purchased from (b) (4) Human pulmonary microsomes from an individual female smoker were also purchased from (b) (4) Microsomal preparations from baculovirus-infected insect cells expressing recombinant human cytochrome P450s (co-expressed with P450 reductase) CYP1A1, CYP1A2, CYP1B1, CYP2C18, CYP2D6, CYP3A5 or CYP4A11 were purchased from (b) (4) The recombinant human cytochrome P450s (co-expressed with P450 reductase and cytochrome b_5) CYP2A6, CYP2B6, CYP2C8, CYP2C9 (Arg_{144}, Ile_{359}), CYP2C19, CYP2E1, and CYP3A4 and recombinant human UDPglucuronosyltransferase (UGT) enzymes were also purchased from (b) (4)

Study Design and Methods

Metabolism of 3H by human liver or pulmonary microsomes:
Human liver microsomes or pulmonary microsomes (1 mg protein·mL^{-1}) were incubated in 100 mM potassium phosphate buffer, pH 7.4 for 15 min on ice. Reactions were pre-incubated with 10 µM (human liver microsomes) [^{3}H]QAB149 and 5 mM $MgCl_2$ for 3 min at 37ºC. Reactions were then initiated by the addition of 1 mM NADPH (and 4 mM UDPGA for glucuronidation reactions) and incubated at 37°C for 30 min in a Thermomixer 5436 at 700 rpm. Human pulmonary microsomes were incubated with 15 µM [^{3}H]QAB149 and 5 mM $MgCl_2$ at 37°C for 30 min. Control incubations were performed by omission of microsomal protein or NADPH/UDPGA from the incubation and quenched immediately. The reactions were quenched by the addition of an equal volume of acetonitrile and the precipitated protein removed by centrifugation at 39,000 x g for 10 min in an Avante 30 high speed microcentrifuge, and the sample (25 µL) was analyzed as described below.

HPLC analysis of [3H]QAB149 and metabolites:
Aliquots of the reaction incubations were analyzed by reversed-phase HPLC. The HPLC chromatographic equipment consisted of a model 2690 separation module, equipped with an autosampler and quartinary pump system. Radioactivity was measured on-line with a β-RAM radioactivity detector, with addition of 3 mL liquid scintillant·min^{-1} (or 2 mL liquid scintillant·min^{-1} for kinetic studies) to the HPLC eluate prior to flow through a liquid flow cell (100 µL or 250 µL for kinetic studies, IN/US Systems). The chromatographic separation was performed on a Kromasil 100 column (3 x 150 mm, 3µm), protected by a guard column cartridge of the same material. Gradient elution consisted of solvent A (20 mM ammonium acetate, 0.2 % acetic acid v/v, pH 3.35), and solvent B (acetonitrile, 0.2% acetic acid, v/v), at a flow rate of 0.3 mL·min^{-1}.

Metabolism of [3H]QAB149 by specific UGT enzymes:
To identify the UGT enzyme(s) involved in the glucuronidation of QAB149 in humans, several recombinant UGT enzymes were tested for QAB149 metabolizing activity. Human UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B15 were pre-incubated with alamethicin and [^{3}H]QAB149 (10 µM) and the reactions were initiated with 4 mM UDPGA. The reactions were incubated for 30 min at 37ºC, quenched, and 100 µL of the sample was analyzed by HPLC.

LC/MS/MS of QAB149 and QAB149-glucuronide metabolite formed in human liver microsomes and by human UGT1A1:
Samples from human liver microsome and UGT1A1 incubations were analyzed by positive ion LC/MS/MS to characterize the structures of the glucuronide metabolites.

Metabolism of [3H]QAB149 by specific cytochrome P450 enzymes:
[^{3}H]QAB149 (10 µM, 0.5% final DMSO concentration, v/v) was incubated with the recombinant human P450 enzymes: CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9(Arg$_{144}$,Ile$_{359}$), CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5 or CYP4A11 (250 pmol P450·mL^{-1}) in potassium phosphate buffer (100 mM, pH 7.4). The reactions were initiated by the addition of a NADPH regenerating system (1 mM NADP-Na_2, 5 mM isocitrate, 5 mM $MgCl_2$, 1 U isocitrate dehydrogenase, and 0.2 mM β-NADPH) and incubated for 30 min at 37°C. The control incubation was performed by omission of microsomal protein from the incubation and quenched immediately. The reactions were quenched by the addition of an equal volume of acetonitrile and the precipitated protein removed by centrifugation and 25 µL of the sample was analyzed by reversed-phase HPLC.

LC/MS/MS of QAB149 metabolites formed by cytochrome P450 enzymes:
Human liver microsomes (1 mg microsomal protein·mL^{-1}), recombinant human CYP2D6 or CYP3A4 (250 pmol P450·mL^{-1}), in potassium phosphate buffer (100 mM, pH 7.4), were incubated with a NADPH regenerating system (1 mM NADP-Na_2, 5 mM isocitrate, 5 mM $MgCl_2$, 1 U isocitrate dehydrogenase, and 0.2 mM β-NADPH) for 30 min at 37°C. The reactions were quenched by the addition of an equal volume of acetonitrile and the precipitated protein removed by centrifugation as described above. The samples were analyzed by positive ion

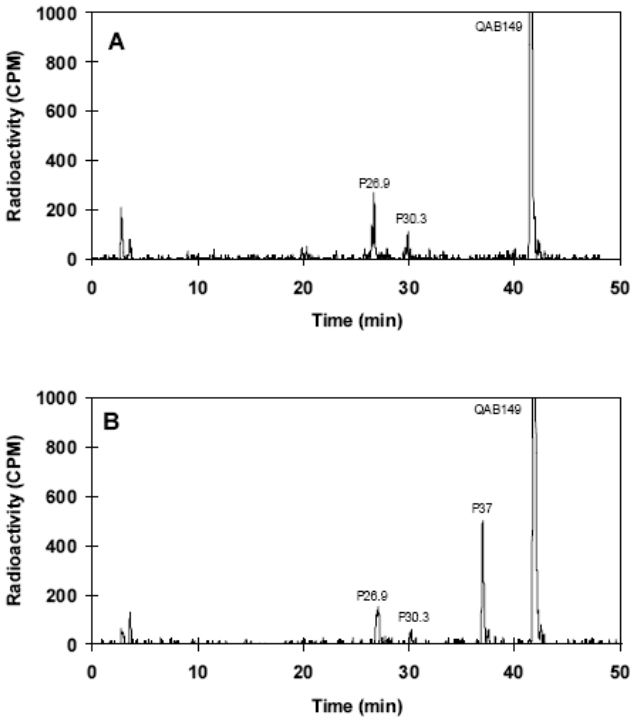
LC/MS and LC/MS/MS to characterize the structures of the QAB149 metabolites. The HPLC eluate was directed entirely into the Finnigan LCQ quadrapole mass spectrometer with the ESI source in positive mode.

Results:

Metabolism of [3H]QAB149 by human liver or pulmonary microsomes:

QAB149 was primarily metabolized by glucuronidation in human liver microsomes, in the presence of UDPGA (Figure 1). In the presence of NADPH and in the absence of UDPGA, the formation of the monooxidation metabolites are P26.9 and P30.3 (Figure 1A). In the presence of UDPGA and NADPH, QAB149 was primarily metabolized to P37 (the phenolic *o*-glucuronide, Figure 1B).

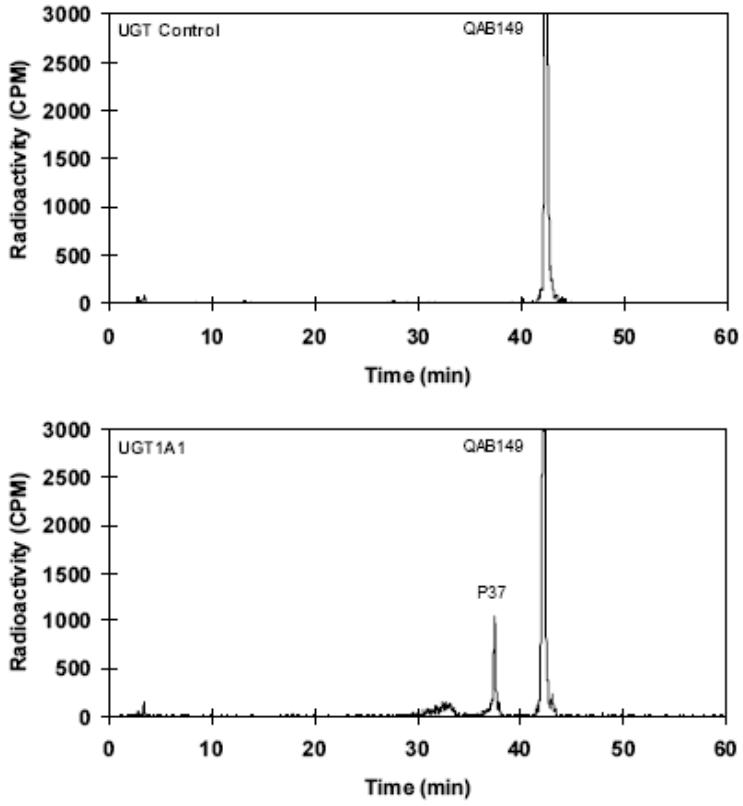
Figure 1: Metabolism of [3H]QAB149 by human liver microsomes



Metabolism of [3H]QAB149 by human recombinant UGT enzymes:

To examine the roles of specific human UGT enzymes in the metabolism of [3H]QAB149, several recombinant UGT enzymes were tested for [3H]QAB149 metabolizing activity. [3H]QAB149 (10 μM) was incubated with nine different human UGT enzymes: UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B15 (at a concentration of 1 mg protein·mL-1). The phenolic *o*-glucuronide metabolite, P37, was predominately formed in reactions with recombinant human UGT1A1 (Figure 2). The structures of QAB149 (P42) and the phenolic *o*-glucuronide (P37) of QAB149 in incubations with human liver microsomes and by recombinant human UGT1A1 were confirmed by LC/MS/MS.

Figure 2 Glucuronidation of [3H] QAB149 by UGT1A1



Metabolism of [3H]QAB149 by specific human cytochrome P450 enzymes

To examine the roles of specific human cytochrome P450 enzymes on the metabolism of [3H]QAB149, several recombinant P450s were tested for [3H]QAB149 metabolizing activity. [3H]QAB149 (10 μM) was incubated with fourteen different P450s (CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9 (Arg144,Ile359), CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5 or CYP4A11) at a concentration of 250 pmol P450·mL-1. Metabolism of [3H]QAB149 above the control (Figure 3) was detectable in incubations with CYP1A1, CYP2D6, and CYP3A4 (Figure 3-6). The metabolites P26.9 and P30.3, formed in reactions with human liver microsomes, were also found in incubations with recombinant human CYP1A1, CYP2D6, and CYP3A4 (Figure 3, 5, 6). The metabolites, P26.9 and P30.3, were examined by LC/MS in incubations with human liver microsomes, CYP3A4 or CYP2D6 and were determined to be monooxidation products (m/z 409). LC/MS3 analysis of P26.9 from incubations with CYP2D6 indicated losses of 1 and 2 H2O (m/z 391 and m/z 373) (Figure 7).

Figure 3 Metabolism of QAB149 by cytochrome P450s CYP1A1, CYP1A2, and CYP1B1

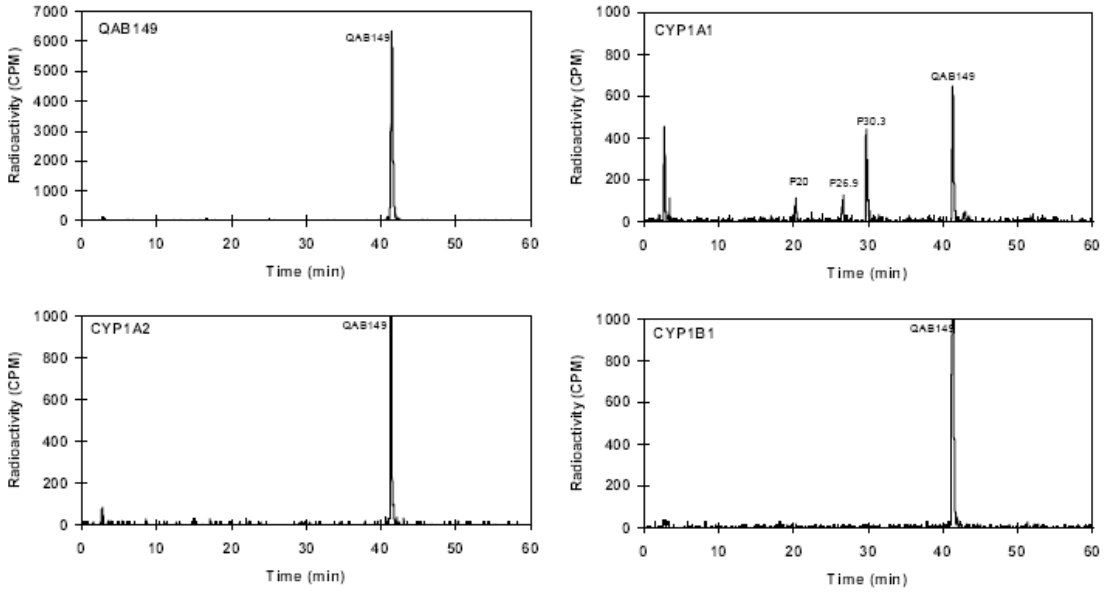


Figure 4 Metabolism of QAB149 by cytochrome P450s CYP2A6, CYP2B6, CYP2C8, and CYP2C9

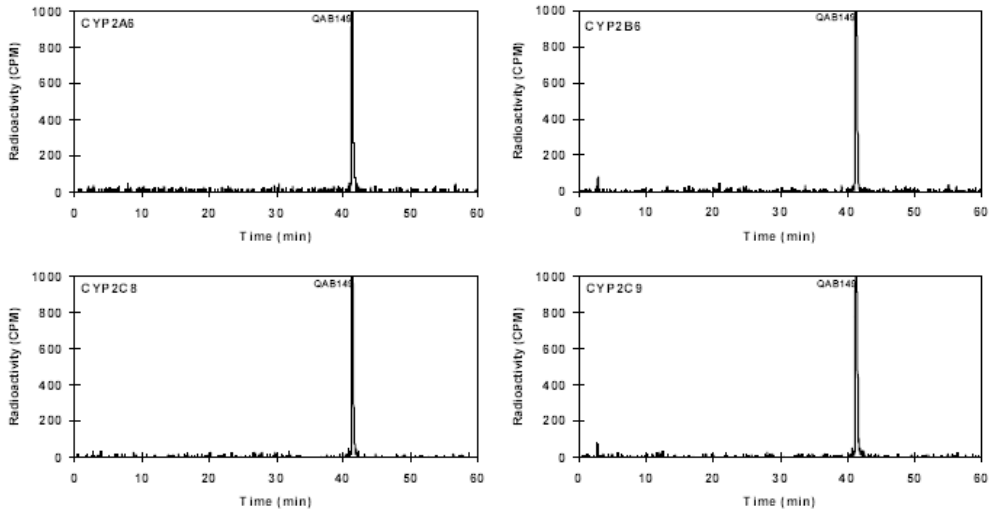


Figure 5 Metabolism of QAB149 by cytochrome P450s CYP2C18, CYP2C19, CYP2D6, and CYP2E1

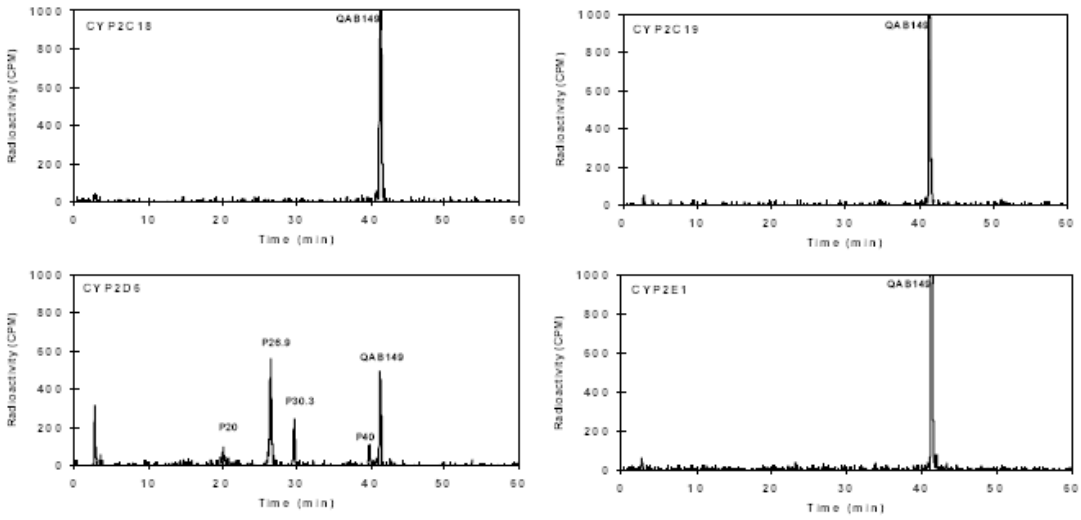


Figure 6 Metabolism of QAB149 by cytochrome P450s CYP3A4, CYP3A5, and CYP4A11

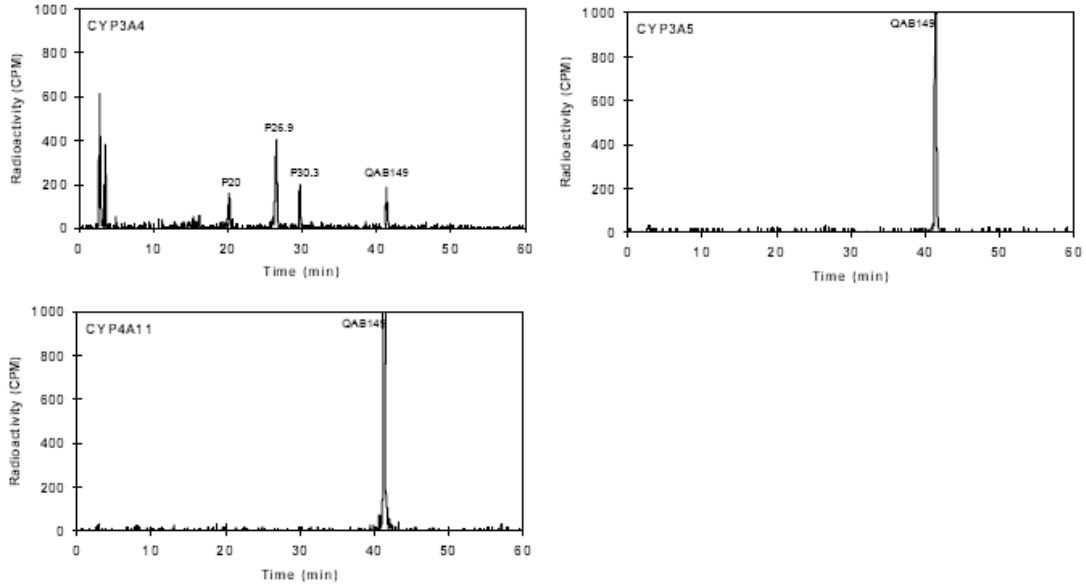
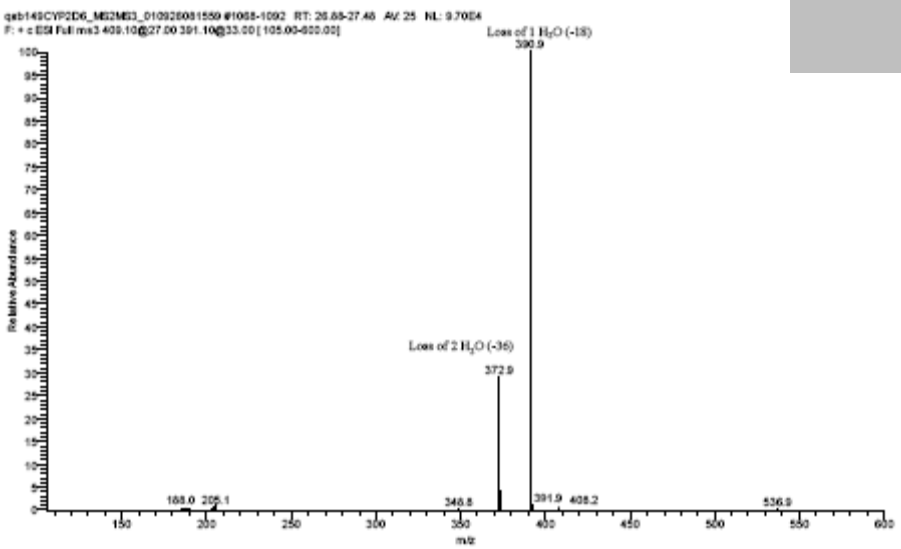


Figure 7 MS product ion spectrum of P26.9 (m/z 409) in incubation with CYP2D6

Best Available Copy



Kinetic analysis of [3H]QAB149 metabolism by human liver microsomes

To define the contributions of glucuronidation and oxidative metabolism to the intrinsic clearance of QAB149, the kinetic parameters (*k*m, Vmax) of QAB149 metabolism in human liver microsomes were determined in the presence or absence of UDPGA (Figure 8, and Figure 9, respectively). Figure 8 A shows a representative HPLC from the kinetic analysis of QAB149 metabolism in the presence of NADPH and UDPGA and Figure 8B is the non-linear regression of the kinetic data. The *K*m value for formation of total metabolites (P37, P26.9, and P30.3) was determined to be 82 ± 12 μM and the Vmax value, 34 ± 3.4 nmol·h-1·mg protein-1 (Table 3). The intrinsic hepatic microsomal clearance (Vmax/*k*m, CLint) was determined to be 0.41 mL·h-1·mg protein-1. Hepatic microsomal clearance of QAB149 was mainly due to formation of P37, the phenolic *o*-glucuronide (Clint 0.34 mL·h-1·mg protein-1), whereas clearance due to oxidative metabolism was at least 5-fold less than clearance due to glucuronidation (CLint by P26.9 formation was 0.065 mL·h-1·mg protein-1). P30.3 kinetic parameters could not be established due to low metabolite formation. In the absence of UDPGA, the *K*m value for formation of total metabolites (P26.9, and P30.3) was determined to be 110 ± 35 μM and the Vmax value, 15 ± 3.5 nmol·h-1·mg protein-1 (Table 4 and Figure 9). The intrinsic hepatic microsomal clearance (Vmax/*K*m, CLint) was determined to be 0.14 mL·h-1·mg protein-1, approximately 3-fold lower than intrinsic clearance in the presence of UDPGA. Clearance was primarily due to formation of P26.9 (CLint 0.10 mL·h-1·mg protein-1).

Table 3 In vitro kinetic parameters of QAB149 metabolism by human liver microsomes in the presence of NADPH and UDPGA

	K_m μM	V_{max} nmol·h^{-1}·mg protein^{-1}	V_{max}/K_m mL·h^{-1}·mg protein^{-1}
Total metabolism[a]	82 ± 12	34 ± 3.4	0.41
P37	59 ± 8.7	20 ± 1.8	0.34
P26.9	200 ± 67	13 ± 3.5	0.065

[a]Total metabolism included metabolites P37, P26.9, and P30.3. P30.3 kinetic parameters could not be determined due to low metabolite formation and large standard error.

Table 4 In vitro kinetic parameters of QAB149 metabolism by human liver microsomes in

the presence of NADPH without UDPGA

	K_m μM	V_{max} nmol·h^{-1}·mg protein^{-1}	V_{max}/K_m mL·h^{-1}·mg protein^{-1}
Total metabolism[a]	110 ± 35	15 ± 3.5	0.14
P26.9	72 ± 19	7.3 ± 1.3	0.10

[a]Total metabolism included metabolites P26.9 and P30.3. P30.3 kinetic parameters could not be determined due to low metabolite formation and large standard error.

Figure 8 Kinetic analysis of [3H]QAB149 metabolism by human liver microsomes in the presence of NADPH and UDPGA

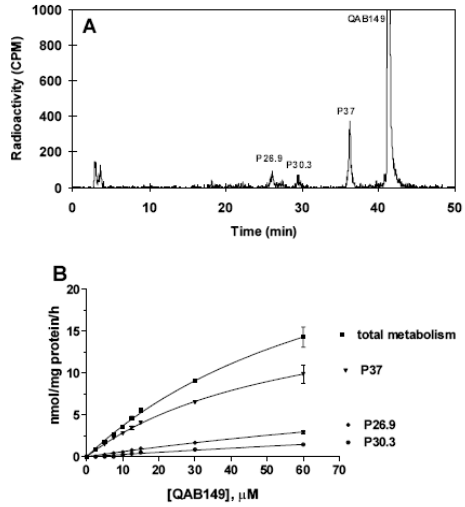
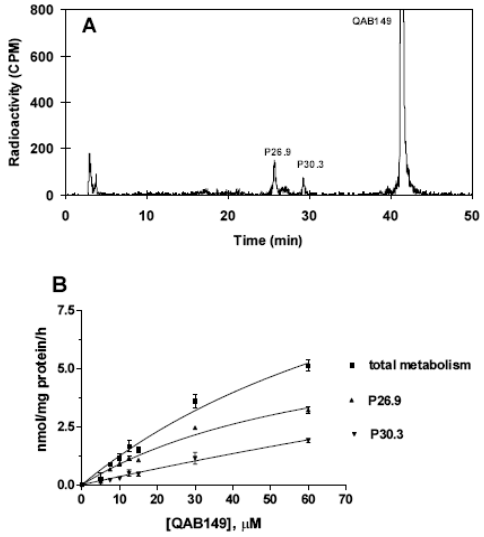


Figure 9 Kinetic analysis of [3H]QAB149 metabolism by human liver microsomes in the presence of NADPH without UDPGA



Kinetic analysis of [3H]QAB149 by recombinant human CYP3A4, CYP2D6, and UGT1A1

Kinetic parameters were established for recombinant human CYP3A4, CYP2D6, and UGT1A1 (Figure 10, 11, 12, and Table 5). CYP3A4 and CYP2D6 primarily metabolized [3H] QAB149 to the oxidative metabolites P26.9 and P30.3. Figure 14 A shows a representative HPLC chromatogram from the kinetic analysis of [3H] QAB149 metabolism by CYP3A4 and Figure 14B is the non-linear regression of the steady-state data. The K_m value for formation of total metabolites (P20, P26.9, and P30.3) by CYP3A4 was determined to be 10 ± 3.7 μM and the V_{max} value, 890 ±170 nmol·h^{-1}·nmol P450^{-1} (Table 5). The efficiency (V_{max}/K_m) of CYP3A4 for [3H] QAB149 metabolism was determined to be 89 mL·h^{-1}·nmol P450^{-1}. The majority of [3H] QAB149 metabolism by CYP3A4 was due to formation of metabolite P26.9. CYP3A4 was 3.6-fold more efficient in formation of P26.9 than P30.3 (V_{max}/K_m, 61 and 17 mL·h^{-1}·nmol P450^{-1}, respectively). The predicted contribution of CYP3A4 to human microsomal oxidative clearance of QAB149 is 2.2 mL·h^{-1}·mg protein^{-1}.

The kinetic analysis of [3H] QAB149 metabolism by human recombinant CYP2D6 is shown in Figure 15. A representative HPLC chromatogram is illustrated in Figure 15A and the non-linear regression of the steady-state data is shown in Figure 15B. CYP2D6 metabolized [3H] QAB149 with 2-fold lower efficiency than CYP3A4 (42 versus 89 mL·h^{-1}·nmol P450^{-1}), primarily due to a lower V_{max} value. The K_m value for formation of total metabolites (P26.9, P30.3, and the minor product, P40) by CYP2D6 was determined to be 2.6 ± 0.57 μM and the V_{max} value, 110 ± 6.8 nmol·h^{-1}·nmol P450^{-1} (Table 5). Formation of P26.9 by CYP2D6 was 7-fold more efficient than formation of P30.3 (V_{max}/K_m, 39 and 5.8 mL·h^{-1}·nmol P450^{-1}, respectively). The predicted contribution of CYP2D6 to human microsomal oxidative clearance of QAB149 is 0.10 mL·h^{-1}·mg protein^{-1}, 22-fold lower than contributions by CYP3A4.

The contributions of the different P450s to the oxidative metabolism of [3H] QAB149 in human liver microsomes can also be estimated from the relative amount of the specific P450 present in human liver microsomes. The contribution of CYP3A4 can be compared to the contributions of CYP2D6 by normalizing the efficiency of [3H] QAB149 metabolism (V_{max}/K_m) of the individual P450s by the relative amount of the specific P450 present in human liver microsomes. This calculation predicts that CYP3A4 would contribute to [3H] QAB149 metabolism by approximately 20-40-fold more than CYP2D6, which is in-line with the 22-fold difference estimated by relative activity factors (Table 5).

Kinetic parameters of QAB149 phenolic *o*-glucuronide (P37) formation by human recombinant UGT1A1 were determined and a representative HPLC chromatogram from the study is shown in Figure 12A. The non-linear regression of the kinetic data is plotted in Figure 12B. The k_m value was found to be high (23 ±1.8 μM) and the V_{max} value was 21 ±0.81 nmol·h^{-1}mg·protein^{-1}.

Figure 10 Kinetic analysis of [3H]QAB149 metabolism by human recombinant CYP3A4

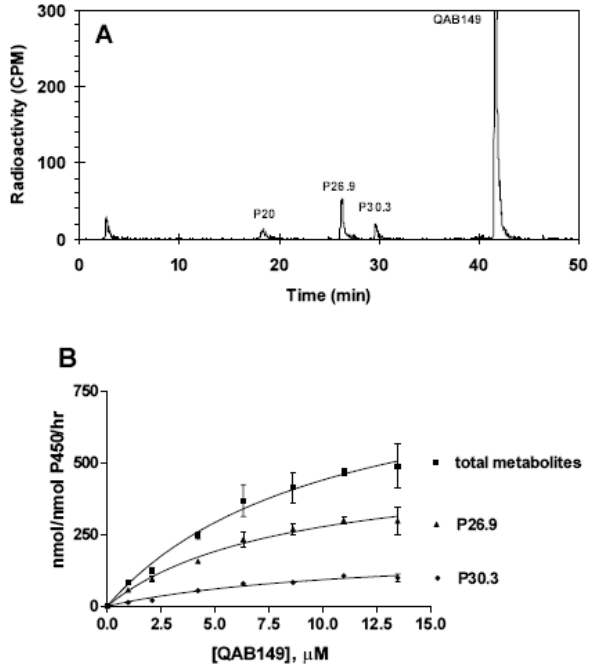


Figure 11 Kinetic analysis of [3H]QAB 149 metabolism by human recombinant CYP2D6

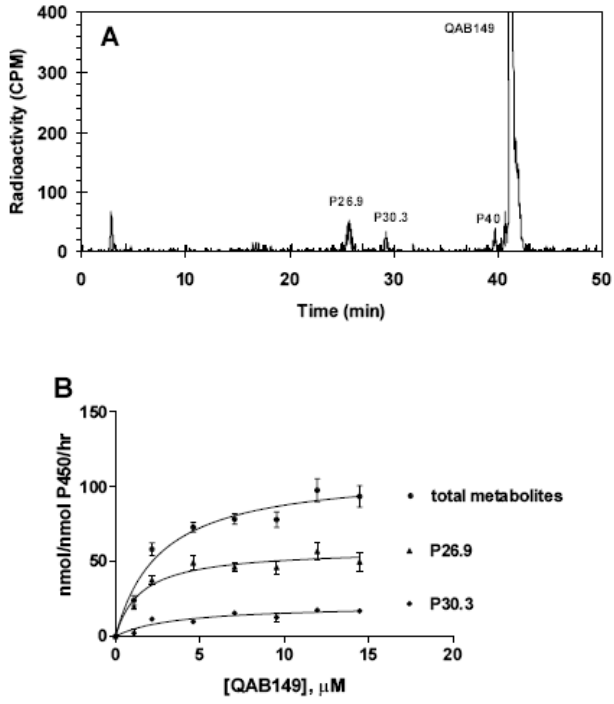
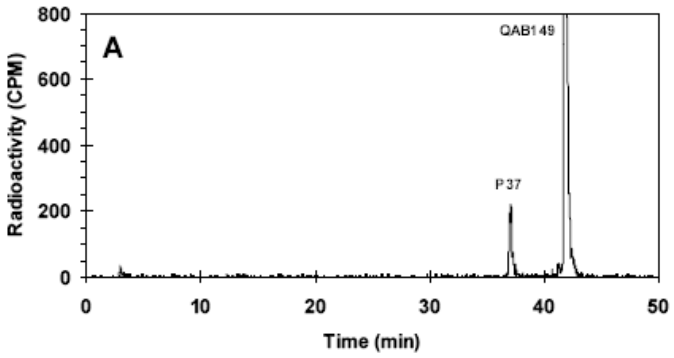


Figure 12 Kinetic analysis of [3H]QAB149 metabolism by human recombinant UGT 1A1



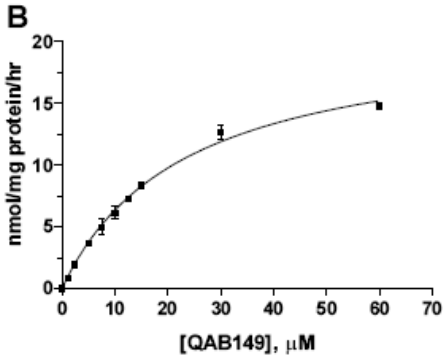


Table 5 *In vitro* kinetic parameters of QAB149 metabolism by recombinant CYP3A4, CYP2D6, and UGT1A1

	K_m μM	V_{max} nmol·h^{-1}·nmol P450^{-1} (nmol·h^{-1}·mg protein^{-1})	V_{max}/K_m mL·h^{-1}·nmol P450^{-1}	Prediction of P450 contribution to human liver microsomal metabolism: V_{max}[a] nmol·h^{-1}·mg protein^{-1}	Prediction of P450 contribution to human liver microsomal metabolism: CL_{int} mL·h^{-1}·mg protein^{-1}
CYP3A4					
Total metabolism[b]	10 ± 3.7	890 ± 170 (84 ± 16)	89	22	2.2
P26.9	8.2 ± 2.5	500 ± 75 (48 ± 7.0)	61	13	1.6
P30.3	12 ± 3.8	200 ± 37 (19 ± 3.5)	17	5.0	0.42
CYP2D6					
Total metabolism[c]	2.6 ± 0.57	110 ± 6.8 (11 ± 0.69)	42	0.26	0.10
P26.9	1.5 ± 0.44	58 ± 3.8 (5.9 ± 0.39)	39	0.14	0.093
P30.3	3.6 ± 1.4	21 ± 2.8 (2.1 ± 0.28)	5.8	0.050	0.014

[a]Determined from the relative activity factors for CYP3A4 = 3.8 and CYP2D6 = 42
[b]Total metabolism represents summation of peaks P30.3, P26.9, and P20
[c]Total metabolism represents summation of peaks P30.3, P26.9, and P40

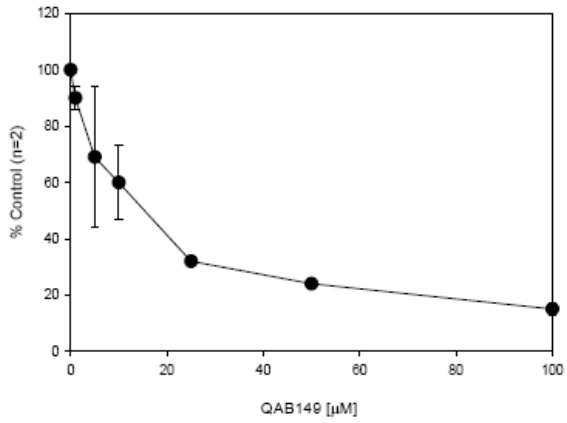
	K_m μM	V_{max} nmol·h^{-1}·mg protein^{-1}	V_{max}/K_m mL·h^{-1}·mg protein^{-1}
UGT1A1			
P37	23 ± 1.8	21 ± 0.81	0.91

Effects of [3H]QAB149 on the metabolism of cytochrome P450 selective substrates

Seven P450 enzyme-selective substrate probes were incubated in the absence and presence of increasing concentrations of QAB149. For the purpose of assessing inhibition, these represented the control values (i.e., 100%). The effect of increasing QAB149 concentration on the above P450 isoform-selective metabolic reactions is shown in Figure 13, Figure 14, Figure 15, Figure 16, Figure 17, Figure 18, and Figure 19.

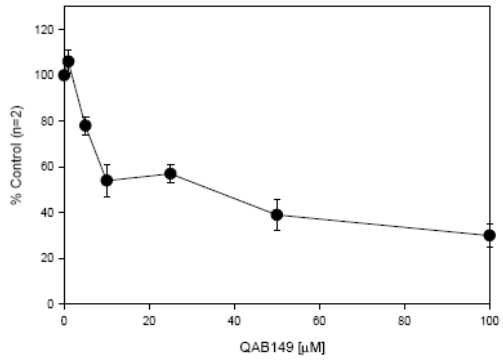
As shown in Figure 13, CYP1A2-mediated deethylation of phenacetin was weakly inhibited by QAB149 with an IC50 value of ~15 μM. Paclitaxel 6 alpha-hydroxylation, catalyzed by CYP2C8, was very weakly inhibited by QAB149 (Figure 14) with an IC50 value of ~30 μM. Diclofenac hydroxylation to yield its 4'-hydroxy metabolite is catalyzed in human liver by CYP2C9. QAB149 was found to not to inhibit this reaction (Figure 15). The 4'-hydroxylation of S-mephenytoin is catalyzed by CYP2C19. QAB149 was found to be a very weak inhibitor of this reaction (Figure 16). Bufuralol 1'-hydroxylation is catalyzed primarily by CYP2D6. QAB149 was found to inhibit bufuralol hydroxylation with an IC50 value ~ 10 μM (Figure 17). Chlorzoxazone 6-hydroxylation is mediated primarily by CYP2E1. QAB149 did not inhibit this reaction (Figure 18). Midazolam 1'-hydroxylation is catalyzed primarily by CYP3A4/5. As shown in Figure 19, QAB149 was found not to be an inhibitor of midazolam 1'-hydroxylation.

Figure 13 Effect of QAB149 on phenacetin deethylation (CYP1A2) in pooled human liver microsomes



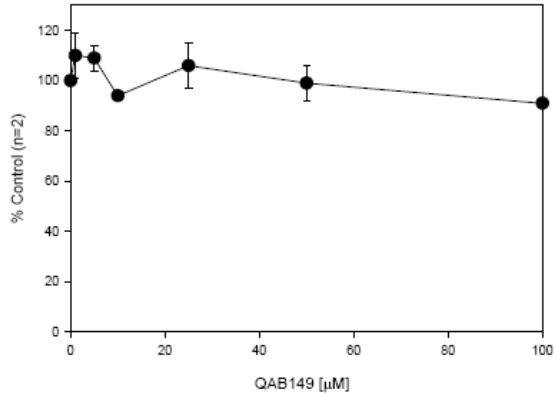
Results represent the mean of two experiments. Error bars indicate the range of values obtained.

Figure 14 Effect of QAB149 on paclitaxel 6alpha-hydroxylation (CYP2C8) in pooled human liver microsomes



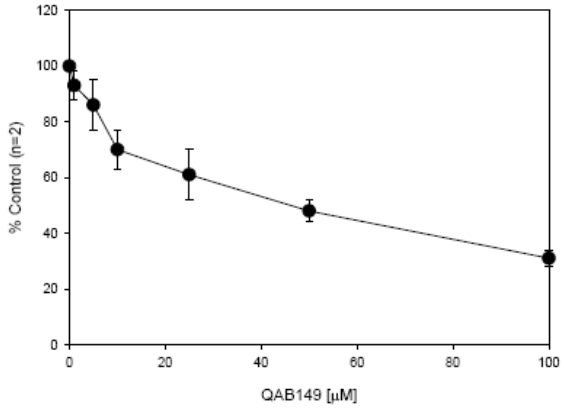
Results represent the mean of two experiments. Error bars indicate the range of values obtained.

Figure 15 Effect of QAB149 on diclofenac 4'-hydroxylation (CYP2C9) in pooled human liver microsomes



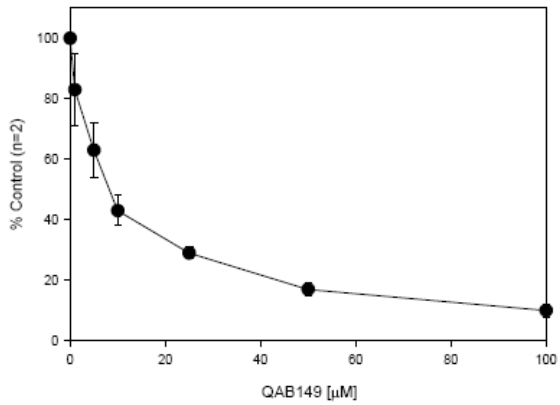
Results represent the mean of two experiments. Error bars indicate the range of values obtained.

Figure 16 Effect of QAB149 on S-mephenytoin 4'-hydroxylation (CYP2C19) in pooled human liver microsomes



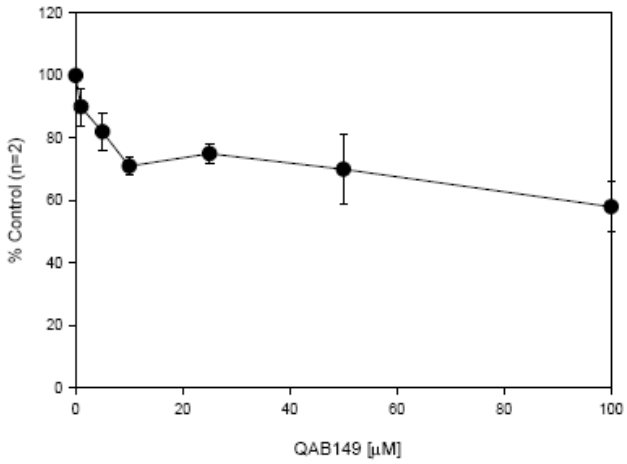
Results represent the mean of two experiments. Error bars indicate the range of values obtained.

Figure 17 Effect of QAB149 on bufuralol 1'-hydroxylation (CYP2D6) in pooled human liver microsomes



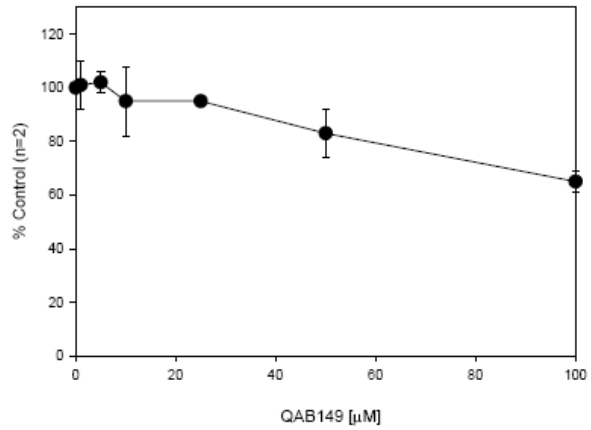
Results represent the mean of two experiments. Error bars indicate the range of values obtained.

Figure 18 Effect of QAB149 on chlorzoxazone 6-hydroxylation (CYP2E1) in pooled human liver microsomes



Results represent the mean of two experiments. Error bars indicate the range of values obtained.

Figure 19 Effect of QAB149 on midazolam 1'-hydroxylation (CYP3A4/5) metabolism in pooled human liver microsomes



Results represent the mean of two experiments. Error bars indicate the range of values obtained.

Conclusion:

QAB149 biotransformation was examined in pooled human liver microsomes to confirm the predominant metabolism by glucuronidation found in human liver slices. QAB149 was primarily metabolized in human liver microsomes, in the presence of NADPH and UDPGA, to the phenolic o-glucuronide (P37), followed by formation of minor monooxygenation products, P26.9 and P30.3. Formation of P37 in human liver microsomes was 5-fold more efficient than formation of the predominant QAB149 monooxygenation product, P26.9 (Vmax/km or CLint, 0.34 versus 0.065 mL·h-1·mg protein-1). Kinetic parameters, *K*m and Vmax, for total QAB149 metabolism in human liver microsomes (with NADPH and UDPGA) were 82 ±12 μM and 34± 3.4 nmol·h-1·mg protein-1, respectively. The phenolic *o*-glucuronide (P37) was found to be formed exclusively by UDP-glucuronosyl transferase 1A1 (UGT1A1), as determined from incubations with nine different recombinant human UGTs (10 μM QAB149). Kinetics of QAB149 glucuronidation by UGT1A1 was examined and the *Km* value for formation of P37 was found to be 23 ± 1.8 μM, similar to the μm value for bilirubin glucuronidation. The two minor monoxygenation metabolites (P26.9 and P30.3) were found to be the primary metabolites formed by recombinant human cytochrome P450s CYP1A1, CYP2D6, and CYP3A4. Kinetic parameters for QAB149 metabolism by CYP3A4 and CYP2D6 were established and CYP3A4 was found to be 2-fold more efficient in formation of total metabolites than CYP2D6 (89 versus 42 mL·h-1·nmol P450-1). As determined by relative activity or abundance of these P450s in human liver microsomes, it was predicted that CYP3A4 would contribute 20 to 40-fold more than CYP2D6 in oxidative metabolism of QAB149 in human liver. However, due to the lack of oxidative metabolism found previously in human liver slices and primary formation of the glucuronidated metabolite in the presence of UDPGA in human liver microsomes, it is predicted that glucuronidation is a major biotransformation pathway of QAB149 in human liver. Substrates of cytochrome P450 are, therefore, predicted to have little effect on the metabolic clearance of QAB149. The actual systemic human exposure to QAB149 by inhalation at therapeutic doses is expected to be at least 3 orders of magnitude lower than the K_m value of UGT1A1 for QAB149 or bilirubin glucuronidation. Due to the high K_m value for glucuronidation of QAB149 by UGT1A1 and expected low QAB149 systemic concentrations, it is unlikely that QAB149 would have an effect on endogenous bilirubin metabolism. QAB149 showed no significant inhibition of P450 enzymes, CYP2C9, CYP2E1 and CYP3A4/5, when tested at concentrations of up to 100 μM. Relatively weak inhibition of P450 enzymes, CYP1A2, CYP2C8, CYP2C19, and CYP2D6 was observed. Based on these inhibition results and the expected low concentrations of QAB149 at therapeutic doses, it is concluded that QAB149 is unlikely to inhibit the metabolic clearance of comedications.

"In vitro assessment of (i) covalent protein binding potential in rat and human liver microsomes and human hepatocytes and (ii) time-dependent cytochrome P450 inhibition"

Study No. R0500025 **Development phase of study**:

Objective

The objectives of this study were to determine (i) if [^{14}C]QAB149 has the potential to bind covalently to protein when incubated with hepatic rat and human microsomal incubations or in human hepatocyte cultures, and (ii) if QAB149 can function as a time-dependent inhibitor of cytochrome P450s, CYP1A2, CYP2C9 or CYP3A4/5, in human liver microsomes.

Study design:

The potential for covalent binding in hepatic microsomes (after incubations had been quenched with acetonitrile) was estimated by measurement of the radioactivity associated with the corresponding exhaustively-washed protein precipitates. The quenched incubation mixtures were transferred to individual wells of a 96-well P3® protein precipitation filter plate. Each well was then exhaustively washed with 20 mL of solvent and the filter insert was punched out into a scintillation vial. The protein associated with each filter was solubilized by treatment with 0.4 mL Solvable®. After solubilization, liquid scintillant was added and radioactivity determined by liquid scintillation counting.

To investigation of the possibility of time-dependent inhibition of CYP1A2, CYP2C9 and CYP3A4/5, QAB149 (10, 25 and 50 μM) was preincubated with human liver microsomes and the enzyme activities remaining at specified timepoints were determined. For activity determinations, aliquots (10 μL) of the preincubation mixture were transferred to a 90 μL enzyme activity assay mixture to determine percent P450 activity remaining. Furafylline (10 μM) and troleandomycin (25 μM) were also tested as positive time-dependent inhibitor controls for CYP3A4/5 and CYP1A2, respectively. No positive control for CYP2C9 was available at the time of this study.

Quantitative analysis of probe substrate metabolites was performed using the LC-MS system.

Results:

3.1 Microsomal binding

The amount of non-extractable radioactivity under various incubation conditions for [^{14}C]QAB149 and the two reference compounds, [^{14}C]diclofenac and [^{14}C]acetaminophen, is summarized in Table 1 and presented graphically in Figure 1. The levels were greater in rat than in human for all compounds and appeared to be NADPH-dependent. Acetaminophen showed the highest binding. In rat, QAB149 had the lowest binding of the three compounds tested. In human,

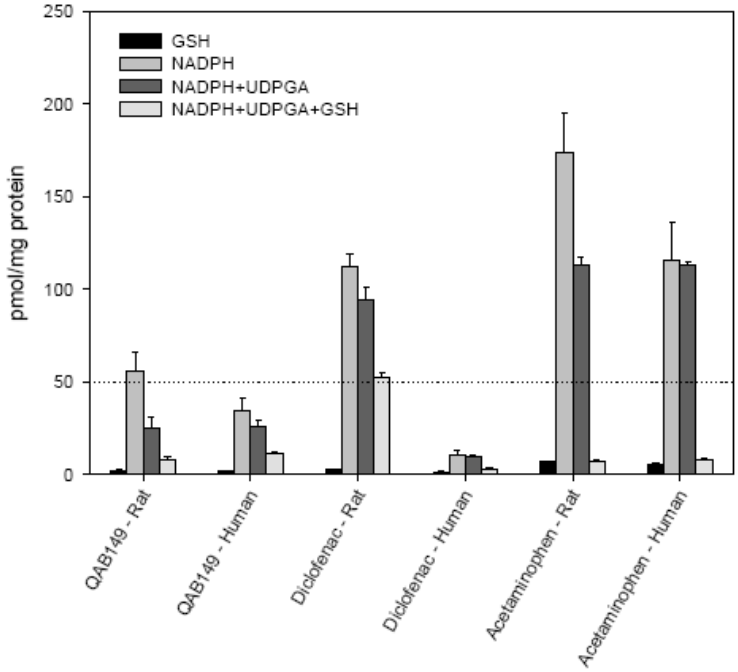
QAB149 was intermediate in binding with diclofenac showing the lowest binding. However, the levels of binding of QAB149 and diclofenac in human were lower than the 50 pmol/mg protein level in all cases (Table 1 and Figure 1). The relative order of apparent binding was Both UDPGA and GSH reduced the apparent levels of binding.

Table 1 Apparent non-extractable radioactivity in liver microsomal incubations after incubation with 14C-labeled test substances

	Cofactors included			
	GSH	NADPH	NADPH+UDPGA	NADPH+UDPGA +GSH
[^{14}C]QAB149	Drug equivalents bound (pmol/mg protein[a])			
Rat	2.1 ± 0.7	56.0 ± 9.9	24.8 ± 5.8	7.9 ± 1.4
Human	1.7 ± 0.4	34.2 ± 7.4	26.2 ± 3.5	11.7 ± 0.4
[^{14}C]Diclofenac				
Rat	2.5 ± 0.4	112 ± 6.8	94.1 ± 6.8	52.0 ± 2.8
Human	1.4 ± 0.4	10.8 ± 2.6	10.0 ± 0.8	2.8 ± 0.7
[^{14}C]Acetaminophen				
Rat	6.7 ± 0.1	174 ± 21.5	113 ± 4.7	7.3 ± 0.9
Human	5.6 ± 0.7	116 ± 20.3	113 ± 1.8	8.1 ± 0.4

[a]Based on nominal microsomal protein included in incubation; values are mean ± SD (n=3), except acetaminophen values which are mean ± range (n=2); all values were rounded to three significant figures or to the nearest 0.1.

Figure 1. Apparent non-extractable radioactivity in liver microsomes after incubation with 14C-labeled QAB149, diclofenac and acetaminophen

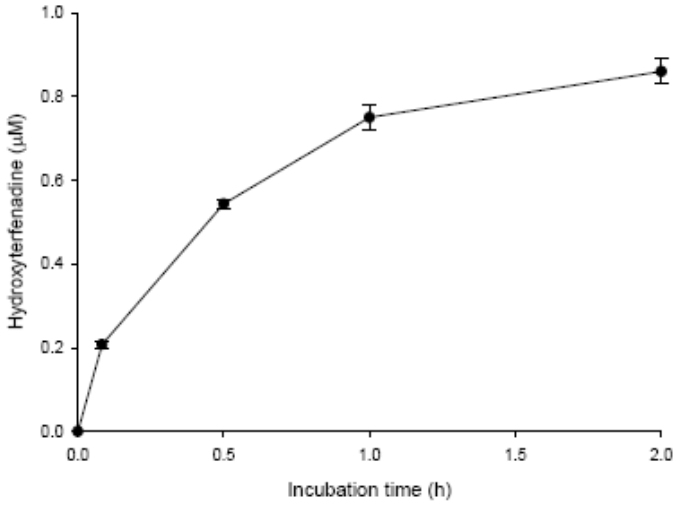


Each bar represents the results from incubations performed in triplicate (mean ± SD), with the exception of acetaminophen which represent the mean (and range) of two incubations. The dashed line illustrates the arbitrary 50 pmol/mg level.

3.2 Human hepatocyte binding

The metabolic activity of the hepatocyte preparation was confirmed by the results of the terfenadine hydroxylation assay (Figure 2). The amount of non-extractable radioactivity in human hepatocytes (cryopreserved) after incubation with the radiolabeled test substances is summarized in Table 2 and presented graphically in Figure 3. For non-extractable radioactivity measurements, an early (5 min) and later time point (120 min) were included to determine if the radioactivity levels increased as function of time. In the present study, [14C]diclofenac produced an extent of binding calculated to be approximately 28 pmol per mg of liver tissue after 120 min incubation. Overall, QAB149 showed approximately 2.2- and 6.4-fold lower binding, respectively, at 120 min than diclofenac and acetaminophen.

Figure 2. Terfenadine hydroxylation in cryopreserved human hepatocytes



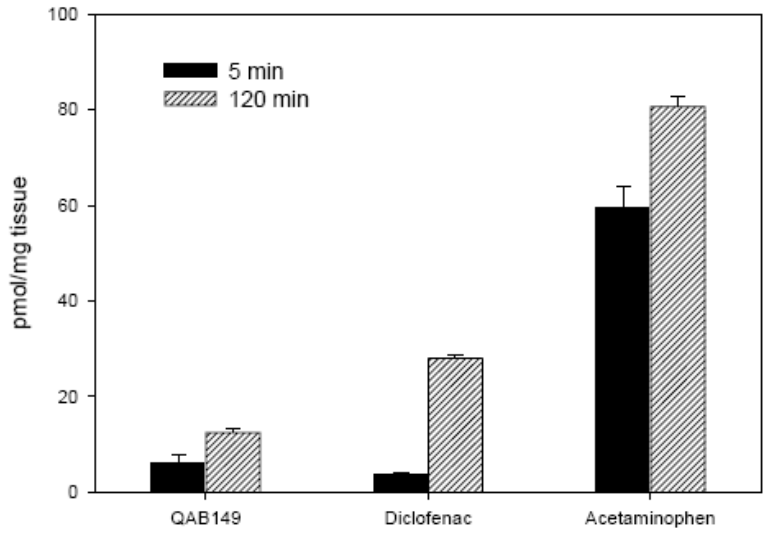
Initial terfenadine concentration was 5 µM. Results are means (± SD) of triplicate determinations.

Table 2 Apparent non-extractable radioactivity in human hepatocytes after incubation with 14C-labeled test substances

	Drug equivalents bound (pmol/mg tissue[a])		
Incubation time	5 min	120 min	Fold difference at 120 min relative to QAB149
[^{14}C]QAB149	6.0 ± 2.0	12.5 ± 0.8	-
[^{14}C]Diclofenac	3.6 ± 0.7	28.0 ± 0.7	2.2
[^{14}C]Acetaminophen	59.5 ± 4.4	80.6 ± 2.2	6.4

[a]Based on 10^7 x 10^6 hepatocytes per gram of tissue

Figure 3 Apparent non-extractable radioactivity in cryopreserved human hepatocytes after incubation with 14C-labeled QAB149, diclofenac and acetaminophen



Each bar represents the results from three incubations (mean ± SD). The mg tissue was calculated based on an estimated 10^7 x 10^6 hepatocytes per gram of liver tissue.

3.3 Time-dependent CYP inhibition

No evidence of time-dependent inhibition of CYP1A2 (Figure 4), CYP2C9 (Figure 5) or CYP3A4/5 (Figure 6) by QAB149 at concentrations of up to 50 µM was observed.

Figure 4 No time-dependent inhibition of CYP1A2 (phenacetin *O*-deethylation) by QAB149 in human liver microsomal incubations

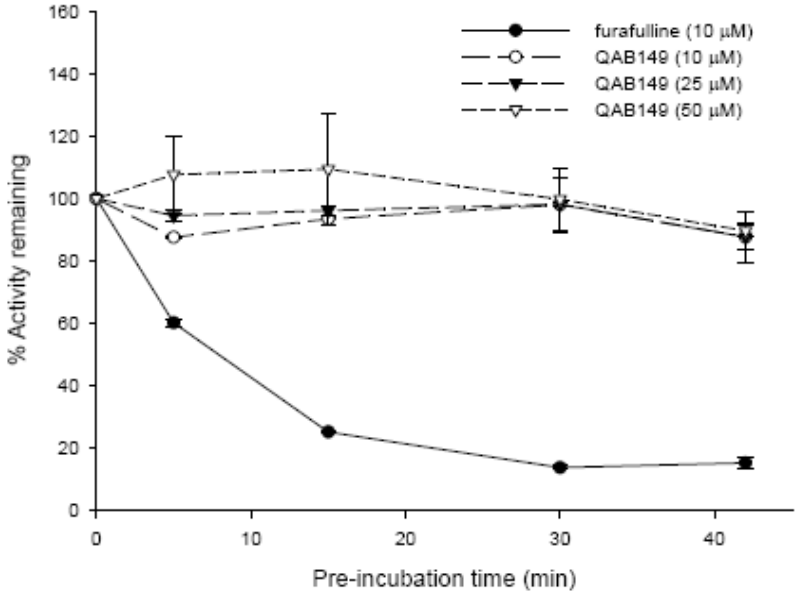


Figure 5 No time-dependent inhibition of CYP2C9 (diclofenac 4′-hydroxylation) in human liver microsomal incubations

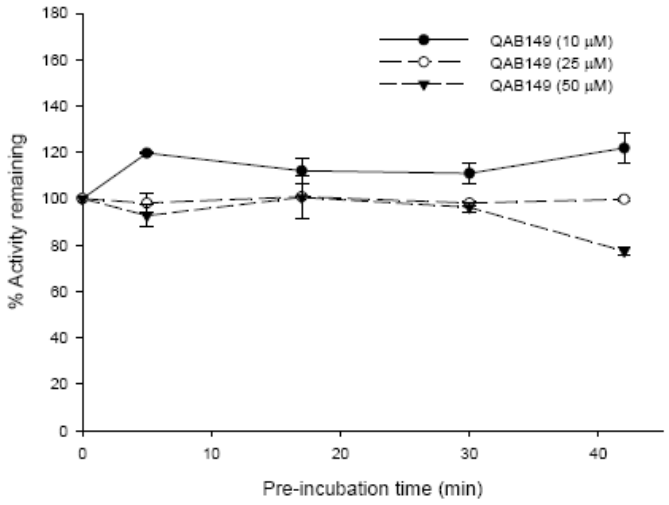
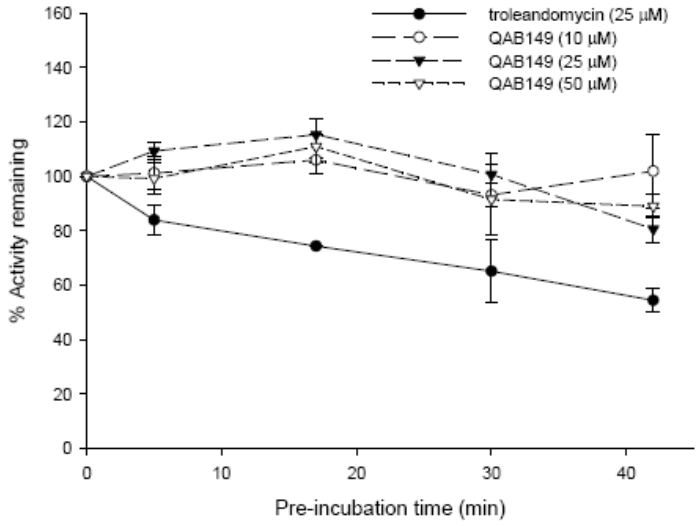


Figure 6 No time-dependent inhibition of CYP3A4/5 (midazolam 1′-hydroxylation) in human liver microsomal incubations



4 Conclusions

QAB149 was found to show relatively low potential for covalent binding to liver microsomes and human hepatocytes, based on non-extractable radioactivity experiments. For all three compounds, the levels of radioactivity associated with the protein isolates from liver microsomes were higher in rat than in human, with the addition of NADPH (cofactor for various oxidative processes) producing the largest increase in apparent binding. The addition of UDPGA (co-substrate for glucuronidation) and GSH (capable of trapping reactive metabolite intermediates and slowing radical reactions) together with NADPH reduced the extent of apparent binding. Relative to the reference compounds, QAB149 in rat liver microsomes was found to show the lowest amount of non-extractable radioactivity. In human liver microsomes, QAB149 produced

levels intermediate to acetaminophen and diclofenac, with acetaminophen having higher levels and diclofenac having lower levels. However, the values for QAB149 and diclofenac binding in human liver microsomes were both below the 50 pmol/mg threshold. In cryopreserved human hepatocytes, the levels of non-extractable radioactivity for QAB149 was also low, being about 2.2- and 6.4-fold less, respectively, than the reference compounds, diclofenac and acetaminophen. QAB149, when preincubated at concentrations of up to 50 μM with human liver microsomes, showed no evidence of time-dependent inhibition of CYP1A2, CYP2C9 or CYP3A4/5 activities.

"*In vitro* binding of ^{3}H-labeled QAB149 to red blood cells, serum and plasma proteins in the rat, dog and human"

Study No. R00594

Objective

To determine the binding of [^{3}H] QAB149 to erythrocytes, and serum and plasma proteins of rat, dog and human in vitro

Study Design and Methods

Blood, plasma and serum collection:
For the binding study with red cells, fresh heparinized blood was obtained from male Wistar-Hanover rats, Beagle dogs and human volunteers (n = 3) who gave written informed consent. Blood from rats and dogs was pooled by species to provide a homogeneous sample of the matrix. The hematocrit value of each blood sample was measured in triplicate by filling individual capillary tubes with blood, sealing one end with clay, and centrifuging the samples in a microcapillary centrifuge. Hematocrit values were obtained using a hematocrit reader. Plasma was obtained by centrifuging blood samples at approximately 3000 g for 15 min. All blood was used within 4 h of collection and the plasma samples were kept at -20°C until analysis. Additional blood was collected without anticoagulant from three male human volunteers. The blood was centrifuged at approximately 3000 g for 15 min to obtain the serum. The serum samples were kept at -20°C until analysis.

Binding to red blood cells:
Distribution of [3H]QAB149 between plasma and red blood cells was determined at concentrations of 1, 10, 100, 500 and 2,000 ng/mL in rat, dog and human blood. Triplicate determinations of the hematocrit were made for each species. Rat and dog samples (1 mL) were prepared in triplicate and a single aliquot (0.1 mL) of blood containing [3H]QAB149 was pipetted for radioactivity analysis. A single sample (1 mL) was prepared from each of the three human volunteers and a single aliquot (0.1 mL) of blood containing [3H]QAB149 was pipetted for radioactivity analysis. The remaining blood was incubated at 37°C in a water bath for 30 min and centrifuged at 3000 rpm for 15 min. The resultant plasma (0.1 mL) was analyzed for radioactivity.

Ultracentrifugation:
Binding of [3H]QAB149 to plasma proteins was determined at concentrations of 1, 10, 100, 500 and 2,000 ng/mL in rat, dog, and human plasma. Samples of pooled rat and dog plasma were prepared in triplicate, while single samples from each of three human subjects were prepared. Approximately two mL of plasma were prepared for each sample. An aliquot (0.1 mL) was pipetted into a vial with appropriate volume of Formula 989 scintillant and counted for radioactivity analysis. A one mL volume of each sample was transferred into a Beckman ultracentrifuge tube and capped. The sample was centrifuged for 3 hours at 37°C at 356,160 x g

using a type 50 rotor. The centrifuge was allowed to stop without using the brake. Aliquots of the supernatant were carefully removed without removing the tube from the rotor. Each supernatant sample was assayed for radioactivity and total protein concentration. For determination of radioactivity, 0.1 mL of the sample was mixed with appropriate volume of Formula 989 scintillant and counted. A 0.1 mL aliquot of each supernatant sample was removed for total protein analysis using a standard curve established with a Sigma Diagnostic Micro Protein Assay Kit on a Spectronic Genesis Spectrophotometer. The Sigma Diagnostic Assay Kit contained a 5-mL protein (human albumin) standard solution at a concentration of 30 mg/dL and a 120- mL protein dye reagent solution.

Calculation:
The fraction of drug in blood that is distributed to red cells (f_{BC}) is calculated as follows:
$f_{BC} = 1-[(1-H)(C_p/C_b)]$

Where H is the hematocrit, C_p and C_b are the concentrations of radioactivity in plasma and blood, respectively.

The fraction of drug bound to plasma proteins (β) equals $(T_t - T_s)/T_t$, where T_t is the concentration of total radioactivity in the uncentrifuged sample and T_s is the concentration of radioactivity in the supernatant.

Results:
Distribution to red blood cells:

The blood:plasma ratios (C_b/C_p) and fractions of [^{3}H]QAB149 to red blood cells (f_{BC}) are shown in Tables 1 and 2, respectively. In general, the compound showed higher affinity to blood cells than plasma in all species. The fraction of QAB149 distributed to red blood cells (f_{BC}) ranged from 0.688-0.742, 0.525-0.608 and 0.499-0.584 in the rat, dog and human, respectively, over the tested concentration range. The binding to red blood cells appeared to be highest in rat, followed by the dog and human where the compound showed only slightly higher distribution to blood cells than plasma. The binding in all species was independent of concentration.

Table 1 Blood: Plasma ratio of [3H]QAB149

Blood concentration, ng/mL	C_b/C_p(mean ± SD)					
	Rat[a,b]	Dog[a,b]	Human Subject 1[c]	Human Subject 2[c]	Human Subject 3[c]	Human Average[d]
1	2.21 ± 0.024	1.22 ± 0.120	1.23	1.12	e	1.18
10	2.15 ± 0.083	1.33 ± 0.091	1.71	1.33	1.14	1.39 ± 0.29
100	2.01 ± 0.056	1.22 ± 0.012	1.27	1.13	1.23	1.21 ± 0.07
500	1.88 ± 0.092	1.18 ± 0.017	1.12	1.07	1.19	1.13 ± 0.06
2,000	1.83 ± 0.086	1.10 ± 0.033	1.24	1.06	1.08	1.13 ± 0.09

[a]data were obtained from triplicate analyses
[b]pooled blood (n ≥3)
[c]data were obtained from single analysis
[d]mean data were obtained from the three individual human subjects
[e]sample was contaminated

Table 2 Fraction of [3H]QAB149 distributed to red blood cells (f_{BC}) at 37°C

Blood concentration, ng/mL	f_{BC} (mean ± SD)[a]					
	Rat[b,c]	Dog[b,c]	Human Subject 1[d]	Human Subject 2[d]	Human Subject 3[d]	Human Average[e]
1	0.742 ± 0.003	0.570 ± 0.042	0.578	0.482	f	0.530
10	0.735 ± 0.010	0.608 ± 0.026	0.696	0.563	0.493	0.584 ± 0.10
100	0.717 ± 0.008	0.573 ± 0.004	0.590	0.488	0.530	0.536 ± 0.05
500	0.705 ± 0.006	0.561± 0.006	0.537	0.459	0.512	0.503 ± 0.04
2,000	0.688 ± 0.015	0.525 ± 0.014	0.580	0.452	0.465	0.499 ± 0.07

[a]hematocrit value was 0.43, 0.48 and 0.44, in rat, dog and human, respectively.
[b]data were obtained from triplicate analyses
[c]pooled blood (n ≥ 3)
[d]data were obtained from single analysis
[e]mean data were obtained from the three individual human subjects
[f]sample was contaminated

Binding to plasma proteins:

The extent of binding of [3H]QAB149 to plasma proteins is summarized in Table 3. The plasma binding ranged from 90.6-92.0% in rat, 92.5-93.5% in dog and 95.1-96.2% in human over the tested concentration range. The binding to plasma proteins appeared to be highest in human, followed by the dog and rat. The protein binding was independent of concentration.

Table 3 Fraction of [3H]QAB149 bound to the plasma protein (ß)

Plasma concentration, ng/mL	β (mean ± SD)					
	Rat[a,b]	Dog[a,b]	Human Subject 1[c]	Human Subject 2[c]	Human Subject 3[c]	Human Average[d]
1	0.906 ± 0.015	0.925 ± 0.012	0.956	0.957	0.956	0.956 ± 0.001
10	0.920 ± 0.006	0.931 ± 0.004	0.942	0.951	0.959	0.951 ± 0.009
100	0.917 ± 0.006	0.931 ± 0.006	0.965	0.960	0.960	0.962 ± 0.003
500	0.917 ± 0.002	0.930 ± 0.008	0.966	0.954	0.966	0.962 ± 0.007
2,000	0.915 ± 0.005	0.935 ± 0.005	0.960	0.965	0.962	0.962 ± 0.003

[a]data were obtained from triplicate analyses
[b]pooled blood (n ≥ 3)
[c]data were obtained from single analysis
[d]mean data were obtained from the three individual human subjects

Serum protein binding:

No effect of heparin on QAB149 protein binding was evident in this study. Over the concentration range tested, the mean fractions of the compound bound to human serum proteins ranged from 94 – 95.3%, as shown in Table 4, which were similar to those bound to plasma proteins.

Table 4 Fraction of QAB149 bound to human serum proteins

Serum concentration, ng/mL	β (mean ± SD)			
	Human Subject 1[a]	Human Subject 2[a]	Human Subject 3[a]	Human Average[b]
1	0.927	0.951	0.946	0.94 ± 0.013
2,000	0.954	0.954	0.950	0.953 ± 0.002

[a]data were obtained from single analysis
[b]mean data were obtained from the three individual human subjects

Conclusion:
Over the concentration range of 1 – 2,000 ng/mL, the compound showed a higher affinity to blood cells than plasma in all species. The binding to red blood cells appeared to be highest in rat, followed by the dog and human where the compound showed only slightly higher distribution to blood cells than plasma. The binding was independent of concentration. The compound was relatively highly bound to plasma proteins (90.6 – 96.2%) in all species and the binding was independent of concentration over the concentration range tested. The anticoagulant, heparin, had no significant effects on the protein binding of QAB149.

"An open-label, single-dose, two-period crossover study in healthy volunteers conducted in two parts to compare the pharmacokinetics of indacaterol (300 µg by inhalation via Concept1) when dosed in the morning and in the evening, and determination of the absolute bioavailability of indacaterol".

Study no.:	CQAB149B2103
Development Phase of Study:	Phase I
Principal investigator:	Dr. Aslak Rautio, Quintiles-Hermelinen, Lulea, Sweden
Study Dates:	28-May-2008/04-Jul-2008

Objectives

Primary objective

- To compare the pharmacokinetics of a single dose of 300 µg of inhaled indacaterol when dosed in the morning and the evening.

Secondary objectives

- To assess the safety and tolerability of a single intravenous infusion of 400 µg indacaterol solution.
- To determine the absolute bioavailability of a single dose of 300 µg of inhaled indacaterol.

Study Population

24 subjects (16 in part 1 and 8 in part 2) were enrolled in the study. All 16 subjects in part 1 completed the study. 4 subjects completed both treatment periods in part 2.

Subjects meeting the following criteria were included:

- Healthy male and female subjects aged 18 to 45 years
- Weight of at least 50 kg and body mass index within the range of 18 to 29 kg/m2
- Healthy as determined by medical history, vital signs, physical examination, ECG and laboratory tests.

The 16 subjects enrolled in Part 1 had a mean age of 22.8 years (range: 18 -31 years) , a mean weight of 71.3 kg (range 54-96 kg), a mean height of 174.1 cm (range: 164-198 cm) and a mean BMI of 23.4 kg/m2 (range: 19-28 kg/m2). The population was predominantly male with only 6 females in the group.

The 8 subjects enrolled in Part 2 had a mean age of 22.8 years (range: 18 -33 years), a mean weight of 72.7 kg (range 60-83 kg), a mean height of 176cm (range: 167-188 cm) and a mean BMI of 23.5 kg/m2 (range: 20-28 kg/m2). The population was predominantly male with only 2 females in the group

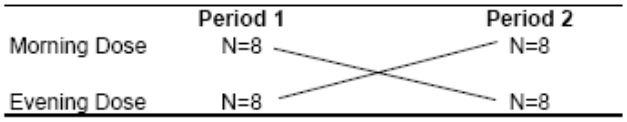
STUDY DESIGN, TREATMENT AND ADMINISTRATION

This was an open label, single-dose, two period crossover study conducted in two parts:

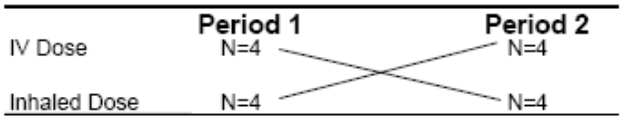
Part 1: Sixteen (16) subjects were randomized to receive inhaled 300 µg indacaterol in the morning and the evening. In periods 1 and 2, they received inhaled 300 µg indacaterol on day 1 with clinical and pharmacokinetic assessments to day 8 (168 hours post dose).

Part 2: Eight (8) subjects were randomized to receive either a single inhaled dose of 300 µg indacaterol or a single intravenous infusion of 400 µg indacaterol administered over 45 minutes. Clinical and pharmacokinetic assessments were performed up to day 8 (168 hours post dose) (see diagram below).

Treatment Schedule for Part 1



Treatment Schedule for Part 2



Test product, dose and mode of administration, batch number

- Inhalation in Part 1 and Part 2: Indacaterol 300 µg capsules for inhalation, Batch Number: XO28AD.
- Concept1 inhaler devices , Batch Number: B03076011001.
- Placebo capsules, Batch Number: X259GC.

PHARMACOKINETIC MEASUREMENTS

Blood samples were taken following inhalation at 0 (predose), 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 8, 10, 24, 48, 72, 96, 144, and 168 hours after inhalation. Blood sampling following intravenous infusion was at 0 (prior to start of infusion), 0.33 (during infusion), 0.75 (at the end of infusion), 0.83, 1, 1.25, 1.75, 2.25, 2.75, 4.75, 8.75, 10.75, 24, 48, 72, 96, 144, and 168 hours after start of infusion. Indacaterol was determined in serum prepared from the blood samples using an LC-MS/MS method. The lower limit of quantification (LLOQ) was 10 pg/mL.

SAFETY MEASUREMENTS

Safety: Vital signs (temperature, blood pressure, pulse rate and ECG), hematology, blood chemistry, urinalysis, serum potassium and plasma glucose evaluation, adverse events and monitoring of concomitant medication use.

Concomitant therapy

There were no concomitant medications reported.

DATA ANALYSIS

Pharmacokinetic Data Analysis

The PK parameters determined using non-compartmental methods and actual sampling times were: AUC0-tlast (area under the serum concentration-time curve from time zero up to the last quantifiable concentration), AUC0-∞ (AUC extrapolated to infinity), Cmax (maximum serum concentration), tmax (time to Cmax), t1/2, Frel (relative BA, Part 1), Fabs (absolute bioavailability, Part 2), CL (systemic clearance after intravenous dosing),Vz (volume of distribution during the terminal elimination phase after intravenous dosing).

Statistical Analysis

All subjects with non-missing values in both periods of either Cmax, AUC0-tlast and/or AUC0-∞ were included in the statistical evaluation of relative bioavailability in Part 1 of the study. Log-transformed Cmax, AUC0-tlast and AUC0-∞ from Part 1 of the study were compared between morning and evening dosing using a linear mixed effects model. The model included treatment and period as fixed effects and subject as a random effect. Point estimates and 90% confidence intervals for the difference of the log-transformed PK parameters – indacaterol evening (test) versus indacaterol morning (reference) – were calculated. Treatment effects were presented as ratios of geometric means by exponentiation of the treatment differences (and associated 90% confidence intervals) on the log scale.

In Part 2 of the study, the absolute BA of indacaterol was calculated employing dose normalized exposure (AUC0-tlast/dose, AUC0-∞/dose) upon inhalation and infusion. The actual infused doses were calculated for as: (100 mL - residual volume in the infusion bag) * 4 µg/mL

RESULTS

Analytical Method

Bioanalytical procedures

Indacaterol was determined in serum samples by an LC-MS/MS method using positive mode electrospray ionization (ESI). Prior to LC-MS/MS analysis serum samples (200 µL each) were subject to liquid-solid extraction followed by evaporation of the extracts to dryness and reconstitution. The lower limit of quantification (LLOQ) using 200 µL of serum was 10 pg/mL.

In-Study Validation for Indacaterol

Matrix	Human Plasma	
Concentration Range	10 to 2000 pg/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.994$	
Between-Batch Accuracy (%Diff)	Qc standards (30, 150, 800, 1800 pg/mL) Cal. Curve standards	-5.44 to -1.3 -2.4-2.0
Between-Batch (% CV)	Cal. Curve standards QCs	3.3-9.0 4-11.6

Pre-Study Validation Report

Reference item	QAB149
Matrix	Human serum
Internal standard	$^{13}CD_3$-QAB149
Sample preparation	Solid-phase extraction on 10 mg Waters MCX plate using an automated Packard Multiprobe II plus system.
Chromatography	Reversed-phase HPLC on a Thermo Hypersil Gold C18 1.9 µm (50 × 2.1 mm) column at 45°C using gradient elution (0.1% formic acid in MeOH-H_2O, 5:95 (v/v)) - (0.1% formic acid in MeOH) at a flow rate of 400 µL/min with at total run-time of 5 min. Special care has to be taken to avoid carryover in the auto-sampler by washing the autosampler system with Acetonitrile-MeOH-H_2O, 70:20:10 (v/v) followed by 0.1% acid formic in MeOH-H_2O, 50:50 (v/v)
Detection	MS/MS TIS source, positive ion mode
Specificity	The method is specific in human serum for QAB149 (maximum interference 5.3% of signal at LLOQ) and for $^{13}CD_3$-QAB149 (maximum interference 0% of signal at working concentration).
Matrix effect	QAB149: mean 108% $^{13}CD_3$-QAB149: mean 137%
Absolute recovery	QAB149: mean 76.9% $^{13}CD_3$-QAB149: mean 58.1%
Calibration curves	Calibration was performed with a first order polynomial within the range of 10.0 pg/mL to 2000 pg/mL, using 1/x weighting. The acceptance criteria for the mean bias were met: -6.6% ≤ mean bias ≤ 4.3%
LLOQ	10.0 pg/mL using 200 µL of human serum (expressed as QAB149 free base)
Intra-day accuracy and precision	Within the acceptance criteria over the entire range.
Inter-day accuracy and precision	Within the acceptance criteria over the entire range.
Dilutions	Results of dilution 1/5 with 1% phosphoric acid were within the acceptance criteria.

Stability of QAB149 in solutions	In (Report DMPK R0300366C): -In stock solutions (100 ng/µL) At least 9 months at 0-8°C At least 24 hours at room temperature - In diluted solutions (1.5 pg/µL to 2.5 ng/µL): At least 5 months at 0-8°C At least 24 hours at room temperature
Stability of QAB149 in extracts	At least 72 hours at about 10°C on the autosampler
Stability of QAB149 in QC samples	At least 24 hours at room temperature and between 0-8°C After 3 freeze-thaw cycles, storage below -18°C At least 23 weeks after storage below -18°C (30 to 1800 pg/mL) In (Report DMPK R0300366A-02): 150 to 40000 pg/mL] At least 15 months and 2 weeks after storage below -18°C or below -70°C
Stability of $^{13}CD_3$-QAB149 in solutions	- In diluted solution (3.12 pg/µL) at least 30 hours at room temperature At least 14 weeks at 0-8°C In (Report DMPK R0300366C): - In stock solutions (31.2 ng/µL) At least 9 months at 0-8°C At least 24 hours at room temperature - In diluted solutions (62.4 pg/µL): At least 5 months at 0-8°C At least 24 hours at room temperature
Cross-check	A cross-check was performed with the previously used LC-MS/MS method. The results of normalized difference were within the acceptance criteria.
Conclusion	The method is suitable for the determination of QAB149 in human serum with an anticipated limit of quantification of 10.0 pg/mL using 200 µL of human serum.

Pharmacokinetic Results

Morning vs. Evening

The mean individual Cmax and AUCt values for indacaterol following single dose administration of the Indacaterol 300 µg in the morning vs. the evening is shown in Figure 1. The mean pharmacokinetic parameters of indacaterol following administration of the treatments are summarized in Table 1. Mean serum Cmax were 475 and 565 pg/mL upon inhalation in the morning and evening, respectively. Mean AUC0-tlast was 5159 pg*h/mL after inhalation in the morning and 5875 pg*h/mL after inhalation in the evening. The mean apparent terminal half-lives (t1/2) were 67.3 and 88.0 h for inhalation in the morning and evening, respectively.

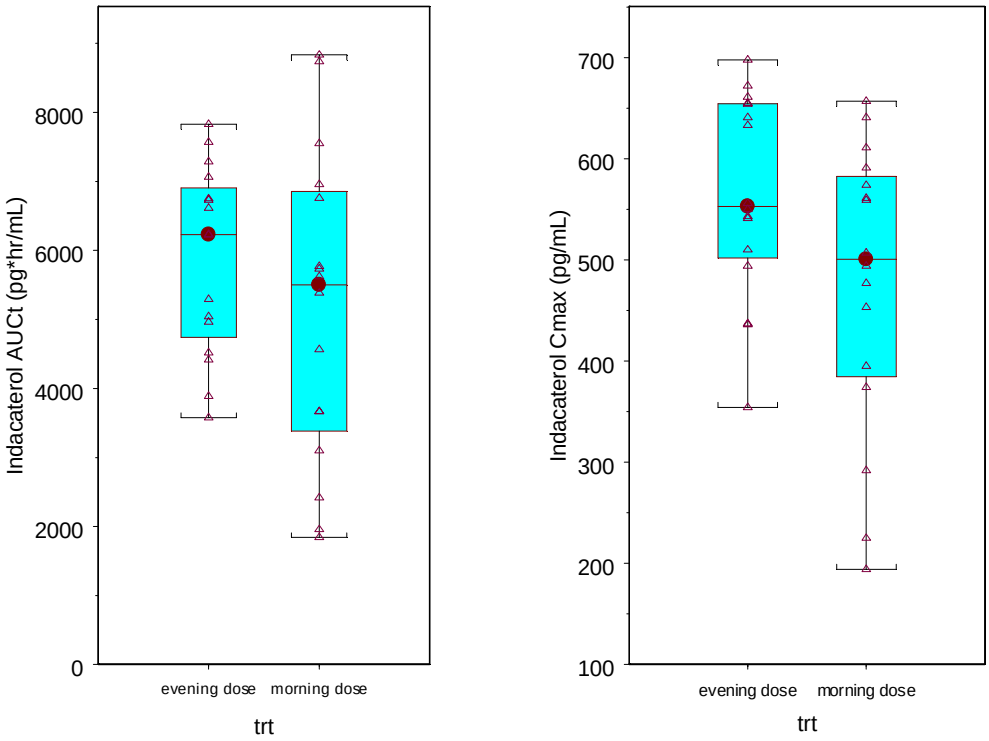


Figure 1. Individual Cmax and AUCt values following single dose administration of indacaterol inhalation aerosol 300 µg in the morning or in the evening (N=16).

Table 1. Mean pharmacokinetic parameters after inhalation of 300 µg indacaterol in the morning and in the evening

	Cmax (pg/mL)	AUC0-tlast (pg*h/mL)	AUC0-∞ (pg*h/mL)	tmax [a)] (h)	t1/2(h)
Morning Dose					
N	16	16	13	16	13
Mean	475	5159	6632	-	67.3
%CV	30.3	43.8	42.3	-	30.0
Min	194	1839	2470	0.25	34.0
Median	501	5502	6738	0.25	69.7
Max	657	8833	11257	0.25	96.8
Evening dose					
N	16	16	16	16	16
Mean	565	5875	7885	-	88.0
%CV	17.8	23.0	26.2	-	27.0
Min	354	3577	4198	0.25	40.6
Median	553	6230	8571	0.25	82.3
Max	698	7829	11473	0.33	138.8

[a)] only median, min and max for tmax

Cmax, AUC0-tlast and AUC0-∞ values of indacaterol were compared between the morning and evening dose by computing the evening to morning ratios in the individual subjects. The results of the statistical analysis, including all subjects, are shown in Table 2. The ratio of the geometric means (evening to morning) were 1.24, 1.23 and 1.26 for Cmax, AUC0-tlast and AUC0-∞, respectively, and the 90% confidence intervals were in the range of 1.04 to 1.46.

According to the sponsor, subjects 5109 and 5115, had atypically low Cmax, AUC0-tlast and AUC0-∞ values following morning dosing relative to their values following evening dosing. Also, these morning dose values were the lowest values of all 16 subjects, whereas the evening dose values of the two subjects were within the range of those seen in the other subjects. Consequently, the evening to morning ratios were considerably larger in these two subjects (ratios were between 2.91 and 3.87) than in all other subjects (ratios were between 0.78 and 1.87). The sponsor stated that there was no evidence for non-compliance of subjects 5109 and 5115.

Table 2. Comparison of exposure upon inhalation of 300 µg indacaterol in the morning and in the evening – all subjects

	Adjusted geometric mean[a)]		geometric mean ratio (evening/morning) [a)]		
	morning	evening	estimate	Lower 90% CL	Upper 90% CL
Cmax (pg/mL)	450	556	1.24	1.06	1.43
AUC0-tlast (pg*h/mL)	4634	5719	1.23	1.04	1.46
AUC0-∞ (pg*h/mL)	6062	7615	1.26	1.09	1.45

In order to assess the influence of the two subjects (subjects 5109 and 5115) with atypically low exposure for the morning dose on the treatment estimates, a sensitivity analysis excluding the data from these two subjects was performed. Exclusion of the two subjects results in ratios between 1.08 and 1.15 for the different PK parameters and confidence intervals all lying between 0.99 and 1.23 (Table 3).

Table 3. Comparison of exposure upon inhalation of 300 µg indacaterol in the morning and in the evening - sensitivity analysis excluding subjects 5109 and 5115

	geometric mean ratio (evening/morning) a)		
	estimate	Lower 90% CL	Upper 90% CL
C_{max} (pg/mL)	1.10	1.02	1.19
$AUC_{0\text{-}tlast}$ (pg*h/mL)	1.08	0.99	1.18
$AUC_{0\text{-}\infty}$ (pg*h/mL)	1.15	1.08	1.23

Inhalation vs. IV Administration

The mean plasma concentration-time profiles of indacaterol following iv administration vs. inhalation is shown in Figure 2. The mean pharmacokinetic parameters of indacaterol following administration of the treatments are summarized in Table 4. Based on the individual dose normalized AUC0-tlast and AUC0-∞ values of the four individuals who received indacaterol by

both routes, the inhaled bioavailability of indacaterol was 43.2%, and 50.7%, respectively. The fraction of extrapolated AUC in AUC0-∞ was <20% in all cases, except for one subject where it was 50% after inhalation. Therefore, the results based on AUC0-tlast, which is based on measured concentrations only, are considered as the primary outcome of this part of the study.

Table 4
Mean [CV%] serum pharmacokinetic parameters after single infusion of 400 µg and inhalation of 300 µg indacaterol

	Infusion	Inhalation
Number of subjects	4	4
Actual dose (µg)	291	300
C_{max} (pg/mL)	4960 [31.3]	502 [19.9]
$AUC_{0\text{-}tlast}$ (pg*h/mL)	11374 [20.1]	5286 [37.3]
$AUC_{0\text{-}\infty}$ (pg*h/mL)	12994 [19.4]	6877 [22.4]
$t_{1/2}$ (h)	76.1 [12.1]	85.8 [27.8]
CL (L/h)	23.3 [31.6]	45.3 [22.5][a)]
V_z (L)	2557 [34.5]	5798 [49.7][b)]
F_{abs} (%), based on individual $AUC_{0\text{-}tlast}$/Dose values (n= 4)		43.2 [24.0]
F_{abs} (%), based on individual $AUC_{0\text{-}\infty}$/Dose values (n= 4)		50.7 [14.5]

a) CL/F; b) Vz/F;

.

Summary of Findings/conclusion

- There was a higher variability (about 40% vs. 20%) in the systemic exposure of indacaterol upon inhalation in the morning compared to that in the evening. This contributed to the lower systemic exposure observed following the morning administration compared to that after the evening administration.
- The absolute bioavailability of an inhaled indacaterol dose was 43.2%

"A randomized, open label, cross-over study to assess the absorption, distribution, metabolism and excretion of QAB149 following a single oral and inhaled dose using non-radiolabeled QAB149 in healthy subjects"

Study no.:	CQAB149A2106
Development Phase of Study:	Phase I
Principal investigator:	Paul Rolan, Joanne Collier, Medeval Ltd, Manchester, UK
Study Dates:	19-Aug-2003/5-Jul-2004

Objectives

Primary objective

- To asses the absorption, distribution, metabolism and excretion of QAB149 and its glucuronide metabolite following oral and inhaled administration.

Secondary objectives

- To investigate the safety and tolerability following single inhaled and oral administration of QAB149

Study Population

Four healthy, non-smoking male subjects, aged 18-45 years were required to complete the study. Due to phenolic O-glucuronidation being the major metabolic pathway subjects with reduced UGT capacity such as those with Crigler-Najjar syndrome or Gilbert's syndrome were excluded from participation in the study.

Subjects meeting the following criteria were included:

- Healthy male subjects aged 18 to 45 years
- Weight of at least 50 kg and body mass index within the range of 18 to 29 kg/m^2
- Healthy as determined by medical history, vital signs, physical examination, ECG and laboratory tests.

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This was a two period, randomized, open label cross over study. Healthy subjects received single doses of QAB149 via inhaled and oral routes. On day 1 following an overnight fast subjects received a single 800 μg dose of QAB149 via the oral or inhaled route. They remained in the study centre until 168 hours post dose for collection of serum, complete 24 h urine and complete 24 h fecal samples for pharmacokinetic and ADME assessments. Safety and tolerability were monitored during this time. Subjects were then discharged from the centre and returned following a minimum 10 day washout for the second period, where identical study assessments, including baseline, were performed.

Test product, dose and mode of administration, batch number

- QAB149 2 x 400 µg aerolizer capsules, administered via the inhaled route using an aerolizer and orally, by swallowing the aerolizer capsules.

PHARMACOKINETIC MEASUREMENTS

Blood Collection

Blood samples for periods 1 and 2 were taken at 0 (predose), 5, 15, 30 minutes, and 1, 2, 3, 4, 8, 12, 24, 30, 48, 72 hours post-dose.

Urine Collection

Urine samples for periods 1 and 2 were taken at 0 (predose), 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 h. Total volume was recorded per collection period.

Feces Collection

Feces samples for periods 1 and 2 were taken at 24 hour collection periods: 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168h.

SAFETY MEASUREMENTS

Safety: Vital signs (temperature, blood pressure, pulse rate and ECG), hematology, blood chemistry, urinalysis, serum potassium and plasma glucose evaluation, adverse events and monitoring of concomitant medication use.

Concomitant therapy

There were no concomitant medications reported.

DATA ANALYSIS

Pharmacokinetic Data Analysis

The following PK parameters for the unchanged and total QAB149 and the glucuronide conjugate(s) of QAB149 were calculated: AUC0-24, AUC0-t, Cmax, tmax from serum concentration-time data; Ae0-24, Ae0-t, absolute amount, CLR. The interpretation of metabolic pathways was derived and % dose of QAB149 (unchanged and total) in the excreta was calculated and was based on the emitted dose of QAB149 from the inhalation device or the known dose (i.e. 800 µg) after oral administration. Disposition parameters were determined using a non-compartmental method.

Statistical Analysis

Safety data are reported descriptively. No formal statistical analyses have been performed on the safety or pharmacokinetic data.

RESULTS

Analytical Method

Bioanalytical procedures

The concentrations of QAB149 in serum were measured by LC/MS/MS and were determined before and after enzymatic hydrolysis of conjugated QAB149. The difference between the

concentration following enzymatic hydrolysis (total QAB149) and QAB149 (before enzymatic hydrolysis) gave the serum concentrations of QAB149 conjugate.

In-Study Validation for Indacaterol

Within-study assay validation was performed by analysis of QC samples together with the study samples. The limits of quantitation before and following enzyme treatment were: 0.07 ng/mL for serum, 0.7 ng/mL for urine and 5 ng/mL for fecal homogenate. The CV for the QC samples in serum was less than 10%. The % accuracy was more than 95%.

Pharmacokinetic Results

The key pharmacokinetic variables of QAB149 and QAB149 glucuronide following a single inhaled dose are shown in Table 1. The AUC of QAB149 glucuronide could only be calculated for subject 5102 since there were insufficient data points for subjects 5101, 5103 and 5104. The serum AUC0-48 h of QAB149 following the oral dose was 2 – 4 fold lower than that following the inhaled dose. Mean peak serum concentrations of conjugated QAB149 following the oral dose were observed over a broad range similar to parent QAB149 (0.1 – 0.4.h). The AUC0-48 h for QAB149 glucuronide which could only be calculated for subjects 5101 and 5102 were similar to the AUC determined in subject 5012 following the inhaled dose. The mass balance results for this study were not included in this review since there is a "pivotal mass balance study" conducted with the appropriate device and using radiolabeled material.

Table 1. Mean pharmacokinetic parameters of QAB149 and QAB149 glucuronide in serum following single 800 μg inhaled dose or single 800 μg oral dose of QAB149 (modified from sponsor's provided tables)

		Inhaled dose of QA149		**Oral dose of QAB149**	
Analyte	**Subject**	**Mean**	**CV(%)**	**Mean**	**CV(%)**
	tmax (h)	0.25	0	1.13	55.9
QAB149	Cmax (ng/mL)	0.928	14.3	0.476	55.3
	AUC1 0-t (ng•h/mL)	4.49	44.1	2.04	38.1
	AUC0-48 h (ng•h/mL)	5.09	42.9	2.33	37.5
QAB149 glucuronide	tmax (h)	0.252 (0.25 – 12)	-	1.13	55.9
	Cmax (ng/mL)	0.174	44.2	0.228	49.6
	AUC1 0-t (ng•h/mL)			2.14	-
	AUC0-48 h (ng•h/mL)	1.25		2.54	-

Summary of Findings/conclusion

- Exposure to QAB149 following the inhaled dose was higher than after the oral dose.
- The relative BA (inhaled/dose= AUC48 inhaled/AUC48hr oral) was 218%. In other words the oral BA of QAB149 was 46% of that after inhalation of the same dose.

- Assuming that following inhalation of QAB149 via the Aerolizer™ device, 27% of the dose was deposited in the lung with the remainder deposited in the stomach, it was estimated that 76% of the systemic exposure was attributed to lung absorption and 24% due to oral absorption.
- The systemic exposure (AUC 0-48hrs) of the parent compound following inhalation was more than 4-fold higher than that observed for the glucoronide metabolite.
- These results should be interpreted with caution since the device used in this study (Aeroliser) is different than the device proposed for marketing (Concept 1).

"A randomized, double-blind, 5-period within-subject placebo-controlled single dose escalation study (400 to 2000 µg) to assess the safety and tolerability of QAB149 dry powder inhaler (RS-01) in Caucasian and Japanese healthy male subject."

Study no.:	CQAB149B2215
Development Phase of Study:	Phase I
Principal investigator:	Dr U. Lorch Richmond Pharmaceutical Incorporated
Study Dates:	15-Apr-2004/30-Jul-2004

Objectives

Primary objective

- Determine the safety and tolerability of single doses of QAB149 from 400 µg up to 2000 µg delivered by the RS-01 device in healthy male Japanese subjects.
- Compare the safety and tolerability of single doses of QAB149 from 400 µg up to 2000 µg delivered by the RS-01 device between Caucasian and Japanese healthy male subjects.

Secondary objectives

- Explore potential differences in the pharmacokinetics of QAB149 from 400 µg up to 2000 µg delivered by the RS-01 device between Caucasian and Japanese healthy male subjects.
- Perform exploratory pharmacogenetic assessments to examine whether individual genetic variation in genes relating to drug metabolism and the drug target pathway confer differential response to QAB149.
- Conduct exploratory genomic studies to identify gene expression patterns that are associated with PD assessments in this study.

Study Population

After screening, a total of 42 male healthy subjects were enrolled (22 Caucasian, 20 Japanese).

Subjects meeting the following criteria were included:

- Healthy male volunteers. Japanese subjects as being born in Japan, having both parents and four grandparents of Japanese origin and having left Japan not more than 10 years ago.
- Caucasian subjects were matched pair wise according to age (+/- 5 years), smoking status and weight (+/- 20 %) of their Japanese counterpart.
- Subjects had a W of at least 50 kg and a body mass index in the range of 19 to 29.

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This study was a double-blind, 5-period, within-subject placebo-controlled single dose escalation design. After screening, a total of 42 male healthy subjects were enrolled (22 Caucasian, 20 Japanese). After they met all the eligibility criteria at baseline, subjects then received single doses of QAB149 from 400 to 2000 µg, and placebo with a washout of at least 7 days between doses. Serial blood collection for PK measurements followed each administration to the subjects. The

study was completed with an end-of-study evaluation after washout of the final dose. The 20 Japanese were equally randomized to one of the 5 sequences. The same was done for the 20 Caucasians.

Test product, dose and mode of administration, batch number

- QAB149 delivered via a single-dose, RS-01device

PHARMACOKINETIC MEASUREMENTS

- **Blood collection** (2 ml blood per sample, preservative-free polypropylene tubes (serum), at each time point as listed):
  - **Period 1 and 2:** Predose, 0.08, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 15, 24 and 36 h post each dose
  - **Period 3 to 5 :** Predose, 0.08, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 15, 24, 36, 48 and 72 h post each dose
- **Urine collection:** (30 ml urine per collection period): - predose, 0-12, 12-24, 24-48 and 48-72 h post each dose.
- Analytes, media and methods: parent drug in serum and urine; LOQ of 0.1 ng/ml in urine and a LOQ of 0.05 ng/ml in serum; LOQ of total drug in urine is 0.7 ng/ml.

SAFETY MEASUREMENTS

Safety: Vital signs (temperature, blood pressure, pulse rate and ECG), hematology, blood chemistry, urinalysis, serum potassium and plasma glucose evaluation, adverse events and monitoring of concomitant medication use.

Concomitant therapy

There were no concomitant medications reported.

DATA ANALYSIS

Pharmacokinetic Data Analysis

PK parameters, AUC0-t, Cmax, tmax, t½, from serum concentration-time data; Ae0-t and CLR from urine concentration and volume-time data were determined using a non-compartmental method (linear log trapezoidal) and evaluated if possible for dose proportionality.

Pharmacogenomics blood collection

A 5-ml blood sample was collected in 2 x 2.5 ml PAXgene tubes at pre-dose, 2 hours and 24 hours after dosing in each of the 5 phases.

Statistical methods

Appropriate summary statistics was calculated for the PK parameters, including mean (arithmetic and/or geometric, or median depending on the variable), standard deviation, coefficient of variation, minimum and maximum for each of the ethnic groups by dose level. The difference in PK parameters for the two ethnic groups was explored for each dose level.

The assessment of safety and tolerability in Japanese subjects was done by listing and summarizing the adverse events and the safety and tolerability assessments by dose level.
For the comparison of safety and tolerability between Japanese and Caucasians, QT and QTc intervals, supine heart rate, blood pressure, plasma potassium, and plasma glucose data were summarized by dose level for each ethnic group. Also, the following exploratory analysis was performed:

- For QT and QTc intervals, at each time-point, the change from baseline was calculated and summarized, by dose level and ethnic group. For each subject, the average time-matched change from baseline was calculated and analyzed with a linear model with ethnic group and dose level as fixed factors, subject as a random factor and the baseline value as covariate. Age and weight may also have been considered as covariates in the model. The differences between the ethnic groups and the 95% confidence intervals was provided.
- For supine heart rate, blood pressure, potassium, and glucose, the AUEC (area under the effect curve), Emax, Emin was calculated and analyzed on the log-scale using a mixed linear model with ethnic group and dose level as fixed factors, subject as a random factor and the baseline value as covariate.

Note: the QT/safety information will not be reviewed in this study since there is a thorough QT study conducted with the to-be marketed formulation and it's under review by the Qt IRT group. In addition, the genomic information will not be reviewed in this study, since there is a dedicated study looking into the effects of genetic variation on the PK of the drug.

RESULTS

Analytical Method

Bioanalytical procedures

Indacaterol was determined in serum samples by an LC-MS/MS method using positive mode electrospray ionization (ESI). Prior to LC-MS/MS analysis serum samples (200 µL each) were subject to liquid-solid extraction followed by evaporation of the extracts to dryness and reconstitution. The lower limit of quantification (LLOQ) using 200 µL of serum was 10 pg/mL.

In-Study Validation for Indacaterol

Matrix	Human Serum	
Concentration Range	0.05 to 100 ng/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.983$	
Between-Batch Accuracy (%bias)	Qc standards in serum (0.15, 25, and 80 ng/mL)	-0.4 to 2
	Cal. Curve standards (0.05, 0.15, 0.5, 1, 25, 50, 100 ng/mL)	-0.8-2.0
Between-Batch (% CV)	Cal. Curve standards QCs	5.7-7.6 The lowest QC sample did not meet the acceptance criteria % CV was about 40%.

Pharmacokinetic Results

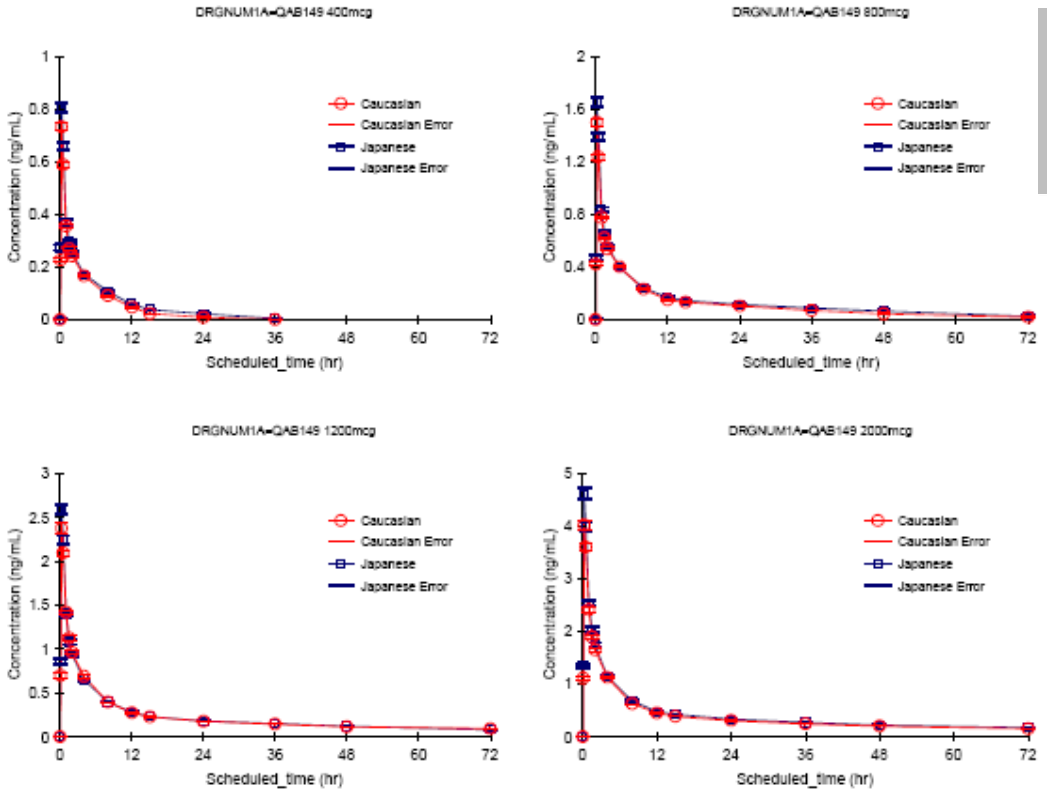
Twenty-one (21) out of 22 Caucasian and 20 Japanese subjects randomized in the study, provided evaluable pharmacokinetic serum and urine data. A total of 20 Caucasian and 20 Japanese subjects completed the study. Table 1 summarizes the mean PK parameters following single dose administration of indacaterol 400 to 300 µg. The plasma concentration-time profile following administration of the treatments is shown in Figure 1.

A non-linearity was observed in the dose normalized concentration profiles (Figure 2). The power model was used to determine dose-proportionally within the dose range considered (ratio highest to lowest dose = 2000/400 = 5) (Figure 2). For all AUC parameters, the estimate of the slope β is always above 1 (Figure 3) as well as the lower 90% confidence intervals for the slopes indicating lack of dose-proportionality in this range of doses tested (Table 2).

There was a numeric trend of lower systemic exposure in Japanese population. The AUC was about 15% lower across doses tested. However, there was not significant difference in the systemic exposure between Caucasians and Japanese population (Table 3).

Table 1	**A summary of pharmacokinetic parameters for QAB149**							
Dose (mg)	**Group**	**C_{max} (ng/mL)**		**t_{max} (hr)**	**AUC0-24 (hr*ng /mL)**	**$t_{1/2}$ (hr)**	**unchange Ae_{0-72} (Dose%)**	**total Ae_{0-72} (Dose%)**
400	Caucasian	N Mean/Median* SD/range* CV%	21 0.734 0.184 25.1	21 0.25 0.25-0.50 27.5	21 2.204 0.740 33.6	20 5.78 2.26 39.1	21 1.199 0.349 29.1	21 1.463 0.575 39.3
	Japanese	N Mean/Median* SD/range* CV%	20 0.812 0.207 25.5	20 0.25 0.25-0.50 21.0	20 2.563 1.160 45.3	19 8.02 4.82 60.1	20 1.564 0.278 17.7	20 1.767 0.470 26.6
800	Caucasian	N Mean/Median* SD/range* CV%	20 1.516 0.304 20.0	20 0.25 0.25-0.50 27.8	20 6.097 1.396 22.9	19 25.78 11.43 44.3	20 1.392 0.433 31.1	20 1.900 0.565 29.8
	Japanese	N Mean/Median* SD/range* CV%	20 1.67 0.39 23.5	20 0.25 0.25-0.50 27.5	20 6.469 1.486 23.0	18 30.21 10.93 36.2	20 1.679 0.337 20.1	20 2.162 0.428 19.8
1200	Caucasian	N Mean/Median* SD/range* CV%	20 2.45 0.59 24.1	20 0.25 0.25-1.00 55.8	20 10.569 2.111 20.0	19 57.07 34.78 60.9	20 1.494 0.374 25.0	20 2.025 0.525 25.9
	Japanese	N Mean/Median* SD/range* CV%	20 2.598 0.663 25.5	20 0.25 0.25-0.52 22.5	20 10.553 2.923 27.7	19 45.51 18.47 40.6	20 1.785 0.384 21.5	20 2.263 0.483 21.3

2000	Caucasian	N Mean/Median* SD/range* CV%	20 4.047 1.049 25.9	20 0.25 0.25-0.52 34.7	20 17.658 4.019 22.8	20 49.86 19.74 39.6	20 1.545 0.365 23.6	20 2.111 0.487 23.1
	Japanese	N Mean/Median* SD/range* CV%	20 4.676 1.294 27.7	20 0.25 0.25-0.50 21.1	20 18.901 5.382 28.5	19 49.57 14.42 29.1	20 1.878 0.377 20.1	20 2.372 0.509 21.5



Best Available Copy

Figure 1. Mean serum concentration time profiles for QAB149 (indacaterol) following single inhaled administration of Indacaterol using the R01 device (taken from sponsor's report).

Best Available Copy

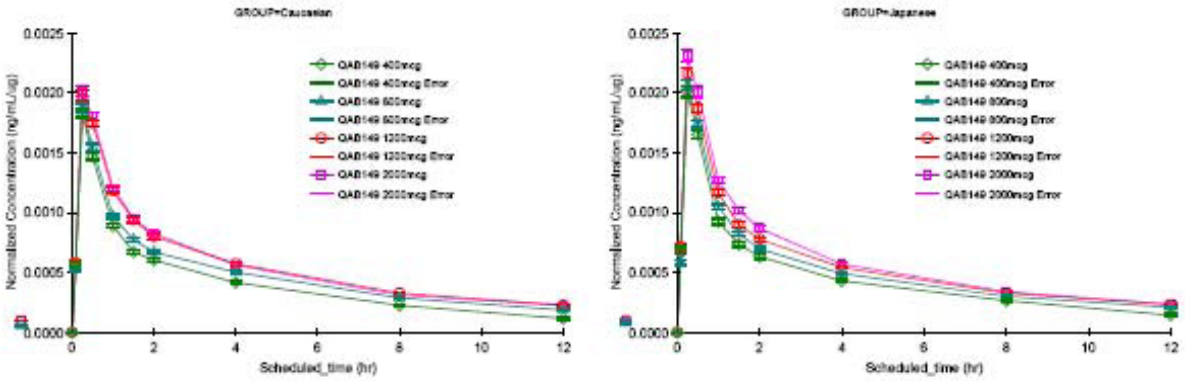


Figure 2. Dose normalized serum concentration time profiles for QAB149 following administration of QAB149 via inhalation

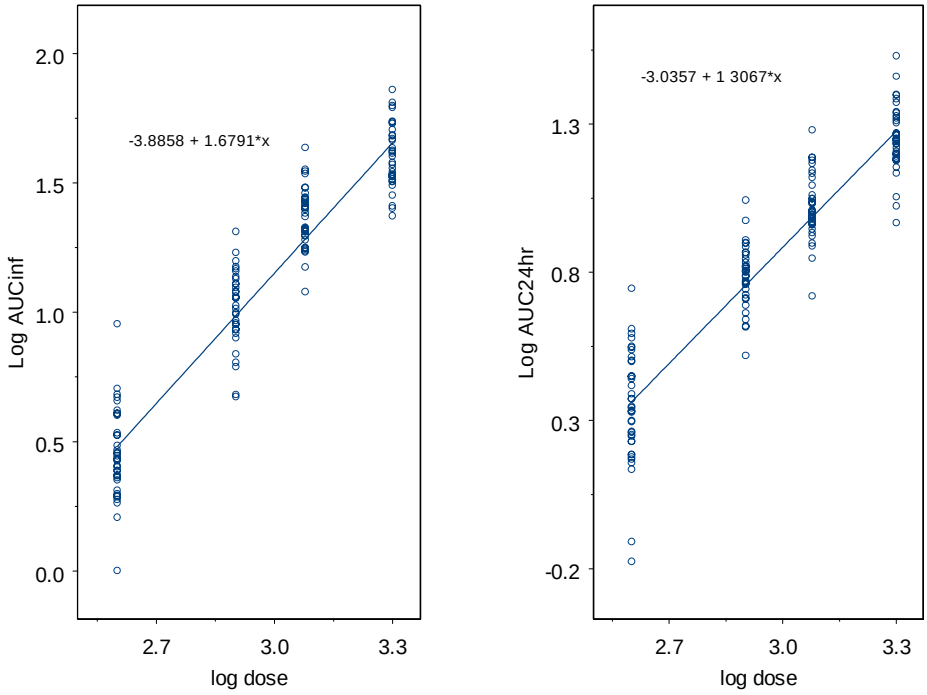


Figure 3. Pooled Individual AUCinf (left panel) and AUC 24hr (right panel) versus dose. Fitted line from power model : AUCinf = $e^{-3\,9}$ * $(strength)^{1\,67}$ and AUC24hr = $e^{-3\,0}$ * $(strength)^{1\,31}$

Table 2. Estimate of the slope for the linear regression between log-pk parameter and log-dose

PK parameter	Race	slope estimate	Lower 90% confidence limit	Upper 90% confidence limit	Dose proportionality across the whole dose range?*
AUC24hrs	Caucasian	1.30	1.24	1.35	No
	Japanese	1.28	1.23	1.34	No
AUCinf	Caucasian	1.70	1.61	1.78	No
	Japanese	1.63	1.55	1.72	No
CMAX	Caucasian	1.04	1.00	1.09	Yes
	Japanese	1.08	1.04	1.12	Yes
Free Ae	Caucasian	1.16	1.12	1.20	No
	Japanese	1.11	1.07	1.16	No
Total Ae	Caucasian	1.24	1.19	1.29	No
	Japanese	1.19	1.14	1.24	No

Table 2. Ratio of PK parameters for QA149 between Caucasian and Japanese Populations

Dose (mg)	Group	C_{max} (ng/mL)	AUC0-24 (hr*ng /mL)	total Ae_{0-72} (Dose%)
400	Japanese/ Caucasian ratio	0.90	0.86	0.83
800	Japanese/ Caucasian ratio	0.91	0.94	0.88
1200	Japanese/ Caucasian ratio	0.94	1.0	0.89
2000	Japanese/ Caucasian ratio	0.87	0.93	0.89

Conclusions

- There was a lack of dose-proportionality in this range of doses tested.
- There was a numeric trend of lower systemic exposure in Japanese population. The AUC was about 15% lower across doses tested. However, there was not significant difference in the systemic exposure between Caucasians and Japanese population.
- The PK results of this study are questionable since the QC samples (150 ng/mL) did not meet the acceptance criteria (%CV was 40%).

"A randomized, multiple-dose, placebo and positive controlled parallel group study to evaluate the effects of indacaterol on cardiac safety in healthy subjects".

Study no.:	CQAB149B2339
Development Phase of Study:	Phase I
Principal investigator:	Dr. Stuart Harris, SeaView Research, Miami, FL, USA (Principal Investigator)
Study Dates:	04-April-2008/14-Aug-2008

Objectives

Primary objective

- To determine the maximum change from baseline in QTcF following multiple dose treatment with indacaterol 150 µg, 300 µg and 600 µg qd for 14 days in healthy subjects, as compared to placebo

Secondary objectives

- To evaluate the potential for effect of indacaterol 150 µg, 300 µg and 600 µg qd multiple-dose treatment for 14 days on uncorrected QT interval duration in healthy subjects.
- To evaluate the potential for effect of multiple dose treatment with indacaterol 150 µg, 300µg and 600 µg for 14 days on cardiovascular safety in healthy subjects.
- To determine the maximum change from baseline in QTcF following single dose treatment with oral moxifloxacin 400 mg in healthy subjects, as compared to placebo.
- To evaluate the pharmacokinetics and dose proportionality of indacaterol during 14 days of qd dosing with indacaterol 150 µg, 300 µg and 600 µg in healthy subjects.
- To evaluate the tolerability of indacaterol in comparison to placebo in healthy subjects. The main tolerability endpoint is cough.

NOTE: This review will focus on the review of the PK portion of this study. The potential effect of indacaterol to prolong QT is under review by the QT IRT group.

Study Population

Four hundred and thirty-five (435) subjects were to be enrolled to ensure 384 completed; 404 subjects were enrolled and dosed; 389 subjects completed 14 days of dosing, 388 subjects completed the study. The PK population for analysis of PK parameters of indacaterol consisted of a subset of 68% of subjects who received the 150 µg and 300 µg dose and 69% of subjects who received the 600 µg dose.

Healthy male and female subjects aged between 18 and 55 years of age (inclusive), in good health with a body mass index of between 18.5 – 32 kg/m2 at screening and weighing at least 50 kg were included in the study.

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This was a single center, randomized, multiple-dose, placebo and positive controlled, five-arm parallel group study in 404 healthy volunteers. Subjects were randomized to one of 5 treatment groups receiving either 150 µg, 300 µg, 600 µg, placebo or placebo-moxifloxacin.

Two strengths of indacaterol (hard gelatin capsule) were supplied for use via a single-dose dry powder inhaler (Concept1) and were manufactured by and supplied to the Investigator by Novartis.

- Indacaterol 150 µg capsules [Batch Number: X272HD/6002099.001; Re-test date: (b) (4) (b) (4)
- Indacaterol 300 µg capsules [Batch Number: X175CD/6001037.003; Re-test date: (b) (4) (b) (4)
- Placebo [Batch Number: X332JC/3760253.004; Re-test date: (b) (4)
- Concept1 Inhalers [Batch Number: B01427011001]
- Avelox® (Moxifloxacin 400 mg tablets po) was purchased by the Investigator as commercial supply. All Avelox® used by the site originated from the same lot.

Duration of treatment: Multiple-dose treatment with indacaterol 150 µg, 300 µg and 600 µg qd administered for 14 days; single dose of moxifloxacin administered to a subset of the placebo group on Day 14.

PHARMACOKINETIC MEASUREMENTS

PK profile samples (serum) were collected on Day 1 and Day 14, and pre-dose samples on Days 7, 10 and 12. Indacaterol and the sum of the diastereomeric metabolites P26.9 and P30.3 (assigned the code QAZ033) were measured in serum by LC/MS/MS methods. PK samples were taken at pre-dose, 0.167, 0.33, 0.67, 1, 2, 3, 4, 6, 12 and 24 hrs post-dose on Days 1 and 14 and at predose on Days 7, 10 and 12.

SAFETY MEASUREMENTS

(SAEs), with their severity and relationship to study drug, and pregnancies. They also included the regular monitoring of hematology, blood chemistry, serum potassium, plasma glucose and urine performed at the local laboratory and regular assessments of vital signs, ECGs, physical condition and body weight. In addition, on each treatment day, following inhalation, an evaluation of tolerability i.e. the occurrence of post-inhalational occurring within 5-minutes of each inhalation was collected. The onset, duration, frequency and severity of PI cough was recorded.

DATA ANALYSIS

Pharmacokinetic Data Analysis

For indacaterol the following PK parameters were determined using non-compartmental methods: AUC0-24, Cmax, and tmax on Day 1 and AUC0-24, Cavg, Cmin, Cmax, CLss/F and tmax on Day 14. R, the accumulation ratio Day 14 to Day 1, was determined for Cmax and AUC0-24, and t1/2.acc, the effective half-life of accumulation, was calculated. For QAZ033 on Day 14, AUC0-24, Cmax, and tmax were determined. In addition, the ratio of metabolites to parent was determined.

For the comparison of the concentrations of indacaterol and QAZ033, mass concentrations were converted to molar concentrations by considering the molecular weight of indacaterol (392.6 g/mol) and QAZ033 (408.5 g/mol). Thus, 1 ng/mL of indacaterol corresponds to 2.547 nM of indacaterol, and 1 ng of QAZ033 correspond to 2.448 nM. Also, the molecular weight corrected Rmet was calculated by multiplying the uncorrected ratios with a factor of 0.961 (=392.6/408.5).

Statistical analysis of dose-PK relationship:
The steady-state dose-PK relationship was assessed by plot of the Day 14 AUC0-24 versus the dose on a log transformed scale and by estimating the regression coefficient to ln(dose) using linear regression of ln(AUC0-24) against ln(dose). The analysis was applied to Day 14 ln(Cmax) as well.

An estimate of the slope including the 90% confidence interval was obtained based upon the log-transformed observations. This estimate and confidence interval were then backtransformed" to the original scale.

The following diagnostics were applied to the model:
Check of log-linear relationship (lack of fit) between dose and PK parameter by first fitting the model with dose as an additional fixed effect for dose and then reducing it to the model above.

Furthermore the variance homogeneity was checked by plotting the predicted values against the residuals. PK dose proportionality can be concluded across the whole dose range, if the 90% confidence interval (βL, βU) for the slope $\exp(\beta 0)$ was completely contained within a pre-specified critical region (bL, bU), where the two limits bL, bU are derived as follows: $bL = 1+\ln(\theta L)/\ln(r)$ and $bU = 1+\ln(\theta U)/\ln(r)$, where r=ratio of doses (highest dose/lowest dose = 600/150 = 4), $\theta L=0.8$, $\theta U=1.25$ being the standard bioequivalence limits. The day 1 (single-dose) dose-PK relationship was assessed as for Day 14.

Statistical analysis of dose-accumulation relationship:
The relationship between indacaterol dose and indacaterol systemic accumulation was assessed by plot of the Day 14 AUC0-24/Day 1 AUC0-24 ratio against the dose; the mean and 90% confidence interval of the dose accumulation ratio was estimated separately for each indacaterol dose. The same analysis was performed for Cmax.

RESULTS
Analytical Method
Bioanalytical procedures
Parent drug and metabolites in serum were determined by a LC/MS/MS method. The LLOQ was 10 pg/mL for indacaterol and 46 pg/mL for metabolites in serum results from benzylic hydroxylation of indacaterol's diethyl-indane moiety. The bioanalytical method used a mixture of the four diastereomers (code: QAZ033) as analytical standard and did not allow to separate the four isomers. Therefore, the sum of the isomers was determined and is denoted in this report as

QAZ033. Of the four possible diastereomers, P26.9 and P30.3 had been identified in humans. Thus, maximum serum QAZ033 (sum of metabolites P26.9 and P30.3) concentrations occurred later than for indacaterol; 2.08 h vs 0.25 h.

In-Study Validation for Indacaterol

Matrix	Human Serum	
Concentration Range	0.05 to 100 ng/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.983$	
Between-Batch Accuracy (%bias)	Qc standards in serum (0.15, 25, and 80 ng/mL) Cal. Curve standards (0.05, 0.15, 0.5, 1, 25, 50, 100 ng/mL)	-0.4 to 2 -0.8-2.0
Between-Batch (% CV)	Cal. Curve standards QCs	5.7-7.6 The lowest QC sample did not meet the acceptance criteria % CV was about 40%.

Pharmacokinetic Results

Parent Compound

Mean serum concentration-time plots for indacaterol following single and multiple dose administration of the treatments is shown on Figures 1. Mean PK parameters of indacaterol is summarized on Table 1. In most subjects, the maximum serum concentration of indacaterol was reached 15 min post-dose on Day 1 and Day 14 (range: 10 min to 3 h; Median tmax was 15 min in all dose groups, both on Day 1 and Day 14.

Between Day 2 and Day 14, mean trough concentrations increased from 20.2 pg/mL to 105.1 pg/mL in the 150 µg dose group, from 45.3 to 216.9 pg/mL in the 300 µg dose group and from 84.9 to 399.0 pg/mL in the 600 µg dose group. In all dose groups, the trough concentrations were similar on Day 12 and Day 14 and the Day14/Day12 mean ratios were close to unity (between 1.03 and 1.09). These findings indicate that steady-state was achieved by Day 12.

The apparent accumulation of indacaterol in serum of each subject during multiple dosing, i.e. between days 1 and 14, was characterized by the accumulation ratios (=R) of Cmax and AUC0-24 (Table 11-9). Cmax increased 1.85-, 1.79- and 1.65-fold and AUC0-24 increased 3.48-, 3.22-, and 2.93-fold in the 150 µg, 300 µg and 600 µg dose groups respectively. The serum concentrations of QAZ033 on Day 14 were considerably lower than that of indacaterol. The metabolites to parent ratio was 0.065 ± 0.029 (mean ± SD) for Cmax and 0.112 ± 0.050 for AUC0-24 (based on mass concentrations).

Dose proportionality over the entire dose range of 150 µg to 600 µg was demonstrated for peak exposure (Cmax) of indacaterol on Day 1 and Day 14 and for total exposure (AUC0-24) on Day

14. For AUC0-24 on Day 1, the increase can be considered as dose-proportional over a dose multiple of up to 2.9.

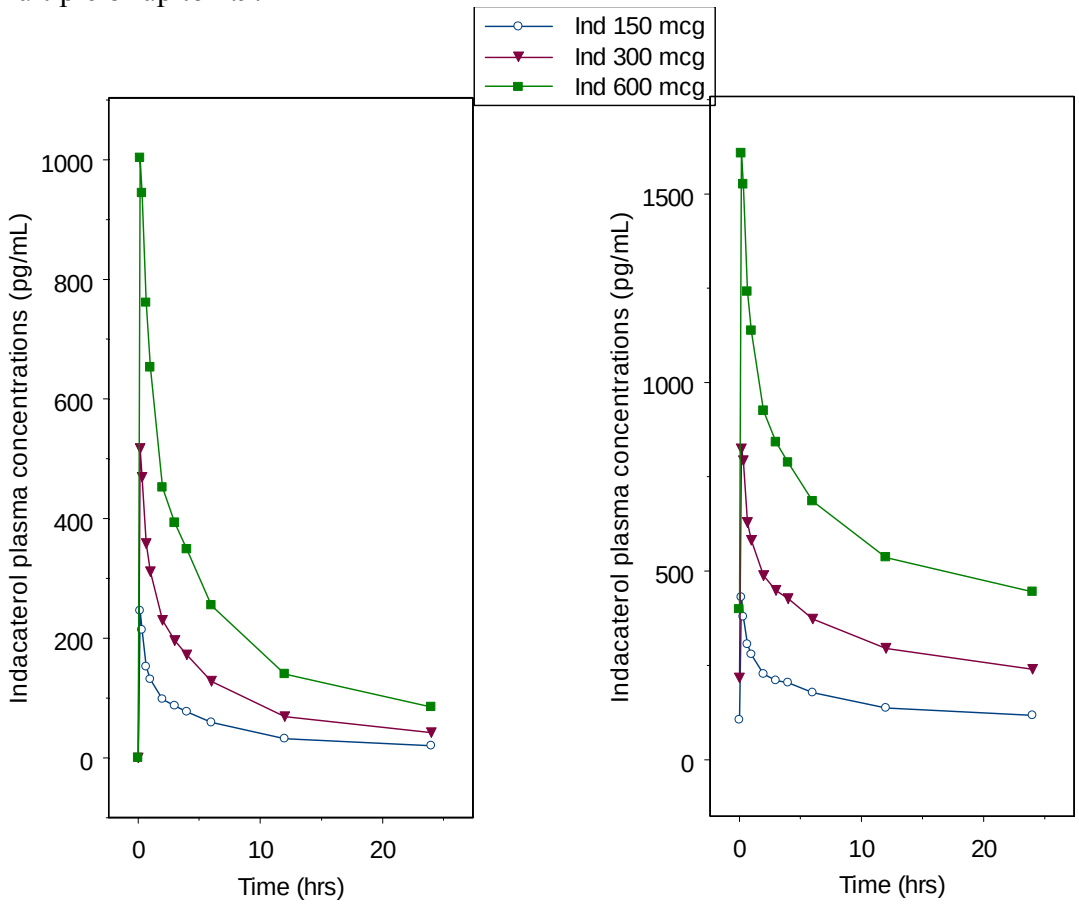


Figure 1. Mean serum concentration-time plots for indacaterol following single and multiple dose administration of the treatments.

Table 1. Summary statistics of indacaterol PK parameters - Day 1				
Dose (µg)	**Statistic**	**[1]tmax (h)**	**Cmax (pg/mL)**	**AUC0-24 (pg h/mL)**
150	N	72	72	72
	Mean/median1 SD/range1	0.25 0.25-0.48	252.9 120.8	1202 554
	CV%	-	47.8	46.1
300	N	73	73	73
	Mean/median1 SD/range1	0.25 0.22-1.08	537.2 224.2	2639 862
	CV%	-	41.7	32.7
600	N	37	37	37
	Mean/median1 SD/range1	0.25 0.25-0.75	1043.8 285.5	5279 1155
	CV%		27.4	21.9

[1]t_{max} – median and range

Table 2. Summary statistics of indacaterol PK parameters - Day 14							
Dose (µg)	Statistic	[1]t_{max} (h)	C_{avg} (pg/mL)	C_{min} (pg/mL)	C_{max} (pg/mL)	AUC_{0-24} (pg h/mL)	CL_{ss}/F (L/h)
150	N	70	70	70	70	70	70
	Mean/median[1] SD/range[1]	0.25 0.22-3.08	161.7 64.4	104.4 43.8	438.6 196.4	3882 1545	45.1 24.2
	CV%	-	39.8	42	44.8	39.8	53.6
300	N	68	68	68	68	68	68
	Mean/median[1] SD/range[1]	0.25 0.17-1.08	339.0 99.5	214.5 68.8	858.6 264.2	8137 2388	40.1 12.0
	CV%	-	29.4	32.1	30.8	29.4	29.9
600	N	37	37	37	37	37	37
	Mean/median[1] SD/range[1]	0.25 0.25-0.42	628.5 142.8	396.8 121.4	1656.6 540.8	15085 3428	42.0 10.7
	CV%	-	22.7	30.6	32.6	22.7	25.4

[1]t_{max} – median and range

Table 3. Indacaterol trough concentration ratios					
Dose (µg)	Statistic	Day10/Day7	Day12/Day10	Day14/Day10	Day14/Day12
150	N	71	71	70	70
	Mean	1.221	1.143	1.168	1.086
	SD	0.240	0.244	0.182	0.507
	CV%	19.6	21.3	15.6	46.7
300	N	69	69	68	68
	Mean	1.219	1.111	1.137	1.033
	SD	0.184	0.159	0.166	0.168
	CV%	15.1	14.3	14.6	16.3
600	N	37	37	37	37
	Mean	1.213	1.090	1.137	1.049
	SD	0.178	0.167	0.293	0.247
	CV%	14.7	15.3	25.8	23.5

Table 4. Summary statistics for accumulation parameters				
Dose (µg)	Statistic	R for C_{max}	R for AUC_{0-24}	$t_{1/2,acc}$ (h)
150	N	69	69	69
	Mean	1.85	3.48	49.1
	SD	0.57	1.03	17.3
	CV%	31.0	29.5	35.2
	90% CI	1.73,1.97	3.31, 3.66	-
300	N	68	68	68
	Mean	1.79	3.22	44.7
	SD	0.67	0.74	12.4
	CV%	37.5	22.9	27.8
	90% CI	1.67, 1.91	3.05, 3.40	-
600	N	37	37	37
	Mean	1.65	2.93	39.8
	SD	0.54	0.72	12.1
	CV%	33.0	24.4	30.3
	90% CI	1.49, 1.82	2.70, 3.17	-

Table 5. Estimate of the slope for the linear regression between log-PK parameter and log-dose

Profile Day	PK parameter	Slope estimate	Lower 90% confidence limit	Upper 90% confidence limit	Dose proportionality across the whole dose range*	Proportionality dose range**
1	AUC_{0-24}	1.124	1.039	1.209	no	2.9
	C_{max}	1.062	0.965	1.160	yes	
14	AUC_{0-24}	1.024	0.946	1.101	yes	
	C_{max}	0.998	0.908	1.088	yes	

* Dose range = ratio highest to lowest dose = 4.00.
** Maximum dose range within which the increase in the pharmacokinetic parameter can still be considered proportional to the increase in dose.
The critical region for the 90% confidence interval for the slope in order to conclude dose-proportionality across the dose range considered is (0.839, 1.161).

PK of Metabolites

Summary of the relevant pharmacokinetic parameters of metabolite are presented in Table 6. The median tmax of QAZ033 occurs after that of indacaterol; 2.08 h vs 0.25 h. Serum concentrations of QAZ033 were considerably lower than that observed for indacaterol. The peak concentration of QAZ033 was approximately 7% of indacaterol Cmax and AUC0-24 was 11% of indacaterol AUC0-24 (Table 6). When molar concentrations were used Cmax and AUC0-24 of QAZ033 were 6% and 11%, respectively, of the relevant indacaterol parameters.

Table 6. Summary statistics of metabolite PK parameters - Day 14					
Statistic	[1]t_{max} (h)	C_{max} (pg/mL)	AUC_{0-24} (pg.h/mL)	[2]$R_{met, Cmax}$	[2]$R_{met, AUC0-24}$
N	32	32	32	32	32
Mean/median[1]	2.08	101.3	1661	0.0654	0.1118
SD/range[1]	0.25-12.08	33.3	665	0.0286	0.0499
CV%	-	32.9	40.0	43.7	44.7

[1]tmax – median and range [2]R_{met} = QAZ033/indacaterol (based on mass concentrations)

Summary of Findings/conclusion

- Peak exposure to indacaterol (serum Cmax AUC24 hrs) increased dose proportionally over the entire dose range on Day 14.
- Steady-state was achieved by Day 12, consistent with the effective half life for accumulation of indacaterol which was, on average, 40 h and 49 h.
- Systemic accumulation of indacaterol at steady state, compared to the first dose, was between 1.65- and 1.85-fold for Cmax and between 2.93- and 3.48-fold for AUC0-24.
- Maximum serum QAZ033 (sum of metabolites P26.9 and P30.3) concentrations occurred later than for indacaterol; 2.08 h vs 0.25 h.
- At steady-state of indacaterol, peak (Cmax) and total exposure (AUC0-24) of QAZ033 (sum of the hydroxy metabolites P26.9 and P30.3) were approximately 7% and 11%, respectively, of the relevant indacaterol exposure.

"An open-label, single dose, parallel-group study to assess the pharmacokinetics of 600 µg indacaterol in subjects with impaired hepatic function in comparison with healthy control subjects"

Study No. A2307 **Development phase of study**: phase III

Objective

Primary objective

• To compare the pharmacokinetics of 600 µg indacaterol administered by oral inhalation in subjects with mild and moderate hepatic impairment with demographically-matched healthy control subjects

Secondary objective

• The secondary objective is to assess and compare the general tolerability and safety of a single dose of 600 µg indacaterol administered by oral inhalation in the study groups

Study Design and Methods

This was a single center, open-label, parallel group, single-dose design in subjects with stable chronic liver disease and demographically-matched healthy controls. All subjects received a single dose of 600 µg indacaterol. A total of 32 subjects were planned to be included in the study consisting of 16 healthy subjects, 8 mild hepatic impaired and 8 moderate hepatic impaired subjects. Child-Pugh Clinical Assessment Score consistent with degree of hepatic impairment. Serum samples were collected pre-dose and 0.083,
0.25, 0.5 h (5, 15, 30 minutes), and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216 and 240 h post dose. At 192, 216 and 240 h post-dose, samples were collected from only the hepatically impaired subjects. Urine was collected pre-dose and through 24 h after dosing. Indacaterol in serum and urine was determined by an LC/MS/MS method. The lower limit of quantification was 0.01 ng/mL for indacaterol in serum and 0.10 ng/mL for indacaterol in urine expressed as free base. For protein binding determination an additional serum samples were collected at 0.25 (15 minutes), 1 and 24 h post dose.

Liver Function assessment:
The sponsor used the following child-pugh system to assess the liver function. The assessment is appropriate.

Child-Pugh Clinical Assessment Score

Assessment	Degree of Abnormality	Score
Encephalopathy *	None	1
	I – II	2
	III	3
Ascites **	Absent	1
	Minimal	2
	Moderate – Severe	3
Bilirubin (mg/dL)	< 2.0	1
	2.0 - 3.0	2
	> 3.0	3
Albumin (g/dL)	> 3.5	1
	2.8 - 3.5	2
	< 2.8	3
Prothrombin Time	0 - 3.9	1
(seconds > control time)	4.0 - 6.0	2
	> 6.0	3

Total the score for all five assessments to determine the clinical group for each subject in subjects with chronic stable liver disease:

Total Score	Group	Severity
5 – 6	2	Mild
7 – 9	3	Moderate
10 – 15	4	Severe

- Signs and symptoms of hepatic encephalopathy by stage are presented on the next page. Symptoms or history of Stage II or worse of encephalopathy within 6 months of study entry is an exclusion criteria.
- Signs and/or symptoms of severe ascites is an exclusion criteria

Results
Pharmacokinetics results
A summary of the key PK parameters for indacaterol is shown in Table 1. The comparison of impaired groups to control groups for AUC0-24, AUC0-168, AUC0-∞, Cmax and Ae0-24 is summarized in Table 2

Serum concentration time profiles were similar between all treatment groups with the last measurable concentration of indacaterol (>LLOQ) found between 96 to 168 hours and 96 to 240 hours, in healthy control and hepatically impaired matched individuals respectively (Figure 1).

Mean systemic exposures (AUC0-24, AUC0-168 and AUC0-∞) were similar between each subject group (Table 1). The mean apparent terminal elimination half-life of indacaterol determined from serum concentrations ranged between 71.1 and 79.6 hours. The mean estimates of total body clearance (CL/F) were 76.2 and 85.9 L/h in hepatically impaired subjects and 73.6 and 88.5 L/h in healthy matched controls. Mean renal clearance of indacaterol ranged from 0.58 to 0.73 L/h

Table 1 Pharmacokinetic parameters of indacaterol (n=8, arithmetic mean, SD (CV%))

Subject group	t_{max}* (h)	C_{max} (pg/mL)	AUC_{0-24} (pg.h/mL)	$AUC_{0-\infty}$ (pg.h/mL)	CL/F (L/h)	$t_{1/2}$ (h)	Ae_{0-24} (µg)	CL_R (L/h)
Control subjects (mild)	0.25 (0.25 – 0.25)	808,323 (39.9)	3926,1939 (49.4)	10028,5313 (53.0)#	73.6,36.3 (49.3)#	79.6,18.9 (23.8)#	2.22,0.90 (40.4)	0.73,0.61 (82.6)
Hepatically impaired (mild)	0.25 (0.25 – 0.5)	790,286 (36.3)	3808,1266 (33.2)	8877, 3255 (36.7)	76.2, 27.6 (36.2)	73.7,19.0 (25.8)	2.19,0.77 (35.2)	0.62,0.29 (46.4)
Control subjects (moderate)	0.25 (0.25 – 0.5)	731,272 (37.1)	3374,1118 (33.1)	7131#, 1791 (25.1)	88.5,20.6 (23.3)#	71.1,19.6 (27.6)#	1.92,0.97 (50.5)#	0.58,0.35 (60.3)#
Hepatically impaired (moderate)	0.25 (0.25 – 2.0)	630,384 (61.0)	3464,2163 (62.4)	8751, 5185 (59.2)	85.9, 39.7 (46.2)	78.6,27.2 (34.6)	1.96,1.65 (84.1)	0.58,0.29 (49.8)

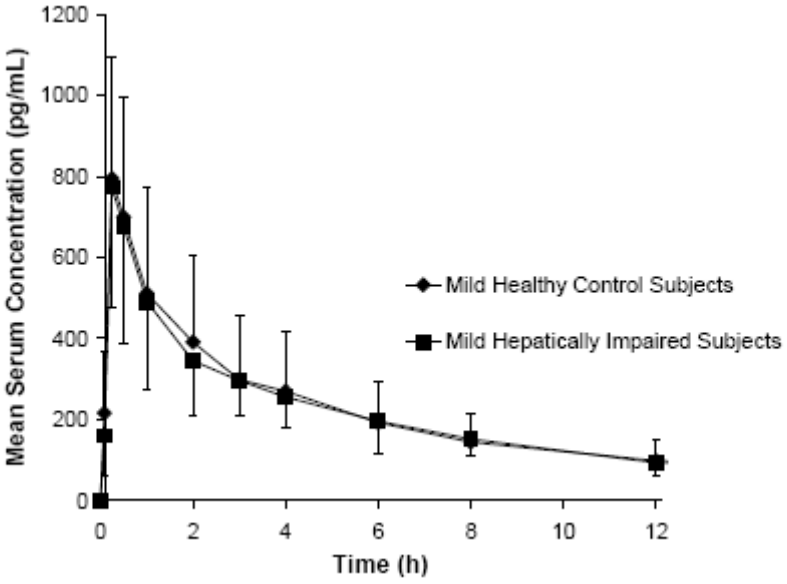
*tmax - median and range; , # n=7;subjects

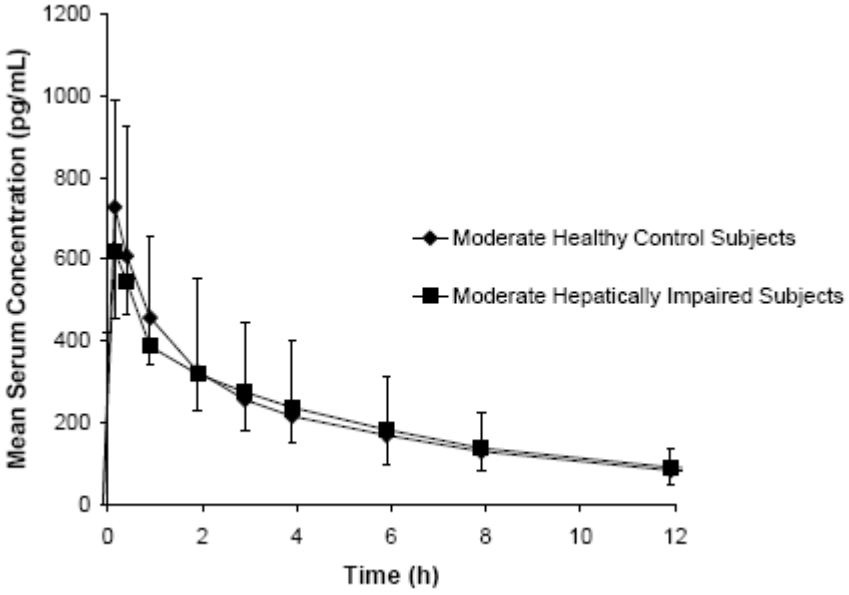
Table 2 Comparison of impaired groups to control groups for AUC0-24, AUC0-168, AUC0-∞, Cmax and Ae0-24

PK Parameter	Group Comparison	Ratio to control (1)	90% Confidence Interval (2)
AUC_{0-24} (pg.h/mL)	Impaired (mild)/Control (mild)	1.012	(0.72,1.42)
	Impaired (moderate)/ Control (moderate)	0.948	(0.67,1.33)
$AUC_{0-\infty}$ (pg.h/mL)	Impaired (mild)/Control (mild)	0.866	(0.59,1.28)
	Impaired (moderate)/ Control (moderate)	1.120	(0.76,1.65)
C_{max} (pg/mL)	Impaired (mild)/Control (mild)	0.978	(0.67,1.43)
	Impaired (moderate)/ Control (moderate)	0.772	(0.53,1.13)
Ae_{0-24} (µg)	Impaired (mild)/Control (mild)	0.984	(0.62,1.57)
	Impaired (moderate)/ Control (moderate)	0.954	(0.58,1.57)

The AUC ratios of the mild and moderate hepatically impaired subjects to matched controls ranged from 0.87 – 1.12. For Cmax the ratios ranged from 0.77 – 0.98, and for Ae0-24 they were close to unity. The analysis indicates that for all the analyzed exposure parameters, the hepatic impaired subjects have similar exposure to their control subjects.

Figure 1 Arithmetic mean (and SD bars) serum concentration-time profiles (0 - 12 h post dose) of indacaterol in hepatically impaired subjects and the matched group of healthy subjects – linear plots





Bioanalytical method Liquid-solid extraction of serum samples followed by evaporation of the extracts to dryness and analysis of the reconstituted samples by LC-MS/MS using electrospray ionization

Method validation report Lower Limit of quantification (LLOQ)
10.0 pg/mL (expressed as base) using 200 µL of serum

Ex vivo protein binding results
The mean serum protein binding of indacaterol was 92.9% (SD=1.6%, n=9) in the patients with mild hepatic impairment and 91.5% (SD=2.2%, n=8) in their healthy control group (Table 3). Binding was 92.6% (SD=1.6%, n=8) in the patients with moderate hepatic impairment and 90.5% (SD=1.9%, n=9) in their control group (Table 4). No significant difference was observed among the time-points in either the hepatically impaired or the healthy subjects (Figure 2).

Table 3. *Ex vivo* serum protein binding of [3H]QAB149 after a 600 µg oral inhalation dose of QAB149 in mild hepatically impaired subjects and fasted healthy volunteers

	Mild hepatically impaired subjects					Healthy Controls				
		DPM/0.05 ml		Bound			DPM/0.05 ml		Bound	
Timepoint (h)	Subj. ID#.	Serum	Supernatant	fraction	Mean ± SD	Subj. ID#	Serum	Supernatant	fraction	Mean ± SD
0.25 h	5101*	616	33.9	0.945	0.939 ± 0.006	5117	478	29.2	0.939	0.928 ± 0.021
1 h		635	41.7	0.934			558	32.5	0.942	
24 h		655	41.5	0.937			467	45.0	0.904	
0.25 h	5102*	557	39.7	0.929	0.937 ± 0.008	5118	546	22.3	0.959	0.940 ± 0.017
1 h		684	37.5	0.945			393	29.4	0.925	
24 h		628	38.9	0.938			561	35.5	0.937	
0.25 h	5103*	582	26.9	0.954	0.944 ± 0.010	5119	513	42.7	0.917	0.906 ± 0.011
1 h		619	40.9	0.934			522	54.7	0.895	
24 h		671	36.9	0.945			548	52.1	0.905	
0.25 h	5104	280	16.9	0.940	0.930 ± 0.010	5120	389	26.4	0.932	0.922 ± 0.010
1 h		310	24.6	0.921			311	24.6	0.921	
24 h		311	22.3	0.928			305	26.8	0.912	
0.25 h	5105	211	20.6	0.902	0.921 ± 0.018	5121	448	46.6	0.896	0.908 ± 0.013
1 h		297	22.8	0.923			529	41.4	0.922	
24 h		294	18.3	0.938			494	46.3	0.906	
0.25 h	5106	285	19.6	0.931	0.938 ± 0.020	5122	474	35.7	0.925	0.921 ± 0.003
1 h		307	12.4	0.960			485	39.1	0.919	
24 h		299	23.3	0.922			490	40.1	0.918	
0.25 h	5107	267	21.0	0.921	0.916 ± 0.019	5123	373	33.7	0.910	0.912 ± 0.013
1 h		305	31.9	0.895			440	43.9	0.900	
24 h		308	21.0	0.932			419	30.7	0.927	
0.25 h	5108	296	16.0	0.946	0.928 ± 0.016	5124	411	63.3	0.846	0.879 ± 0.031
1 h		295	22.3	0.924			423	48.0	0.887	
24 h		310	26.6	0.914			518	48.8	0.906	
0.25 h	6106	281	26.8	0.905	0.910 ± 0.007					
1 h		311	25.5	0.918						
24 h		283	26.6	0.906						
Ave ± SD					0.929 ± 0.016					0.915 ± 0.022

* DPM count was from 0.1 ml serum and supernatant.

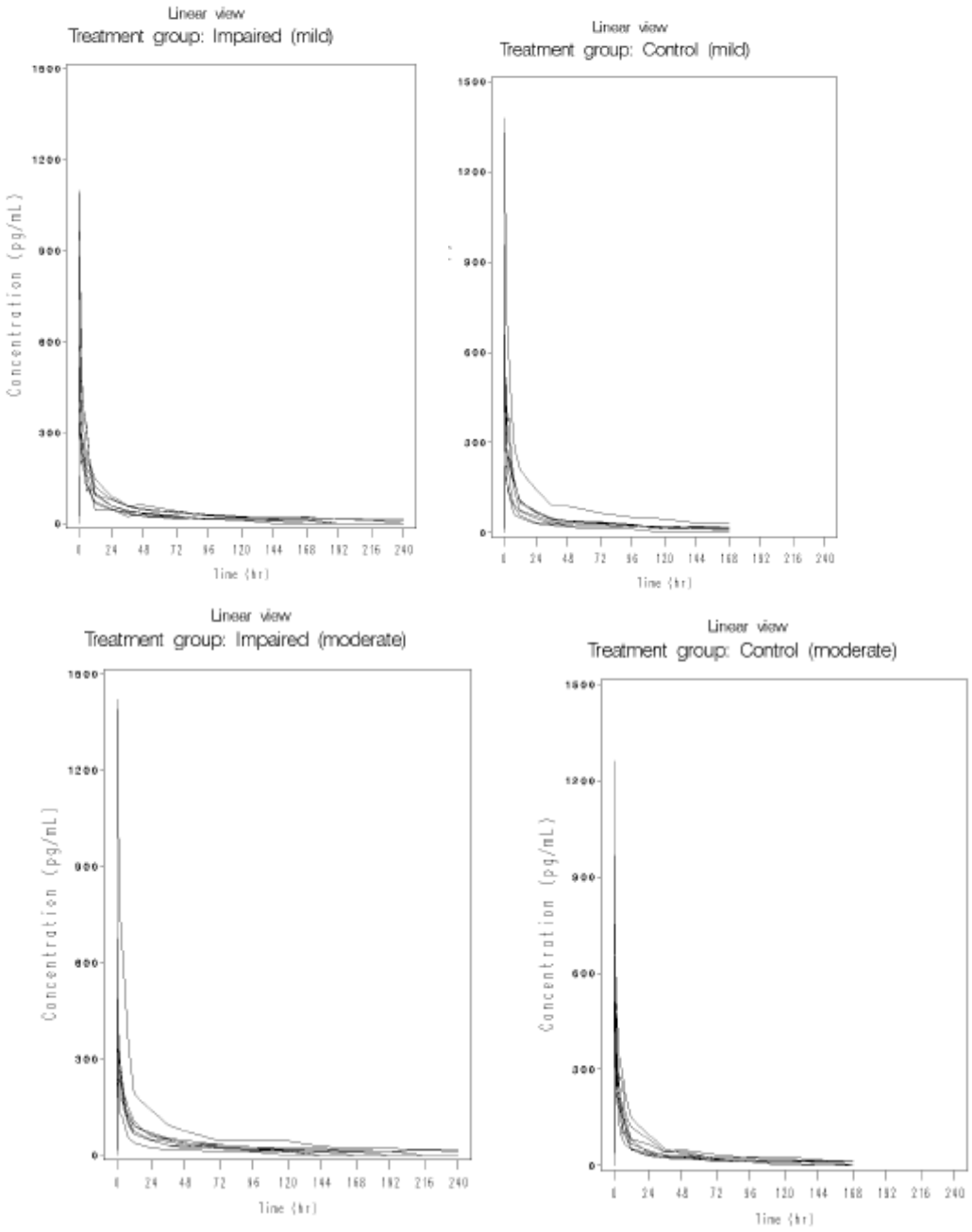
Table 4 *Ex vivo* serum protein binding of [3H]QAB149 after a 600 µg oral inhalation dose of QAB149 in moderate hepatically impaired subjects and fasted healthy volunteers

	Moderate hepatically impaired subjects					Healthy Controls				
		DPM/0.05 ml		Bound			DPM/0.05ml		Bound	
Timepoint (h)	Subj. ID#.	Serum	Supernatant	fraction	Mean ± SD	Subj. ID#.	Serum	Supernatant	fraction	Mean ± SD
0.25 h	5109	387	42.0	0.891	0.903 ± 0.010	5125	515	38.1	0.926	0.922 ± 0.005
1 h		482	44.9	0.907			446	34.3	0.923	
24 h		456	40.5	0.911			510	42.3	0.917	
0.25 h	5110	440	22.7	0.948	0.934 ± 0.016	5126	460	38.7	0.916	0.915 ± 0.010
1 h		430	26.7	0.938			507	38.2	0.925	
24 h		462	38.6	0.916			471	44.6	0.905	
0.25 h	5111	498	31.7	0.936	0.934 ± 0.002	5127	385	40.6	0.895	0.895 ± 0.017
1 h		422	28.8	0.932			472	41.5	0.912	
24 h		461	31.1	0.933			381	46.6	0.878	
0.25 h	5112	421	42.0	0.900	0.906 ± 0.006	5128	322	44.8	0.861	0.882 ± 0.028
1 h		441	38.4	0.913			436	56.4	0.871	
24 h		461	43.5	0.906			514	44.2	0.914	
0.25 h	5113	425	28.3	0.933	0.938 ± 0.006	5129	534	44.4	0.917	0.901 ± 0.018
1 h		500	31.5	0.937			451	53.6	0.881	
24 h		549	30.2	0.945			435	41.2	0.905	
0.25 h	5114	471	29.9	0.937	0.929 ± 0.022	5130	435	36.4	0.916	0.912 ± 0.006
1 h		508	27.5	0.946			454	43.0	0.905	
24 h		411	39.3	0.904			462	40.0	0.913	

Table continued on next page

	Moderate hepatically impaired subjects					Healthy Controls				
		DPM/0.05 ml		Bound			DPM/0.05 ml		Bound	
Timepoint (h)	Subj ID#.	Serum	Supernatant	fraction	Mean ± SD	Subj ID#.	Serum	Supernatant	fraction	Mean ± SD
0.25 h	5115	444	27.1	0.939	0.933 ± 0.005	5131	364	38.1	0.895	0.893 ± 0.026
1 h		431	29.7	0.931			410	55.1	0.866	
24 h		437	30.6	0.930			526	43.1	0.918	
0.25 h	5116	444	35.6	0.920	0.929 ± 0.008	5132	509	38.6	0.924	0.918 ± 0.006
1 h		458	29.3	0.936			493	40.1	0.919	
24 h		446	31.2	0.930			537	46.9	0.913	
0.25 h						6131	550	46.4	0.916	0.905 ± 0.010
1 h							473	46.4	0.902	
24 h							527	54.5	0.897	
Ave ± SD					0.926 ± 0.016					0.905 ± 0.019

Figure 2 Overlaying individual concentration– time profiles



Conclusion:
Indacaterol exhibited comparable pharmacokinetics and systemic exposure in hepatically impaired mild and moderate impairment and healthy control subjects.

Mild and moderate hepatic impairment did not significantly affect the binding of indacaterol to serum proteins.

Discussion:

The dose used in this study (600 μg) was much higher than the proposed dose regimen (300 μg once daily). Because one of the purposes of the study is to assess the tolerability and safety of the drug, the dose used seems appropriate.

The pharmacokinetic parameters the sponsor compared are the 'arithmetic mean', which is not the right mean they should use. Therefore, their conclusion about the comparable PK and systemic exposure are questionable.

"An open-label, single-dose, two period, single sequence crossover study to assess the pharmacokinetic interaction of QAB149 (300 µg via inhalation) with ketoconazole (200 mg tablet BID) in healthy adult subjects″

Study No. A2311 **Development phase of study**: phase III

Objective

The primary objective of this study was to compare the pharmacokinetics of a single 300 µg dose of indacaterol administered alone and in the presence of ketoconazole (at steady state) in healthy adult subjects.

The secondary objective was to assess the safety of a single 300 µg dose of indacaterol given via inhalation in the presence of ketoconazole at steady state in healthy adult subjects.

Study Design and Methods

This study was an open-label, single dose, two-period, single sequence crossover design. Twenty healthy male subjects were to receive a single inhaled dose of indacaterol (300 µg) in period 1. After a washout of 14 day period, in period 2, ketoconazole BID 200 mg was administered for 7 days (till day 21) and on the 4th day (day 17), once steady state of ketoconazole was attained, a single inhaled dose of indacaterol (300 µg) was administered to all subjects. After each dose of indacaterol, three mL of blood was collected into a polypropylene tube spray coated with silica at each of the following time points: pre-dose (i.e. pre – indacaterol dose), 0.083, 0.25, 0.5 h (5, 15, 30 minutes), and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96 and 120 h post-dose. Serum was obtained from all blood samples. Indacaterol in serum was determined by LC/MS/MS. The lower limit of quantification (LLOQ) was 0.010 ng/mL.

Results:

Mean log-linear indacaterol concentration-time plot and a summary of the pharmacokinetic parameters for indacaterol are given in Figure 1 and Table 1, respectively.

Systemic exposure to indacaterol was consistently higher after coadministration with ketoconazole as compared with the administration of indacaterol alone. The mean increase (calculated as mean of the individual ratios) of indacaterol following co-administration with ketoconazole in terms of Cmax, AUC0-24, AUC0-tlast and AUC0-∞ was 1.31, 1.88, 1.95 and 1.92-fold, respectively. The statistical analyses of the data produced very similar mean ratios, as can be seen in Table 2. The treatment differences were statistically significant for all the parameters tested ($P < 0.001$).

Figure 1 Arithmetic mean serum concentration-time profiles of indacaterol administered alone (N=20) and together with ketoconazole (N=18)

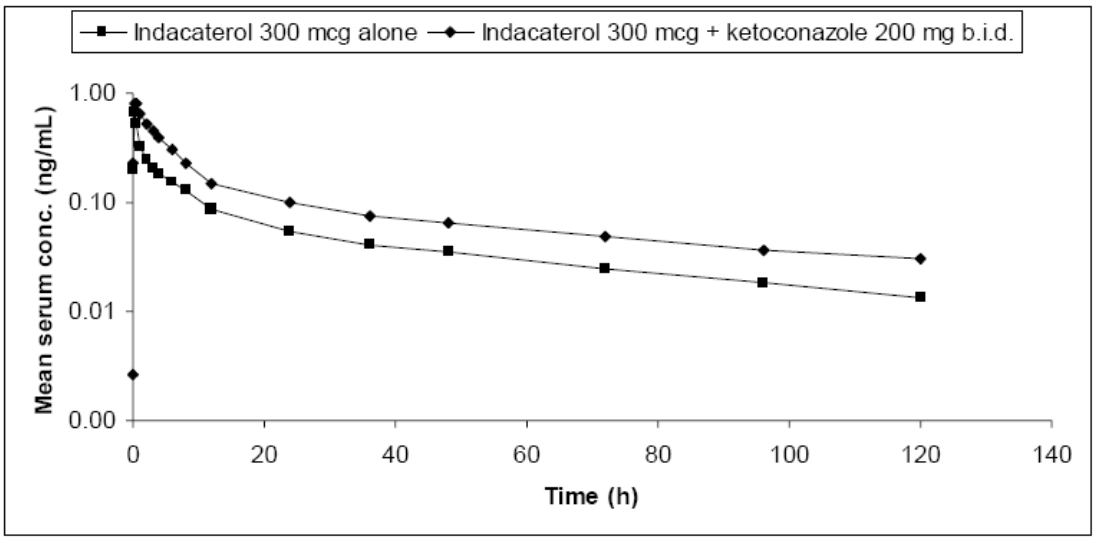


Table 1 Serum pharmacokinetic parameters of indacaterol administered alone and together with ketoconazole (arithmetic mean, SD (CV %))

Treatment	t_{max}* (h)	C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)	$AUC_{0-tlast}$ (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)
Indacaterol alone (N=20)	0.25 (0.25-0.50)	0.682, 0.217 (32)	3.03, 0.87 (29)	5.64, 1.83 (33)	7.25, 2.26 (31)	63.2, 21.1 (33)
Indacaterol + ketoconazole (N=18)	0.50 (0.25-1.00)	0.863, 0.266 (31)	5.65, 1.79 (32)	10.73, 3.56 (33)	13.80, 4.63 (34)	69.4, 23.1 (33)

*tmax – median and range

Table 2 Statistical results for PK parameters of indacaterol

PK parameter (unit)	Treatment group	N	Geometric mean (1)	Ratio (2)	90% CI	P value
C_{max} [ng/mL]	Indacaterol	18	0.63			
	Indacaterol + Ketoconazole	18	0.82	1.31	1.16, 1.48	0.001
AUC_{0-24} [ng.h/mL]	Indacaterol	18	2.85			
	Indacaterol + Ketoconazole	18	5.35	1.88	1.73, 2.04	<0.001
$AUC_{0-tlast}$ [ng.h/mL]	Indacaterol	18	5.19			
	Indacaterol + Ketoconazole	18	10.12	1.95	1.78, 2.13	<0.001
$AUC_{0-\infty}$ [ng.h/mL]	Indacaterol	18	6.78			
	Indacaterol + Ketoconazole	18	12.99	1.92	1.76, 2.09	<0.001

Note: (1) Obtained from analysis of variance of logarithmically transformed values.
(2) Ratio = indacaterol+ketoconazole/indacaterol.

Conclusion:
• PK parameters (AUC and Cmax) showed an increase in exposure to indacaterol when indacaterol was given with ketoconazole compared to when given alone ($P < 0.001$). AUC's (i.e. AUC0-24, AUC0-tlast and AUC0-∞) were approximately doubled and Cmax increased about 31%.

• Median time to maximum serum concentration (Tmax) was delayed by 15 minutes when indacaterol was co-administered with ketoconazole.

• The terminal elimination half-lives of indacaterol were similar for both treatments: on average, 63.2 h for indacaterol alone and 69.4 h for indacaterol + ketoconazole.

"An open-label, single-dose, two-period, single sequence study to assess the pharmacokinetic interaction of indacaterol (300 µg via inhalation) with verapamil (80 mg tablet t.i.d) in healthy adult subjects"

Study no.:	CQAB149B2216
Development Phase of Study:	Phase I
Principal investigator:	Dr. Shoba Rajagopal, Lotus Labs Pvt. Ltd., Lotus House, No. 7, Jasma Bhavan Road, Millers Tank Bed Area, Opp. Gurunanak Bhavan, Vasanthnagar, Bangalore 560052, Karnataka, India
Study Dates:	18-Apr-2008/26-May-2008

Objectives

Primary objective

- To compare the pharmacokinetics of a single 300 µg dose of indacaterol administered alone and in the presence of verapamil (at steady state) in healthy adult subjects..

Secondary objectives

- To assess the safety of a single 300 µg dose of indacaterol given via inhalation in the presence of verapamil at steady state in healthy adult subjects.

Study Population

Twelve healthy male subjects were enrolled, 12 subjects completed the first period and 11 completed both periods. All pharmacokinetic samples from both treatment periods were analyzed.

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This study was an open-label, single dose, two-period, single sequence design. Twelve healthy males were enrolled. Each subject participated in a screening period (day -21 to day - 2), two baseline periods (day -1), two treatment periods, a washout period of at least fifteen days between the two treatment periods, and a study completion evaluation. Eleven (11) of the 12 subjects received both treatments and completed the study. Subjects were randomized to the following treatments:

Treatment A: Indacaterol 300 µg capsule for inhalation administered using the Concept1 device as a single dose under fasted conditions.

Treatment B. Verapamil 80 mg tablet administered orally as a t.i.d. dosing for four days. On the third day of verapamil treatment (day 3), a single dose of indacaterol 300 µg capsules for inhalation administered using the Concept1 device under fasted conditions.

Test product, dose and mode of administration, batch number

- Indacaterol 300 µg capsules for oral inhalation (Batch #: X174CD)
- Placebo capsules for oral inhalation (Batch #: X134EC)-used for training purpose only

The above mentioned study drugs were administered via inhalation by Concept1 inhaler devices (Batch #: B01437011001).

- Verapamil 80 mg tablets (Calaptin®, Batch #: EC0017) for oral administration..

PHARMACOKINETIC MEASUREMENTS

Blood samples were taken following inhalation at 0 (predose), 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 8, 10, 24, 48, 72, 96, 144, and 168 hours after inhalation. Indacaterol was determined in serum prepared from the blood samples using an LC-MS/MS method. The lower limit of quantification (LLOQ) was 10 pg/mL.

SAFETY MEASUREMENTS

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine performed at study center laboratory and regular assessments of vital signs, physical condition and body weight.

Concomitant therapy

There were no concomitant medications reported.

DATA ANALYSIS

Pharmacokinetic Data Analysis

Standard pharmacokinetic parameters were determined using noncompartmental methods: Cmax (maximum serum concentration), tmax (time to Cmax), AUC0-24 (area under the serum concentration-time curve from time 0 to 24 h post-dose), AUC0-48 (AUC from time 0 to 48 h post-dose), AUC0-tlast (AUC up to the last quantifiable concentration), AUC0-∞ (AUC extrapolated to infinity) and t1/2 (terminal elimination half-life).

Statistical Analysis

Statistical methods: Log transformed values of Cmax, AUC0-24, AUC0-48, AUC0-tlast and AUC0-∞ were analyzed using a linear mixed effects model in order to assess whether the co-administration of verapamil to steady-state with indacaterol administered as a single dose altered the pharmacokinetics of indacaterol. The model included the treatment as a fixed effect and subject as a random effect. These analyses are summarized by point estimates and 90% confidence intervals (CI) of the geometric mean ratios of the treatment means (indacaterol + verapamil / indacaterol alone), back transformed from the log scale.

RESULTS

Analytical Method

Bioanalytical procedures

The analytical method consisted on liquid-solid extraction of plasma samples followed by evaporation of the extracts to dryness and analysis of the reconstituted samples by LC-MS/MS using electrospray ionization. The lower limit of quantification (LLOQ) was 0.010 ng/mL (10

pg/mL) using 0.2 mL of serum. All concentrations refer to indacaterol free base. The assays were performed at the Bioanalytics laboratories of DMPK, Novartis, in Rueil-Malmaison, France.

In-Study Validation for Indacaterol

Matrix	Human Plasma	
Concentration Range	10 to 2000 pg/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.997$	
Between-Batch Accuracy (%Diff)	Qc standards (30, 150, 800, 1800 pg/mL) Cal. Curve standards	-7.4 to -4.4 -4.0-3.0
Between-Batch (% CV)	Cal. Curve standards QCs	2.5-7.2 3.7-12.1

Pharmacokinetic Results

The mean indacaterol concentration time profile following single dose administration of Indacaterol 300 µg with and without verapamil is shown in Figure 1. The individual Cmax and AUCt values for indacaterol following single dose administration of the Indacaterol 300 µg with and without verapamil are shown in Figures 2 and 3. A summary of the key serum PK parameters for indacaterol and indacaterol with verapamil is shown in Table 1. The statistical comparison of indacaterol + verapamil to indacaterol given alone using the PK parameters Cmax, AUC0-24, AUC0-48, AUC0-tlast, and AUC0-∞, is summarized in Table 2.

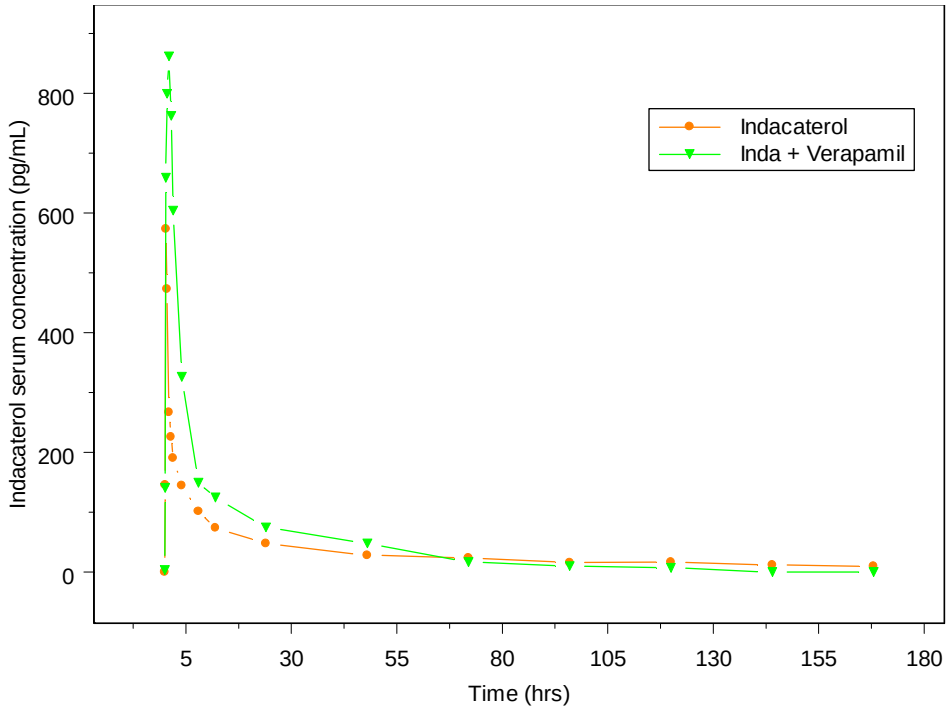


Figure 1. Mean concentration time profile for indacaterol following single dose administration of indacaterol inhalation aerosol 300 µg with and without verapamil 800 mg t.i.d for 4 days.

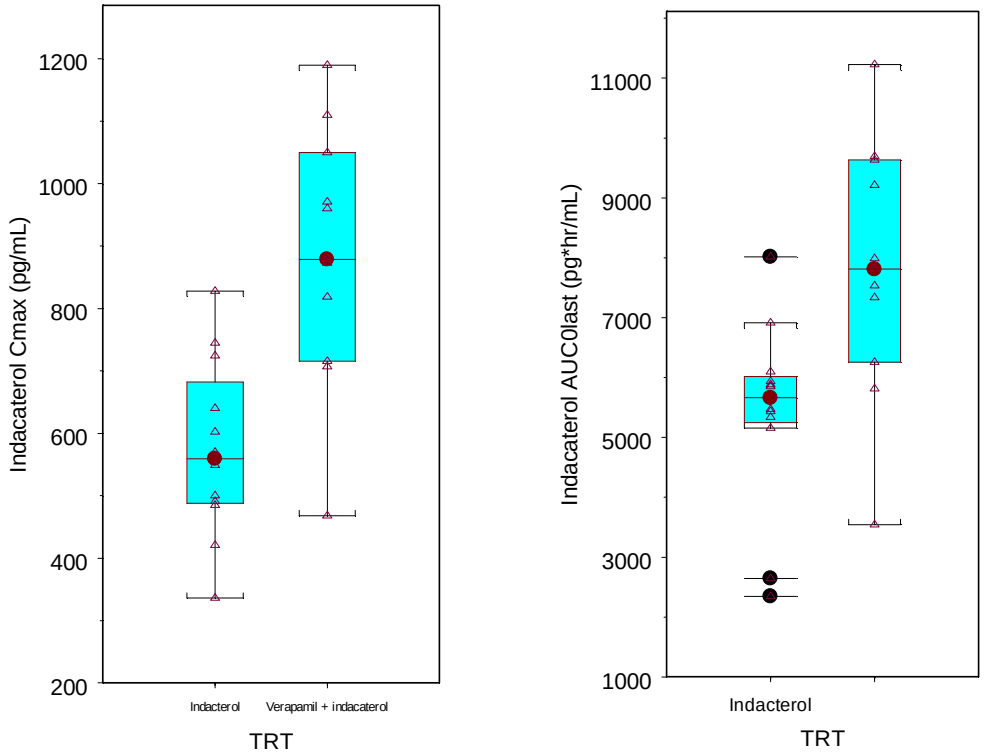


Figure 2. Individual Cmax and AUCt values following single dose administration of indacaterol inhalation aerosol 300 µg with and without verapamil 800 mg t.i.d for 4 days.

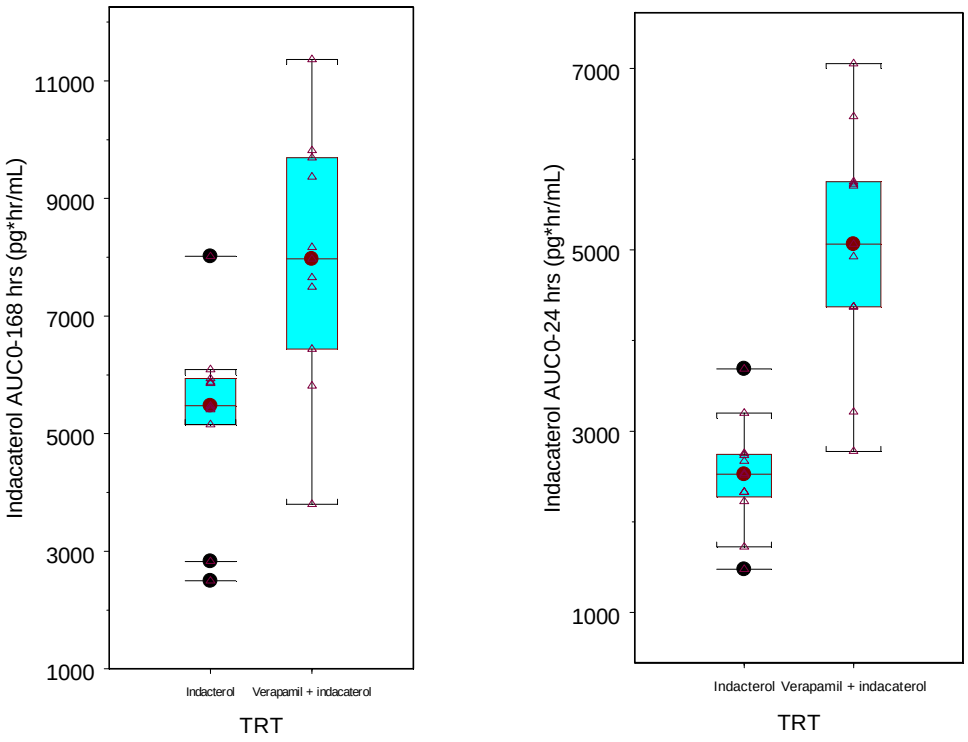


Figure 3. Individual AUC168 hrs and AUC24hrs values following single dose administration of indacaterol inhalation aerosol 300 µg with and without verapamil 800 mg t.i.d..

Table 1. Mean pharmacokinetic parameters after inhalation of 300 µg indacaterol with and without verapamil

Table 1. Serum pharmacokinetic parameters of indacaterol after administration alone and together with verapamil (arithmetic mean, SD and CV%)								
Treatment	Stat	t_{max} * [h]	C_{max} [pg/mL]	AUC_{0-24} [pg*h/mL]	AUC_{0-48}[Pg*h/mL]	$AUC_{0-tlast}$ [pg*h/mL]	$AUC_{0-\infty}$ [pg*h/mL]	$t_{1/2}$ [h]
Indacaterol alone (n=12)	Mean	0.25 0.25–0.50	574	2514	3420	5424	6634[a)]	78.7 [a)]
	SD	-	142	591	802	1575	2308	33.0
	%CV	-	25	24	24	29	35	42
Indacaterol + verapamil (n=11)	Mean	1.0 0.50–1.5	886	5038	6505	7823	8511 [a)]	50.5 [a)]
	SD	-	206	1300	1670	2131	2098	56.1
	%CV	-	23	26	26	27	25	111

*t_{max} = median and range, [a)] N= 10

Table 2. Statistical results for PK parameters of indacaterol – ratios of geometric means and 90% confidence intervals

			Pharmacokinetic parameter		
C_{max}		AUC_{0-24}	AUC_{0-48}	$AUC_{0-tlast}$	$AUC_{0-\infty}$
Ratio [1)]	1.53	2.00	1.90	1.47	1.35
90 % CI	1.34, 1.76	1.80, 2.23	1.71, 2.11	1.32, 1.64	1.20, 1.52

1) Ratio = indacaterol+verapamil/indacaterol alone (using geometric means), back transformed from log scale

Summary of Findings/Conclusion

- The treatment ratios of the geometric means (indacaterol + verapamil to indacaterol alone) ranged between 1.35 (for $AUC_{0-\infty}$) and 2.00 (for AUC_{0-24}).
- The 90% confidence intervals for the geometric mean ratios of C_{max}, $AUC_{0-tlast}$ and $AUC_{0-\infty}$ were within the range 1.20 to 1.76.
- The 90% confidence intervals for the geometric mean ratios of AUC_{0-24} and AUC_{0-48} the 90% confidence intervals were contained within the range of 1.71 to 2.23.
- In general, one can conclude that the indacaterol systemic exposure in the presence of verapamil increased by about 2 fold.
- Since multiple doses up to 1200 µg of indacaterol were found to be safe, no dose adjustment is needed when coadministering these two drugs.

"An open-label, two-period, single sequence study to assess the pharmacokinetic interaction of a single-dose of indacaterol (300 µg via oral inhalation) with multiple, daily doses of erythromycin ethylsuccinate (400 mg tablet q.i.d) in healthy adult subjects"

Study no.:	CQAB149B2220
Development Phase of Study:	Phase I
Principal investigator:	Dr. Anton Drollmann, (Head Respiratory Profiling), Novartis Institutes for Biomedical Research, Translational Science, Basel, Switzerland)
Study Dates:	12-may-2008/12-Jun-2008

Objectives

Primary objective

- to compare the pharmacokinetics of a single 300 µg dose of indacaterol administered alone and in the presence of erythromycin (at steady state) in healthy adult subjects.

Secondary objectives

- To assess the safety of a single 300 µg dose of indacaterol given via inhalation in the presence of erythromycin at steady state in healthy adult subjects.

Study Population

Twelve male patients were enrolled into this study, 12 subjects completed the first period and eleven (11) subjects completed both periods, one subject withdrew (during washout) due to the occurrence of an adverse event (plasmodium infestation).

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This was on open-label, single-dose (indacaterol), two-period, single sequence design. Each subject participated in a screening period (day -21 to day -2), two baseline periods (day -1), two treatment periods, a washout period of at least fifteen days between the two treatment periods and a study completion evaluation.

Treatment A: Indacaterol 300 µg capsule for inhalation administered using the Concept1 device as a single dose under fasted conditions.

Treatment B. Erythromycin ethylsuccinate 400 mg tablet was administered orally as q.i.d. dosing for seven (7) days. On the third day of erythromycin ethylsuccinate treatment (day 3), a single dose of indacaterol 300 µg capsule for oral inhalation was administered using the Concept1 device under fasted conditions.

Test product, dose and mode of administration, batch number

- Indacaterol 300 µg capsule for oral inhalation (Batch No. X174CD) administered using the Concept1 inhaler device.

- Erythromycin ethylsuccinate 400 mg tablet (Batch No. 60988CG21) manufactured by Abbott and administered orally.

PHARMACOKINETIC MEASUREMENTS

Blood samples were taken following inhalation at 0 (predose), 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after inhalation (Treatment periods 1 and 2). Indacaterol was determined in serum prepared from the blood samples using an LC-MS/MS method. The lower limit of quantification (LLOQ) was 10 pg/mL.

SAFETY MEASUREMENTS

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine performed at study center laboratory and regular assessments of vital signs, physical condition and body weight.

Concomitant therapy

There were no concomitant medications reported.

DATA ANALYSIS

Pharmacokinetic Data Analysis

Log-transformed Cmax, AUC0-24, AUC0-tlast and AUC0-∞ were analyzed using a linear mixed effects model in order to assess whether the co-administration of erythromycin to steadystate with indacaterol administered as a single dose altered the pharmacokinetics of indacaterol. The model included treatment as a fixed factor and subject as a random factor. These analyses are summarized by point estimates and 90% confidence intervals (CI) for the geometric mean ratios of the treatments (indacaterol with erythromycin / indacaterol alone), back transformed from the log scale.

Statistical Analysis

Statistical methods: Log transformed values of Cmax, AUC0-24, AUC0-48, AUC0-tlast and AUC0-∞ were analyzed using a linear mixed effects model in order to assess whether the co-administration of erythromycin to steady-state with indacaterol administered as a single dose altered the pharmacokinetics of indacaterol. The model included the treatment as a fixed effect and subject as a random effect. These analyses are summarized by point estimates and 90% confidence intervals (CI) of the geometric mean ratios of the treatment means (indacaterol + erythromycin / indacaterol alone), back transformed from the log scale.

RESULTS

Analytical Method

Bioanalytical procedures

The analytical method consisted on liquid-solid extraction of plasma samples followed by evaporation of the extracts to dryness and analysis of the reconstituted samples by LC-MS/MS using electrospray ionization. The lower limit of quantification (LLOQ) was 0.010 ng/mL (10

pg/mL) using 0.2 mL of serum. All concentrations refer to indacaterol free base. The assays were performed at the Bioanalytics laboratories of DMPK, Novartis, in Rueil-Malmaison, France.

In-Study Validation for Indacaterol

Matrix	Human Plasma	
Concentration Range	10 to 2000 pg/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.997$	
Between-Batch Accuracy (%Diff)	Qc standards (30, 150, 800, 1800 pg/mL) Cal. Curve standards	-7.4 to -4.4 -4.0-3.0
Between-Batch (% CV)	Cal. Curve standards QCs	2.5-7.2 3.7-12.1

Pharmacokinetic Results

The mean indacaterol concentration time profile following single dose administration of Indacaterol 300 µg with and without erythromycin is shown in Figure 1. A summary of the key serum PK parameters for indacaterol and indacaterol with erythromycin is shown in Table 1. The statistical comparison of indacaterol + erythromycin to indacaterol given alone using the PK parameters Cmax, AUC0-24, AUC0-tlast, and AUC0-∞, is summarized in Table 2.

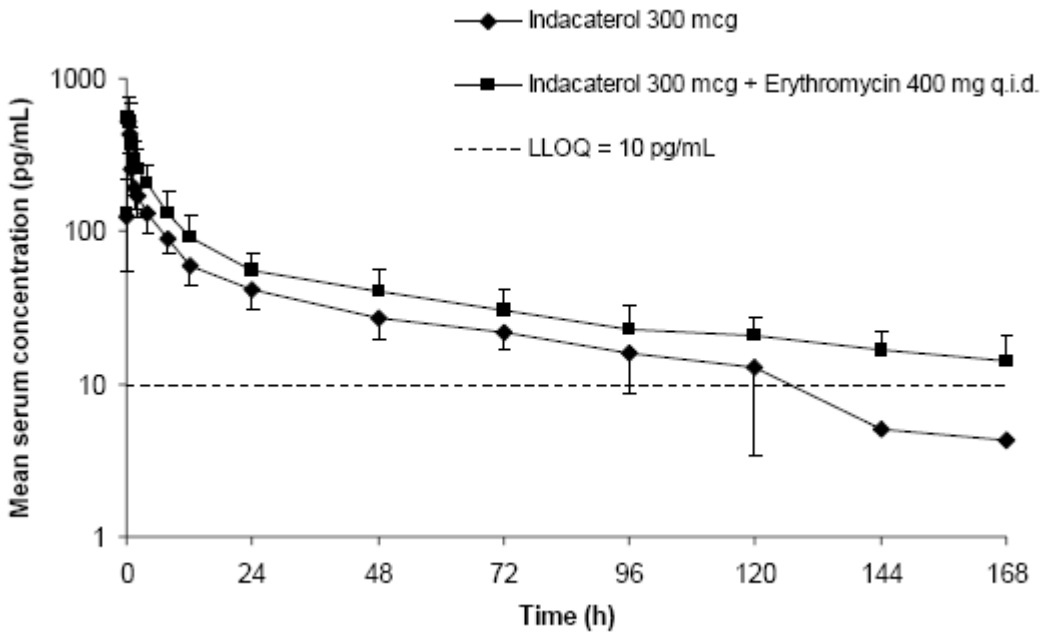


Figure 1. Mean concentration time profile for indacaterol following single dose administration of indacaterol inhalation aerosol 300 µg with and without erythromycin 400 mg q.i.d for 7 days.

Table 1. Serum pharmacokinetic parameters of indacaterol administered alone and together with erythromycin (arithmetic mean, SD (CV%))

Treatment	tmax * (h)	Cmax (pg/mL)	AUC0-24 (pg h/mL)	AUC0-last (pg h/mL)	AUC0-∞ (pg.h/mL)	t1/2 (h)
Indacaterol alone (N=12)	0.25 (0.25-0.27)	524, 196 (37)	2204, 518 (24)	4617, 1357 (29)	5821, 1763 (30)	70.9, 21.0 (30)
Indacaterol + erythromycin (N=11)	0.27 (0.25-0.52)	561, 196 (35)	3183, 1049 (33)	7172, 2418 (34)	9762, 2885 (30)	93.5, 32.2 (34)

*t_{max} = median and range

Table 2. Statistical results for PK parameters of indacaterol – ratios of geometric means and 90% confidence intervals

	Pharmacokinetic parameter			
	Cmax	AUC0-24	AUC0-tlast	AUC0-∞
Ratio [1)]	1.15	1.44	1.59	1.61
90 % CI	1.00, 1.32	1.26, 1.65	1.41, 1.80	1.38, 1.89

1) Ratio = indacaterol+erythromycin/indacaterol alone (using geometric means), back transformed from log scale

Summary of Findings/Conclusion

- The treatment ratios of the geometric means (indacaterol + erythromycin to indacaterol alone) ranged between 1.44 (for AUC_{0-24}) and 1.61 (for $AUC_{0-\infty}$).

- The 90% confidence intervals for the geometric mean ratios of AUC_{0-24} and AUC_{0-inf} the 90% confidence intervals were contained within the range of 1.26 to 1.89.
- In general, one can conclude that the indacaterol Cmax and AUC 0-24hr in the presence of erythromycin increased by 15% and 44 %, respectively.
- Since multiple doses up to 1200 µg of indacaterol were found to be safe, no dose adjustment is needed when coadministering these two drugs.

"An open label, randomized, single-dose, five-way crossover study to compare the pharmacokinetics of a single inhaled dose of mometasone furoate and indacaterol when administered alone, in free or in fixed combination in healthy male and female, non-smoking subjects"

Study no.:	CQMF149A2206
Development Phase of Study:	Phase II
Principal investigator:	Dr. C. James Kissling, MDS Pharma Services (US) Inc., Lincoln, NE, USA (Principal Investigator)
Study Dates:	03-Nov-2007/12-Jan-2008

Objectives:
Primary objective

- To compare the systemic exposure (with focus on relative bioavailability) to indacaterol when indacaterol is given alone by inhalation either via the single dose dry powder inhaler Concept1, or given alone via the multidose dry powder inhaler Twisthaler™, or when given as a fixed dose combination with mometasone furoate via the multidose dry powder inhaler Twisthaler™ in healthy male and female, non-smoking subjects.

Secondary objectives

- To compare the systemic exposure resulting from inhalation of mometasone furoate via Twisthaler™ versus exposure to mometasone furoate resulting from inhalation of a fixed dose combination of mometasone furoate and indacaterol in the same device in healthy male and female, non-smoking subjects.
- To monitor the safety and tolerability of a single inhaled dose of mometasone furoate and indacaterol when administered alone, in free or in fixed combination in healthy male and female, non-smoking subjects.

STUDY DESIGN, TREATMENT AND ADMINISTRATION
This was a single-center, randomized, five-period, crossover design trial evaluating the pharmacokinetics of 5 treatments of indacaterol and mometasone administered in various combinations or alone after single dose administration.

Treatment A: QMF149 (fixed dose combination of 250 µg indacaterol and 200 µg mometasone furoate) dry powder inhaler formulation administered via Twisthaler™ as a single dose under fasted conditions.

Treatment B: free combination of 1 x 250 µg indacaterol administered via Twisthaler™ and 1 x 200 µg mometasone furoate* dry powder inhaler formulation administered via Twisthaler™ as a single dose under fasted conditions.

Treatment C: 1 x 200 µg mometasone furoate* dry powder inhaler formulation administered via Twisthaler™ as a single dose under fasted conditions.

Treatment D: 1 x 250 µg indacaterol dry powder inhaler formulation administered via Twisthaler™ device as a single dose under fasted conditions.

Treatment E: 1 x 300 µg indacaterol dry powder inhaler formulation administered via Concept1 device as a single dose under fasted conditions

Mometasone furoate is supplied as 220 µg, however, only 200 µg is inhaled.

Test product, dose and mode of administration, batch number

- QMF149 (indacaterol/mometasone furoate) 250/200 µg Twisthalers™ [Batch: H384CD #7006608.001; Re-test date: (b) (4)]
- QAB149 (indacaterol) 250 µg Twisthalers™ [Batch: H395ED #7006617.002; Re-test date: (b) (4)]
- QAB149 (indacaterol) 300 µg capsules (administered via Concept1) [Batch: X164EC #6001037.003; Re-test date: (b) (4)
- Asmanex® (mometasone furoate) 220 µg Twisthalers™ [Batch: 7-JS-10; Re-test date: (b) (4)

PHARMACOKINETIC MEASUREMENTS

PK samples for indacaterol (3 mL blood) were collected from each subject at the following timepoints in all treatment periods involving dosing with indacaterol:

- pre-dose, 5 minutes, and 0.25, 0.5, 1, 2, 3, 6, 12, 24, 36, 48, 72, 96, 120 and 144 hours post-dose

PK samples for mometasone furoate (6 mL blood) were collected from each subject at the following timepoints in all treatment periods involving dosing with mometasone furoate:

- pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 6, 12 and 24 hours post-dose.

SAFETY MEASUREMENTS

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine performed at study center laboratory and regular assessments of vital signs, physical condition and body weight.

DATA ANALYSIS

Pharmacokinetic Data Analysis

Standard pharmacokinetic parameters were determined using noncompartmental methods: Cmax (maximum serum concentration), tmax (time to Cmax), AUC0-24 (area under the serum concentration-time curve from time 0 to 24 h post-dose), AUC0-48 (AUC from time 0 to 48 h post-dose), AUC0-tlast (AUC up to the last quantifiable concentration), AUC0-∞ (AUC extrapolated to infinity) and t1/2 (terminal elimination half-life).

Statistical Analysis
A mixed linear model was used to analyze log transformed PK parameters applying with Sequence, Period, and Treatment as fixed effects and Subject as a random effect. The bioavailability ratio was estimated using least squares mean estimates of the treatment contrasts from the statistical model with the corresponding 90% CI. Results are presented using the original scale.

The primary comparisons for indacaterol were the comparisons of bioavailability, measured as the ratio between the AUC0-tlast of indacaterol for the treatment given in fixed combination with mometasone furoate, and the treatments given alone, either via Concept1 or via Twisthaler™. The primary comparison for mometasone furoate was the comparison of bioavailability, measured as the ratio between the AUC0-tlast of mometasone furoate for the treatment given in fixed combination with indacaterol, and the treatment given alone.
The above comparisons were repeated on AUC0-∞ (mometasone furoate only), AUC0-6, AUC0-24 and Cmax (for both indacaterol and mometasone furoate).

RESULTS
Analytical Method

Bioanalytical procedures
Pharmacokinetics: The determination of indacaterol in plasma was performed by Novartis DMPK/BA in France using a LC-MS/MS method with a lower limit of quantification (LLOQ) of 10 pg/mL.
Mometasone furoate was determined in plasma by [redacted] (b) (4) using a LC-MS/MS method with a LLOQ of 0.25 pg/mL.

In-Study Validation for Indacaterol

Matrix	Human Plasma	
Concentration Range	10 to 2000 pg/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.991$	
Between-Batch Accuracy (%Diff)	Qc standards (30, 150, 800, 1800 pg/mL) Cal. Curve standards	-2.2 to 0.0 -2.1-2.4
Between-Batch (% CV)	Cal. Curve standards QCs	4-8.6 5.2-7.9

In-Study Validation for Mometasone

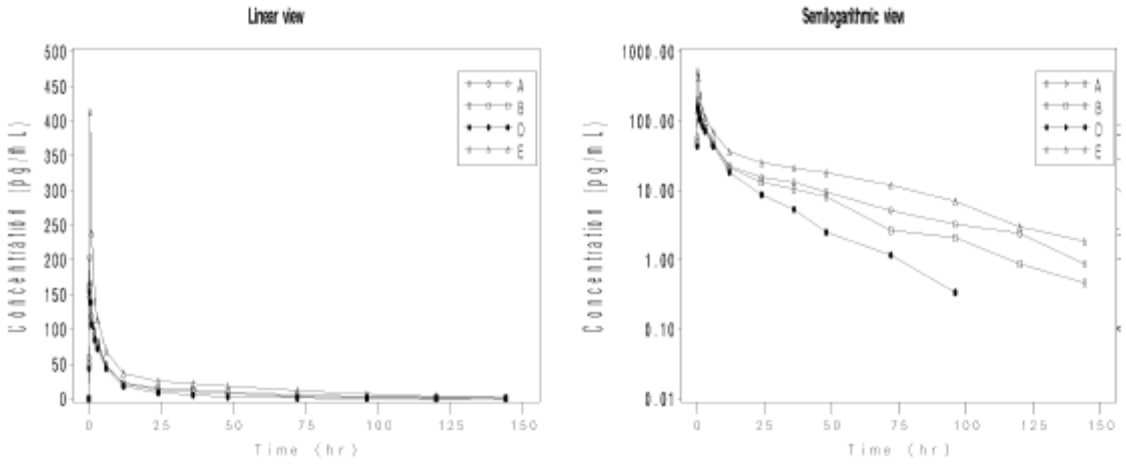
Matrix	Human Plasma	
Concentration Range	0.25 to 25 pg/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.991$	
Between-Batch Accuracy (%Diff)	Qc standards (0.5 to 19.0 pg/mL) Cal. Curve standards	-4.7 to 1.2 -0.2 to 0.4
Between-Batch (% CV)	Cal. Curve standards QCs	2.9 to 9.6 3.1 to 10.2

Pharmacokinetic Results

The mean indacaterol concentration time profile following single dose administration of the treatments is shown in Figure 1. Mean plasma mometasone furoate concentrations versus time profiles for the three treatments involving mometasone furoate are shown in Figure 2.

A summary of the key serum mean PK parameters for indacaterol is shown in Table 1. Likewise, summary of PK parameters for mometasone is shown in Table 2. The results of inferential statistics (adjusted geometric means of the parameters, geometric mean ratios and 90% confidence intervals) are detailed in Table 3 and 4 for indacaterol and mometasone furoate, respectively.

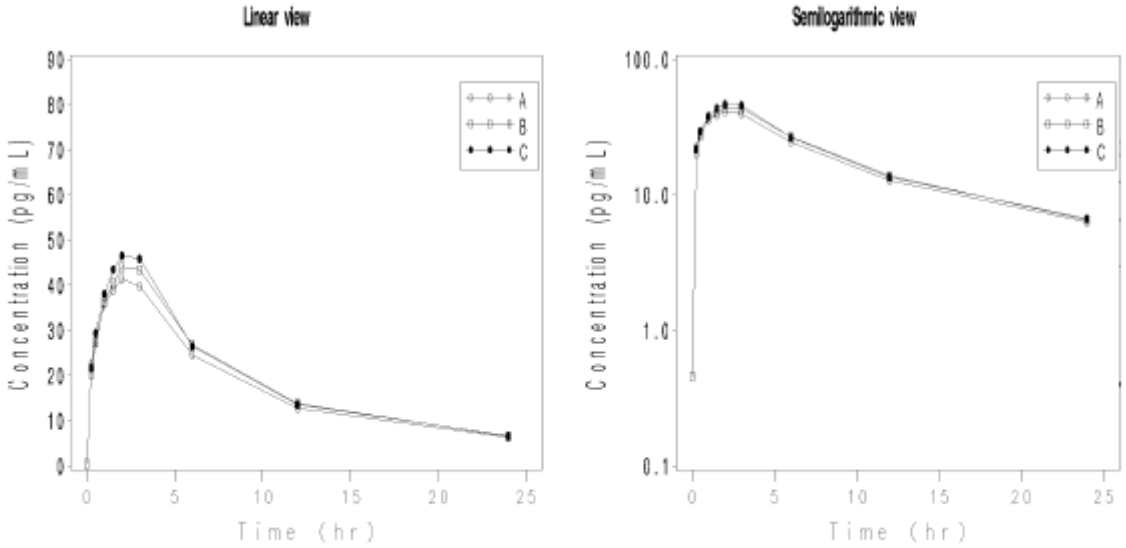
Best Available Copy



Treatment A, QMF149 (fixed combination indacaterol 250 µg / mometasone furoate 200 µg) via Twisthaler™.
Treatment B, Free combination (indacaterol 250 µg / mometasone furoate 200 µg) via Twisthaler™.
Treatment D, Indacaterol (250 µg) via Twisthaler™.
Treatment E, Indacaterol (300 µg) via Concept1.

Figure 1. Arithmetic mean indacaterol concentration - time profiles for all treatments

Best Available Copy



Treatment A, QMF149 (fixed combination indacaterol 250 µg / mometasone furoate 200 µg) via Twisthaler™.

Treatment B, Free combination (indacaterol 250 µg / mometasone furoate 200 µg) via Twisthaler™.

Treatment C, Mometasone furoate (200 µg) via Twisthaler™.

Figure 2. Arithmetic mean mometasone concentration - time profiles for all treatments

Table 1. Summary of pharmacokinetic parameters of indacaterol: mean (standard deviation)				
Parameter	**Treatment**			
	QMF149	Free combination via Twisthaler™	Indacaterol via Twisthaler™	Indacaterol via Concept1
$AUC_{0\text{-}tlast}$ (pg.hr/mL)	1547 (975)	1307 (830)	917 (583)	2767 (1237)
Cmax (pg/mL)	208 (81.39)	176 (61.9)	161 (70.2)	538 (208)
$AUC_{0\text{-}6}$ (pg hr/mL)	526 (172)	508 (164)	466 (168)	932 (316)
$AUC_{0\text{-}24h}$ (pg.hr/mL)	953 (332)	923 (322)	813 (331)	1616 (551)
T_{max} (hr)*	0.250 (0.23, 0.52)	0.250 (0.23, 2.05)	0.250 (0.23, 2.08)	0.250 (0.23, 0.52)
$t_{½}$, (hr)	53.9 (40.3)	47.8 (38.9)	19.5 (20.6)	72.6 (32.6)

Table 2. Summary of pharmacokinetic parameters of mometasone furoate: mean (standard deviation)			
Parameter	**Treatment**		
	QMF149	Free combination via Twisthaler™	Mometasone furoate via Twisthaler™
$AUC_{0\text{-}tlast}$ (pg.hr/mL)	428 (142)	457 (139)	462 (181)
Cmax (pg/mL)	43(17.2)	45.7 (15.7)	49.5 (20.9)
$AUC_{0\text{-}\infty}$ (pg.hr/mL)	517 (169)	545 (169)	553 (224)
$AUC_{0\text{-}6}$ (pg hr/mL)	201 (74.6)	214 (68)	224 (87.8)
$AUC_{0\text{-}24h}$ (pg.hr/mL)	428 (142)	457(139)	462 (181)
T_{max} (hr)*	2.03 (0.53, 3.05)	2.10 (1.00, 3.03)	2.067 (1.00, 3.02)
$t_{½}$, (hr)	9.07 (1.26)	9.12 (1.39)	9.11 (1.56)

Table 3. Geometric mean ratio and 90% confidence intervals for indacaterol PK parameters

		--Adjusted geo-mean*--	Ratio of geometric means treatment/comparator Estimate (90% C.I.)		
Treatment	**Parameter**				
QMF149	$AUC_{0\text{-tlast}}$ (pg.hr/mL)	1258.38	1.15 (0.97, 1.37)	1.63 (1.37, 1.94)	0.52 (0.44, 0.62)
	Cmax (pg/mL)	189.40	1.14 (1.01, 1.29)	1.27 (1.12, 1.44)	0.38 (0.34, 0.43)
	$AUC_{0\text{-}6}$ (pg.hr/mL)	497.79	1.03 (0.93, 1.14)	1.14 (1.02, 1.26)	0.57 (0.51, 0.63)
	$AUC_{0\text{-}24}$ (pg.hr/mL)	892.14	1.03 (0.91, 1.16)	1.19 (1.05, 1.34)	0.59 (0.52, 0.67)
Free combination via Twisthaler™	$AUC_{0\text{-tlast}}$ (pg.hr/mL)	1093.38		1.41 (1.19, 1.68)	0.45 (0.38, 0.54)
	Cmax (pg/mL)	166.44		1.12 (0.99, 1.27)	0.34 (0.30, 0.38)
	$AUC_{0\text{-}6}$ (pg.hr/mL)	483.84		1.10 (1.00, 1.22)	0.55 (0.50, 0.61)
	$AUC_{0\text{-}24}$ (pg.hr/mL)	869.07		1.16 (1.02, 1.31)	0.58 (0.51, 0.65)
Indacaterol via Twisthaler™	$AUC_{0\text{-tlast}}$ (pg.hr/mL)	773.32			0.32 (0.27, 0.38)
	Cmax (pg/mL)	148.94			0.30 (0.26, 0.34)
	$AUC_{0\text{-}6}$ (pg.hr/mL)	438.25			0.50 (0.45, 0.55)
	$AUC_{0\text{-}24}$ (pg.hr/mL)	751.67			0.50 (0.44, 0.56)
Indacaterol via Concept1	$AUC_{0\text{-tlast}}$ (pg.hr/mL)	2419.17			
	Cmax (pg/mL)	496.01			
	$AUC_{0\text{-}6}$ (pg.hr/mL)	876.02			
	$AUC_{0\text{-}24}$ (pg.hr/mL)	1505.98			
Comparator			Free combination via Twisthaler™	Indacaterol via Twisthaler™	Indacaterol via Concept1

Table 4. Geometric mean ratio and 90% confidence intervals for mometasone furoate PK parameters

Treatment	Parameter	--Adjusted geo-mean*--	Ratio of geometric means treatment/comparator Estimate (90% C.I.)	
QMF149	$AUC_{0\text{-tlast}}$ (pg.hr/mL)	406.67	0.93 (0.83, 1.05)	0.95 (0.85, 1.07)
	Cmax (pg/mL)	39.87	0.93 (0.81, 1.06)	0.88 (0.77, 1.00)
	$AUC_{0\text{-}\infty}$ (pg.hr/mL)	492.11	0.94 (0.84, 1.06)	0.97 (0.86-1.08)
	$AUC_{0\text{-}6}$ (pg.hr/mL)	187.56	0.92 (0.82, 1.04)	0.91 (0.80, 1.03)
	$AUC_{0\text{-}24}$ (pg.hr/mL)	406.67	0.93 (0.83, 1.05)	0.95 (0.85, 1.07)
Free combination via Twisthaler™	$AUC_{0\text{-tlast}}$ (pg.hr/mL)	437.29		1.02 (0.91, 1.15)
	Cmax (pg/mL)	42.98		0.95 (0.83, 1.08)
	$AUC_{0\text{-}\infty}$ (pg.hr/mL)	521.42		1.02 (0.92-1.14)
	$AUC_{0\text{-}6}$ (pg.hr/mL)	203.33		0.98 (0.87, 1.11)
	$AUC_{0\text{-}24}$ (pg.hr/mL)	437.29		1.02 (0.91, 1.15)
Mometasone furoate via Twisthaler™	$AUC_{0\text{-tlast}}$ (pg.hr/mL)	426.69		
	Cmax (pg/mL)	45.28		
	$AUC_{0\text{-}\infty}$ (pg.hr/mL)	509.42		
	$AUC_{0\text{-}6}$ (pg.hr/mL)	206.62		
	$AUC_{0\text{-}24}$ (pg.hr/mL)	426.69		
Comparator			Free combination via Twisthaler™	Mometasone furoate via Twisthaler™

Summary of Findings/Conclusion

- Indacaterol exposure was 50% to 65% lower after dosing with all three of the Twisthaler™ treatments compared to the Concept1 formulation.
- Indacaterol exposures after dosing with the two combination treatments (fixed dose and free) were similar.
- Comparison of the two combination treatments with indacaterol alone via Twisthaler™ showed that exposure was higher after the combination treatments.
- Mometasone furoate increased the bioavailability of indacaterol. The increase ranged from 63% to 27% in $AUC_{0\text{-tlast}}$ and C_{max} respectively for the fixed dose combination, compared to 41% to 12% in $AUC_{0\text{-tlast}}$ and C_{max} respectively for the free combination.
- The exposures to mometasone furoate were similar regardless of dosing with the two combination treatments or mometasone furoate alone. Therefore, it appeared that indacaterol did not affect the bioavailability of mometasone furoate.

"A randomized, double-blind, double-dummy, active (formoterol 12 µg BID) and placebo controlled, multi-center, 5 period crossover, dose-ranging study to assess the bronchodilatory efficacy and safety of single doses of indacaterol 150 µg, 300 µg and 600 µg delivered via single dose dry powder inhaler (SDDPI) vs. placebo in patients with moderate to severe chronic obstructive pulmonary disease (COPD)″

Study no.:	CQAB149B2212
Development Phase of Study:	Phase IIb
Principal investigator:	Dr Vincent Ninane, C.H.U. St Pierre, Rue Haute 322, Bruxelles, Belgium
Study Dates:	31-Oct-2006/31-Jan-2007

Objectives

Primary objective

- to assess the bronchodilatory efficacy of single doses of indacaterol 150 µg, 300 µg and 600 µg via SDDPI in patients with moderate to severe COPD as compared to placebo in terms of 24 h post-dose (trough) FEV1.

Secondary objectives

- to assess the safety of single doses of indacaterol 150 µg, 300 µg and 600 µg via SDDPI compared to placebo in patients with COPD in terms of adverse events, laboratory analysis, vital signs (blood pressure and pulse rate) and ECGs, and
- to evaluate the bronchodilatory efficacy measures of single doses of indacaterol 150 µg, 300 µg and 600 µg via SDDPI compared to placebo in terms of: Time to peak FEV1, percent change in FEV1 compared to baseline at each time point post-dose, FEV1 and FVC at each time point post-dose and standardized FEV1 AUC between baseline (pre dose) and 4 h postdose.

Study Population

It was planned that 60 patients should be randomized into the study with 12 in each treatment arm. A total of 51 patients were randomized to treatment, with 47 completing the study.

Male and female adults aged 40-75 years inclusive, who had signed an Informed Consent Form prior to initiation of any study-related procedure (which included any adjustment to their current COPD treatment), were eligible for this study. Patients had to have a clinical diagnosis of COPD according to the GOLD Guidelines and a history of characteristic COPD symptoms (such as cough, sputum production, dyspnea), and additionally meet the following criteria: Smoking history of at least 10 pack years, FEV1 at Visit 1 and Visit 2 <65% of the predicted normal value and at least 0.75 L and a prebronchodilator FEV1/FVC at Visit 1 and Visit 2 < 70%.

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This study was of a 5 period crossover design. A 14 day run-in period (Visit 1 to 2) was used to confirm patients were stable on allowable COPD therapy. At Visit 2, patients whose eligibility was confirmed were randomized to one of 5 treatment sequences and entered the first of five

double blind, double-dummy 1 day treatment periods. Patients received a different 1 day treatment at Visits 2, 4, 6, 8 and 10 according to their treatment sequence: one of 3 doses of indacaterol 150, 300, or 600 μg (QD); formoterol 12 μg (BID); or placebo.

Patients were assessed on the day of each treatment and also returned for further assessments the following day (approx 23 h post dose). After each treatment patients entered a minimum 6 day washout period during which they received allowable COPD treatment and short-acting β2-agonist rescue medication

Test product, dose and mode of administration, batch number
Treatment consisted of indacaterol 150, 300 and 600 μg delivered by SDDPI (150 and 300 μg capsules), formoterol 12 μg delivered via the Aerolizer and placebo to both active agents with the appropriate inhaler device. Patients were assigned to one of 5 treatment sequences in a 1:1:1:1:1 ratio. The morning dose consisted of inhalation of capsules from each of 3 devices labeled at the study site at the time of the morning dose. The evening dose was of a capsule from an Aerolizer inhaler only. Study drugs were identical in packaging, labeling and appearance.

Medication	KN No.	Batch No.s
Indacaterol 150 μg	6002099.001	X260GC
Indacaterol 300 μg	6001037.003	X164EC
Formoterol 12 μg	3746732.001	S0054
Indacaterol placebo	3760253.004	X134EC
Formoterol placebo	3751443.002	X016AB

PHARMACOKINETIC MEASUREMENTS
Blood samples were taken following inhalation on Treatment Period Days 1 (Visits 2, 4, 6, 8 & 10) at -15 min pre-dose, and 30 min, 1 and 4 h post-dose, and on Treatment Period Day 2 (Visits 3, 5, 7, 9 & 11) at 23h 45min post-dose.

SAFETY MEASUREMENTS
Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine performed at the study center, and regular assessments of vital signs, physical condition, ECG and body weight.

Efficacy evaluation
The primary variable, 24-hour trough in FEV1 following inhalation of study drug, was summarized by treatment for the mITT population. The comparison of indacaterol 150 μg or 300 μg or 600 μg to placebo was evaluated by testing the following null hypothesis (Ho) versus the alternative hypothesis (Ha) using the mITT population.

DATA ANALYSIS

Pharmacokinetic Data Analysis

AUC0-24, Cmax, and tmax were determined by noncompartmental analysis from serum concentration-time data using WinNonlin v5.01 software. Actual times were used to calculate PK parameters. AUC0-24 was calculated using the "AUCall" method of the PK software. Descriptive statistics of pharmacokinetic parameters included arithmetic means, SD, CV, median, minimum and maximum (only median, minimum, and maximum for tmax). Concentration-time data was presented graphically for each subject.

An exploratory analysis of the relationship between dose and Cmax as well as AUC0-24 was performed with a graphical approach (on the basis of dose-normalized parameters) and descriptive statistics. The analysis used was changed from that originally planned. Dose-proportionality of the parameters was statistically analyzed on the basis of the slope of a linear regression of log-transformed geometric means by fitting the following 'dose division' model:
log(Response) from= logB + (C-1)*log(Dose) where 'B' is the gradient of the response versus possible linear dose trend and 'C' is the power term. Confidence intervals (90%) were produced for the slope of the linear regression of the log-transformed pharmacokinetic parameters and critical regions for acceptability of dose-proportionality were calculated.

Statistical Analysis

Statistical methods:
The modified intention-to-treat (mITT) population included all randomized patients who received at least one dose of study drug. Patients were analyzed according to the treatment they received. All efficacy variables, including the primary efficacy variables, were analyzed on the modified intent-to-treat population. The per-protocol (PP) population included all patients in the mITT population without any major protocol violations. The safety population included all patients who received at least one dose of study drug.

RESULTS

Analytical Method

Bioanalytical procedures
The analytical method consisted on liquid-solid extraction of plasma samples followed by evaporation of the extracts to dryness and analysis of the reconstituted samples by LC-MS/MS using electrospray ionization. The lower limit of quantification (LLOQ) was 0.010 ng/mL (10 pg/mL).

In-Study Validation for Indacaterol

Matrix	Human Plasma	
Concentration Range	10 to 2000 pg/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.992$	
Between-Batch Accuracy (%Diff)	Qc standards (30, 150, 800, 1800 pg/mL) Cal. Curve standards	-3.3 to 3.4 -4.7 to 2.0
Between-Batch (% CV)	Cal. Curve standards QCs	3.9 to 10.2 5.1 to 10.2

Dose-Response Results

The primary efficacy result (24 hour post-dose, trough, FEV1) for the mITT population showed that all doses of indacaterol showed statistically significant differences to placebo ($p< 0.001$) (Table 1). The least squares mean difference to placebo was greatest with indacaterol 600 µg (0.18 L), although that with indacaterol 300 µg was similar (0.17 L). An exploratory analysis of treatment contrasts showed that the trough FEV1 for indacaterol 600 µg was statistically significantly greater than that for formoterol 12 µg (LS mean difference of 50 mL) and indacaterol 150 µg (LS mean difference 40 mL). The treatment contrast between indacaterol 300 µg and formoterol 12 µg was also statistically significant in favor of indacaterol (Figure 1).

There was a numerical trend for dose-response relationship in the range of indacaterol doses tested (150 to 600 µg). The mean difference to placebo in through FEV1 increased from 0.14 to 0.18 L for the 150 µg and 600 µg, respectively. However, the treatment contrast between indacaterol doses showed no statistically significant difference between indacaterol 600 µg vs. 300 µg and indacaterol 300 µg vs. 150 µg ($p>0.57$).

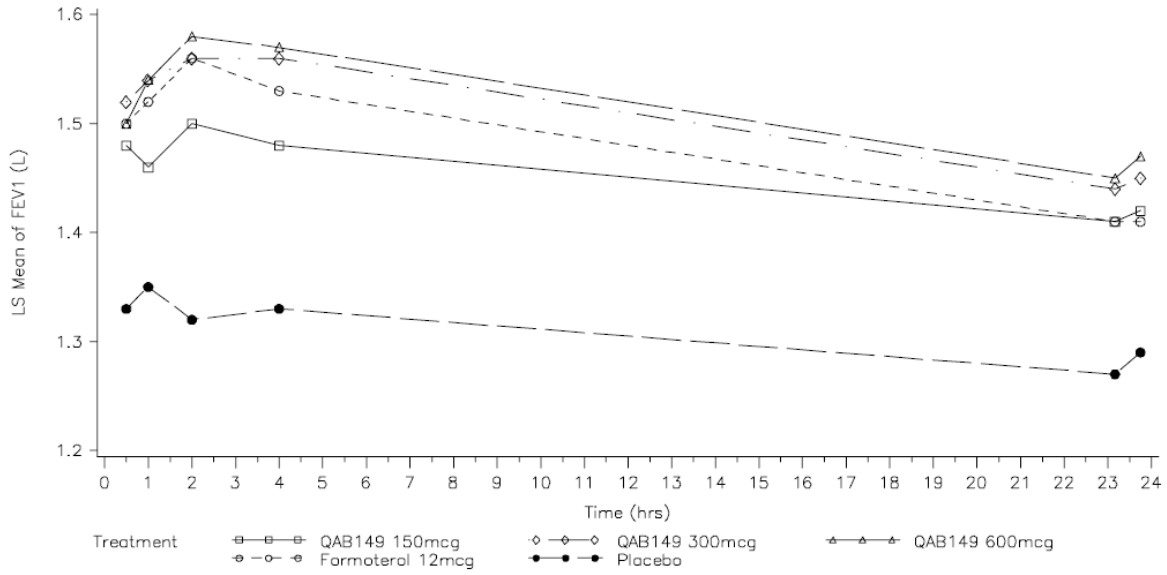


Figure 1. 24-hour profile of LS Mean FEV_1 (Modified intent-to-treat population)

Table 1. Analysis of covariance of 24 h post-dose (trough) FEV_1 (L) (modified **ITT population)**

	n	LSMean	SE	95% CI*	p-value*	SS 95% CI**	SD p-value (2-sided)**
Treatment Effect							
Indacaterol 600 µg	50	1.46	0.014	(1.43, 1.49)			
Indacaterol 300 µg	49	1.45	0.015	(1.42, 1.48)			
Indacaterol 150 µg	47	1.42	0.015	(1.39, 1.45)			
Formoterol 12 µg	50	1.41	0.014	(1.38, 1.43)			
Placebo	48	1.28	0.015	(1.25, 1.31)			
Treatment Contrast (Primary Analysis)							
Indacaterol 600 µg-Placebo		0.18	0.021	(0.14, 0.22)	<0.001	(0.13, 0.23)	<0.001
Indacaterol 300 µg-Placebo		0.17	0.020	(0.13, 0.21)	<0.001	(0.12, 0.22)	<0.001
Indacaterol 150 µg-Placebo		0.14	0.020	(0.10, 0.18)	<0.001	(0.09, 0.19)	<0.001
Treatment Contrast (Secondary / Exploratory Analysis)							
Indacaterol 600 µg-300 µg		0.01	0.020	(-0.03, 0.05)	0.5690		
Indacaterol 600 µg-150 µg		0.04	0.020	(0.00, 0.08)	0.0428		
Indacaterol 600 µg-Formoterol 12 µg		0.05	0.020	(0.01, 0.09)	0.0089		
Indacaterol 300 µg-150 µg		0.03	0.020	(-0.01, 0.07)	0.1382		
Indacaterol 300 µg-Formoterol 12 µg		0.04	0.020	(0.00, 0.08)	0.0426		
Indacaterol 150 µg-Formoterol 12 µg		0.01	0.020	(-0.03, 0.05)	0.5925		
Formoterol 12 µg-Placebo		0.13	0.020	(0.09, 0.17)	<0.001		

*95% CIs and p-values are calculated without multiplicity adjustment
** SS 95% CIs are based on a single step Dunnett procedure implemented using % SimIntervals SAS macro. The SD p-values are based on stepdown Dunnett procedure implemented using % SimTests SAS macro

Pharmacokinetic Results

A summary of the key serum PK parameters for indacaterol is shown in Table 1. Exposure (C_{max} and AUC_{0-24}) increased with increasing doses but dose proportionality across the entire dose range (dose range=4) could not be concluded from the statistical analysis (data not shown) because the upper 90 % confidence intervals of the slopes of the log-transformed model-derived geometric means of AUC_{0-24} as well as C_{max} were slightly outside the pre-specified ranges of dose-proportionality. However the PK parameters can be considered dose-proportional over a dose range of 3.27 (AUC_{0-24}) and 3.58 (C_{max}).

Table 2. Summary of pharmacokinetic parameters of serum indacaterol after single inhaled doses of 150 ug, 300 ug, and 600 ug

Dose	Statistic	tmax[h]	Cmax[pg/mL]	Cmax/Dose [pg/mL/µg]	AUC0-24 [pg*h/mL]	AUC0-24/Dose [pg*h/mL/µg]
150 µg (N=47)	Mean SD	--	145.4 65.2	0.97 0.434	1284 646	8.56 4.3
	Min	0.48	23.9	0.159	201	1.34
	Median	0.58	142	0.947	1145	7.63
	Max	1.25	367	2.447	3370	22.47
	CV%	-	44.8	44.8	50.3	50.3
	Geo. Mean	-	131.8	0.879	1140	7.60
300 µg (N=46)	Mean SD Min	--0.5	327.9 151.4 35.3	1.093 0.505 0.118	2975 1663 213	9.92 5.54 0.71
	Median	0.59	325	1.083	2670	8.9
	Max	4.12	751	2.503	8142	27.14
	CV%	-	46.2	46.2	55.9	55.9
	Geo. Mean	-	287.9	0.96	2406	8.45
600 µg (N=50)	Mean SD Min	0.42	680.5 331.7 213	1.134 0.553 0.355	6017 3161 1162	10.03 5.27 1.94
	Median	0.58	610.5	1.018	5550	9.25
	Max	1.15	1730	2.883	18330	30.55
	CV%	-	48.7	48.7	52.5	52.5
	Geo. Mean	-	609.6	1.016	5344	8.91

Summary of Findings/Conclusion

- There was a numerical trend for dose-response relationship in the range of indacaterol doses tested (150 to 600 µg). The mean difference to placebo in through FEV1 increased from 0.14 to 0.18 L for the 150 µg and 600 µg, respectively. However, the treatment contrast between indacaterol doses showed no statistically significant difference between indacaterol 600 µg vs. 300 µg and indacaterol 300 µg vs. 150 µg ($p>0.57$).
- Cmax and AUC24hrs increased more than proportional to the dose in the range of doses tested (150 to 600 µg).

" A randomized, double-blind, placebo-controlled, parallel group, multi-center, multiple dose (7 days) dose-ranging study, to assess the efficacy and safety of 4 doses of QAB149 (50, 100, 200 & 400 µg) delivered via a multiple dose inhaler and 1 dose of QAB149 (400 µg) delivered via a single dose inhaler in patients with chronic obstructive pulmonary disease (COPD)"

Study no.:	CQAB149B2205
Development Phase of Study:	Phase IIb
Principal investigator:	Bantje Th.A et al.
Study Dates:	01-July-2004/24-Dec-2004

Objectives

Primary objective

- to evaluate the bronchodilatory efficacy of QAB149 in patients with moderate to severe COPD by comparing four doses of QAB149 (50, 100, 200 & 400 µg QD) via MDDPI versus placebo in terms of FEV1 standardized area under the curve (AUC) between 22 and 24 h on Day 1 of treatment.

Secondary objectives

- On Day 1 and Day 7, to evaluate for all six treatment groups, in terms of standardized FEV1 AUC between 22 to 24 h, all additional comparisons (within day only) not covered by the primary objective.
- To compare each active treatment group with placebo and with each other on Day 1 and Day 7 with respect to:
  - Peak FEV1
  - Percentage change in FEV1 at each individual time point post-dosing
  - FEV1, FVC, and FEF25-75% at each individual time point post dosing
  - To explore the safety and tolerability in all six treatment groups following 7 days of treatment.
  - To explore the pharmacokinetics of QAB149, in a subset of patients, on the first and last day of the 7 day treatment period.

Study Population

The study planned to randomize approximately 660 patients (110 per dose) aged 40-75 years with moderate to severe COPD. Approximately 260 patients who completed the core protocol were recruited to the open label treatment period. Male and female patients aged 40-75 years with moderate to severe COPD and smoking history of at least 20 pack years, whose FEV1 at Visit 1 and 2 was ≥ 40 % of the predicated normal value and ≥ 1.0 L demonstrated after a washout period of at least 6 h during which no short-acting β2-agonist had been inhaled and 24 h for long-acting β2-agonists and a pre-bronchodilator FEV1/FVC<70%.

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This was a double-blind, parallel group study. Following a 14 (±2) day run-in period to assess eligibility of patients for the study and to allow patients to be transferred from prohibited COPD therapy to allowable COPD therapy, patients were randomized to one of six treatments arms QAB149 50 µg, 100 µg, 200 µg, or 400 µg via the MDDPI, QAB149 400 µg via the SDDPI or placebo. Patients took study medication for 7 days and were assessed on Day 1 both pre-treatment and then up to 24 h post first dose, then again on Day 7.

Test product, dose and mode of administration, batch number

Patients were randomized to the following treatments.

Medication	KN No.	Batch Numbers
QAB149 50 µg (MDDPI)	7004920.001	X037 0104
QAB149 100 µg (MDDPI	7004919.001	X038 0104
QAB149 200 µg (MDDPI)	7004918.001	X039 0204
Placebo (MDDPI)	3757192.004	X005 0204
QAB149 400 µg capsules (SDDPI)	3760188.004	X242 0903
Placebo capsules (SDDPI)	3760253.002	X200 0803

PHARMACOKINETIC MEASUREMENTS

Blood samples were collected from a subset of patients (approximately 120 in total, i.e. 20 patients per dose group) for pharmacokinetic analysis at per-dose, 15 min, 1 h and 4 h postdose.
Urine was collected for 4 h post-dose at Visits 2 and 3, the patient having voided their bladder before study drug administration.

SAFETY MEASUREMENTS

Safety assessments included recording all adverse events including serious adverse events, pregnancies, the regular monitoring of hematology, blood chemistry and urine performed at a central laboratory, and regular assessments or vital signs, physical examinations and ECG.

Efficacy evaluation

The primary efficacy variable was the standardized AUC of FEV1 between 22 and 24 h postdose on Day 1.
Secondary efficacy variables were:

- Standardized AUC of FEV1 between 22 and 24 h post-dose on Day 7.
- FEV1, FEF25-75% and FVC at time points: 5, 10, 15, 30 min, and 1, 2, 3, 4, 8, 12, 22, 23 and 24 h post dosing on Day 1.
- FEV1, FEF25-75% and FVC at time points: 5, 10, 15, 30 min, and 1, 2, 3, 4, 22, 23 and 24 h post dosing on Day 7.
- Open label treatment period variables were:
- Standardized AUC of FEV1 between 22 and 24 h post-dose on Day 8
- Standardized AUC of FEV1 between 0 and 4 h post-dose on Day 8
- Standardized AUC of FEV1 between 0 and 4 h post-dose on Day 1

DATA ANALYSIS

Statistical Analysis

The primary efficacy variable was the FEV1 standardized AUC calculated between 22 and 24 h post-dose on Day 1 of treatment. Any spirometry measurements taken up to 6 h following the administration of rescue medication were excluded from calculations of AUC.

Two-sided hypothesis testing was performed on the ITT population at a significance level of 0.05 for the following four contrasts:

1. MDDPI QAB149 400 μg versus placebo;
2. MDDPI QAB149 200 μg versus placebo;
3. MDDPI QAB149 100 μg versus placebo;
4. MDDPI QAB149 50 μg versus placebo

The SAS procedure PROC MIXED was used to obtain estimates of the pair wise contrasts and associated 95% confidence intervals from an ANCOVA model, with treatment groups and center nested within country included as fixed effects and baseline FEV1 included as a covariate.

All secondary efficacy variables were subjected to two-sided hypothesis testing at a significance level of 0.05 for all fifteen possible pair wise contrasts. The estimates of the pair wise contrasts and associated 95% confidence intervals were calculated from an analysis of covariance (ANCOVA) model.

RESULTS

Dose-Response Results

Following single dose administration, the trough FEV1 values were significantly higher in all QAB149 MDDPI groups compared to placebo, with the largest difference seen between the 400 μg dose and placebo (Table 1). There was a numerical trend for dose-response relationship in the range of indacaterol doses tested (50 to 400 μg). The mean difference to placebo in trough FEV1 increased from 0.1 to 0.17 L for the 50 μg and 400 μg, respectively. However, the treatment contrast between indacaterol doses showed no statistically significant difference between indacaterol 400 μg vs. 200 μg and indacaterol 200 μg vs. 100 μg or 50 μg ($p>0.57$). Also there was not statistically significant difference between the 100 μg dose and 50 μg dose (Table 1).

At Day 7, there was also a trend for dose-response relationship (Figure 1). The mean difference to placebo in trough FEV1 increased from 0.14 to 0.21 L for the 50 μg and 400 μg, respectively. However, only the differences between the 400 μg dose and the 100 μg dose, and between the 400 μg dose and the 50 μg dose were statistically significant ($P<0.007$).

Table 1. Analysis of covariance of 24 h post-dose (trough) FEV1 (L) (modified ITT population)

	LSM	**SE**	**95% CI**	**P value 2-sided**
Treatment effect				
QAB149 400 µg MDDPI	1.83	0.020	(1.79, 1.87)	
QAB149 200 µg MDDPI	1.79	0.020	(1.75, 1.83)	
QAB149 100 µg MDDPI	1.74	0.021	(1.70, 1.78)	
QAB149 50 µg MDDPI	1.76	0.020	(1.71, 1.80)	
QAB149 400 µg SDDPI	1.87	0.021	(1.83, 1.91)	
Placebo	1.65	0.020	(1.62, 1.69)	
QAB149 Treatment contrast (Primary analysis)				
400 µg MDDPI -Placebo	0.17	0.027	(0.12, 0.23)	<0.0001
200 µg MDDPI -Placebo	0.13	0.027	(0.08, 0.19)	<0.0001
100 µg MDDPI -Placebo	0.08	0.027	(0.03, 0.14)	0.0023
50 µg MDDPI -Placebo	0.10	0.027	(0.05, 0.15)	0.0002
QAB149 Treatment contrast (Secondary analysis)				
400 µg MDDPI -200 µg MDDPI	0.04	0.027	(-0.01, 0.09)	0.1524
400 µg MDDPI -100 µg MDDPI	0.09	0.027	(0.04, 0.14)	0.0009
400 µg MDDPI -50 µg MDDPI	0.07	0.027	(0.02, 0.13)	0.0070
400 µg MDDPI -400 µg SDDPI	-0.05	0.027	(-0.10, 0.01)	0.0929
200 µg MDDPI -100 µg MDDPI	0.05	0.027	(0.00, 0.10)	0.0587
200 µg MDDPI -50 µg MDDPI	0.03	0.027	(-0.02, 0.09)	0.2079
200 µg MDDPI -400 µg SDDPI	-0.08	0.027	(-0.14, -0.03)	0.0023
100 µg MDDPI -50 µg MDDPI	-0.02	0.027	(-0.07, 0.04)	0.5262
100 µg MDDPI -400 µg SDDPI	-0.14	0.027	(-0.19, -0.08)	<0.0001
50 µg MDDPI - 400 µg SDDPI	-0.12	0.027	(-0.17, -0.06)	<0.0001
400 µg SDDPI - Placebo	0.22	0.027	(0.16, 0.27)	<0.0001

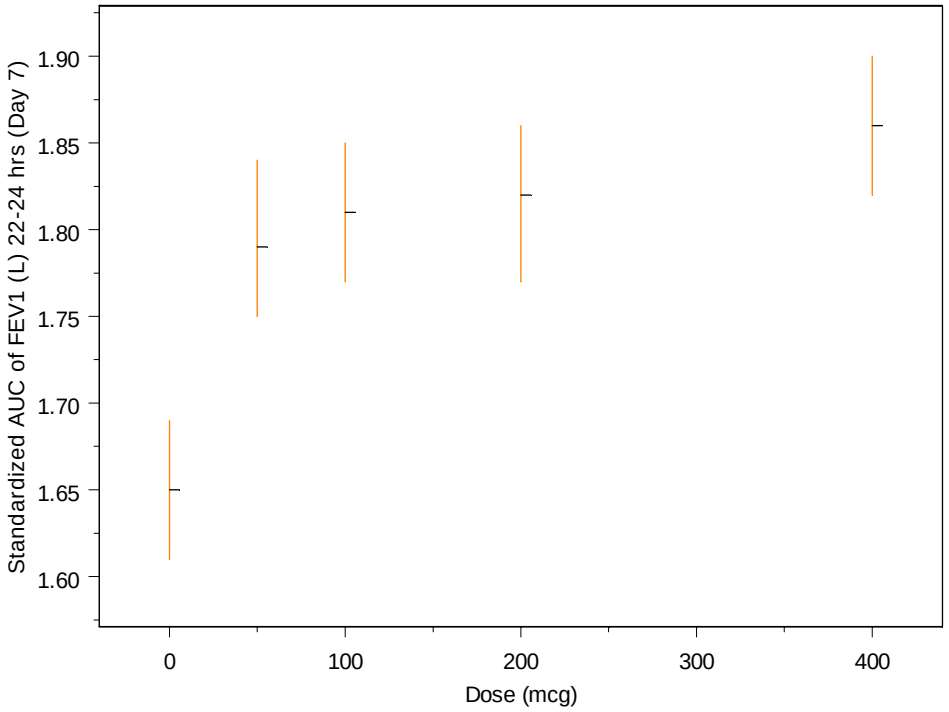


Figure 1. Standardized AUC of FEV1 (L) 22-24 h post-dose at Day 7/Day 8 following multiple dose administration (QD) of the treatments (0=PLB)

Pharmacokinetic Results

The sponsor did not present the PK results as part of this report.

Dose-Response---Safety Results

The most common adverse event overall was headache and occurred at a similar frequency in each of the QAB149 treatment groups, with the exception of the QAB149 200 µg MDDPI group where the frequency was somewhat higher. Cough occurred at a higher frequency in the active drug treatment groups compared to placebo (2.9-12.4% vs 0.9%) with evidence that this was a dose related response (Figure 2). The rate of other adverse events was low and there were no meaningful differences between treatment groups.

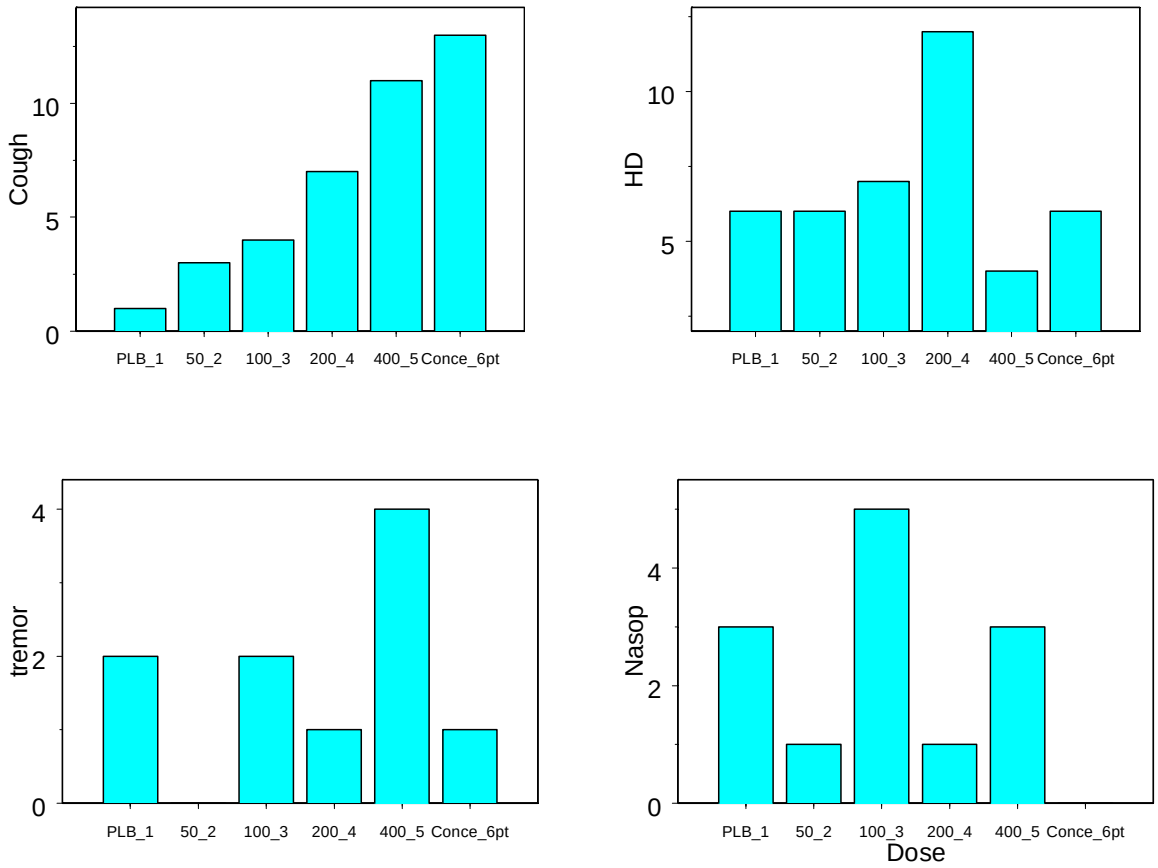


Figure 2. Number (%) of patients with most frequent AEs (> 1 patient for any group) (Safety population) (HD=headache, Nasop=nasopharyngitis).

Potassium levels

There were no significant differences between treatment groups except at Day 1 (1 h) between 400 µg MDDPI and placebo groups. There were no significant differences between treatments groups with respect to the minimum serum potassium value recorded post-dose. There was no evidence of dose-response relationship for serum potassium (Table 2).

Table 2. Number (%) of patients with serum potassium (mmol/L) below lower limit of normal (LLN) by treatment (Safety population)						
	400 µg MDDPI	**200 µg MDDPI**	**100 µg MDDPI**	**50 µg MDDPI**	**400 µg SDDPI**	**Placebo**
	N=110	**N=105**	**N=105**	**N=103**	**N=105**	**N=107**
Day, time point	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Day 1						
Pre-dose	0	0	0	1 (1.3)	1 (1.3)	0
15 min	0	0	1 (1.4)	0	1 (1.3)	0
1 h	2 (2.7)	0	0	0	2 (2.7)	0
4 h	2 (2.7)	0	0	2 (2.8)	2 (2.7)	0
24 h	0	0	0	1 (1.2)	2 (2.4)	1 (1.1)
Day 7						
Pre-dose	0	0	0	2 (2.6)	0	0
15 min	0	0	0	2 (2.7)	0	0
1 h	1 (1.3)	0	0	0	0	0
4 h	2 (2.6)	0	1 (1.4)	3 (4.1)	4 (5.5)	0
24 h	0	0	1 (1.3)	1 (1.2)	0	0
Minimum post-dose value	6 (5.9)	0	3 (3.1)	4 (4.2)	7 (7.2)	1 (1.0)

Glucose Levels

There was a numerical trend for dose-response relationship for serum glucose. The 400 µg MDDPI group blood glucose was significantly higher compared to the 200 µg MDDPI and 50 µg MDDPI groups (Table 3).

Table 3. Number (%) of patients with blood glucose (mmol/L) above upper limit of normal (ULN) by treatment (Safety population)

Day, time point	QAB149 400 µg MDDPI N=110 n (%)	QAB149 200 µg MDDPI N=105 n (%)	QAB149 100 µg MDDPI N=105 n (%)	QAB149 50 µg MDDPI N=103 n (%)	QAB149 400 µg SDDPI N=105 n (%)	Placebo N=107 n (%)
Day 1						
Pre-dose	6 (5.6)	3 (2.9)	5 (4.8)	6 (5.9)	1 (1.0)	4 (3.8)
15 min	5 (4.6)	4 (3.9)	2 (2.0)	5 (5.0)	3 (2.9)	4 (3.7)
1 h	4 (3.7)	5 (4.9)	8 (7.7)	7 (7.0)	8 (8.0)	3 (2.8)
4 h	12 (11.0)	9 (8.7)	11 (10.6)	8 (8.0)	8 (7.9)	10 (9.3)
24 h	7 (6.6)	3 (3.0)	4 (4.0)	7 (6.9)	1(1.0)	5 (4.8)
Day 7						
Pre-dose	4 (3.8)	3 (2.9)	5 (4.9)	7 (6.9)	3 (3.0)	5 (4.7)
15 min	3 (2.9)	3 (3.0)	6 (5.9)	6 (5.9)	3 (3.0)	2 (1.9)
1 h	3 (2.8)	5 (5.0)	7 (6.9)	7 (7.0)	9 (9.0)	4 (3.9)
4 h	12 (11.2)	9 (9.8)	12 (11.8)	8 (8.0)	10 (10.2)	7 (6.7)
24 h	7 (6.6)	6 (6.0)	4 (4.0)	6 (5.9)	5 (5.1)	5 (4.7)
Maximum post-dose value	31 (28.4)	17 (16.2)	29 (27.6)	22 (21.4)	29 (28.2)	23 (21.5)

Summary of Findings/Conclusion

- There was a numerical trend for dose-response relationship in the range of indacaterol doses tested (50 to 400 µg). The mean difference to placebo in through FEV1 increased from 0.14 to 0.21 L for the 50 µg and 400 µg, respectively. However, only the differences between the 400 µg dose and the 100 µg dose, and between the 400 µg dose and the 50 µg dose were statistically significant ($P<0.007$).
- There was a trend for the rate of some side effects (headache, cough, etc) to be lower at smaller doses.
- There was a dose-response for serum glucose levels, but not for potassium levels. The 400 µg MDDPI group blood glucose was significantly higher compared to the 200 µg MDDPI and 50 µg MDDPI groups.

Office of clinical Pharmacology:
Pharmacometric review

Summary of Findings

Key Review Questions

The purpose of this review is to address the following key questions.

Is there any significant covariate which affects Indacaterol PK?

Yes. Weight, age and gender were found to be significant factors for CL/F. However, it is not necessary to adjust dose based on these covariates as dose-response relationship appeared to be shallow and these covariates showed relatively small effects.

The population PK analysis estimated that the AUC (μg·hr/mL) increases by an average of 28% and 21% between 48 and 78 years (90% age range) and 50 and 107 kg (90%weight range) in COPD patients, respectively. Also AUC (μg·hr/mL) is an average 7% greater in female COPD patients than in male COPD patients.

Is the proposed dosing regimen (150μg QD) acceptable?

No, the sponsor's analyses did not fully justify 150μg QD as an optimal dosing regimen.
The sponsor submitted a separate report titled 'the dose-response and frequency of dosing for indacaterol' to justify their dosing regimen. This report includes dose-response analysis for the justification of the proposed dose (150μg) and peak-to-trough ratio analysis for the justification of dosing interval (QD).
Based on the sponsor's dose-response analysis (meta-analysis) of trough response, the doses of 75,150,300 and 600μg were predicted to correspond to the ED78, ED88, ED93, and ED97, respectively. The sponsor claimed that indacaterol 75μg, dosed once daily, provided less complete bronchodilation in the typical patient compared with 150 μg or 300 μg doses. However, the sponsor's Emax model did not fit the observed data especially well at lower dose due to the lack of data, which made ED50 estimates unreliable due to the large uncertainty (Figure, Table 2.2.4.4.1).
In addition, the sponsor's minimum clinically important difference (MCID, 0.12 L) is not justified according to the medical team's opinion. Dose of 75 μg clearly showed the effectiveness compared to placebo even though the lower bound of 95% confidence interval is lower than 0.12L. Furthermore, the paper[2] published by the authors from the sponsor demonstrated that the sponsor's rule for finding the minimum effective dose (MED) based on the lower bound of 95% confidence interval tends to overestimate the target dose.

In order to justify the dosing interval (QD), the sponsor performed the peak-to-trough ratio analysis. As shown in Figure 2.2.4., peak-to-trough ratio at 12 h for a twice-daily drug such as formoterol or salmeterol should be greater than that for indacaterol. However, it could be argued that the extended duration of effect might be a result of simply increasing the dose to artificially extend the duration of action. To address this question, the sponsor assessed two different metrics of the dose-response: the peak response and the trough response. Similar estimates of the ED50 for the respective metrics would

[2] Combining Multiple Comparisons and Modeling Techniques in Dose-Response Studies, F.Brets, J.C.Pinheiro and M.Branson. Biometrics, 2005,61, p.738-748.

provide evidence that the once daily property of indacaterol is not achieved at the expense of elevating the dose to artificially extend the duration of action.
However, the sponsor's claim on dosing interval (once daily) could not be supported by the sponsor's analysis mainly due to the large uncertainty in ED50 estimates for trough FEV1 and especially peak FEV1 (**Table 2.2.4.4.1**).

Recommendations

The Office of Clinical Pharmacology has reviewed the submission (NDA 22383) and has the following recommendation:

- The sponsor's dose-response modeling analysis does not fully address minimum effective dose issue
- The sponsor needs to explore lower doses than 75µg given the safety concern with LABA.

Pertinent Regulatory Background

The sponsor is seeking the approval for indacaterol (Arcapta™ (b) (4)), which is a long-acting inhaled β2-agonist (LABA), for the treatment in patients with chronic obstructive pulmonary disease (COPD).
Long-acting inhaled β2-agonists (LABAs) such as formoterol and salmeterol have been available for approximately 12 years, and are recommended to be used twice daily (BID) for regular maintenance treatment in both asthma and COPD. In addition, the long acting antimuscarinic (anticholinergic) antagonist, tiotropium is recommended to be used once daily (QD) for regular maintenance treatment in COPD.
Following approval of the first LABA drug (salmeterol) in 1994, post-marketing and phase IV commitment results showed the rate of severe asthma exacerbations including death increased with LABA treatment compared to placebo. As a result, boxed warning was added in the label of all LABA products and currently LABAs are recommended to be co-administered with an inhaled corticosteroid (ICS).

Results of Sponsor's Analysis

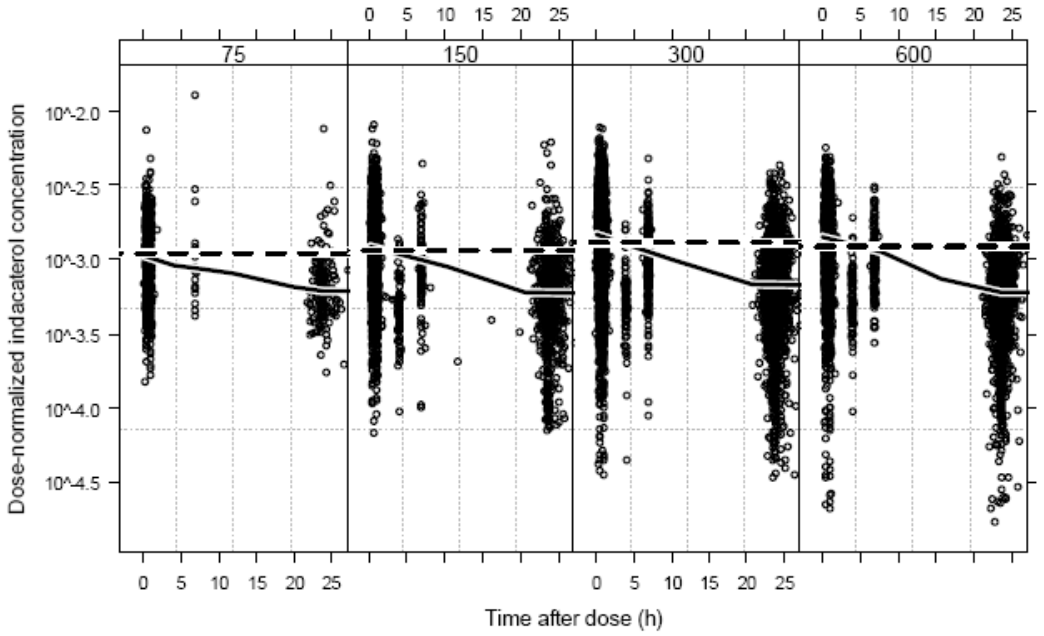
The sponsor conducted population PK analysis to address the effects of covariates on indacaterol PK. Also the sponsor submitted a separate dose-response analysis to justify the dosing regimen (150µg QD).

PK analysis

Data from two Phase II studies (CQAB149A2228, CQAB149B2212) and three phase III trials (CQAB149B2334, CQAB149B2335S, CQAB149B2338) were included in the population PK analysis. Studies were selected on the basis of inhalation device (Concept1 SDDPI devices only), disease status (only studies that included COPD or asthma patients were included and no healthy volunteer studies were considered), and whether PK data had been collected.
Two-compartment model with first-order elimination and drug administered as an instantaneous input into the systemic circulation was chosen as a final model. A plot of dose-normalized indacaterol

concentration against time after dose revealed no apparent nonlinearity in kinetics at the doses studied (Figure 1).

Figure 1. Plot of dose normalized indacaterol concentration .vs. time after dose, conditioned by dose. The solid line is an average (loess) smooth through the data; the dashed line is mean concentration.



Source: the sponsor's report, pharmacokinetic modeling of indacaterol, page 26.

The population PK analysis showed that weight, age and gender were found to be significant factors for CL/F. AUC (μg·hr/mL) increases by an average of 28% and 21% between 48 and 78 years (90% age range) and 50 and 107 kg (90%weight range) in COPD patients, respectively. Also AUC (μg·hr/mL) is 7% greater in female COPD patients than in male COPD patients. Exposure in Black patients was lower than in other ethnic group but this effect could not be determined with acceptable statistical significance in the full population PK model due to the relatively low number of Black patients in the data.

Overall, it is not necessary to adjust dose based on these covariates as dose-response relationship appeared to be shallow and these covariates showed relatively small effects.

Reviewer's comments:
Sponsor's population PK analysis is acceptable.

Dose-response analyses

The sponsor submitted a separate report titled 'the dose-response and frequency of dosing for indacaterol' to justify their dosing regimen. This report includes dose-response analysis for the justification of the proposed starting dose (150µg) and peak-to-trough ratio analysis for the justification of dosing interval (QD).
For the dose-response analysis, the sponsor performed two separate model-based analyses: 1) a Bayesian meta-analysis including data from 7 studies in COPD patients (CQABB2205, CQABB2212, CQABB2305, CQABB2334, CQABB2335S, CQABB2340 and CQABB2346) and 4 studies in Asthma patients (CQABA2208, CQABA2216, CQABA2218 and CQABA2228); 2) a non-linear mixed effect modeling (hereafter NLME) analysis using one pivotal study (CQABB2335S). Three studies (CQABB2334, CQABB2335S and CQABB2340) were included for the peak-to-trough ratio analysis.

Three different endpoints were used for dose-response analysis; trough FEV1 (defined as the average of the FEV1 measurements typically obtained around 23.25 h and 23.75 h post-dose), observed peak FEV1 (0-4h, determined as the maximum FEV1 value measured within the first 4 hours post-dose), peak average response (AUC0-4) which is AUC taken between 5min and 4 hour post-dose, standardized by dividing by 4 hour.

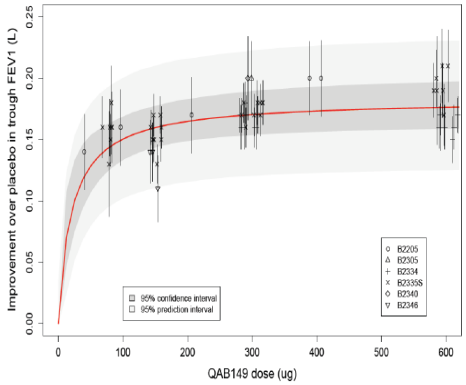
Based on the meta-analysis of trough values, the doses of 75,150,300 and 600µg were predicted to correspond to the ED78, ED88, ED93, and ED97, respectively. The sponsor claimed that indacaterol 75µg, dosed once daily, provided less complete bronchodilation in the typical patient compared with 150µg or 300µg doses. Both analyses showed similar estimates (Table 2.2.4.4.1).

Table 2. The parameter estimates from meta-analysis and NLME analysis. The numbers in parenthesis indicate 90% CI.

	Meta-analysis			NLME analysis		
	Trough FEV1	Peak average (AUC0-4)	Observed Peak FEV1	Trough FEV1	Peak average (AUC0-4)	Observed Peak FEV1
Emax	0.18 (0.12-0.20)	0.27 (0.23-0.30)	0.26 (0.22-0.30)	0.18 (0.16-0.21)	0.23 (0.19-0.26)	0.22 (0.18-0.25)
ED50	22 (10-35)	25 (11-42)	35 (10-69)	22 (7-68)	14 (3-73)	12 (2-93)
%max effect at 75µg	78 (68-88)	76 (64-87)	70 (52-88)	78 (53-92)	84 (57-95)	86 (53-97)
%max effect at 150µg	88 (81-94)	86 (78-93)	82 (69-94)	87 (69-96)	91 (73-98)	93 (69-99)
%max effect at 300µg	93 (90-97)	92 (88-97)	90 (81-97)	93 (82-98)	95 (84-99)	96 (82-99)
%max effect at 600µg	97 (94-98)	96 (93-98)	95 (90-98)	97 (90-99)	98 (91-99)	98 (90-99)

The prediction of the dose response relationship in the meta-analysis of the 24 h trough values is presented in Figure 2. All trough values were taken between week 1 and 26.
Most data points were derived from Study CQAB149B2335S.
It should be noted that the standard error bars for the CQAB149B2335S observations at 150 and 300 µg are the narrowest, reflecting the fact that the underlying number of patients observed at these doses was greatest. Most data were available on the plateau of the predicted dose response, with little in the ascending part of the curve.

Figure 2. Prediction of dose response for trough FEV1 at steady state. The data points and the corresponding vertical lines represent the least-squares means and standard errors as determined for each visit and treatment arm of the respective study. The solid line and the inner and outer shaded areas represent the mean dose response curve, its 95% confidence interval and 95% prediction interval, respectively.

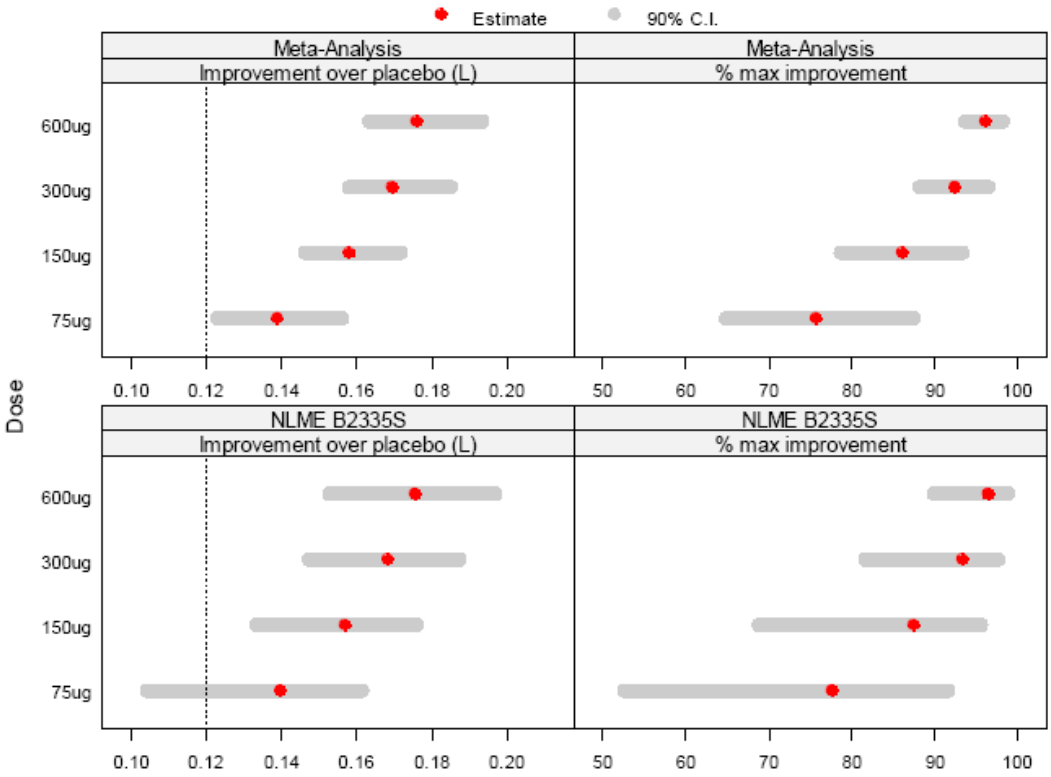


Best Available Copy

Source: the sponsor's report, dose-response and regimen modeling report. Page 27

Figure 3 provides direct comparisons between the respective model fits with respect to predicted improvement in response and percent of maximum improvement in trough FEV1. The two model-based analyses produce almost identical point estimates. The only key difference between the two analyses is the degree of uncertainty: the meta-analysis, which draws on more data, has narrower confidence intervals in comparison to the mixed-effects analysis of a single study.

Figure 3. Meta-analysis (top) and NLME analysis of CQAB149B2335S (bottom) predicted improvement over placebo and percentage maximum improvement in trough FEV1 for the doses tested in Phase 3.

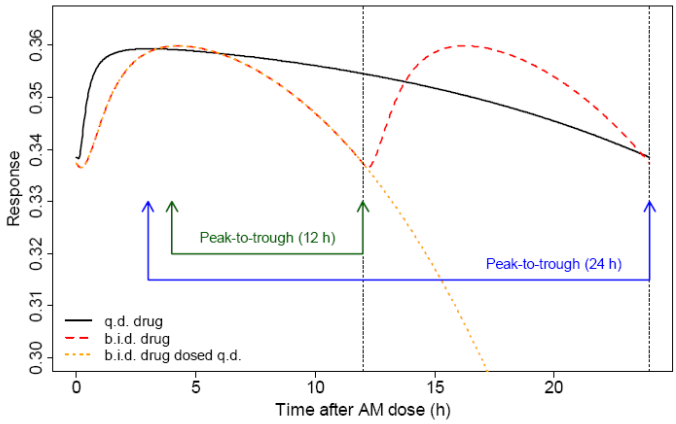


Source: the sponsor's report, dose-response and regimen modeling report. Page 41

Refer to Appendix 1 for the analyses results from other analyses.

Figure 2.2.4. presents the systematic illustration for the concept of QD. vs. BID dosing interval, provided by the sponsor. The primary metrics in the assessment of once-daily versus twice-daily drugs are responses measured at 24 hours and 12 hours post-dose – the trough values for the respective regimens.

Figure 4. The sponsor's schematic presentation of the peak-to-trough concept at steady-state (not based on real data).



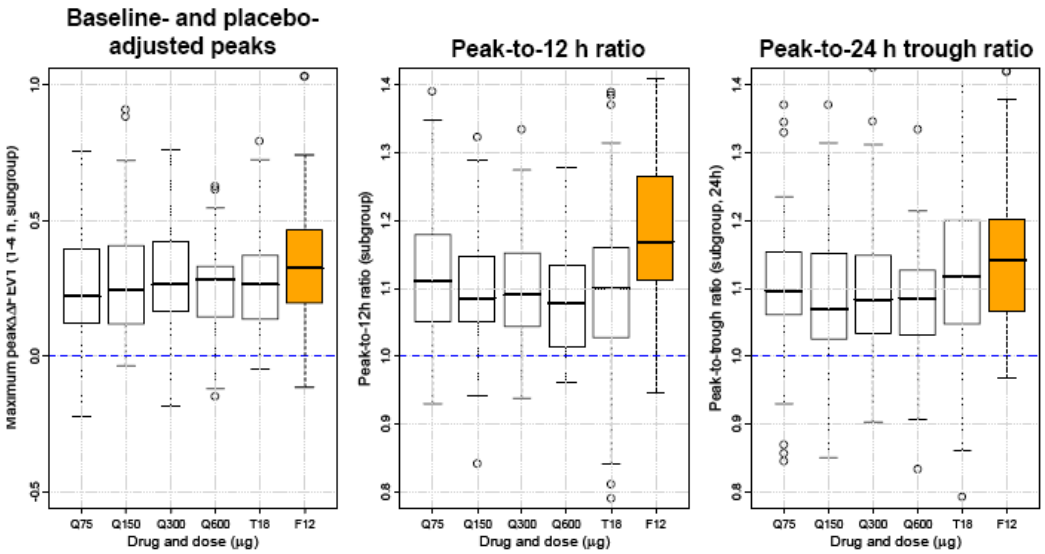
Best Available Copy

Source: the sponsor's report, dose-response and regimen modeling report. Page 13.

It is expected that the response for indacaterol at 12 h should be superior to the response of a twice-daily drug such as formoterol or salmeterol. Since the peak effects for the respective drugs should be comparable, the peak-to-trough ratio may be an ideal metric for this comparison. However, it could be argued that the extended duration of effect might be a result of simply increasing the dose to artificially extend the duration of action. To address this question, the sponsor assessed two different metrics of the dose-response: the peak response and the trough response. Similar estimates of the ED50 for the respective metrics would provide evidence that the once daily properties of indacaterol is not achieved at the expense of elevating the dose to artificially extend the duration of action. Refer to Table 2.2.4.4.1 for the parameter estimates for ED50.

Figure 5 shows the baseline- and placebo-adjusted peaks at Day 14 in study CQAB149B2335S for each treatment arm. Baseline was defined as the average of the
FEV1 measurements taken in the clinic in the hour prior to first dose of study drug at Day 1, and normalization was carried out by subtracting each individual's baseline from each of their associated FEV1 observations. Since within-patient placebo response data were not available for the studies included in this analysis, mean baseline-adjusted FEV1 by nominal time and visit number from the placebo arm of the relevant study was used for placebo adjustment.
Once-daily administration of indacaterol was shown to have significantly smaller peak-to-12 h trough FEV1 ratios than formoterol and salmeterol BID. The sponsor claimed that this analysis along with similar ED50 estimates in both trough and peak FEV1 responses confirmed the intrinsic difference between indacaterol and the BID bronchodilators in terms of their FEV1 profiles.

Figure 5. Boxplots of Peak to Trough Ratios in individual patients for Study CQAB149B2335S on Day 14.



Best Available Copy

Source: the sponsor's report, the dose-response and regimen modeling report, page 44.

Reviewer's comments:

- *The sponsor does not fully address the justification of 150µg as an optimal dose.*
  - *The sponsor's MCID is not justified according to the medical review team's opinion*
  - *As shown in the paper*[1]*, the sponsor's rule for finding the minimum effective dose (MED) based on the lower bound of 95% confidence interval tends to overestimate the target dose.*
- *The sponsor's Emax model does not fit the observed data well, especially at lower doses due to the lack of data.*
- *The sponsor's* ED50 *estimates are not reliable due to the large uncertainty.*
- *Even though there is certain evidence to support the once daily properties of indacaterol, the large uncertainty on* ED_{50} *estimates, especially for peak FEV1 response, makes it difficult to fully rule out the possibility of a BID regimen being the appropriate dosing regimen.*

Appendix 1

1. Model specification in the Bayesian meta-analysis

$$E = \frac{E_{max} \times dose}{ED_{50} + dose}.$$

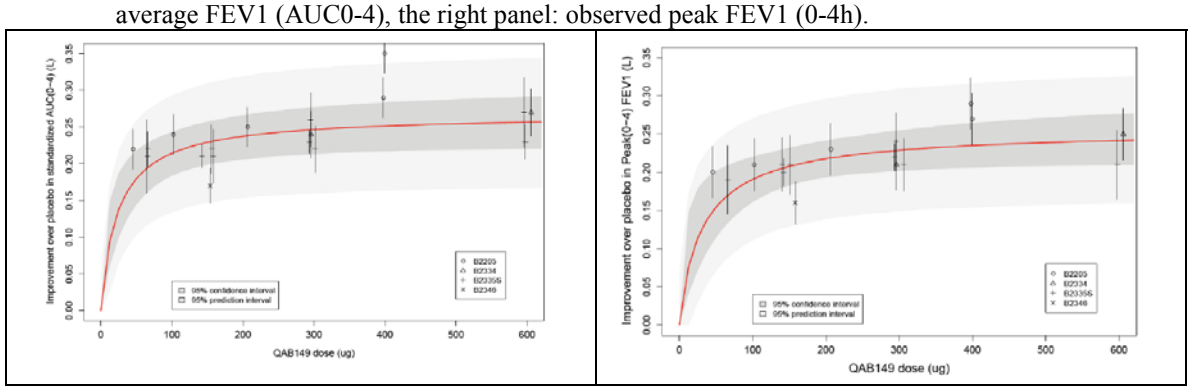
- Between-study variability: Emax, i = Emax + δi, where δi represents the (random) deviation for study i relative to the population effect (Emax). δi is assumed normally distributed as N(0, σEmax^2), i.e. a normal distribution with mean 0 and standard deviation (SD) σEmax.
- Uncertainty in least-squares (LS) estimates: yij ~ N(μij,σij^2) where yij is the LS mean contrast to placebo at visit j for study i and σij the corresponding estimated standard error (SE) which, as in standard meta-analysis, are assumed known.
- To complete the model specification, prior distributions were specified for all model parameters:
    - Emax ~ N(0, 100^2)
    - ED50 ~ unif(0, 600) i.e. a uniform distribution over the dose range 0 to 600 μg.
    - σEmax ~ exp(45) i.e. an exponential distribution with rate parameter equal to 45.

2. Model specification in NLME analysis

$$y_{ij} = \left[(E_0 + b_i) + \mathbf{x}_i^t \boldsymbol{\beta} + \frac{E_{max} \times dose_i}{ED_{50} + dose_i} \right] \varepsilon_{ij}$$

where y_{ij} represents the FEV1 metric measured on patient i at day j, E_0 is the intercept fixed effect and b_i a random effect to account for between-patient variation in response, assumed to be independently normally distributed with mean 0 and standard deviation σ_b.
the **β xti** term accounts for the baseline covariates adjustment (baseline FEV1, FEV1 reversibility components, smoking status, and country a re included in **x**i).
Finally, ε_{ij} denotes the within-patient multiplicative errors, assumed to be independently distributed as lognormal (0, σ) variables.

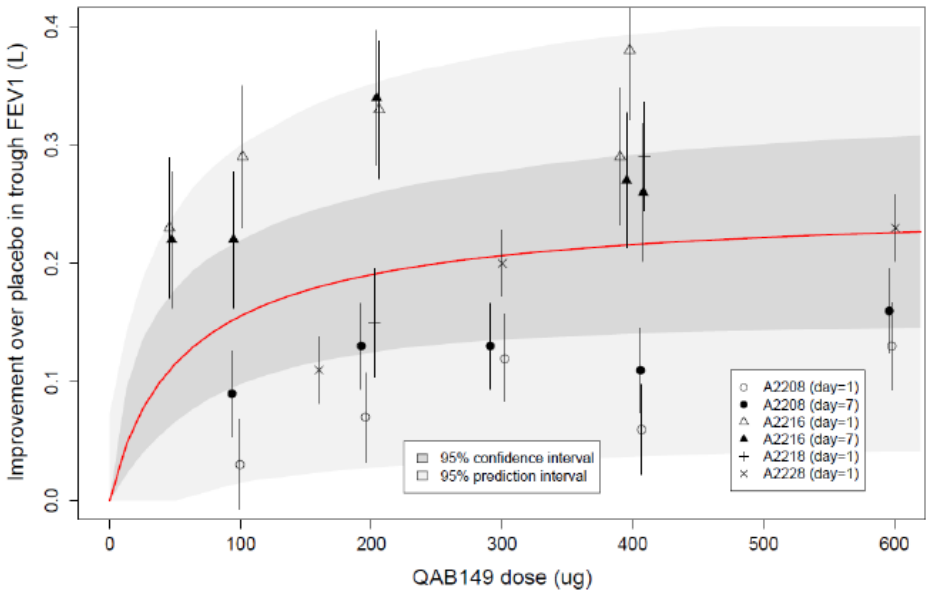
3. Prediction of dose-response relationship for other endpoints from both meta-analysis. The left panel: peak average FEV1 (AUC0-4), the right panel: observed peak FEV1 (0-4h).



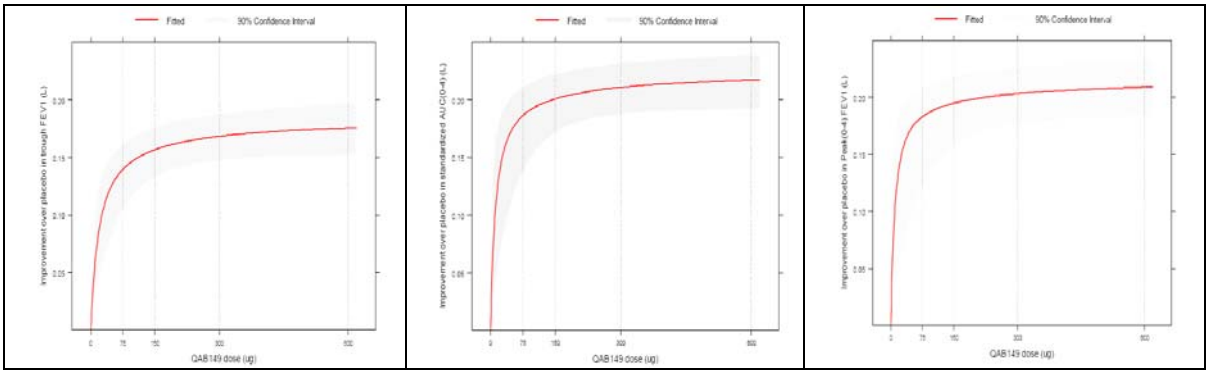
Best Available Copy

4. Prediction of dose-response relationship (trough FEV1) at day 1 and 7 in asthma patients from meta-analysis.

Best Available Copy



5. Prediction of dose-response relationship from NLME analyses. The left panel: trough FEV1, the middle panel: peak average FEV1 (AUC0-4), the right panel: observed peak FEV1 (0-4h).



CLINICAL PHARMACOLOGY GENOMICS GROUP REVIEW

NDA Number	22,383
Submission Type	Standard
Applicant Name	Novartis
Submission Date	12/18/09
Brand Name	Arcapta
Generic Name	Indacaterol
Proposed Indication	COPD
Genomics Reviewer	Mike Pacanowski, Pharm.D., M.P.H.
Team Leader	Issam Zineh, Pharm.D., M.P.H.

1. BACKGROUND

Indacaterol is a long-acting beta2-adrenergic receptor agonist. The applicant is seeking approval for the use of indacaterol in the treatment of chronic obstructive pulmonary disease (COPD).

The sponsor's proposed labeling contains language concerning the effect of polymorphisms in the UGT1A1 drug metabolism gene on the pharmacokinetics (PK) of indacaterol as follows:

(b) (4)

This language is based on a prospective study with UGT1A1 genotype-based enrollment study that was conducted as part of the Novartis exploratory development program.

The purpose of this review is to 1) evaluate heterogeneity in indacaterol exposure and/or response, 2) evaluate the sponsor's proposed labeling regarding the impact of UGT1A1 polymorphisms on indacaterol PK and 3) evaluate other potential sources of heterogeneity in indacaterol disposition or response.

2. NDA CONTENT RELATED TO GENOMICS

The pharmacogenetic effects of UGT1A1 polymorphisms on indacaterol exposure and response were evaluated in a single, prospective, open-label, cohort study that enrolled a balanced number of subjects with the UGT1A1 (TA)6/(TA)6 (also referred to as *1/*1; normal activity) or (TA)7/(TA)7 (also referred to as *28/*28; reduced activity) genotypes: Study A2221.

DNA samples were collected in the pivotal efficacy studies (e.g., A2335S) on a voluntary basis to explore pharmacogenetic predictors of indacaterol PK and pharmacodynamics. No data other than the UGT1A1 data were submitted as part of Study A2221 were included in the regulatory submission.

The sponsor's pivotal efficacy studies were reviewed to evaluate individual responses to indacaterol and heterogeneity in the PK profile of indacaterol.

3. KEY QUESTIONS AND SUMMARY OF GENOMICS FINDINGS

3.1. Are individual indacaterol exposures or responses heterogeneous?

Yes. The PK of indacaterol was not excessively variable in densely sampled healthy volunteer studies. However, marked variability was evident in the changes in FEV1 following at least 12 weeks of per-protocol indacaterol treatment in the 3 pivotal studies. Approximately 50% of patients demonstrated less than a 10% improvement in FEV1. Non-response rates were similar or greater for formoterol and tiotropium, indicating the response heterogeneity may be typical of other inhaled agents used in COPD.

The PK of indacaterol was evaluated in 41 studies. The distribution and dispersion of PK parameters based on multiple dose studies with dense PK sampling is depicted in the following table. The coefficient of variations ranged from 15% to 45% for AUC_{0-24}, C_{max}, and $t_{1/2}$.

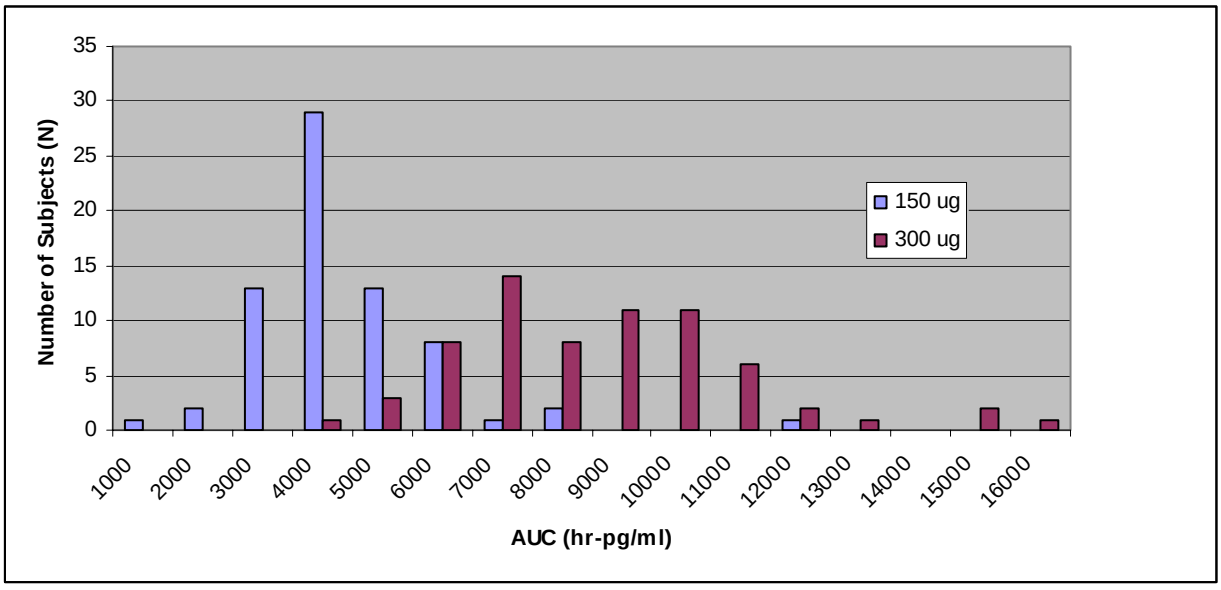
Table 1. PK variability of indacaterol delivered via Concept1 inhaler in healthy volunteer, multiple-dose studies with dense sampling (sponsor's analysis)

Study	Dose	Follow-up (days)	N	Variable	Mean at Follow-up	SD	CV (%)
A2221*	200 µg	14	12	C_{max} (ng/mL)	0.553	0.084	15
	(Aerolizer)		12	AUC_{0-24} (ng-h/ml)	4.26	0.67	16
			12	$t_{1/2}$ (h)	126	23	18
			12	$t_{1/2}$* (h)	42.3	8.3	20
B2339	150 mcg	14	70	C_{max} (pg/mL)	438.6	196.4	45
			70	AUC_{0-24} (pg-h/ml)	3882	1545	40
			70	$t_{1/2}$* (h)	44.7	12.4	28
	300 mcg		68	C_{max} (pg/mL)	858.6	264.2	31
			68	AUC_{0-24}	8137	2388	29
			68	$t_{1/2}$* (h)	44.7	12.4	28
* only data for (TA)6 homozygotes presented							

Source Sponsor's Reports for Study A2221 and A2339

The distributions of exposures are shown in the following figure. Exposures following the 150 mcg dose appeared to have wider variability in exposure and higher maximum exposures when compared with the 300 mcg dose.

Figure 1. Distribution of indacaterol AUC0-24 after 14 days in Study 2339



Source Genomics Reviewer

The efficacy and safety of indacaterol in COPD patients was studied in 3 trials using 150 mcg vs. tiotropium (B2335S), placebo (B2346), and formoterol (B2334) as controls. Supportive evidence is provided from 3 additional studies, B2305, B2307, and B2340. Other endpoints included exacerbations, peak expiratory flow, rescue medication use, days of poor control, quality of life, among others. In the 3 pivotal trials, the primary endpoint was FEV1 trough after 12 weeks of indacaterol treatment. Treatment differences for indacaterol relative to controls were the primary comparison in the sponsor's analyses.

The following table displays summary statistics for FEV1 responses following at least 12 weeks of indacaterol for the per-protocol populations in the pivotal studies. The CV% ranged from 132% to 1245% FEV1 changes. Formoterol and tiotropium responses were comparably variable.

Table 2. Pharmacodynamic variability of indacaterol in COPD patients (per-protocol)

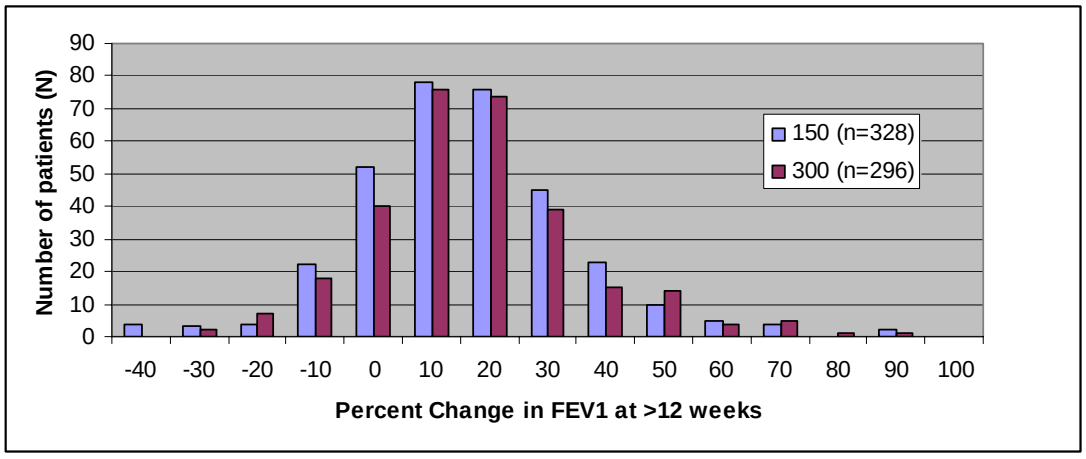
Study	Drug	N	Follow-up (weeks)	Absolute Change from Baseline	SD	CV%	Percent Change from Baseline	SD	CV%
B2346	Ind 150 mcg	182	12	0.13	0.30	223	12.8	19.99	156
B2334	Ind 300 mcg	148	12	0.16	0.23	138	13.8	18.95	137
	Ind 600 mcg	145	12	0.12	0.22	179	11.7	20.28	174
	Formoterol	147	12	0.02	0.23	1245	2.4	16.71	707
B2335 S	Ind 150 mcg	146	26	0.10	0.25	252	9.1	18.64	206
	Ind 300 mcg	149	26	0.13	0.24	183	11.8	20.28	172
	Ind 75 mcg*	27	12	0.11	0.21	194	9.1	15.69	172
	Ind 600 mcg*	27	12	0.19	0.27	146	13.9	18.32	132
	Tiotropium	145	26	0.10	0.22	212	10.3	19.68	190
	Formoterol	28	12	0.14	0.20	147	11.7	18.56	158

*Individuals with data at 12 weeks

Source Genomics Reviewer

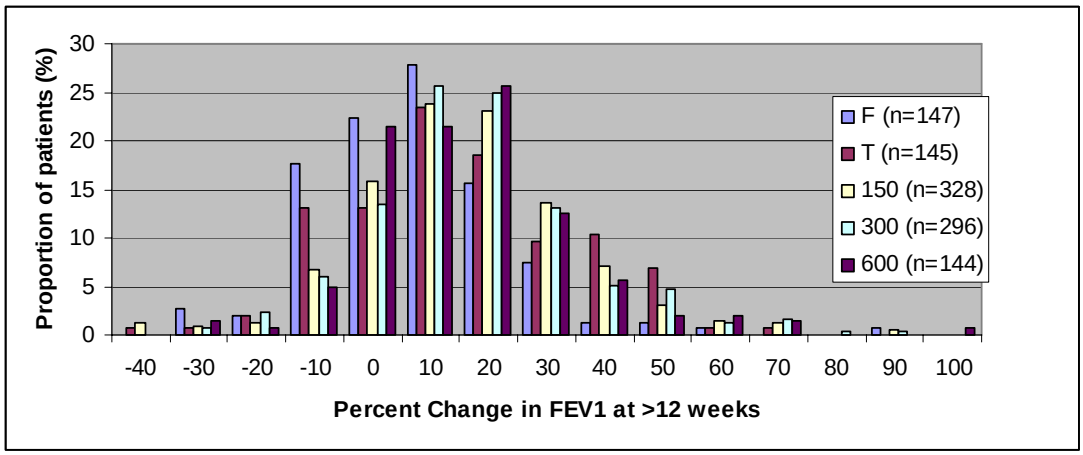
A pooled analysis of per-protocol patients in the 3 pivotal studies was performed to evaluate response rates at 12 weeks or greater (with non-response defined as <10% change in FEV1). As shown in the following histograms, 49.7% of patients treated with 150 mcg and 48.3% of patients treated with 300 mcg demonstrated less than a 10% change or an increase in FEV1. Non-response rates were similar for 600 mcg of indacaterol (50%) and tiotropium (53.1%), but were higher for formoterol (72.8%).

Figure 2. Number of patients by trough FEV1 response after at least 12 weeks of indacaterol at 150 mg and 300 mg



Source Genomics Reviewer

Figure 3. Proportion of treated patients by trough FEV1 response category after at least 12 weeks of indacaterol as compared to formoterol and tiotropium



Source Genomics Reviewer

It is noted that COPD treatments were withheld for a drug-specific washout period in each study (notably, long-acting β_2-agonists were withheld for 48 hours and corticosteroids for 1 month).

The reviewer performed linear regression to identify covariates that predict the absolute change in FEV1 at 3 months. Variables entered into this analysis included age, baseline FEV1, inhaled corticosteroid use, race, baseline COPD severity, sex, and smoking history. Significant covariates are highlighted in the following table. These factors account for a small portion of the overall variability in treatment response (R^2 approximately 4%).

Table 3: Linear regression model for absolute change in FEV1 after 12 weeks of indacaterol treatment

	150 mcg (n=531)			300 mcg (n=720)		
Variable	**Parameter estimate**	**SE**	**P**	**Parameter estimate**	**SE**	**P**
Age	-0.00397	0.00138	0.0042	-0.00502	0.00123	<.0001
Baseline FEV1	-0.15676	0.03091	<.0001	-0.12304	0.02931	<.0001
Inhaled corticosteroid use	-0.02847	0.02311	0.2186	0.02227	0.01994	0.2645
Race	-0.02948	0.01861	0.1137	-0.01852	0.01448	0.2013
COPD Severity (<mod vs. >sev)	-0.08506	0.02755	0.0021	-0.12339	0.02554	<.0001
Sex (F vs. M)	-0.1268	0.02672	<.0001	-0.06909	0.0254	0.0067
Smoking history	0.01264	0.02378	0.5954	-0.04202	0.02087	0.0445
	Adjusted R^2 = 0.0426			*Adjusted R^2 = 0.0457*		
Analysis based on 3-month data from Integrated Summary of Efficacy dataset						

Source Genomics reviewer

3.2. Do UGT1A1 polymorphisms affect the indacaterol PK or responses?

Nonsignificant trends toward higher C_{max} and AUC_{0-24} (19% and 20%, respectively) were noted in patients with the (TA)7 genotype. These findings are consistent with the reduced metabolic function of this form of the enzyme. The magnitude of the difference may greater at higher doses, However, Cmax and AUC values following the 200 mcg dose in (TA)7 subjects did not exceed those of the 300 mcg dose in other studies. The alleles assessed in this study were appropriate given that the population was predominantly white. Non-white subjects and their respective variants of UGT1A1 have not been evaluated, although the findings for (TA)6/7 are likely representative.

UGT1A1 is a polymorphic enzyme. UGT1A1 is the only UGT isoenzyme involved in indacaterol metabolism (1A1, 1A3, 1A4, 1A6, 1A8, 1A9, 1A10, 2B7, 2B15 tested). In individuals of European descent, a repeat polymorphism in the promoter region of *UGT1A1*, (TA)6→(TA)7 ((TA)7 also referred

to as *28) decreases UGT1A1 transcription rates. This allele is present in approximately 26-31% of European chromosomes, but is more common in individuals of African descent and less common in Asians. Other alleles found in non-European populations decrease UGT1A1 metabolic capacity. The *6 allele which reduces *UGT1A1* gene expression to approximately 30% of normal is unique to and common in Asian patients (allele frequency of 0.13-0.23). Unique to African individuals are the *36 allele, which increases transcription, and the *37 allele, which decreases transcription.

The impact of UGT1A1 TA6 genotype on indacaterol PK was evaluated in a prospective, open-label, parallel-arm, healthy volunteer study with genotype-based enrollment (A2221). The study details are described in ***Section 6***. Briefly, subjects who were homozygous for 7 TA repeats ((TA)7) or 6 TA repeats ((TA)6) were enrolled in a balanced fashion and treated with 200 mcg of indacaterol daily via Aerolizer for 14 days. Dense PK sampling was performed over the first 24 hours after the initial dose and until 168 hours after the last of 14 daily doses. Trough samples were collected on Day 4, 6, 8, 10 and 13.

The study population consisted of 12 subjects in each genotype group. All except 2 subjects with the (TA)7/(TA)7 genotype were white, and all were male except 2 subjects in each genotype group. The sponsor provided the following results for PK parameters for study subjects according to (TA)7 genotype as follows:

Table 4. Plasma PK parameters for unchanged indacaterol (arithmetic mean, SD (CV%))

	Day	t_{max}* (h)	C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)	$t_{1/2}$ (h)	$t_{1/2,acc}$ (h)	R for C_{max}	R for AUC_{0-24}
$A(TA)_6TAA$ (n=12)	1	0.25 (0.25-0.50)	0.346, 0.076 (22)	1.42, 0.34 (24)	-	-	-	-
	14	0.25 (0.25-0.25)	0.553, 0.084 (15)	4.26, 0.67 (16)	126, 23 (18) **	42.3, 8.3 (20)	1.64, 0.29 (17)	3.08, 0.49 (16)
$A(TA)_7TAA$ (n=12)	1	0.25 (0.20-0.50)	0.311, 0.067 (21)	1.44, 0.43 (30)	-	-	-	-
	14	0.25 (0.25-0.50)	0.660, 0.194 (29)	5.11, 1.41 (28)	125, 27 (22)	51.6, 9.7 (19)	2.17, 0.66 (30)	3.63, 0.58 (16)

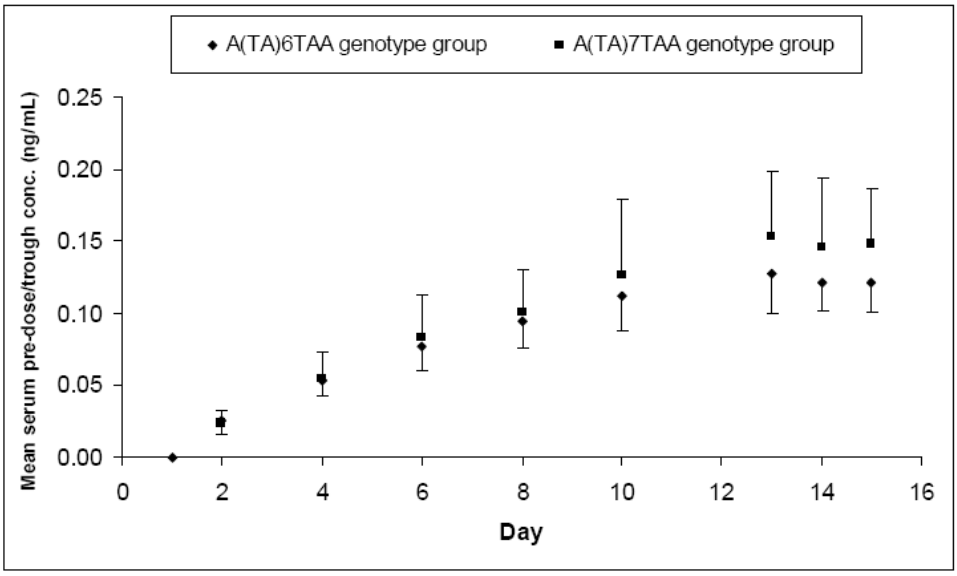
*t_{max} - median and range; ** n=11

Source: Sponsor's report Study A2221

T_{max} and the observed half-life were similar at day 14 for both genotype groups. The AUC, C_{max}, and accumulation factor were modestly higher in subjects with the (TA)7/(TA)7 genotype.

The trough concentrations over the study period are shown in the following figure. The observed troughs were variable, but tended to be higher in the (TA)7 group. The trough concentrations appeared to plateau at approximately 2 weeks.

Figure 4. Arithmetic mean (and SD bars) pre-dose trough concentrations of indacaterol (ng/ml)



Day 15 concentration is the 24 h concentration of Day 14. Source: Appendix 16.2.5-2 Table 16.2.5-2.2 to Table 16.2.5-2.7

Source: Sponsor's report Study A2221

The age- and body weight-adjusted ratios (95%CI) of (TA)7/(TA)6 C_{max} and AUC_{0-24} were 1.15 (0.93-1.42) and 1.16 (0.96-1.40), respectively, after 2 weeks of treatment. The upper-bound of the 95%CI was less than 2 for both parameters.

Reanalysis by the reviewer confirmed the sponsor findings. Based on statistical reanalysis, trends toward a difference in AUC_{0-24} (P=0.07, t-test; P=0.19, Wilcoxon) and Cmax (P=0.1, t-test; P=0.14, Wilcoxon) were noted. The magnitude of the difference was approximately 1.2-fold, and is thus of questionable clinical relevance.

No deaths or SAEs occurred during the study and no subject discontinued due to AEs. The sponsor reported that no tolerability issues appeared to differentiate across the genotype groups.

3.3. What other biomarkers may predict response to indacaterol?

Indacaterol may be metabolized by CYP3A5 and this should be explored as a potential source of PK variability. The drug target, ADRB2, is known to have functional polymorphisms that have demonstrated effects on β_2-agonist responses in asthma. The sponsor should assess responses according to ADRB2 polymorphisms in the pivotal studies and subsequent efficacy studies to assess their contribution to response variability.

Drug metabolism and transport

Indacaterol is a CYP3A4 substrate. The sponsor did not evaluate whether indacaterol is also metabolized by CYP3A5. Substrates for CYP3A4 and CYP3A5 often overlap, and CYP3A5 is polymorphic. Indacaterol is a low affinity substrate for P-glycoprotein.

Drug target/ disease markers

The gene encoding the target of β_2-adrenergic receptor agonists, *ADRB2*, contains numerous, common single nucleotide polymorphisms (SNPs). Many of the SNPs alter receptor function, including Gly16Arg, Gln27Glu, and Thr164Ile. The Arg16 form of the receptor has been shown to exhibit diminished agonist-stimulated downregulation, although some controversy remains concerning the functionality of the codon 16 and 27 polymorphisms. Thr164Ile is less common (<5% allele frequency), but has been shown to alter binding affinity for β_2-agonists.(Brodde, PMID: 18353108)

The impact of *ADRB2* variants on β_2-agonist responses has not been extensively studied in COPD. A study carried out in Korean subjects (n=104) suggested no differences across *ADRB2* codon 16 or 27 genotypes in the percent change in FEV1 following 12 weeks of salmeterol. A prospective, genotype-stratified study demonstrated that asthma patients with the Gly16 form of the receptor respond favorably to short-acting β_2-agonist, whereas those with the Arg16 form of the receptor have worsening in PEFR and FEV1 (Israel, PMID 15500895). Other studies evaluating the pharmacogenetics of long-acting β2-agonists in asthma patients have been contradictory (Bleecker, PMID 18156033; Bleecker, PMID 17030231; Wechsler, PMID 16322642; Taylor, PMID 10950895).

It is notable that the *ADRB2* polymorphisms are expressed in the heart and vasculature and genetic variations have been associated with sudden cardiac death and various other cardiovascular phenotypes (Brodde, PMID: 18353108). Consequently, cardiovascular effects of indacaterol may in part depend on the variability in this receptor.

4. COMMENTS

Indacaterol responses are highly variable.

UGT1A1 does not appear to be a major contributor to variable indacaterol PK, although trends were evident such that UGT1A1 reduced metabolizers (i.e., (TA)7) had higher $AUC_{0\text{-}24}$ and C_{max} (approximately 1.2-fold)

DNA samples were collected in the phase III studies.

5. RECOMMENDATIONS

The applicant's proposed labeling concerning UGT1A1 pharmacogenetics is acceptable based on the results of study A2221 provided the Agency and the applicant can agree on the language.

The applicant should explore *CYP3A5* and *ADRB2* gene variation as additional intrinsic factors to account for the excessive variability in indacaterol responses.

5.1. Labeling Recommendations

(b) (4)

6. INDIVIDUAL STUDY REVIEW(S)

"An open label, multiple dose study to compare the pharmacokinetics of QAB149 in subjects with genetic variants of UDP-glucuronosyltransferase 1 enzyme: comparison of A(TA)$_7$TAA and A(TA)$_6$TAA genotypes"

Study No. A2221 **Development phase of study**: phase III

Primary Review: Ying Fan, Ph.D.
Secondary Review: Mike Pacanowski, Pharm.D., M.P.H.

Objective
To compare the pharmacokinetics of QAB149 in subjects with genetic variants of UDP-glucuronosyltransferase 1 enzyme: comparison of A(TA)7TAA and A(TA)6TAA genotypes

Results:
Pharmacokinetic results:
A summary of the key PK parameters for indacaterol is shown in Table 1. Mean pre-dose or trough concentration ratios Day 14/Day 13, Day 15/Day 13 and Day 15/Day 14 tended to 1.0 in both genotype groups (Table 2). Thus, steady-state was achieved by Day 13.

Arithmetic mean serum concentration-time profiles on Day 1 and Day 14 for the A(TA)6 TAA and A(TA)7TAA genotype groups are shown in Figure 1. Indacaterol was absorbed rapidly following inhalation. The maximum serum concentration of indacaterol was reached between 15 min and 30 min in the individual profiles; the median Tmax was at 15 minutes, in both genotype groups and after single and repeated dosing.

On Day 1, concentration-time profiles were similar in both genotype groups, and mean AUC0-24 values were close together (1.42 vs. 1.44 ng.h/mL in the A(TA)$_6$ TAA and the A(TA)7TAA group, respectively). By Day 14, the concentration-time profiles are slightly separated (Figure 1). There were minor differences in Cmin, Cavg, Cmax AUC0-24 between the genotype groups; mean exposure was 1.2-fold higher in the A(TA)7TAA group than the A(TA)$_6$TAA group, and indacaterol accumulation was slightly higher in the A(TA)7TAA group (AUC accumulation ratio was 3.63 in the A(TA)7TAA group vs. 3.08 in the A(TA)$_6$TAA group).

The terminal elimination half-life of indacaterol determined from the serum concentrations up to 168 h after the last dose on Day 14 were similar; on average, 125 h for the A(TA)6TAA genotype group and 126 h for the A(TA)7TAA genotype group.

The effective half-life for indacaterol accumulation, calculated from the AUC accumulation ratio, was 42.3 h for the A(TA)6TAA genotype group and 51.6 h for the A(TA)7TAA genotype group.

Table 5 Plasma PK parameters for unchanged indacaterol (Arithmetic mean, SD (CV%))

	Day	t_{max}* (h)	C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)	$t_{1/2}$ (h)	$t_{1/2,acc}$ (h)	R for C_{max}	R for AUC_{0-24}
$A(TA)_6TAA$ (n=12)	1	0.25 (0.25-0.50)	0.346, 0.076 (22)	1.42, 0.34 (24)	-	-	-	-
	14	0.25 (0.25-0.25)	0.553, 0.084 (15)	4.26, 0.67 (16)	126, 23 (18) **	42.3, 8.3 (20)	1.64, 0.29 (17)	3.08, 0.49 (16)
$A(TA)_7TAA$ (n=12)	1	0.25 (0.20-0.50)	0.311, 0.067 (21)	1.44, 0.43 (30)	-	-	-	-
	14	0.25 (0.25-0.50)	0.660, 0.194 (29)	5.11, 1.41 (28)	125, 27 (22)	51.6, 9.7 (19)	2.17, 0.66 (30)	3.63, 0.58 (16)

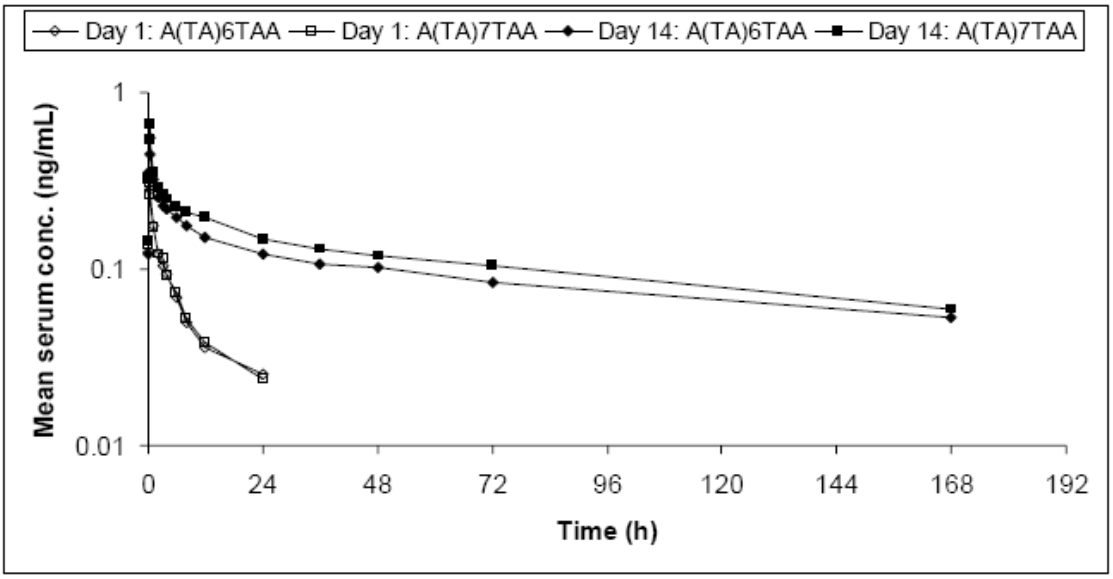
*tmax - median and range; ** n=11

Table 6 Pre-dose or trough concentration ratios for subjects with the 6/6 and 7/7 genotypes (Arithmetic Mean, SD (CV%))

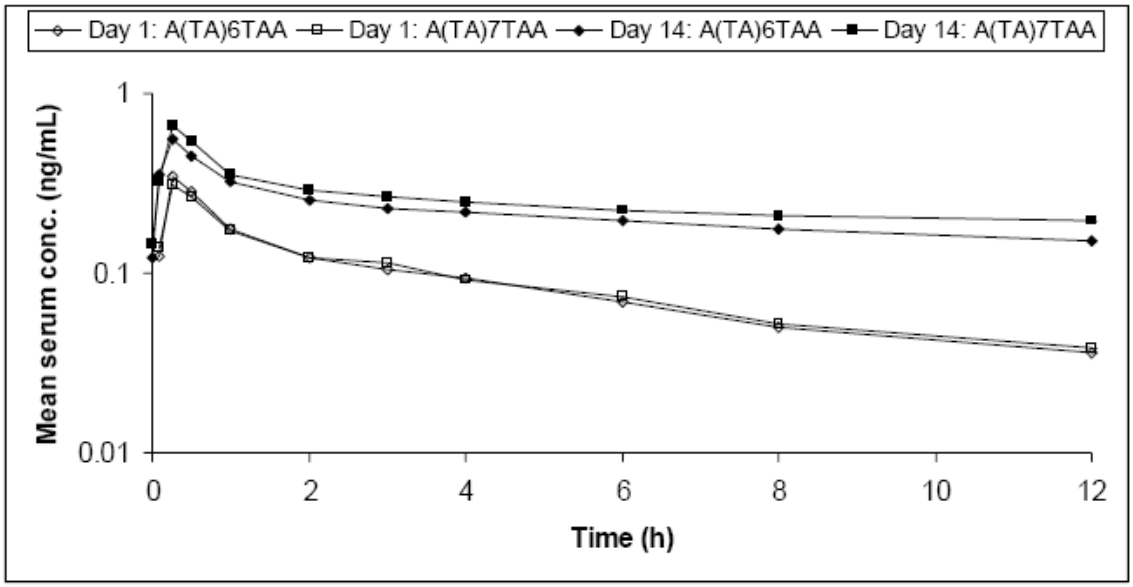
Genotype	Day13/Day8	Day13/Day10	Day14/Day13	Day15/Day13*	Day15/Day14*
$A(TA)_6TAA$	1.35, 0.20 (15)	1.14, 0.09 (8)	0.97, 0.15 (16)	0.98, 0.16 (16)	1.02, 0.18 (18)
$A(TA)_7TAA$	1.56, 0.33 (21)	1.27, 0.24 (19)	0.96, 0.20 (21)	0.98, 0.11 (12)	1.07, 0.30 (28)

*Day 15 concentration is the 24 h concentration of Day 14

Figure 5. Arithmetic mean serum concentration-time profiles of indacaterol on Day 1 and Day 14 for the A(TA)6TAA and A(TA)7TAA genotype group
Concentrations 0 to 24 h after inhalation on Day 1 and 0 to 168 h after inhalation on Day 14



Concentrations 0 to 12 h after inhalation on both days



Sponsor's Conclusions:

• The difference in systemic exposure (as measured by Cmax and AUC0-24) to indacaterol between genotype groups was minor. After repeated dosing exposure was on average 20% higher in the homozygous A(TA)7TAA group than in the homozygous A(TA)6TAA group.

• Accumulation of serum indacaterol was 1.64- and 2.17-fold for Cmax and 3.08- and 3.63-fold for AUC0-24 for the A(TA)6TAA and A(TA)7TAA group, respectively.

• Steady-state was achieved by Day 13, consistent with the effective half life for accumulation of indacaterol which was, on average, 42 h and 52 h for the A(TA)6TAA and the A(TA)7TAA group, respectively.

• There was no evidence of newly emerging adverse effects of indacaterol in either study group.
• Indacaterol was well tolerated by both groups.

_____ _____

Michael A. Pacanowski, Pharm.D., M.P.H. Date
Primary Reviewer, Genomics Group
Office of Clinical Pharmacology

_____ _____

Issam Zineh, Pharm.D., M.P.H. Date
Associate Director for Genomics, Genomics Group
Office of Clinical Pharmacology

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology Tracking/Action Sheet for Formal/Informal Consults	
From: **Sandra Suarez-Sharp**		**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE OF SUBMISSION: December 18, 2008	**NDA No.:** 22-383 **Serial No.:** S-001	BLA No.	**DATE OF REVIEW:** January 30, 2009
NAME OF DRUG: Arcapta™ (b) (4) (indacaterol maleate inhalation powder, QAB149)	**PRIORITY CONSIDERATION:** **S or P**		***Date of informal/Formal Consult*:** December 23, 2008

NAME OF THE SPONSOR: Novartis

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ SAFETY PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POP PK ISSUES	☐ MEETING PACKAGE	☒ OTHER *(SPECIFY BELOW):* *NDA Filing Review*
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated) ☐ E-mail comments to: ☐Medical ☐Chemist ☐Pharm-Tox ☐Micro ☐Pharmacometrics ☐ Others (Check as appropriate and attach e-mail)	☐ Oral communication with Name: [ ] ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☒ Formal Review/Memo (attached) ☐See comments below ☐See submission cover letter ☐ OTHER *(SPECIFY BELOW)*: [Please see attached memo]

REVIEW COMMENT(S)

☒ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

1. Executive Summary

This NDA filing review is for Arcapta ™ (b) (4) (Proposed) (indacaterol maleate inhalation powder, QAB149). Indacaterol Inhalation Powder is a novel long-acting inhaled β2-adrenergic agonist intended for long-term, once daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease

(COPD). The proposed starting dose is 150 µg once-daily administered by the orally inhaled route via inhalation powder hard capsules in a single dose dry powder inhaler. The maximum dose proposed is 300 µg once-daily.

In support of this submission, the sponsor included the results from 36 clinical studies that contain pharmacokinetic information collected from healthy volunteers (14 studies), patients with COPD (10 studies), and asthma patients (12 studies). In these studies indacaterol was administered via the inhaled route using either single dose dry powder inhaler (SDDPI) devices, a pressurized metered dose inhaler (pMDI) device, or a multi dose dry powder inhaler (MDDPI) device. The development of the pMDI and the MDDPI was discontinued and the device used in the to-be marketed formulation is an SDDPI variant called Concept1.

Pharmacokinetic data after inhalation via Concept1 was collected in studies in healthy subjects and patients with COPD and in studies in asthmatic patients. The studies conducted in asthma patients (12 studies) will not be reviewed as part of this submission because of their lack of relevance of the approval of this NDA for COPD. There were three studies conducted in healthy volunteers to assess drug-drug interactions (DDI), Study CQAB149A2311, Study CQAB149B2216, and Study CQAB149B2220. Special populations were investigated in Study CQAB149A2307 which studied hepatic impairment and Study CQAB149A2221 which investigated UGT1A1 genotype. Ethnic differences between Japanese and Caucasian subjects were addressed in healthy subjects (Study CQAB149A2215) as well as in asthmatics (Study CQAB149A2219). Information about covariates that may have an impact on pharmacokinetics such as age, gender, body weight, body mass index and race were investigated using a population PK modeling approach with pooled pharmacokinetic data from Study CQAB149B2212, Study CQAB149A2228, Study CQAB149B2334, Study CQAB149B2335S, and Study CQAB149B2338 (population-pk-indacaterol). According to the sponsor, because renal clearance plays a very minor role in elimination of indacaterol a study in renally impaired subjects was not conducted.

The bronchodilator effects of indacaterol were investigated in COPD patients up to doses of 3000 µg in single dose and 800 µg in repeated dose studies. Common endpoints were trough FEV1 to characterize the bronchodilator effect of indacaterol at the end of the 24 h dosing interval and peak FEV1. Two short term efficacy studies were undertaken in patients with COPD and characterized the bronchodilator effects of indacaterol over 24 h. These studies helped to determine the doses evaluated in the Phase III clinical development program.

Study CQAB149B2212 was a Phase II multi-center, randomized, placebo controlled, double-dummy, crossover design study and compared the efficacy and safety of single doses of indacaterol 150, 300 and 600 µg with placebo, using formoterol 12 µg b.i.d. as active control. Study CQAB149B2205 was a 7-day dose-ranging study carried out in COPD patients who were randomized to receive indacaterol at 50, 100, 200 or 400 µg *via* MDDPI, indacaterol 400 µg via SDDPI, or placebo.

Three studies were undertaken as part of the efficacy program for Phase III clinical development. Study CAQB149B2307 investigated the onset of bronchodilator action, Study CQAB149B2305 compared the bronchodilator effect of indacaterol when administered in the morning or in the evening, and Study CQAB149B2340 evaluated the bronchodilator response profile of inhaled indacaterol over the whole dosing interval. For the precise characterization of the effects of indacaterol on the QT-interval a large thorough QT-study (Study CQAB149B2339) was conducted in 404 healthy subjects.

According to the sponsor, indacaterol represents a typical inhaled drug product with low systemic concentrations reached early after inhalation and a lack of clinically relevant drug-interaction potential. The sponsor stated that in general, dose-proportionality of key pharmacokinetic parameters is given at least over a range of doubling doses. Biliary clearance appears to be the major contributor to elimination of drug related material. The impact of age, gender and race on the pharmacokinetics of indacaterol in COPD patients does not warrant dose-adjustments. Mild or moderate hepatic impairment does not alter the pharmacokinetics of indacaterol.

This reviewer's Comments
No information was included on the following:

- Effect of renal impairment of the PK of indacaterol/major metabolites. According to the sponsor, renal clearance plays a very minor role in elimination of indacaterol. Therefore, a study in renally impaired subjects was not conducted. The relevance of the renal impairment information on the PK of the drug/major metabolites will be a review issue.
- **The potential effect of indacaterol/major metabolites to induce major CYP P450 enzymes. The sponsor is inquired about this information.**

The sponsor has submitted a reviewable package for this NDA and therefore, there are no filing issues. The table below summarizes the clinical pharmacology studies included in the present submission and that are considered relevant for the approval of this NDA.

Study	Design	Tabular listing/ PK summary	Analytical method	PK parameters	Statistical analysis
CQAB149A2307: Hepatic impairment study with 600 µg indacaterol in matched pairs of subjects with hepatic impairment and healthy controls	Open label, single dose, parallel groups (17 subjects with mild and moderate hepatic impairment) (17 healthy controls)	√	√	√	√
CQAB149B2339: Thorough QTc study with 150, 300 & 600 µg indacaterol	Randomized, multiple dose, placebo controlled, parallel	√	√	√	√
CQAB149B2103: am / pm and absolute bioavailability with 300 µg inhaled and 400 µg intravenous indacaterol	Open label, single dose, 2 period cross-over (20)	√	√	√	√
CQAB149A2106: Inhaled vs oral administration of 800 µg indacaterol	Randomized, open label, cross-over, single dose (4)	√	√	√	√
CQAB149A2223: Human ADME (II) with 800 µg indacaterol	Open label, single dose (4)	√	√	√	√
CQAB149A2311: Drug interaction of 300 µg indacaterol with ketoconazole	Open label, single dose, cross-over (18)	√	√	√	√
CQAB149B2216: Drug interaction of 300 µg indacaterol with verapamil	Open label, single dose, 2 period, single sequence (12)	√	√	√	√
CQAB149B2220: Drug interaction of 300 µg indacaterol with erythromycin	Open label, 2 period, single sequence (12)	√	√	√	√
CQAB149A2215: Single dose study with 400, 800, 1200 & 2000 µg indacaterol in Japanese & Caucasians	Randomized, double blind, placebo controlled, multiple dose (40)	√	√	√	√

	population-pk-indacaterol]: Pharmacokinetic modeling of indacaterol, with special reference to the potential influences of covariates	CQAB149A2228, CQAB149B2212, CQAB149B2334, CQAB149B2335S, CQAB149B2338	NONMEM model, R-code, output and datasets				
	CQAB149B2202: Dose escalation safety & tolerability with 400, 1000, 2000 & 3000 µg indacaterol in patients with mild to moderate	Open label, non-randomized, single dose escalation (18)	√	√	√	√	
	CQAB149B2201: Four week safety, tolerability and PK of 400 and 800 µg indacaterol via SDDPI in patients with moderate COPD	Randomized, double blind, placebo controlled, parallel group, multiple dose study (163)	√	√	√	√	
	CQVA149A2101: Comparative PK of 300 µg indacaterol with the antimuscarinic bronchodilator NVA237	Randomized, open label, single dose, 4 way cross-over (28)	√	√	√	√	
	CQAB149B2212: Dose ranging (150, 300 and 600 µg) for indacaterol delivered via Concept1 in patients with moderate to severe COPD	Randomized, double blind, double-dummy, placebo and active treatment (formoterol) controlled, cross-over, single dose (51)	√	√	√	√	
	CQAB149A2211: Safety and tolerability of 400 µg, 1000 µg, 2000 µg and 3000 µg indacaterol in patients with persistent asthma	Open label, dose escalation, ascending single dose in persistent asthma (20)	√	√	√	√	
	CQAB149A2221: UGT1A1 genotype study with 200 µg indacaterol	Open label, multiple dose (24)	√	√	√	√	
	Study R00-594: In vitro binding of 3H-labeled QAB149 to red blood cells, serum and plasma proteins in the rat, dog and human	In vitro study	√	√	NA	NA	
	R0301281: Oxidative metabolism of [3H]QAB149 in human, rat, and mouse liver microsomes	In vitro study	√	√	NA	NA	
	R01-994: Metabolic profile in human liver microsomes and potential to inhibit cytochrome P450-mediated reactions	In vitro study	√	√	NA	NA	
	DMPK R0500761: *In vitro* assessment of [14C]QAB149 permeability and interactions with drug transporters across Caco-2 cell monolayers	In vitro study	√	√	NA	NA	

DMPK(US) R00-397: Comparative metabolism of [3H]QAB149 in rat, dog and human liver slice culture and metabolism in human lung slice culture	In vitro study	√	√	NA	NA
DMPK R0500025: In vitro assessment of (i) covalent protein binding potential in rat and human liver microsomes and human hepatocytes and (ii) time-dependent cytochrome P450 inhibition.	In vitro study	√	√	NA	NA

1.1 Recommendation

The Division of Clinical Pharmacology 2 (DCP2) has reviewed NDA 22-383 (S001) submitted on December 16, 2008 for filing purposes. The NDA is filable from a clinical pharmacology perspective. The following comments should be conveyed to the sponsor:

- Submit information on the potential of indacaterol/major metabolites to induce the major CYP P450 enzymes.
- Submit SAS transport files, containing ID, TRT, DOSE, individual CONC, TIME, individual PK Parameters, and other relevant study information for the following PK studies:
  - CQAB149A2106, CQAB149A2311, CQAB149B2216, CQAB149B2220, CQAB149A2215, CQAB149B2202, CQAB149A2211, CQAB149A2221, CQAB149B2201,CQAB149A2307, CQAB149B2103, CQAB149A2212
- Submit SAS transport files, containing ID, TRT, DOSE, individual CONC, TIME, individual PD Parameters, and other relevant study information for the following PD studies:
  - CQAB149B2202, CQAB149B2201, CQAB149B2217

SIGNATURE OF REVIEWER: *Sandra Suarez-Sharp, Ph.D.* _____ **SIGNATURE OF TEAM LEADER (acting):** Sally Choe, Ph.D. _____	Date _____ Date _____
CC.: HFD # [ ]; TL: [ ]; DD: [ ]	***Project Manager:*_____ *Date* _____**

Background

Chemistry/Drug Product

Arcapta™ (b) (4) (Proposed) (indacaterol maleate inhalation powder, QAB149). Indacaterol Inhalation Powder is a novel long-acting inhaled β2-adrenergic agonist intended for long-term, once daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The proposed starting dose is 150 µg once-daily administered by the orally inhaled route via inhalation powder hard capsules in a single dose dry powder inhaler. The maximum dose proposed is 300 µg once-daily.

Phase III clinical development of indacaterol was completed using hard gelatin capsules containing a dry powder formulation of indacaterol in lactose administered via a single-dose dry powder inhalation device (SDDPI) called Concept1. The dose strengths used in the Phase III clinical development of inhaled indacaterol via Concept1 device were manufactured as 75, 150 and 300 µg dosage strengths. (b) (4) The delivered dose (ex-mouth piece) from this inhaler is approximately (b) (4) of the nominal dose of the capsule.

Multiple dosage strengths of QAB149 inhalation powder hard capsules were developed for administration via a single dose dry powder inhaler (SDDPI). SDDPI devices for the clinical development of QAB149 included the marketed Aerolizer® device for an initial clinical Proof of Concept study, and its further redesign, i.e. the so-called RS01 device and the so-called Concept1 device.

(b) (4)

Clinical Pharmacology Findings

The following is a summary of clinical Pharmacology finding reported by the sponsor:

After oral inhalation from an SDDPI device such as Concept1, indacaterol was rapidly absorbed and achieved peak serum levels (Cmax) in the majority of subjects within the first 30 minutes after administration. Thereafter, indacaterol concentrations declined in a multi-phasic manner with an apparent terminal half-life that ranged from 45.5 to 126 h. From the multiple dose inhalation study (Study CQAB149B2339) the effective half-life for accumulation was determined to be in the range of 40 to 52 hours which was consistent with the observation that steady state was achieved between 12 and 14 days of o.d. dosing. As evidenced by the results of Study CQAB149B2339 the increase in steady state indacaterol AUC and Cmax was dose-proportional in the dose range of 150 μg to 600 μg and there was no change in the clearance of indacaterol on repeated once-daily dosing via Concept1. At steady state (Day 14) accumulation factors (Racc; i.e Day 14/Day 1 ratios) in that study for AUC and Cmax were in the range of 2.9 to 3.5 and 1.7 to 1.9 respectively. Absolute bioavailability of an inhaled dose was on average 43.2% (n=4). There was no clinically meaningful difference in systemic exposure when comparing dosing via Concept1 in the morning versus evening. After intravenous administration, serum clearance was moderate (23.3 L/h), and a large volume of distribution was observed (Vz=2557 L) (Study CQAB149B2103). Relative bioavailability of an oral dose compared to an inhaled dose was 46% (Study CQAB149A2106). The bioavailability data together suggest that systemic exposure to indacaterol after inhalation is a composite of pulmonary and intestinal absorption.

Since indacaterol is an inhaled drug, a formal food effect study was not conducted. In the pivotal studies of the clinical development program indacaterol was administered as a morning dose regardless of the timing of food intake. Indacaterol is highly bound to plasma and serum proteins. The *in vitro* human serum and plasma protein binding was high, ranging from 94.1 to 95.3 and 95.1 to 96.2% respectively. *In vitro* protein binding results were consistent with *ex-vivo* protein binding measurements. Mild-to-moderate hepatic impairment did not alter the protein binding of indacaterol [Study CQAB149B2339]. Indacaterol had an *in vitro* blood-to-plasma concentration ratio of 1.2 (Study R00-594).

.

Renal clearance of serum indacaterol was on average between 0.5 and 1.2 L/h in healthy subjects and COPD patients. After inhaled administration of indacaterol, generally less than 2% of the inhaled dose was excreted into urine. In a human ADME study (Study CQAB149A2223) the majority of the orally administered radioactive dose was excreted into feces and only a minor fraction was found in the urine. Indacaterol does not undergo stereoconversion *in-vivo*. Analysis of urine samples from (Study CQAB149A2211) provided evidence that stereochemical conversion of indacterol (the pure R-enantiomer) to the S-enantiomer *in vivo* does not happen to any significant extent.

The primary metabolic pathways of indacaterol in human involved monohydroxylation, and N-glucuronidation, and both C- and N-dealkylation. After oral administration of indacaterol in the human ADME study [Study CQAB149A2223] unchanged indacaterol was the main circulating component in human serum, accounting for 32.5% of the total drug related AUC0-24h. The

contribution of individual metabolites to the total drug-related AUC0-24h in human serum ranged from 4.2% to 12% with the hydroxylated metabolite P26.9 being the most prominent. All of the metabolites identified in humans were found in one or more of the animal species tested. Conversely, there were no metabolites observed in the animal species investigated that were not detected in human.
The key enzymes responsible for metabolic clearance of indacaterol are UGT1A1 and CYP3A4. *In vitro* investigations indicated that UGT1A1 was the only UGT isoform that metabolized indacaterol to the phenolic-O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6 and CYP3A4. CYP3A4 was predicted to be by far the most predominant isoenzyme responsible for hydroxylation of indacaterol. The hydroxylated metabolites P26.9 and P30.3 were found to have similar *in vitro* affinity to human beta-2-receptors than indacaterol itself. However the hydroxylated metabolites could not compete with indacaterol's duration of action in functional assays. The hydroxylated metabolites were found to represent no more than 11% of the steady state AUC0-24h and 6% of Cmax of parent indacaterol after inhalation via Concept1 (Study CQAB149B2339). Given the inferior activity profile and low *in vivo* abundancy, the hydroxylated metabolites are not expected to contribute significantly to pharmacological activity of indacaterol.

Indacaterol showed no significant inhibition of the P450 enzymes: CYP2C9, CYP2E1 and CYP3A4/5, when tested at concentrations of up to 100 μM. Relatively weak inhibition of the P450 enzymes: CYP1A2 ($IC_{50} \approx 10$ μM), CYP2C8 ($IC_{50} \approx 25$ μM), CYP2C19 ($IC_{50} \approx 25$-50 μM), and CYP2D6 ($IC_{50} \approx$ 5-10 μM), was observed. The sponsor stated that based on the low nanomolar maximum indacaterol serum concentrations observed at a therapeutically relevant dose of 300 μg, it is unlikely that indacaterol could act as an inhibitor of any of the cytochrome P450 enzyme activities in the clinic.

Indacaterol is a low affinity substrate for the efflux pump P-gp. *In-vitro* investigations in Caco-2 monolayer systems characterized indacaterol as a medium to high permeability drug substance that is also a low affinity substrate for P-gp mediated efflux. Inhibition of the key contributors of indacaterol clearance, i.e. UGT1A1, CYP3A4 and P-gp have no impact on the clinical safety of therapeutic doses of indacaterol.

The pharmacokinetics of indacaterol was studied in populations with different UGT1A1 genotypes – the fully functional [(TA)6,(TA)6] genotype and the low activity [(TA)7, (TA)7] genotype (i.e. Gilbert Syndrome genotype) (Study CQAB149A2221). The study demonstrated that steady state AUC0-24h as well as Cmax were 1.2-fold higher in the low activity UGT1A1 genotype group, indicating that systemic exposure to indacaterol is not significantly affected by UGT1A1-genotype.

Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e. ketoconazole (Study CQAB149A2311), erythromycin (Study CQAB149B2220) and verapamil (Study CQAB149B2216). Verapamil was used as the prototypic inhibitor of P-gp and resulted in 1.4- to two-fold increase in AUC and 1.5-fold increase in Cmax. Coadminstration of erythromycin resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2 fold for Cmax. Combined inhibition of P-gp and CYP3A4 by the very strong dual inhibitor ketoconazole caused

a 2-fold and 1.4-fold increase in AUC and Cmax respectively. Taken together the data suggest that systemic clearance is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold AUC increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition. Given the safety data of [Study CQAB149B2339] and of the pivotal studies (which both confirmed safe use of a 600 µg dosage regimen) the magnitude of exposure increases due to drug-interactions do not raise any safety concerns for therapeutic doses of 150 µg or 300 µg.

Indacaterol pharmacokinetics shows no difference between Japanese and Caucasian subjects and is not different amongst COPD patients of different ethnicities. Comparison of the pharmacokinetics between Japanese and Caucasian healthy subjects after single inhaled doses via a SDDPI device was conducted in (Study CQAB149A2215). No notable differences between Japanese and Caucasian populations were observed across the studies.

Further exploration of ethnic factors as covariates of systemic exposure in COPD patients and patients with asthma was done using a population PK modeling approach. Within the limits of the sensitivity of that analysis no ethnic factor was identified in the COPD analysis population that would impact systemic exposure to indacaterol after inhalation via Concept1 [population-pk-indacaterol]. Covariate analysis on age, gender, body weight, body mass index did not indicate a need for change in dosage regimen. The population PK analysis indicated that within the COPD analysis population the systemic exposure increased with increasing age (41% increase in peak exposure and 23% increase in steady state AUC0-24h within the age range of 48 to 78 years). When body weight increased from 50 to 107 kg in the COPD analysis population, peak concentrations decreased by 25% and AUC0-24h decreased by 21%. Female COPD patients had on average 7%-11% higher systemic exposure than males [population-pk-indacaterol].

Mild and moderate hepatic impairment does not alter indacaterol pharmacokinetics or protein binding. Study CQAB149A2307 studied the impact of mild and moderate (Child Pugh 5-6 and 7-9, respectively) hepatic impairment on the pharmacokinetics of single inhaled doses of 600 µg indacaterol delivered via Concept1. The study could not detect any relevant changes in pharmacokinetics or ex-vivo protein binding of indacaterol in either of the two groups when compared to healthy, demographically-matched control subjects. The effect of severe hepatic impairment on indacaterol pharmacokinetics was not studied.

Because renal clearance plays a very minor role in elimination of indacaterol a study in renally impaired subjects was not conducted.

Study CQAB149B2339, a thorough QTc study in 404 healthy subjects. The primary objective of the thorough QT study was to characterize the maximum mean QTcF prolongation following multiple doses of indacaterol for 14 days. With indacaterol treatment at multiple daily doses of 150, 300 and 600 µg maximum mean prolongations of QTcF intervals were below <5 ms (the regulatory threshold of concern) and the upper limit of the 90% confidence intervals was below 10 ms for all comparisons vs. placebo. This shows that there is no concern for a proarrhythmic potential in the investigated dose range. Study CQAB149B2202 investigated single doses of

indacaterol up to 3000 μg in patients with COPD. The maximal increase from baseline in QTcF in this study was 9.10 ms at 8 hours after the inhalation of 2000 μg indacaterol.

Study CQAB149B2201 investigated repeat doses of indacaterol up to 800 μg in patients with COPD. In this study there was an increase in QTcB versus placebo (60-minutes postdose) on Day 1 of 8.7 ms and 8.5 ms for the 400 μg and 800 μg doses respectively. The corresponding changes on Day 28 of treatment were 12.6 ms and 18.5 ms. The indacaterol QT-effects in asthma patients were largely consistent with those in COPD patients.

Overall the effects on heart rate appeared to be marginal and inconsistent with doses up to 800 μg indacaterol, so that it is unlikely that doses up to 800μg will produce relevant effects on heart rate.

There is an indication of potential heart rate effects at very high overdoses such as 3000 μg indacaterol. In Study CQAB149B2202 with single doses of indacaterol, there was a dose-dependent increase in heart rate up to 3000 μg indacaterol which produced a maximum heart rate change versus placebo of 12.4 bpm. In Study CQAB149B2201 repeat doses of 400 and 800 μg indacaterol for 28 days produced a maximum heart rate change versus placebo of 2.9 bpm 1 hour post-dose with the 800 μg dose. Changes in blood glucose and serum potassium associated with indacaterol administration in COPD were small, variable and not dose-related in all doses close to the clinical dose level.

Analytical Methods

According to the sponsor, currently QAB149 (indacaterol free base) is analyzed in serum and urine using a specific HPLC-MS/MS method with a lower limit of quantification (LLOQ) of 10 pg/mL using 200 μL serum (100 μL with online SPE) and of 50 pg/mL using 100 μL urine, respectively. In early phases of development indacaterol was analyzed with bioanalytical methods that were less sensitive (e.g. 250 pg/mL, 70 pg/mL and 50 pg/mL in serum). Methods for the analysis of indacaterol glucuronide in serum and urine were based on the determinations of "total indacaterol (i.e. the sum of parent and conjugated indacaterol) after sample treatment with glucuronidase followed by subtraction of the concentration of indacaterol measured in untreated samples. For the determination of potential enantiomeric conversion of indacaterol, in-vivo using urine samples from [Study CQAB149A2211], an enantio-selective bioanalytical method for the determination of the S-enantiomer was developed that allowed chromatographic separation of the S- and R-enantiomers. A specific bioanalytical method for analysis of oxidative metabolites (P26.9 and P30.3) in serum samples of [Study CQAB149B2339] was developed as well. According to the sponsor, all pivotal trials and the majority of PK studies used the most sensitive method with an LLOQ of 10 pg/mL. The table below shows a summary of analytical methods used in the analysis of indacaterol and its metabolites in this NDA submission.

Table 2-3 Summary of analytical methods

Analyte	Matrix	Method	Method-ID	LLOQ	Reference Validation report
Indacaterol	Serum	HPLC-MS/MS	A	10 pg/mL	[R0300366D] [R0300366D-01] [R0300366D-02] [R0300366D-03] [R0300366D-04] [R0400092B] [R0701007-01]
Indacaterol	Serum	HPLC-MS/MS (online SPE)	B	10 pg/mL	[R0701007]
Indacaterol	Plasma	HPLC-MS/MS	C	10 pg/mL	[R0300366G]
Indacaterol	Serum	HPLC-MS/MS	D	50 pg/mL	[R0300366A] [R0300366A-01] [R0300366A-02]
Indacaterol	Serum	HPLC-MS/MS	E	70 pg/mL	[R99-2520] [R0200492]
Indacaterol	Serum	HPLC-MS/MS	F	250 pg/mL	[R99-2520]
Hydroxy-indacaterol	Serum	HPLC-MS/MS	G	46 pg/mL	[R0700802]
Indacaterol	Urine	HPLC-MS/MS	H	100 pg/mL	[R0300366C] [R0300366C-01] [R0300366C-02] [R0300366C-03]
Indacaterol	Urine	HPLC-MS/MS	I	100 pg/mL	[R0400150]
S-enantiomer to indacaterol	Urine	HPLC-MS/MS	J	200 pg/mL	[R0300366F]
Total indacaterol [1)]	Urine	HPLC-MS/MS	K	250 pg/mL	[R99-2520]
Total indacaterol [1)]	Urine	HPLC-MS/MS	L	700 pg/mL	[R00-2189] [R0300366C-01] [R0400083] [R0400150]

A summary (reported by the sponsor) of the relevant methods is as follows:
Method A for indacaterol in serum with LLOQ of 10 pg/mL: The linearity of the analytical method for analysis of indacaterol in serum was validated (linear regression) in the range 10 pg/mL to 2000 pg/mL. The method is specific in human serum (maximum interference 5.1 % of signal at LLOQ). The inter-day accuracy and precision of the method was evaluated as the mean bias and precision of quality control samples analyzed during 3 validations days: bias at LLOQ was 4.2 %, and precision was 10.9 %. Above LLOQ, the biases were within the range -0.8 % to 1.8 % and the precisions were within the range 2.2 % to 9.9 %.

Method G for hydroxy-indacaterol in serum with LLOQ of 46 pg/mL: The linearity of the analytical method for analysis of hydroxy-indacaterol in serum was validated (linear regression) in the range 46 pg/mL to 460 pg/mL. The method quantified the sum of four enantiomers potentially resulting from hydroxylation at the ethyl-indan moiety of indacaterol. Out of the four enantiomers a pair of two diastereomers were observed in feces samples from the human ADME (i.e. P26.9 and P30.3 at a ratio of 1/3; see CTD section 4.2.2).The method is specific in human serum (maximum interference 5.0 % of signal at LLOQ). The inter-day accuracy and precision of the method was evaluated as the mean bias and precision of quality control samples analyzed

during 3 validations days: bias at LLOQ was 13.9 %, and precision was 7.1 %. Above LLOQ, the biases were within the range 4.1 % to 6.5 % and the precisions were within the range 6.8 % to 10.2 %.

Method H for indacaterol in urine with LLOQ of 100 pg/mL: The linearity of the analytical method in urine without glucuronidase/sulfatase sample treatment was validated (quadratic regression) in the range 0.1 ng/mL to 100 ng/mL. The method is specific in human urine (maximum interference 6.7 % of signal at LLOQ). The inter-day accuracy and precision of the method was evaluated as the mean bias and precision of quality control samples analyzed during one validation day: bias at LLOQ was -1.3 %, and precision was 10.3 %. Above LLOQ, the biases were within the range -12.5 % to 3.0 % and the precisions were within the range 1.3 % to 3.8 %.

Method J for S-enantiomer to indacaterol in urine with LLOQ of 200 pg/mL: The linearity of the analytical method in urine was validated (quadratic regression) in the range 0.2 ng/mL to 20 ng/mL. The method is specific in human urine (maximum interference 0.4 % of signal at LLOQ). The inter-day accuracy and precision of the method was evaluated as the mean bias and precision of quality control samples analyzed during 2 validation days: bias at LLOQ was -2.5 %, and precision was 8.2 %. Above LLOQ, the biases were within the range - 4.0 % to 5.5 % and the precisions were within the range 2.2 % to 4.4 %.

Table 1 shows the clinical studies (in healthy subjects and COPD patients) that contained PK information. Table 2 shows a list of studies that will be reviewed as part of this submission.

Table 1. Clinical studies that contained PK information

Study overview of clinical pharmacology studies in healthy subjects				
Study Code	**Short Title**	**Design Number of subjects (n = completed)**	**Device**	**PK sampling[1)]**
[CQAB149A2307]	Hepatic impairment study with 600 µg indacaterol in matched pairs of subjects with hepatic impairment and healthy controls	Open label, single dose, parallel groups (17 subjects with mild and moderate hepatic impairment) (17 healthy controls)	Concept1 SDDPI	dense
[CQAB149A2311]	Drug interaction of 300 µg indacaterol with ketoconazole	Open label, single dose, cross-over (18)	Concept1 SDDPI	dense
[CQAB149B2103]	am / pm and absolute bioavailability with 300 µg inhaled and 400 µg intravenous indacaterol	Open label, single dose, 2 period cross-over (20)	Concept1 SDDPI & intravenous infusion	dense
[CQAB149B2216]	Drug interaction of 300 µg indacaterol with verapamil	Open label, single dose, 2 period, single sequence (12)	Concept1 SDDPI	dense
[CQAB149B2220]	Drug interaction of 300 µg indacaterol with erythromycin	Open label, 2 period, single sequence (12)	Concept1 SDDPI	dense
[CQAB149B2339]	Thorough QTc study with 150, 300 & 600 µg indacaterol	Randomized, multiple dose, placebo controlled, parallel	Concept1 SDDPI	dense
[CQAB149A2106]	Inhaled vs oral administration of 800 µg indacaterol	Randomized, open label, cross-over, single dose (4)	Aerolizer™ SDDPI & oral dose	dense
[CQAB149A2221]	UGT1A1 genotype study with 200 µg indacaterol	Open label, multiple dose (24)	Aerolizer™ SDDPI	dense
[CQAB149A2215]	Single dose study with 400, 800, 1200 & 2000 µg indacaterol in Japanese & Caucasians	Randomized, double blind, placebo controlled, multiple dose (40)	RS01 SDDPI	dense
[CQAB149A2214]	Human ADME (I) with 800 µg indacaterol	Open label, single dose (3)	Oral dose	dense
[CQAB149A2223]	Human ADME (II) with 800 µg indacaterol	Open label, single dose (4)	Oral dose	dense
[CQVA149A2101]	Comparative PK of 300 µg indacaterol with the antimuscarinic bronchodilator NVA237	Randomized, open label, single dose, 4 way cross-over (28)	Concept1 SDDPI	dense
[CQMF149A2206]	Comparative PK with QMF149 (200 µg mometasone & 250 µg indacaterol)	Randomized, open label, single dose, 5 way, cross-over (32)	Concept1 SDDPI & Twisthaler™ MDDPI	dense
Study overview of clinical pharmacology studies in COPD Patients				
Study Code	Short Title	Design Number of subjects (n)	Device	PK sampling[1)]

[CQAB149B2212]	Dose ranging (150, 300 and 600 µg) for indacaterol delivered via Concept1 in patients with moderate to severe COPD	Randomized, double blind, double-dummy, placebo and active treatment (formoterol) controlled, cross-over, single dose (51)	Concept1 SDDPI	semi
[CQAB149B1202]	Efficacy & safety of 150, 300 & 600 µg indacaterol in Japanese COPD patients under exercise & and salbutamol co-administration	Randomized, double blind, placebo controlled, 4 period cross-over, single dose, dose-ranging study (45) (salmeterol) controlled, cross-over, single dose (21)	Concept1 SDDPI	semi
[CQAB149B2305]	Efficacy and safety of indacaterol 300 µg o.d. dosed in the morning or evening in patients with moderate to severe COPD	Phase III randomized, double-blind, double dummy, placebo controlled, multicenter, 4 treatments, 3 period incomplete block crossover study (83)	Concept1 SDDPI	compliance
[CQAB149B2201]	Four week safety, tolerability and PK of 400 and 800 µg indacaterol via SDDPI in patients with moderate COPD	Randomized, double blind, placebo controlled, parallel group, multiple dose study (163)	RS01 SDDPI	sparse
[CQAB149B2202]	Dose escalation safety & tolerability with 400, 1000, 2000 & 3000 µg indacaterol in patients with mild to moderate COPD	Open label, non-randomized, single dose escalation (18)	RS01 SDDPI	dense
[CQAB149B2205]	Dose ranging & device comparison with 50, 100, 200 & 400 µg indacaterol in patients with moderate to severe COPD	Randomized, double blind, placebo controlled, parallel group, multiple dose (623)	Certihaler™ MDDPI & RS01 SDDPI	semi
[CQAB149A2105]	Safety & tolerability of multiple 800 µg indacaterol doses	Randomized, double blind, placebo controlled, parallel group, multiple dose (10)	HFA pMDI	dense

1) > 6 samples per 24-hour period = dense; 4 - 6 samples per 24-hour period = semi; < 4 samples per 24-hour period = sparse; 1 single sample = compliance

Table 2. Clinical pharmacology and in vitro studies relevant to NDA submission.

Study	Design	Tabular listing/ PK summary	Analytical method	PK parameters	Statistical analysis
CQAB149A2307: Hepatic impairment study with 600 µg indacaterol in matched pairs of subjects with hepatic impairment and healthy controls	Open label, single dose, parallel groups (17 subjects with mild and moderate hepatic impairment) (17 healthy controls)	√	√	√	√
CQAB149B2339: Thorough QTc study with 150, 300 & 600 µg	Randomized, multiple dose, placebo controlled, parallel	√	√	√	√

indacaterol					
CQAB149B2103: am / pm and absolute bioavailability with 300 µg inhaled and 400 µg intravenous indacaterol	Open label, single dose, 2 period cross-over (20)	√	√	√	√
CQAB149A2106: Inhaled vs oral administration of 800 µg indacaterol	Randomized, open label, cross-over, single dose (4)	√	√	√	√
CQAB149A2223: Human ADME (II) with 800 µg indacaterol	Open label, single dose (4)	√	√	√	√
CQAB149A2311: Drug interaction of 300 µg indacaterol with ketoconazole	Open label, single dose, cross-over (18)	√	√	√	√
CQAB149B2216: Drug interaction of 300 µg indacaterol with verapamil	Open label, single dose, 2 period, single sequence (12)	√	√	√	√
CQAB149B2220: Drug interaction of 300 µg indacaterol with erythromycin	Open label, 2 period, single sequence (12)	√	√	√	√
CQAB149A2215: Single dose study with 400, 800, 1200 & 2000 µg indacaterol in Japanese & Caucasians	Randomized, double blind, placebo controlled, multiple dose (40)	√	√	√	√
population-pk-indacaterol]: Pharmacokinetic modeling of indacaterol, with special reference to the potential influences of covariates	CQAB149A2228, CQAB149B2212, CQAB149B2334, CQAB149B2335S, CQAB149B2338	NONMEM model, R code, output and datasets			
CQAB149B2202: Dose escalation safety & tolerability with 400, 1000, 2000 & 3000 µg indacaterol in patients with mild to moderate	Open label, non-randomized, single dose escalation (18)	√	√	√	√
CQAB149B2201: Four week safety, tolerability and PK of 400 and 800 µg indacaterol via SDDPI in patients with moderate COPD	Randomized, double blind, placebo controlled, parallel group, multiple dose study (163)	√	√	√	√
CQVA149A2101: Comparative PK of 300 µg indacaterol with the antimuscarinic bronchodilator NVA237	Randomized, open label, single dose, 4 way cross-over (28)	√	√	√	√
CQAB149B2212: Dose ranging (150, 300 and 600 µg) for indacaterol delivered via Concept1 in patients with moderate to severe	Randomized, double blind, double-dummy, placebo and active treatment (formoterol) controlled, cross-over, single dose (51)	√	√	√	√

COPD					
CQAB149A2211: Safety and tolerability of 400 µg, 1000 µg, 2000 µg and 3000 µg indacaterol in patients with persistent asthma	Open label, dose escalation, ascending single dose in persistent asthma (20)	√	√	√	√
CQAB149A2221: UGT1A1 genotype study with 200 µg indacaterol	Open label, multiple dose (24)	√	√	√	√
In vitro binding of 3H-labeled QAB149 to red blood cells, serum and plasma proteins in the rat, dog and human	In vitro study	√	NA	NA	NA
R0301281: Oxidative metabolism of [3H]QAB149 in human, rat, and mouse liver microsomes	In vitro study	√	NA	NA	NA
R01-994: Metabolic profile in human liver microsomes and potential to inhibit cytochrome P450-mediated reactions	In vitro study	√	NA	NA	NA
DMPK R0500761: *In vitro* assessment of [14C]QAB149 permeability and interactions with drug transporters across Caco-2 cell monolayers	In vitro study	√	NA	NA	NA
DMPK(US) R00-397: Comparative metabolism of [3H]QAB149 in rat, dog and human liver slice culture and metabolism in human lung slice culturea	In vitro study	√	NA	NA	NA
DMPK R0500025: In vitro assessment of (i) covalent protein binding potential in rat and human liver microsomes and human hepatocytes and (ii) time-dependent cytochrome P450 inhibition.	In vitro study	√	√	NA	NA

This reviewer's Comments

The sponsor has submitted a reviewable package for this NDA and therefore, there are no filing issues.

4.2 Filing Review

Office of Clinical Pharmacology			
New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	22-383	**Brand Name**	Arcapta (b) (4)
OCP Division	II	**Generic Name**	Indacaterol maleate
Medical Division	DPAP	**Drug Class**	**LABA**
OCP Reviewer	**Sandra Suarez-Sharp**	**Indication(s)**	Maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
OCP Team Leader (acting)	**Sally Choe**	**Dosage Form**	Inhalation Powder
PM Reviewer	TBD	**Dosing Regimen**	150 mcg once daily. The maximum dose is 300 mcg once daily.
Date of Submission	December 18, 2008	**Route of Administration**	Oral Inhalation
Estimated Due Date of OCP Primary Review	**August 25, 2009**	**Sponsor**	Novartis
PDUFA Due Date	Oct 18, 2009	**Priority Classification**	**s**
Division Due Date	**Oct 16, 2009**		

3 Clin. Pharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any. Study number**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**x**	**2**	**1**	[CQAB149A2214] [CQAB149A2223]
Isozyme characterization:	**x**	**4**	**3**	R0301281, R01-994, R0500761, R0500025
Blood/plasma ratio:	**x**	**1**	**1**	R00-594
Plasma protein binding:	**x**	**1**	**1**	R00-594
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**x**	**3**	**3**	[CQVA149A2101], [CQMF149A2206], [CQAB149B2201]
multiple dose:	x	**1**	**1**	[CQAB149A2105]
Patients-				
single dose:	**x**	**2**	1	[CQAB149B2212], [CQAB149B1202]
multiple dose:	**x**	**3**	3	[CQAB149B2305], [CQAB149B2202], [CQAB149B2205]

Dose proportionality -				
fasting / non-fasting single dose:	**x**	**1**	1	CQAB149B2339
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**x**	**3**	3	[CQAB149A2311], [CQAB149B2216], and [CQAB149B2220]
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	**x**	**1**	1	[CQAB149A2215]
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	**x**	**1**	1	[CQAB149A2307]
PD:				
Phase 2:	**x**	**2**	**2**	CQAB149B2212 CQAB149A2211
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Meta analysis:				
Data sparse:	**x**	**1**	1	Pop PK of indacaterol
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	**x**	**1**	1	[CQAB149B2103]
alternate formulation as reference:	**x**	**1**	**1**	[CQAB149A2106]
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	**x**	**1**	**1**	[CQAB149A2221]
QTC STUDIES (PHASE 1)	**x**	**1**	**1**	[CQAB149B2339]
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**x**	**31**	**28**	

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. • Submit information on the potential of indacaterol/major metabolites to induce the major CYP P450 enzymes. See executive summary for other comments.		
QBR questions (key issues to be considered)	**1. What is the optimal dose base on dose-response studies?** **2. Is dose adjustment needed on special populations (gender, race, hepatic impairment, age, renal impairment)?** **3. Is dose adjustment, warning or contraindication warranted based on DDI information?** **4. Was the metabolic pathway adequately characterized for indacaterol?** **5. Is the systemic exposure to indacaterol affected by UGT1A1 genotypic variation?** **6. Do indacaterol inhibit/induct the major P450 CYP enzymes?** **7. Was the to-be marketed formulation used in key PK studies?**			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22383	ORIG 1	NOVARTIS PHARMACEUTICALS CORP	INDACATEROL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDRA SUAREZ
08/25/2009

MICHAEL A PACANOWSKI
08/25/2009

ISSAM ZINEH
08/25/2009

JOO YEON LEE
08/25/2009

YANING WANG
08/25/2009

DAKSHINA M CHILUKURI
08/25/2009

The OCP Briefing will take place during the first week of September. The Secondary Review (if needed) will include any recommendations/changes, based on the feedback received at the OCP Briefing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology Tracking/Action Sheet for Formal/Informal Consults	
From: **Sandra Suarez-Sharp**		**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE OF SUBMISSION: December 18, 2008	**NDA No.:** 22-383 **Serial No.:** S-001	BLA No.	**DATE OF REVIEW:** January 30, 2009
NAME OF DRUG: Arcapta™ (b) (4) (indacaterol maleate inhalation powder, QAB149)	**PRIORITY CONSIDERATION:** **S or P**		**Date of informal/Formal Consult**: December 23, 2008

NAME OF THE SPONSOR: Novartis

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ SAFETY PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POP PK ISSUES	☐ MEETING PACKAGE	☒ OTHER *(SPECIFY BELOW):* *NDA Filing Review*
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated) ☐ E-mail comments to: ☐Medical ☐Chemist ☐Pharm-Tox ☐Micro ☐ Pharmacometrics ☐Others (Check as appropriate and attach e-mail)	☐ Oral communication with Name: [ ] ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☒ Formal Review/Memo (attached) ☐See comments below ☐See submission cover letter ☐ OTHER *(SPECIFY BELOW)*: [Please see attached memo]

REVIEW COMMENT(S)

☒ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

1. Executive Summary

This NDA filing review is for Arcapta ™ (b) (4) (Proposed) (indacaterol maleate inhalation powder, QAB149). Indacaterol Inhalation Powder is a novel long-acting inhaled β2-adrenergic agonist intended for

long-term, once daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The proposed starting dose is 150 µg once-daily administered by the orally inhaled route via inhalation powder hard capsules in a single dose dry powder inhaler. The maximum dose proposed is 300 µg once-daily.

In support of this submission, the sponsor included the results from 36 clinical studies that contain pharmacokinetic information collected from healthy volunteers (14 studies), patients with COPD (10 studies), and asthma patients (12 studies). In these studies indacaterol was administered via the inhaled route using either single dose dry powder inhaler (SDDPI) devices, a pressurized metered dose inhaler (pMDI) device, or a multi dose dry powder inhaler (MDDPI) device. The development of the pMDI and the MDDPI was discontinued and the device used in the to-be marketed formulation is an SDDPI variant called Concept1.

Pharmacokinetic data after inhalation via Concept1 was collected in studies in healthy subjects and patients with COPD and in studies in asthmatic patients. The studies conducted in asthma patients (12 studies) will not be reviewed as part of this submission because of their lack of relevance of the approval of this NDA for COPD. There were three studies conducted in healthy volunteers to assess drug-drug interactions (DDI), Study CQAB149A2311, Study CQAB149B2216, and Study CQAB149B2220. Special populations were investigated in Study CQAB149A2307 which studied hepatic impairment and Study CQAB149A2221 which investigated UGT1A1 genotype. Ethnic differences between Japanese and Caucasian subjects were addressed in healthy subjects (Study CQAB149A2215) as well as in asthmatics (Study CQAB149A2219). Information about covariates that may have an impact on pharmacokinetics such as age, gender, body weight, body mass index and race were investigated using a population PK modeling approach with pooled pharmacokinetic data from Study CQAB149B2212, Study CQAB149A2228, Study CQAB149B2334, Study CQAB149B2335S, and Study CQAB149B2338 (population-pk-indacaterol). According to the sponsor, because renal clearance plays a very minor role in elimination of indacaterol a study in renally impaired subjects was not conducted.

The bronchodilator effects of indacaterol were investigated in COPD patients up to doses of 3000 µg in single dose and 800 µg in repeated dose studies. Common endpoints were trough FEV1 to characterize the bronchodilator effect of indacaterol at the end of the 24 h dosing interval and peak FEV1. Two short term efficacy studies were undertaken in patients with COPD and characterized the bronchodilator effects of indacaterol over 24 h. These studies helped to determine the doses evaluated in the Phase III clinical development program.

Study CQAB149B2212 was a Phase II multi-center, randomized, placebo controlled, double-dummy, crossover design study and compared the efficacy and safety of single doses of indacaterol 150, 300 and 600 µg with placebo, using formoterol 12 µg b.i.d. as active control. Study CQAB149B2205 was a 7-day dose-ranging study carried out in COPD patients who were randomized to receive indacaterol at 50, 100, 200 or 400 µg *via* MDDPI, indacaterol 400 µg via SDDPI, or placebo.

Three studies were undertaken as part of the efficacy program for Phase III clinical development. Study CAQB149B2307 investigated the onset of bronchodilator action, Study CQAB149B2305 compared the bronchodilator effect of indacaterol when administered in the morning or in the evening, and Study CQAB149B2340 evaluated the bronchodilator response profile of inhaled indacaterol over the whole dosing interval. For the precise characterization of the effects of indacaterol on the QT-interval a large thorough QT-study (Study CQAB149B2339) was conducted in 404 healthy subjects.

According to the sponsor, indacaterol represents a typical inhaled drug product with low systemic

concentrations reached early after inhalation and a lack of clinically relevant drug-interaction potential. The sponsor stated that in general, dose-proportionality of key pharmacokinetic parameters is given at least over a range of doubling doses. Biliary clearance appears to be the major contributor to elimination of drug related material. The impact of age, gender and race on the pharmacokinetics of indacaterol in COPD patients does not warrant dose-adjustments. Mild or moderate hepatic impairment does not alter the pharmacokinetics of indacaterol.

This reviewer's Comments
No information was included on the following:

- Effect of renal impairment of the PK of indacaterol/major metabolites. According to the sponsor, renal clearance plays a very minor role in elimination of indacaterol. Therefore, a study in renally impaired subjects was not conducted. The relevance of the renal impairment information on the PK of the drug/major metabolites will be a review issue.
- The potential effect of indacaterol/major metabolites to induce major CYP P450 enzymes. The sponsor is inquired about this information.

The sponsor has submitted a reviewable package for this NDA and therefore, there are no filing issues. The table below summarizes the clinical pharmacology studies included in the present submission and that are considered relevant for the approval of this NDA.

Study	Design	Tabular listing/ PK summary	Analytical method	PK parameters	Statistical analysis
CQAB149A2307: Hepatic impairment study with 600 µg indacaterol in matched pairs of subjects with hepatic impairment and healthy controls	Open label, single dose, parallel groups (17 subjects with mild and moderate hepatic impairment) (17 healthy controls)	√	√	√	√
CQAB149B2339: Thorough QTc study with 150, 300 & 600 µg indacaterol	Randomized, multiple dose, placebo controlled, parallel	√	√	√	√
CQAB149B2103: am / pm and absolute bioavailability with 300 µg inhaled and 400 µg intravenous indacaterol	Open label, single dose, 2 period cross-over (20)	√	√	√	√
CQAB149A2106: Inhaled vs oral administration of 800 µg indacaterol	Randomized, open label, cross-over, single dose (4)	√	√	√	√
CQAB149A2223: Human ADME (II) with 800 µg indacaterol	Open label, single dose (4)	√	√	√	√
CQAB149A2311: Drug interaction of 300 µg indacaterol with ketoconazole	Open label, single dose, cross-over (18)	√	√	√	√
CQAB149B2216: Drug interaction of 300 µg indacaterol with verapamil	Open label, single dose, 2 period, single sequence (12)	√	√	√	√
CQAB149B2220: Drug	Open label, 2 period,	√	√	√	√

interaction of 300 µg indacaterol with erythromycin	single sequence (12)				
CQAB149A2215: Single dose study with 400, 800, 1200 & 2000 µg indacaterol in Japanese & Caucasians	Randomized, double blind, placebo controlled, multiple dose (40)	√	√	√	√
population-pk-indacaterol]: Pharmacokinetic modeling of indacaterol, with special reference to the potential influences of covariates	CQAB149A2228, CQAB149B2212, CQAB149B2334, CQAB149B2335S, CQAB149B2338	NONMEM model, R-code, output and datasets			
CQAB149B2202: Dose escalation safety & tolerability with 400, 1000, 2000 & 3000 µg indacaterol in patients with mild to moderate	Open label, non-randomized, single dose escalation (18)	√	√	√	√
CQAB149B2201: Four week safety, tolerability and PK of 400 and 800 µg indacaterol via SDDPI in patients with moderate COPD	Randomized, double blind, placebo controlled, parallel group, multiple dose study (163)	√	√	√	√
CQVA149A2101: Comparative PK of 300 µg indacaterol with the antimuscarinic bronchodilator NVA237	Randomized, open label, single dose, 4 way cross-over (28)	√	√	√	√
CQAB149B2212: Dose ranging (150, 300 and 600 µg) for indacaterol delivered via Concept1 in patients with moderate to severe COPD	Randomized, double blind, double-dummy, placebo and active treatment (formoterol) controlled, cross-over, single dose (51)	√	√	√	√
CQAB149A2211: Safety and tolerability of 400 µg, 1000 µg, 2000 µg and 3000 µg indacaterol in patients with persistent asthma	Open label, dose escalation, ascending single dose in persistent asthma (20)	√	√	√	√
CQAB149A2221: UGT1A1 genotype study with 200 µg indacaterol	Open label, multiple dose (24)	√	√	√	√
Study R00-594: In vitro binding of 3H-labeled QAB149 to red blood cells, serum and plasma proteins in the rat, dog and human	In vitro study	√	√	NA	NA
R0301281: Oxidative metabolism of [3H]QAB149 in human, rat, and mouse liver microsomes	In vitro study	√	√	NA	NA
R01-994: Metabolic profile in human liver microsomes and potential to inhibit cytochrome	In vitro study	√	√	NA	NA

P450-mediated reactions					
DMPK R0500761: *In vitro* assessment of [14C]QAB149 permeability and interactions with drug transporters across Caco-2 cell monolayers	In vitro study	√	√	NA	NA
DMPK(US) R00-397: Comparative metabolism of [3H]QAB149 in rat, dog and human liver slice culture and metabolism in human lung slice culture	In vitro study	√	√	NA	NA
DMPK R0500025: In vitro assessment of (i) covalent protein binding potential in rat and human liver microsomes and human hepatocytes and (ii) time-dependent cytochrome P450 inhibition.	In vitro study	√	√	NA	NA

1.1 Recommendation

The Division of Clinical Pharmacology 2 (DCP2) has reviewed NDA 22-383 (S001) submitted on December 16, 2008 for filing purposes. The NDA is filable from a clinical pharmacology perspective. The following comments should be conveyed to the sponsor:

- Submit information on the potential of indacaterol/major metabolites to induce the major CYP P450 enzymes.
- Submit SAS transport files, containing ID, TRT, DOSE, individual CONC, TIME, individual PK Parameters, and other relevant study information for the following PK studies:
  - CQAB149A2106, CQAB149A2311, CQAB149B2216, CQAB149B2220, CQAB149A2215, CQAB149B2202, CQAB149A2211, CQAB149A2221, CQAB149B2201,CQAB149A2307, CQAB149B2103, CQAB149A2212
- Submit SAS transport files, containing ID, TRT, DOSE, individual CONC, TIME, individual PD Parameters, and other relevant study information for the following PD studies:
  - CQAB149B2202, CQAB149B2201, CQAB149B2217

SIGNATURE OF REVIEWER: Sandra Suarez-Sharp, Ph.D. _____ **SIGNATURE OF TEAM LEADER (acting):** Sally Choe, Ph.D. _____	Date _____ Date _____
CC.: HFD # [ ]; TL: [ ]; DD: [ ]	**Project Manager:_____ Date _____**

Background

Chemistry/Drug Product

Arcapta [TM] [(b) (4)] (Proposed) (indacaterol maleate inhalation powder, QAB149). Indacaterol Inhalation Powder is a novel long-acting inhaled β2-adrenergic agonist intended for long-term, once daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The proposed starting dose is 150 µg once-daily administered by the orally inhaled route via inhalation powder hard capsules in a single dose dry powder inhaler. The maximum dose proposed is 300 µg once-daily.

Phase III clinical development of indacaterol was completed using hard gelatin capsules containing a dry powder formulation of indacaterol in lactose administered via a single-dose dry powder inhalation device (SDDPI) called Concept1. The dose strengths used in the Phase III clinical development of inhaled indacaterol via Concept1 device were manufactured as 75, 150 and 300 µg dosage strengths. [(b) (4)] The delivered dose (ex-mouth piece) from this inhaler is approximately [(b) (4)] of the nominal dose of the capsule.

Multiple dosage strengths of QAB149 inhalation powder hard capsules were developed for administration via a single dose dry powder inhaler (SDDPI). SDDPI devices for the clinical development of QAB149 included the marketed Aerolizer® device for an initial clinical Proof of Concept study, and its further redesign, i.e. the so-called RS01 device and the so-called Concept1 device.

[(b) (4)]

Clinical Pharmacology Findings
The following is a summary of clinical Pharmacology finding reported by the sponsor:

After oral inhalation from an SDDPI device such as Concept1, indacaterol was rapidly absorbed and achieved peak serum levels (Cmax) in the majority of subjects within the first 30 minutes after administration. Thereafter, indacaterol concentrations declined in a multi-phasic manner with an apparent terminal half-life that ranged from 45.5 to 126 h. From the multiple dose inhalation study (Study CQAB149B2339) the effective half-life for accumulation was determined to be in the range of 40 to 52 hours which was consistent with the observation that steady state was achieved between 12 and 14 days of o.d. dosing. As evidenced by the results of Study CQAB149B2339 the increase in steady state indacaterol AUC and Cmax was dose-proportional in the dose range of 150 µg to 600 µg and there was no change in the clearance of indacaterol on repeated once-daily dosing via Concept1. At steady state (Day 14) accumulation factors (Racc; i.e Day 14/Day 1 ratios) in that study for AUC and Cmax were in the range of 2.9 to 3.5 and 1.7 to 1.9 respectively. Absolute bioavailability of an inhaled dose was on average 43.2% (n=4). There was no clinically meaningful difference in systemic exposure when comparing dosing via Concept1 in the morning versus evening. After intravenous administration, serum clearance was moderate (23.3 L/h), and a large volume of distribution was observed (Vz=2557 L) (Study CQAB149B2103). Relative bioavailability of an oral dose compared to an inhaled dose was 46% (Study CQAB149A2106). The bioavailability data together suggest that systemic exposure to indacaterol after inhalation is a composite of pulmonary and intestinal absorption.

Since indacaterol is an inhaled drug, a formal food effect study was not conducted. In the pivotal studies of the clinical development program indacaterol was administered as a morning dose regardless of the timing of food intake. Indacaterol is highly bound to plasma and serum proteins. The *in vitro* human serum and plasma protein binding was high, ranging from 94.1 to 95.3 and 95.1 to 96.2% respectively. *In vitro* protein binding results were consistent with *ex-vivo* protein binding measurements. Mild-to-moderate hepatic impairment did not alter the protein binding of indacaterol [Study CQAB149B2339]. Indacaterol had an *in vitro* blood-to-plasma concentration ratio of 1.2 (Study R00-594).

.

Renal clearance of serum indacaterol was on average between 0.5 and 1.2 L/h in healthy subjects and COPD patients. After inhaled administration of indacaterol, generally less than 2% of the inhaled dose was excreted into urine. In a human ADME study (Study CQAB149A2223) the majority of the orally administered radioactive dose was excreted into feces and only a minor fraction was found in the urine. Indacaterol does not undergo stereoconversion *in-vivo*. Analysis of urine samples from (Study CQAB149A2211) provided evidence that stereochemical conversion of indacterol (the pure R-enantiomer) to the S-enantiomer *in vivo* does not happen to any significant extent.

The primary metabolic pathways of indacaterol in human involved monohydroxylation, and N-glucuronidation, and both C- and N-dealkylation. After oral administration of indacaterol in the human ADME study [Study CQAB149A2223] unchanged indacaterol was the main circulating component in human serum, accounting for 32.5% of the total drug related AUC0-24h. The contribution of individual metabolites to the total drug-related AUC0-24h in human serum ranged from 4.2% to 12% with the hydroxylated metabolite P26.9 being the most prominent. All of the metabolites identified in humans were found in one or more of the animal species tested. Conversely, there were no metabolites observed in the animal species investigated that were not detected in human.
The key enzymes responsible for metabolic clearance of indacaterol are UGT1A1 and CYP3A4. *In vitro* investigations indicated that UGT1A1 was the only UGT isoform that metabolized indacaterol to the phenolic-O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6 and CYP3A4. CYP3A4 was predicted to be by far the most predominant isoenzyme responsible for hydroxylation of indacaterol. The hydroxylated metabolites P26.9 and P30.3 were found to have similar *in vitro* affinity to human beta-2-receptors than indacaterol itself. However the hydroxylated metabolites could not compete with indacaterol's duration of action in functional assays. The hydroxylated metabolites were found to represent no more than 11% of the steady state AUC0-24h and 6% of Cmax of parent indacaterol after inhalation via Concept1 (Study CQAB149B2339). Given the inferior activity profile and low *in vivo* abundancy, the hydroxylated metabolites are not expected to contribute significantly to pharmacological activity of indacaterol.

Indacaterol showed no significant inhibition of the P450 enzymes: CYP2C9, CYP2E1 and CYP3A4/5, when tested at concentrations of up to 100 μM. Relatively weak inhibition of the P450 enzymes: CYP1A2 ($IC_{50} \approx 10$ μM), CYP2C8 ($IC_{50} \approx 25$ μM), CYP2C19 ($IC_{50} \approx$ 25-50 μM), and CYP2D6 ($IC_{50} \approx$ 5-10 μM), was observed. The sponsor stated that based on the low nanomolar maximum indacaterol serum concentrations observed at a therapeutically relevant dose of 300 μg, it is unlikely that indacaterol could act as an inhibitor of any of the cytochrome P450 enzyme activities in the clinic.

Indacaterol is a low affinity substrate for the efflux pump P-gp. *In-vitro* investigations in Caco-2 monolayer systems characterized indacaterol as a medium to high permeability drug substance that is also a low affinity substrate for P-gp mediated efflux. Inhibition of the key contributors of indacaterol clearance, i.e. UGT1A1, CYP3A4 and P-gp have no impact on the clinical safety of therapeutic doses of indacaterol.

The pharmacokinetics of indacaterol was studied in populations with different UGT1A1 genotypes – the fully functional [(TA)6,(TA)6] genotype and the low activity [(TA)7, (TA)7] genotype (i.e. Gilbert Syndrome genotype) (Study CQAB149A2221). The study demonstrated that steady state AUC0-24h as well as Cmax were 1.2-fold higher in the low activity UGT1A1 genotype group, indicating that systemic exposure to indacaterol is not significantly affected by UGT1A1-genotype.

Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e. ketoconazole (Study CQAB149A2311), erythromycin (Study CQAB149B2220) and verapamil (Study CQAB149B2216). Verapamil was used as the prototypic inhibitor of P-gp and resulted in 1.4- to two-fold increase in AUC and 1.5-fold increase in Cmax. Coadminstration of erythromycin resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2 fold for Cmax. Combined inhibition of P-gp and CYP3A4 by the very strong dual inhibitor ketoconazole caused a 2-fold and 1.4-fold increase in AUC and Cmax respectively. Taken together the data suggest that systemic clearance is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold AUC increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition. Given the safety data of [Study CQAB149B2339] and of the pivotal studies (which both confirmed safe use of a 600 μg dosage regimen) the magnitude of exposure increases due to drug-interactions do not raise any safety concerns for therapeutic doses of 150 μg or 300 μg.

Indacaterol pharmacokinetics shows no difference between Japanese and Caucasian subjects and is not different amongst COPD patients of different ethnicities. Comparison of the pharmacokinetics between Japanese and Caucasian healthy subjects after single inhaled doses via a SDDPI device was conducted in (Study CQAB149A2215). No notable differences between Japanese and Caucasian populations were observed across the studies.

Further exploration of ethnic factors as covariates of systemic exposure in COPD patients and patients with asthma was done using a population PK modeling approach. Within the limits of the sensitivity of that analysis no ethnic factor was identified in the COPD analysis population that would impact systemic exposure to indacaterol after inhalation via Concept1 [population-pk-indacaterol]. Covariate analysis on age, gender, body weight, body mass index did not indicate a need for change in dosage regimen. The population PK analysis indicated that within the COPD analysis population the systemic exposure increased with increasing age (41% increase in peak exposure and 23% increase in steady state AUC0-24h within the age range of 48 to 78 years). When body weight increased from 50 to 107 kg in the COPD analysis population, peak concentrations decreased by 25% and AUC0-24h decreased by 21%. Female COPD patients had on average 7%-11% higher systemic exposure than males [population-pk-indacaterol].

Mild and moderate hepatic impairment does not alter indacaterol pharmacokinetics or protein binding. Study CQAB149A2307 studied the impact of mild and moderate (Child Pugh 5-6 and 7-9, respectively) hepatic impairment on the pharmacokinetics of single inhaled doses of 600 μg indacaterol delivered via Concept1. The study could not detect any relevant changes in pharmacokinetics or ex-vivo protein binding of indacaterol in either of the two groups when compared to healthy, demographically-matched control subjects. The effect of severe hepatic impairment on indacaterol pharmacokinetics was not studied.

Because renal clearance plays a very minor role in elimination of indacaterol a study in renally impaired subjects was not conducted.

Study CQAB149B2339, a thorough QTc study in 404 healthy subjects. The primary objective of the thorough QT study was to characterize the maximum mean QTcF prolongation following multiple doses of indacaterol for 14 days. With indacaterol treatment at multiple daily doses of 150, 300 and 600 µg maximum mean prolongations of QTcF intervals were below <5 ms (the regulatory threshold of concern) and the upper limit of the 90% confidence intervals was below 10 ms for all comparisons vs. placebo. This shows that there is no concern for a proarrhythmic potential in the investigated dose range. Study CQAB149B2202 investigated single doses of indacaterol up to 3000 µg in patients with COPD. The maximal increase from baseline in QTcF in this study was 9.10 ms at 8 hours after the inhalation of 2000 µg indacaterol.

Study CQAB149B2201 investigated repeat doses of indacaterol up to 800 µg in patients with COPD. In this study there was an increase in QTcB versus placebo (60-minutes postdose) on Day 1 of 8.7 ms and 8.5 ms for the 400 µg and 800 µg doses respectively. The corresponding changes on Day 28 of treatment were 12.6 ms and 18.5 ms. The indacaterol QT-effects in asthma patients were largely consistent with those in COPD patients.

Overall the effects on heart rate appeared to be marginal and inconsistent with doses up to 800 µg indacaterol, so that it is unlikely that doses up to 800µg will produce relevant effects on heart rate.

There is an indication of potential heart rate effects at very high overdoses such as 3000 µg indacaterol. In Study CQAB149B2202 with single doses of indacaterol, there was a dose-dependent increase in heart rate up to 3000 µg indacaterol which produced a maximum heart rate change versus placebo of 12.4 bpm. In Study CQAB149B2201 repeat doses of 400 and 800 µg indacaterol for 28 days produced a maximum heart rate change versus placebo of 2.9 bpm 1 hour post-dose with the 800 µg dose. Changes in blood glucose and serum potassium associated with indacaterol administration in COPD were small, variable and not dose-related in all doses close to the clinical dose level.

Analytical Methods

According to the sponsor, currently QAB149 (indacaterol free base) is analyzed in serum and urine using a specific HPLC-MS/MS method with a lower limit of quantification (LLOQ) of 10 pg/mL using 200 µL serum (100 µL with online SPE) and of 50 pg/mL using 100 µL urine, respectively. In early phases of development indacaterol was analyzed with bioanalytical methods that were less sensitive (e.g. 250 pg/mL, 70 pg/mL and 50 pg/mL in serum). Methods for the analysis of indacaterol glucuronide in serum and urine were based on the determinations of "total indacaterol (i.e. the sum of parent and conjugated indacaterol) after sample treatment with glucuronidase followed by subtraction of the concentration of indacaterol measured in untreated samples. For the determination of potential enantiomeric conversion of indacaterol, in-vivo using urine

samples from [Study CQAB149A2211], an enantio-selective bioanalytical method for the determination of the S-enantiomer was developed that allowed chromatographic separation of the S- and R-enantiomers. A specific bioanalytical method for analysis of oxidative metabolites (P26.9 and P30.3) in serum samples of [Study CQAB149B2339] was developed as well. According to the sponsor, all pivotal trials and the majority of PK studies used the most sensitive method with an LLOQ of 10 pg/mL. The table below shows a summary of analytical methods used in the analysis of indacaterol and its metabolites in this NDA submission.

Table 2-3 Summary of analytical methods

Analyte	Matrix	Method	Method-ID	LLOQ	Reference Validation report
Indacaterol	Serum	HPLC-MS/MS	A	10 pg/mL	[R0300366D] [R0300366D-01] [R0300366D-02] [R0300366D-03] [R0300366D-04] [R0400092B] [R0701007-01]
Indacaterol	Serum	HPLC-MS/MS (online SPE)	B	10 pg/mL	[R0701007]
Indacaterol	Plasma	HPLC-MS/MS	C	10 pg/mL	[R0300366G]
Indacaterol	Serum	HPLC-MS/MS	D	50 pg/mL	[R0300366A] [R0300366A-01] [R0300366A-02]
Indacaterol	Serum	HPLC-MS/MS	E	70 pg/mL	[R99-2520] [R0200492]
Indacaterol	Serum	HPLC-MS/MS	F	250 pg/mL	[R99-2520]
Hydroxy-indacaterol	Serum	HPLC-MS/MS	G	46 pg/mL	[R0700802]
Indacaterol	Urine	HPLC-MS/MS	H	100 pg/mL	[R0300366C] [R0300366C-01] [R0300366C-02] [R0300366C-03]
Indacaterol	Urine	HPLC-MS/MS	I	100 pg/mL	[R0400150]
S-enantiomer to indacaterol	Urine	HPLC-MS/MS	J	200 pg/mL	[R0300366F]
Total indacaterol [1)]	Urine	HPLC-MS/MS	K	250 pg/mL	[R99-2520]
Total indacaterol [1)]	Urine	HPLC-MS/MS	L	700 pg/mL	[R00-2189] [R0300366C-01] [R0400083] [R0400150]

A summary (reported by the sponsor) of the relevant methods is as follows:
Method A for indacaterol in serum with LLOQ of 10 pg/mL: The linearity of the analytical method for analysis of indacaterol in serum was validated (linear regression) in the range 10 pg/mL to 2000 pg/mL. The method is specific in human serum (maximum interference 5.1 % of signal at LLOQ). The inter-day accuracy and precision of the method was evaluated as the mean bias and precision of quality control samples analyzed during 3 validations days: bias at LLOQ was 4.2 %, and precision was 10.9 %. Above

LLOQ, the biases were within the range -0.8 % to 1.8 % and the precisions were within the range 2.2 % to 9.9 %.

Method G for hydroxy-indacaterol in serum with LLOQ of 46 pg/mL: The linearity of the analytical method for analysis of hydroxy-indacaterol in serum was validated (linear regression) in the range 46 pg/mL to 460 pg/mL. The method quantified the sum of four enantiomers potentially resulting from hydroxylation at the ethyl-indan moiety of indacaterol. Out of the four enantiomers a pair of two diastereomers were observed in feces samples from the human ADME (i.e. P26.9 and P30.3 at a ratio of 1/3; see CTD section 4.2.2).The method is specific in human serum (maximum interference 5.0 % of signal at LLOQ). The inter-day accuracy and precision of the method was evaluated as the mean bias and precision of quality control samples analyzed during 3 validations days: bias at LLOQ was 13.9 %, and precision was 7.1 %. Above LLOQ, the biases were within the range 4.1 % to 6.5 % and the precisions were within the range 6.8 % to 10.2 %.

Method H for indacaterol in urine with LLOQ of 100 pg/mL: The linearity of the analytical method in urine without glucuronidase/sulfatase sample treatment was validated (quadratic regression) in the range 0.1 ng/mL to 100 ng/mL. The method is specific in human urine (maximum interference 6.7 % of signal at LLOQ). The inter-day accuracy and precision of the method was evaluated as the mean bias and precision of quality control samples analyzed during one validation day: bias at LLOQ was -1.3 %, and precision was 10.3 %. Above LLOQ, the biases were within the range -12.5 % to 3.0 % and the precisions were within the range 1.3 % to 3.8 %.

Method J for S-enantiomer to indacaterol in urine with LLOQ of 200 pg/mL: The linearity of the analytical method in urine was validated (quadratic regression) in the range 0.2 ng/mL to 20 ng/mL. The method is specific in human urine (maximum interference 0.4 % of signal at LLOQ). The inter-day accuracy and precision of the method was evaluated as the mean bias and precision of quality control samples analyzed during 2 validation days: bias at LLOQ was -2.5 %, and precision was 8.2 %. Above LLOQ, the biases were within the range - 4.0 % to 5.5 % and the precisions were within the range 2.2 % to 4.4 %.

Table 1 shows the clinical studies (in healthy subjects and COPD patients) that contained PK information. Table 2 shows a list of studies that will be reviewed as part of this submission.

Table 1. Clinical studies that contained PK information

Study overview of clinical pharmacology studies in healthy subjects				
Study Code	**Short Title**	**Design Number of subjects (n = completed)**	**Device**	**PK sampling[1)]**
[CQAB149A2307]	Hepatic impairment study with 600 µg indacaterol in matched pairs of subjects with hepatic impairment and healthy controls	Open label, single dose, parallel groups (17 subjects with mild and moderate hepatic impairment) (17 healthy controls)	Concept1 SDDPI	dense
[CQAB149A2311]	Drug interaction of 300 µg indacaterol with ketoconazole	Open label, single dose, cross-over (18)	Concept1 SDDPI	dense
[CQAB149B2103]	am / pm and absolute bioavailability with 300 µg inhaled and 400 µg intravenous indacaterol	Open label, single dose, 2 period cross-over (20)	Concept1 SDDPI & intravenous infusion	dense
[CQAB149B2216]	Drug interaction of 300 µg indacaterol with verapamil	Open label, single dose, 2 period, single sequence (12)	Concept1 SDDPI	dense
[CQAB149B2220]	Drug interaction of 300 µg indacaterol with erythromycin	Open label, 2 period, single sequence (12)	Concept1 SDDPI	dense
[CQAB149B2339]	Thorough QTc study with 150, 300 & 600 µg indacaterol	Randomized, multiple dose, placebo controlled, parallel	Concept1 SDDPI	dense
[CQAB149A2106]	Inhaled vs oral administration of 800 µg indacaterol	Randomized, open label, cross-over, single dose (4)	Aerolizer™ SDDPI & oral dose	dense
[CQAB149A2221]	UGT1A1 genotype study with 200 µg indacaterol	Open label, multiple dose (24)	Aerolizer™ SDDPI	dense
[CQAB149A2215]	Single dose study with 400, 800, 1200 & 2000 µg indacaterol in Japanese & Caucasians	Randomized, double blind, placebo controlled, multiple dose (40)	RS01 SDDPI	dense
[CQAB149A2214]	Human ADME (I) with 800 µg indacaterol	Open label, single dose (3)	Oral dose	dense
[CQAB149A2223]	Human ADME (II) with 800 µg indacaterol	Open label, single dose (4)	Oral dose	dense
[CQVA149A2101]	Comparative PK of 300 µg indacaterol with the antimuscarinic bronchodilator NVA237	Randomized, open label, single dose, 4 way cross-over (28)	Concept1 SDDPI	dense
[CQMF149A2206]	Comparative PK with QMF149 (200 µg mometasone & 250 µg indacaterol)	Randomized, open label, single dose, 5 way, cross-over (32)	Concept1 SDDPI & Twisthaler™ MDDPI	dense
Study overview of clinical pharmacology studies in COPD Patients				
Study Code	Short Title	Design Number of subjects (n)	Device	PK sampling[1)]

[CQAB149B2212]	Dose ranging (150, 300 and 600 µg) for indacaterol delivered via Concept1 in patients with moderate to severe COPD	Randomized, double blind, double-dummy, placebo and active treatment (formoterol) controlled, cross-over, single dose (51)	Concept1 SDDPI	semi
[CQAB149B1202]	Efficacy & safety of 150, 300 & 600 µg indacaterol in Japanese COPD patients under exercise & and salbutamol co-administration	Randomized, double blind, placebo controlled, 4 period cross-over, single dose, dose-ranging study (45) (salmeterol) controlled, cross-over, single dose (21)	Concept1 SDDPI	semi
[CQAB149B2305]	Efficacy and safety of indacaterol 300 µg o.d. dosed in the morning or evening in patients with moderate to severe COPD	Phase III randomized, double-blind, double dummy, placebo controlled, multicenter, 4 treatments, 3 period incomplete block crossover study (83)	Concept1 SDDPI	compliance
[CQAB149B2201]	Four week safety, tolerability and PK of 400 and 800 µg indacaterol via SDDPI in patients with moderate COPD	Randomized, double blind, placebo controlled, parallel group, multiple dose study (163)	RS01 SDDPI	sparse
[CQAB149B2202]	Dose escalation safety & tolerability with 400, 1000, 2000 & 3000 µg indacaterol in patients with mild to moderate COPD	Open label, non-randomized, single dose escalation (18)	RS01 SDDPI	dense
[CQAB149B2205]	Dose ranging & device comparison with 50, 100, 200 & 400 µg indacaterol in patients with moderate to severe COPD	Randomized, double blind, placebo controlled, parallel group, multiple dose (623)	Certihaler™ MDDPI & RS01 SDDPI	semi
[CQAB149A2105]	Safety & tolerability of multiple 800 µg indacaterol doses	Randomized, double blind, placebo controlled, parallel group, multiple dose (10)	HFA pMDI	dense

1) > 6 samples per 24-hour period = dense; 4 - 6 samples per 24-hour period = semi; < 4 samples per 24-hour period = sparse; 1 single sample = compliance

Table 2. Clinical pharmacology and in vitro studies relevant to NDA submission.

Study	Design	Tabular listing/ PK summary	Analytical method	PK parameters	Statistical analysis
CQAB149A2307: Hepatic impairment study with 600 µg indacaterol in matched pairs of subjects with hepatic impairment and healthy controls	Open label, single dose, parallel groups (17 subjects with mild and moderate hepatic impairment) (17 healthy controls)	√	√	√	√
CQAB149B2339: Thorough QTc study with 150, 300 & 600 µg	Randomized, multiple dose, placebo controlled, parallel	√	√	√	√

indacaterol					
CQAB149B2103: am / pm and absolute bioavailability with 300 µg inhaled and 400 µg intravenous indacaterol	Open label, single dose, 2 period cross-over (20)	√	√	√	√
CQAB149A2106: Inhaled vs oral administration of 800 µg indacaterol	Randomized, open label, cross-over, single dose (4)	√	√	√	√
CQAB149A2223: Human ADME (II) with 800 µg indacaterol	Open label, single dose (4)	√	√	√	√
CQAB149A2311: Drug interaction of 300 µg indacaterol with ketoconazole	Open label, single dose, cross-over (18)	√	√	√	√
CQAB149B2216: Drug interaction of 300 µg indacaterol with verapamil	Open label, single dose, 2 period, single sequence (12)	√	√	√	√
CQAB149B2220: Drug interaction of 300 µg indacaterol with erythromycin	Open label, 2 period, single sequence (12)	√	√	√	√
CQAB149A2215: Single dose study with 400, 800, 1200 & 2000 µg indacaterol in Japanese & Caucasians	Randomized, double blind, placebo controlled, multiple dose (40)	√	√	√	√
population-pk-indacaterol]: Pharmacokinetic modeling of indacaterol, with special reference to the potential influences of covariates	CQAB149A2228, CQAB149B2212, CQAB149B2334, CQAB149B2335S, CQAB149B2338	NONMEM model, R code, output and datasets			
CQAB149B2202: Dose escalation safety & tolerability with 400, 1000, 2000 & 3000 µg indacaterol in patients with mild to moderate	Open label, non-randomized, single dose escalation (18)	√	√	√	√
CQAB149B2201: Four week safety, tolerability and PK of 400 and 800 µg indacaterol via SDDPI in patients with moderate COPD	Randomized, double blind, placebo controlled, parallel group, multiple dose study (163)	√	√	√	√
CQVA149A2101: Comparative PK of 300 µg indacaterol with the antimuscarinic bronchodilator NVA237	Randomized, open label, single dose, 4 way cross-over (28)	√	√	√	√
CQAB149B2212: Dose ranging (150, 300 and 600 µg) for indacaterol delivered via Concept1 in patients with moderate to severe	Randomized, double blind, double-dummy, placebo and active treatment (formoterol) controlled, cross-over, single dose (51)	√	√	√	√

COPD					
CQAB149A2211: Safety and tolerability of 400 µg, 1000 µg, 2000 µg and 3000 µg indacaterol in patients with persistent asthma	Open label, dose escalation, ascending single dose in persistent asthma (20)	√	√	√	√
CQAB149A2221: UGT1A1 genotype study with 200 µg indacaterol	Open label, multiple dose (24)	√	√	√	√
In vitro binding of 3H-labeled QAB149 to red blood cells, serum and plasma proteins in the rat, dog and human	In vitro study	√	NA	NA	NA
R0301281: Oxidative metabolism of [3H]QAB149 in human, rat, and mouse liver microsomes	In vitro study	√	NA	NA	NA
R01-994: Metabolic profile in human liver microsomes and potential to inhibit cytochrome P450-mediated reactions	In vitro study	√	NA	NA	NA
DMPK R0500761: *In vitro* assessment of [14C]QAB149 permeability and interactions with drug transporters across Caco-2 cell monolayers	In vitro study	√	NA	NA	NA
DMPK(US) R00-397: Comparative metabolism of [3H]QAB149 in rat, dog and human liver slice culture and metabolism in human lung slice culturea	In vitro study	√	NA	NA	NA
DMPK R0500025: In vitro assessment of (i) covalent protein binding potential in rat and human liver microsomes and human hepatocytes and (ii) time-dependent cytochrome P450 inhibition.	In vitro study	√	√	NA	NA

This reviewer's Comments

The sponsor has submitted a reviewable package for this NDA and therefore, there are no filing issues.

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-383	**Brand Name**	Arcapta (b) (4)
OCP Division	II	**Generic Name**	Indacaterol maleate
Medical Division	DPAP	**Drug Class**	LABA
OCP Reviewer	Sandra Suarez-Sharp	**Indication(s)**	Maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
OCP Team Leader (acting)	Sally Choe	**Dosage Form**	Inhalation Powder
PM Reviewer	TBD	**Dosing Regimen**	150 mcg once daily. The maximum dose is 300 mcg once daily.
Date of Submission	December 18, 2008	**Route of Administration**	Oral Inhalation
Estimated Due Date of OCP Primary Review	August 25, 2009	**Sponsor**	Novartis
PDUFA Due Date	Oct 18, 2009	**Priority Classification**	s
Division Due Date	Oct 16, 2009		

Clin. Pharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any. Study number**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**x**	**2**		[CQAB149A2214] [CQAB149A2223]
Isozyme characterization:	**x**	**5**		R0301281, R01-994, R0500761, R00-397 R0500025
Blood/plasma ratio:	**x**	**1**		R00-594
Plasma protein binding:	**x**	**1**		R00-594
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**x**	**3**		[CQVA149A2101], [CQMF149A2206], [CQAB149B2201]
multiple dose:	x	**1**		[CQAB149A2105]
Patients-				
single dose:	**x**	**2**		[CQAB149B2212], [CQAB149B1202]
multiple dose:	**x**	**3**		[CQAB149B2305], [CQAB149B2202], [CQAB149B2205]
Dose proportionality -				

fasting / non-fasting single dose:	**x**	**1**		CQAB149B2339
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**x**	**3**		[CQAB149A2311], [CQAB149B2216], and [CQAB149B2220]
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	**x**	**1**		[CQAB149A2215]
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	**x**	**1**		[CQAB149A2307]
PD:				
Phase 2:	**x**	**2**		CQAB149B2212 CQAB149A2211
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Meta analysis:				
Data sparse:	**x**	**1**		Pop PK of indacaterol
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	**x**	**1**		[CQAB149B2103]
alternate formulation as reference:	**x**	**1**		[CQAB149A2106]
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	**x**	**1**		[CQAB149A2221]
QTC STUDIES (PHASE 1)	**x**	**1**		[CQAB149B2339]
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**x**	**31**		

Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. • Submit information on the potential of indacaterol/major metabolites to induce the major CYP P450 enzymes. See executive summary for other comments.		
QBR questions (key issues to be considered)		**1. What is the optimal dose base on dose-response studies?** **2. Is dose adjustment needed on special populations (gender, race, hepatic impairment, age, renal impairment)?** **3. Is dose adjustment, warning or contraindication warranted based on DDI information?** **4. Was the metabolic pathway adequately characterized for indacaterol?** **5. Is the systemic exposure to indacaterol affected by UGT1A1 genotypic variation?** **6. Do indacaterol inhibit/induct the major P450 CYP enzymes?** **7. Was the to-be marketed formulation used in key PK studies?**		
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sandra Suarez
2/20/2009 01:15:47 PM
BIOPHARMACEUTICS

Sally Choe
2/20/2009 01:17:03 PM
BIOPHARMACEUTICS