Predicted heart rate effect of inhaled PF-00610355, a long acting β -adrenoceptor agonist, in volunteers and patients with chronic obstructive pulmonary disease

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

Patients with chronic obstructive pulmonary disease (COPD) suffer from various cardiovascular complications, such as ischaemic heart disease, right ventricular hypertrophy and arrhythmias. Inhaled long-acting β_2 -adrenergic drugs (LABAs) exert their pharmacological effects in the lungs, but particles may be absorbed into the systemic circulation via sputum that is swallowed and enters the GI tract. Increase in heart rate as a result of systemic exposure to LABAs may result in additional or increased cardiovascular safety concerns in this patient population.

WHAT THIS STUDY ADDS

An integrated model of the cardiovascular effects of PF-00610355 was constructed on the basis of available phase I and phase II clinical trial data collected in the development programme of PF-00610355. Although substantial increases in heart rate were observed in healthy volunteers, significant pharmacokinetic and pharmacodynamic differences between healthy volunteers and COPD patients were identified. Subsequent model-based simulations indicate that the median expected placebo-corrected maximum increase in heart rate is 2.7 beats min⁻¹ (95% confidence interval 0.90, 4.82 beats min⁻¹) in COPD patients following a daily PF-00610355 dose of 280 μ g, which is considered not clinically relevant.

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AIM

To assess the cardiovascular effects of a new inhaled long-acting β -adrenoceptor agonist PF-00610355 in COPD patients.

METHODS

Thirteen thousand and sixty-two heart rate measurements collected in 10 clinical studies from 579 healthy volunteers, asthma and COPD patients were analyzed. The relationship between heart rate profiles and predicted plasma concentration profiles, patient status, demographics and concomitant medication was evaluated using non-linear mixed-effects models. The median heart rate increase in COPD patients for doses of PF-00610355 up to 280 μ g once daily was simulated with the final pharmacokinetic/pharmacodynamic (PKPD) model.

RESULTS

An $E_{\max}$ model accounting for delayed on-and off-set of the PF-00610355-induced change in heart rate was developed. The predicted potency in COPD patients was three-fold lower compared with healthy volunteers, while no difference in maximum drug effect was identified. Simulations suggested a maximum placebo-corrected increase of 2.7 (0.90–4.82) beats min⁻¹ in COPD patients for a PF-00610355 dose of 280 μ g once daily, with 19% subjects experiencing a heart rate increase of more than 20 beats min⁻¹ compared with 8% in the placebo group.

CONCLUSIONS

This PKPD analysis supports the clinical observation that no relevant effects of PF-00610355 on heart rate in COPD patients should be expected for doses up to 280 μ g once daily.

Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the airways characterized by a progressive decline in lung function that is accompanied by cough, excess sputum production and breathlessness. Airflow obstruction in COPD includes reversible components such as smooth muscle contraction and airway inflammation as well as irreversible components such as small airway fibrosis and narrowing [1]. Bronchodilators, such as β_2 -adrenoceptor agonists, represent an important pharmacological therapy for COPD and affect the reversible component of COPD by stimulating β_2 -adrenergic receptors. This results in relaxation of airway smooth muscle and improvement of symptoms. Short acting β_2 -adrenoceptor agonists (SABAs), such as salbutamol and terbutaline, were the first available agents in the class for the treatment of COPD. In the late 1990s, the relatively short duration of action of these agents (~4 h) lead to the development of long acting β_2 -adrenoceptor agonists (LABAs), such as salmeterol and formoterol. These agents have a 12 h duration of action [2, 3], are given in a twice daily regimen and have been found to be more effective and convenient than SABAs. Currently, indacaterol has been approved as a once daily LABA [4, 5] and may therefore further improve patient convenience and adherence over twice-daily LABAs. PF-00610355 is a new inhaled LABA that is also being developed for the once daily treatment of COPD [6]. Human liver microsome experiments indicate that PF-00610355 is mainly eliminated through phase II conjugation (mainly glucuronidation), but also via CYP3A4 and CYP2D6 metabolism. Caco-2 cells have indicated low to moderate cell permeability with high transporter mediated efflux [7]. PF-00610355 is highly bound to plasma proteins (>99.9% bound in human plasma), and no active metabolites have been identified. PF-00610355 is delivered through a multi-dose dry powder inhalation device (CRC-749) which is capable of delivering mono, double or triple therapy, with the potential of improving patient convenience and adherence over available therapies.

Although inhaled PF-00610355 exert its beneficial effects in the lungs, systemic exposure of PF-00610355 is expected to be responsible for certain drug-related side effects, in particular increase in heart rate. This is particularly relevant in COPD, as cardiac co-morbidities such as ischaemic heart disease, right ventricular hypertrophy and arrhythmias are relatively common in these patients [8–10]. Therefore such patients may be at an increased risk of cardiovascular complications resulting from β -adrenoceptor stimulation with these agents [11]. Although these cardiovascular effects may be reduced in combination with inhaled corticosteroids (ICS) [12], there is also evidence that LABAs and ICS may interact in a synergistic way [13]. As such, it was appropriate to assess the intrinsic cardiovascular safety of PF-00610355 in a systematic way.

An integrated analysis of the cardiovascular effects of PF-00610355 was performed on the basis of relevant phase I and phase II clinical trial data collected in the development programme of PF-00610355. The purpose of this analysis was to understand the relationship between heart rate and drug exposure (plasma concentrations over time), patient status and other patient variables, such as patient demographics, concomitant medication, etc. In this analysis, a previously developed pharmacokinetic model was used to describe the time course of PF-00610355 concentrations in plasma as a function dose/dosing regimen, fine particle dose, patient status and demographics [14].

The developed PKPD model for heart rate was subsequently used to simulate expected effects on heart rate for various dosing regimen of PF-00610355 in COPD patients. The goal of this work was to identify the cardiovascular effects, with respect to changes in heart rate, for a selected set of PF-00610355 dosing regimens that are being considered in subsequent trials. Furthermore, it allowed the evaluation of the impact of clinically relevant factors that may affect heart rate in COPD patients. In combination with a similar data analysis effort to identify the optimal efficacious treatment regimen for PF-00610355 in COPD patients [15], an optimal safe and efficacious treatment regimen for the drug may be proposed.

Methods

Data

Individual time profiles of heart rate based on means of (mostly) triplicate ECG measurements in 10 clinical trials of PF-00610355 (seven phase I, two phase IIa and one phase IIb) were used in this analysis. All ECG measurements were 12-lead ECGs, measured after the subject had been rested quietly for at least 10 min in the supine position. Triplicate ECGs were generally recorded 2–4 min apart with no PK samples taken during the resting period or in between replicate measurements. In these studies, both the improved CRC-749 as well as the standard MIAT (Miat monodose inhaler, model 5) inhalation devices were used. Study design information, including doses, inhalation devices and treatment regimen, is presented in Table 1. The phase I clinical trials included single dose crossover and/or multiple dose data in healthy subjects while the phase IIa studies comprised of single dose crossover studies in patients with asthma or moderate COPD. The phase IIb study in moderate COPD patients comprised of a 6 week multiple dose study of three active doses of PF-00610355 vs. placebo and active control (inhaled salmeterol, twice daily: Diskus® in US, Accuhaler™ elsewhere). Included COPD patients were all moderate in severity and either current or former smokers with a history of smoking (10 pack years at minimum). Exclusion criteria included: (i) respiratory failure, cor pulmonale or right ventricular failure, respiratory disorders (e.g. bronchiectasis, pulmonary fibro-

Table 1

Study design, dose regimens and inhalation devices used in the studies used in the analysis

Study (phase)	Design	PF-00610355 dose (μg)	Device	Regimen
A7881001 (I)	Double-blind, placebo controlled, dose escalation	0, 15, 45, 90, 150, 450, 900, 1500, 2 200, 3000	MIAT	Single × 5
A7881002 (I)	Randomized, double-blind, placebo controlled, multiple dose	0, 150, 450, 900, 1 200, 1800	MIAT	Once daily
A7881003 (I)	Open, randomized, placebo controlled, two-way crossover, ketoconazole interaction	368	CRC-749	Single × 2
A7881007 (I)	Randomized, double-blind, placebo/active controlled	0, 15, 60, 150, 300, 450	MIAT	Single × 5
A7881014 (I, TQT)	Double blind, randomized incomplete block, multiple dose, placebo/active controlled, four-way cross-over, thorough QT (TQT)	0, 450, 1 200	CRC-749	Once daily, 4 days × 4
A7881004 (IIa)	Randomized, double-blind, placebo/active controlled, five-way crossover, asthma patients	0, 108, 368, 736, 1472	CRC-749	Single × 5
A7881010 (IIa)	Double-blind, four-way crossover, placebo controlled, moderate COPD patients	0, 368, 736, 1472	CRC-749	Single × 4
A7881013 (IIb)	Parallel, double blind, placebo/active controlled, moderate COPD patients	0, 100, 300, 600	CRC-749	Once daily, 6 weeks
B0751001 (I)	Open, randomized, five-way crossover	0, 1350	CRC-749	Single
A9001181 (I)	Randomized, double-blind, four-way crossover, salmeterol effect	0	Other	Single

sis, pneumoconiosis), (ii) within the previous year: myocardial infarction, cardiac arrhythmia, left ventricular failure, unstable angina, coronary angioplasty, coronary artery bypass grafting (CABG) or cerebrovascular accident and (iii) resting heart rate outside the 50–100 beats min⁻¹ range or ECG abnormalities. Patients with certain chronic conditions such as hypertension, thyroid disease, type 1 or type 2 diabetes, hypercholesterolaemia, gastroesophageal reflux or depression were included in the study as long as the conditions were well controlled and medications relating to the condition were stable and would not be predicted to compromise safety or interfere with the tests and interpretations of the studies. These studies were approved by an Ethics Committee or Institutional Review Board and were conducted in accordance with the current revision of the Declaration of Helsinki [16]. Informed consent, in compliance with ICH GCP, was obtained from every participant at or ahead of the initial screening visit.

Software

Heart rate data were analyzed using the NONMEM software (v7.1.2) for non-linear mixed effects models, running under PsN (Perl-speaks-NONMEM) 3.2.12 [17] on a grid of CentOS 5.6 linux servers. Data management, exploratory analysis and graphical representations (model diagnostics, simulations results) were performed using the data analysis software R 2.12 [18].

Data analysis

Strategy A subject and treatment period specific random effects model was used to characterize over time the relationship between observed heart rate and PF-00610355 concentrations in plasma. First, a placebo model component for heart rate, including a circadian pattern as a function of clock time, was constructed on the basis of placebo

data only. Next, the drug exposure model component was included in the model by relating the subject and treatment specific time course of heart rate to the respective time course of PF-00610355 plasma concentrations in a sequential pharmacokinetic–pharmacodynamic (PKPD) model. These concentration–time profiles were calculated from subject/treatment specific PK parameters that were obtained from a previously developed mixed-effects PK model of PF-00610355 plasma exposure data that were available from the clinical trial database [14]. This exposure–response model served as the base model for the final step in the model development process, which focused on the identification of additional significant and clinically relevant variables (covariates) that determine the pharmacodynamic (PD) effects of PF-00610355 with respect to heart rate. The forward model was built by adding all statistically significant univariate covariates to the base model. Covariates in the forward model were then qualified by multivariate backward elimination. Continuous covariates were included using power functions, while binary covariates entered as factors:

$$\text{Parm} = \text{Parm}_{\text{Pop}} \cdot (\text{Cov}_{\text{Cont}} / \text{median}(\text{Cov}_{\text{Cont}}))^{\theta_1} \cdot (1 + \text{Cov}_{\text{Cat}} \cdot \theta_2) \quad (1)$$

Parm is the typical parameter defined as a function of the population typical value, Parm_{Pop}, and the contribution from the continuous covariate, Cov_{Cont}, and the binary covariate (with values 0 and 1), Cov_{Cat}. θ₁ and θ₂ are the respective covariate coefficients.

Model building criteria

Goodness of fit of different models and hypothesis testing were evaluated with the use of the change in NONMEM

objective function (OFV), consideration of the level of uncertainty in the parameter estimates and visual inspection of the goodness of fit. Individual and population predicted heart rate values were directly compared with observed data. Conditional weighted residuals were plotted vs. time and population predicted heart rate to check for possible bias. Distributions of random effects were tested for normality, and finally, a visual predictive check (VPC) was performed on the basis of 1000 model-based simulations to test the model's ability to describe the observed mean heart rate and inter-individual variability. In order to remove the influence in this VPC from independent variables other than dose in this graphical representation, observed and simulated heart rate data were corrected for the model population prediction [19].

For the likelihood ratio test used in covariate selection, nominal significance levels were set to $P = 0.01$ for addition of univariate covariates to the base model and $P = 0.001$ for backward elimination of non-significant multivariate covariates from the forward model. The corresponding change in OFV is 6.63 and 10.83, respectively, for 1 d.f. Besides a statistically significant outcome in the likelihood ratio test, none of the 95% confidence intervals of included covariates was allowed to include 0 in the final model. A bootstrap based on 500 resampled replicates of the original dataset was used to assess the robustness of the final model, and to derive the 95% confidence interval of model parameters.

Model-based simulations

The final PKPD model developed for heart rate was used to evaluate the expected steady-state effects of PF-00610355 on heart rate following multiple dosing at clinically relevant doses. For this purpose, 250 replicates of a virtual 43 day, parallel arm study were simulated. Dose levels were placebo and 56, 112.4, 140, 200 and 280 µg PF-00610355 administered once daily using the CRC-749 inhaler. Each dose was received by 250 healthy volunteers and 250 COPD patients. The heart rate was observed at 11 time points on day 43 (0, 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h post-dose). The fixed effect point estimates and the associated covariance matrix of the parameters of the final model were used to account for their uncertainty in the simulations. Inter- and intra-individual variances were defined by their point estimates. Subject level covariate values were simulated on the basis of distributions observed in the analysis data set, stratified by patient status (COPD vs. healthy volunteers). For the analysis of simulated heart rate, each simulated individual subjects' maximum absolute and change from baseline heart rate was derived on days 1 and 43. Subsequently, the median and 95% prediction interval was derived for each treatment arm. Finally, the median and 95% prediction interval of the medians across all replicates was derived in order to quantify the impact of parameter uncertainty.

Results

The analysis dataset consisted of 13 062 heart rate measurements (mean value of mostly triplicate ECG recordings), collected from 579 subjects in 10 studies. In order to implicitly account for inter-occasional variability, different periods in crossover studies were assigned different NONMEM subject identifiers resulting in 1006 unique NONMEM subject IDs. Characteristics of the patient population are summarized in Table 2. Data on prior and concomitant medication were available from study A7881013 only (phase 2b in COPD). In this study, the prevalence of previous use of LABAs, anticholinergics (LAAC) and corticosteroids was 6.2%, 3.1%, and 39.3%, respectively. A plot of observed heart rate change from baseline (HR_{CFB}) as a function of dose and predicted plasma concentration for different subject populations and inhalation devices is presented in Figure 1. The plots show that in the dose range up to 1200 µg, the effects of heart rate in both asthma and COPD patients (both using the CRC-749 inhalation device) is much less pronounced than in healthy volunteers, regardless of the inhalation device used. A separate analysis indicated that a distinct pharmacokinetic difference exists between healthy volunteers, asthma patients and COPD patients [14]. In the present analysis, this was specifically accounted for by relating subject specific heart rate-time profiles to the individually predicted profiles for PF-00610355 concentrations.

Model development

Placebo model On the basis of the placebo data, various model structures were explored to capture the circadian pattern in the heart rate data. A negative Gaussian function was preferred over a cosine function on the basis of likelihood considerations:

$$Y_{ij} = \text{INTC} - \text{CAMP} \cdot \exp\left(-(\text{CTIM}_{ij} - \text{CPHS})^2 / \text{CSTP}\right) + \eta_i + \varepsilon_{ij}, \quad \eta_i \sim N(0, \omega^2), \quad \varepsilon_{ij} \sim N(0, \sigma^2) \quad (2)$$

Y_{ij} and CTIM_{ij} are the observed heart rate and clock time for placebo subject i at the j^{th} time point, respectively. $\text{INTC} + \eta_i$ is the individual intercept. CAMP , CPHS , and CSTP are the amplitude, the phase, and a slope parameter of the Gauss function describing the circadian variation. ε_{ij} is an independently, normally distributed residual error. This model was able to describe adequately the circadian fluctuations in heart rate in the time frame between 7.00 and 21.00 h, in which ~95% of the heart rate data were collected in the studies. Note that unlike the PKPD model described below, the placebo model did not depend on the observed HR baseline.

PKPD model Starting from the placebo model described in the previous section, plasma concentrations were introduced into the model to account for the drug effect of

Table 2
Population characteristics. Mean (SD) of continuous and fraction of categorical covariates

Study (phase)	Population	n	Age (years)	Body weight (kg)	% male	Race	Smoker (No/Yes/Ex)	Baseline HR (beats min ⁻¹)
A7881001 (I)	HV	21	25.5 (5.17)	71.2 (11.3)	100	White: 4.76% Asian: 95.2%	No: 90.5% Ex: 9.52%	56.8 (5.7)
A7881002 (I)	HV	60	34.1 (8.95)	75.3 (10.8)	71.7	White: 88.3% Black: 11.7%	No: 91.7% Ex: 8.33%	61.5 (9.34)
A7881003 (I)	HV	14	32.3 (7.82)	69.1 (8.63)	100	Asian: 100%	No or Ex: 100%	62.2 (14.1)
A7881007 (I)	HV	18	27.7 (5.93)	76.8 (9)	100	White: 88.9% Black: 5.56% Other: 5.56%	No: 94.4% Ex: 5.56%	57.2 (8.17)
A7881014 (I, TQT)	HV	48	38.9 (8.16)	72.2 (12)	50	White: 97.9% Other: 2.08%	No: 89.6% Ex: 10.4%	60.5 (8.85)
A7881004 (IIa)	Asthma	43	39.7 (12.7)	81.2 (13.1)	65.1	White: 95.3% Other: 4.65%	No: 83.7% Ex: 16.3%	62.1 (8.32)
A7881010 (IIa)	COPD	20	59.4 (8.8)	73.3 (13.9)	60	White: 100%	Yes or Ex: 100%	69 (8.32)
A7881013 (IIb)	COPD	323	61.9 (8.55)	80.1 (17.3)	63.8	White: 94.1% Black: 3.1% Other: 2.79%	Yes: 48.9% Ex: 51.1%	71.7 (11.1)
B0751001 (I)	HV	20	37 (7.89)	66.3 (11.1)	70	Asian: 100%	No: 90% Ex: 10%	61.2 (8.41)
A9001181 (I)	HV	12	24.1 (5.92)	83.3 (12)	100	White: 91.7% Asian: 8.33%	No: 58.3% Ex: 41.7%	57.4 (6.23)

HV, human volunteers.

Figure 1
Mean (95% CI) observed HR_{CFB} for four different subpopulations in the analysis dataset. There is no overlap between the populations. Observations are binned into groups by dose (A) or predicted plasma concentration (B). The dashed lines show E_{max} functions fitted to the data. —, human volunteers; —, asthma; —, COPD; —, human volunteers, MIAT (Miat monodose inhaler, model 5)

PF-00610355. The apparent delay in the onset and offset of the effect of PF-00610355 on heart rate compared with the time course of PF-00610355 concentrations was accounted for by introducing a hypothetical effect compartment [20]. Next, various linear and non-linear relation-

ships were evaluated in order to relate the time course of changes in heart rate to the time course of (effect compartment) PF-00610355 concentrations. The heart rate data were best described by the pharmacologically meaningful E_{max} pharmacodynamic model.

$$\begin{aligned}
Y_{ij} &= \text{BASE}_i + \text{NDEF}_{ij} + \text{DEFF}_{ij} + \varepsilon_{ij}, \varepsilon_{ij} \sim N(0, \sigma^2) \\
\text{NDEF}_{ij} &= \text{TVPLC} - \text{CAMP} \cdot \exp(-(CTIM_{ij} - \text{CPHS})^2 / \text{CSTP}) \\
\text{DEFF}_{ij} &= E_{\max i} \cdot \text{CPE}_{ij} / (EC_{50i} + \text{CPE}_{ij}), \\
E_{\max i} &= E_{\max \text{Pop}} + \eta_{1,i}, \eta_{1,i} \sim N(0, \omega_1^2) \\
EC_{50i} &= EC_{50 \text{Pop}} + \eta_{2,i}, \eta_{2,i} \sim N(0, \omega_2^2) \\
\text{BASE}_i &= \text{BASE}_{\text{Obs},i} + \eta_{3,i}, \eta_{3,i} \sim N(0, \sigma^2)
\end{aligned} \tag{3}$$

Y_{ij} is the observed absolute heart rate for subject i at the j^{th} time point. $\text{BASE}_{\text{Obs},i}$ and BASE_i are the individually observed and predicted HR baseline (see discussion on the modelling of observed baseline, below), respectively, NDEF_{ij} is the placebo model as defined above with TVPLC representing the difference between the baseline and individual intercept, and DEFF_{ij} is the effect of PF-00610355 concentration in the effect compartment, CPE_{ij} .

The development of tolerance/desensitization following continuous PF-00610355-induced adrenergic stimulation was evaluated in the development model using various approaches. A mathematical approach as proposed by Porchet *et al.* [21] resulted in an adequate description of the decline in the effect of PF-00610355 on heart rate, and reflected a 13% reduction in the maximum effect of PF-00610355. Although this tolerance effect was found to be statistically significant, the impact of the tolerance on the overall effect of PF-00610355 on heart rate was limited, and it was decided that the estimated tolerance was insufficient to warrant the added complexity to the model. This decision was supported by the finding that adding the tolerance component to the final model including covariates did not result in a statistically significant reduction in OFV.

Modelling observed baseline The change from baseline, rather than the absolute heart rate was relevant for the objective of this evaluation. Various approaches for the implementation of observed baseline, as suggested by Dansirikul *et al.* [22], were therefore considered, and these all led to considerable improvements in model fit. A baseline model was selected that described the observed baseline plus an individual-specific measurement error corresponding to the residual variability on post-baseline heart rate observations (see Dansirikul *et al.* [22], method 'B2' and Equation 3 above). Following these considerations with respect to placebo model, drug model, tolerance development and baseline heart rate correction, the base PKPD model consisted of a baseline component depending on the observed baseline with error, a circadian variability component implemented as a negative Gaussian function, and an $E_{\max}$ pharmacodynamic drug component of delayed plasma concentration for the PF-00610355-induced drug effect. The model contained random effects on $E_{\max}$, EC_{50} , and baseline, while the residual variability was described using an additive error model.

Forward model Clinically relevant subject variables (covariates) were explored for inclusion into the forward model in a univariate manner. Subsequently, the forward model was defined by adding all statistically significant covariates to the base model. The demographic covariates, gender, age, body weight and race, as well as the disease status (COPD, asthma or healthy) and previous medication with corticosteroids, LAACs and LABAs were tested on pharmacodynamic model parameters $E_{\max}$ and EC_{50} . The demographic covariates and disease status were tested on the amplitude of circadian variability. Binary covariates indicating if the number of repeated HR measurements underlying each observation record was less than three, and indicating the thorough QT (TQT) study (A7881014), were tested on the residual error variability. Following the univariate test, the following significant (nominal $P < 0.01$) relations were included in the forward model: age, body weight, COPD status, previous corticosteroid use on $E_{\max}$, age, race, asthma status, COPD status, previous corticosteroid use on EC_{50} , age and asthma status on circadian amplitude and TQT study on residual error.

During the stepwise, backwards elimination, covariates not significant at the nominal $P = 0.001$ level were removed. Following the backward elimination of covariates, the following covariates were included in the final model: age and asthma status on the amplitude of circadian variability, age and COPD status on EC_{50} and a reduction in residual error variability in the TQT study.

Patient status (COPD vs. non-COPD) was included as a covariate on the drug potency (EC_{50}). However, due to the lower concentrations observed in COPD patients compared with healthy volunteers it was not possible to estimate simultaneously separate maximum drug effect ($E_{\max}$) for these subgroups. Nevertheless, this approach resulted in an adequate description of the concentration–effect relationship of PF-00610355 in both populations (see below) and resulted in typical values of 23.9 beats min^{-1} for $E_{\max}$, and 1480 pg ml^{-1} and 5353 pg ml^{-1} for EC_{50} in non-COPD and COPD patients, respectively.

Final model evaluation Base and final model parameter estimates and uncertainties are listed in Table 3. The symmetric, parametric 95% confidence intervals of final model parameter estimates (based on the standard errors of the parameter estimates) indicated model parsimony. While the relative standard errors were substantial (>50%) on EC_{50} and the parameter describing delay in the onset and offset of drug effect relative to PF-00610355 plasma concentrations (KEO), the bootstrap-based confidence intervals established that these parameters were in fact significantly different from 0 (Table 3).

A plot of observed vs. population and individual model predicted heart rate is shown in Figure 2 (left) and indicates that most HR observations are well described by the model. The overall distribution of points around the line of unity is symmetric, indicating an unbiased model. This is

Table 3

Parameter estimates and uncertainties in the final HR model based on the original dataset, and bootstrap results based on 500 replicates of the final model. Fixed effects with relative standard errors larger than 50% are indicated in italics. All parameters are significantly different from 0 according to the bootstrap confidence intervals

Parameter (unit)	Final model (%SE)	Bootstrap (95% CI)
TVPLC (beats min ⁻¹)	3.128 (11.55)	3.151 (2.625, 3.687)
CAMP (beats min ⁻¹)	5.695 (4.723)	5.731 (5.313, 6.109)
CPHS (h)	11.24 (1.826)	11.23 (11.05, 11.4)
CSTP (h)	7.905 (12.24)	7.972 (6.797, 9.441)
E _{maxPop} (beats min)	23.93 (33.83)	23.76 (20.65, 26.81)
EC _{50Pop} (pg ml ⁻¹)	1479 (77.1)	1457 (935.3, 1938)
KEO (1 h ⁻¹)	0.0978 (85.3)	0.09812 (0.05313, 0.138)
CAMP(AGE)	-0.3401 (33.89)	-0.3263 (-0.4961, -0.1739)
CAMP(ASTHMA)	-0.8971 (23.46)	-0.8838 (-1.081, -0.663)
EC ₅₀ (AGE)	1.047 (38.04)	1.037 (0.5328, 1.602)
EC ₅₀ (COPD)	2.744 (39.17)	2.819 (1.485, 5.54)
ω(log(E _{max}))	0.3444 (26.68)	0.1161 (0.0652, 0.1755)
ω(log(EC ₅₀))	0.9586 (51.1)	0.9151 (0.6174, 1.531)
σ (beats min ⁻¹)	5.703 (1.846)	5.697 (5.481, 5.887)
σ (TQT)	-0.2408 (10.87)	-0.2379 (-0.2866, -0.1903)

supported by the conditional weighted residuals (Figure 2, right) which show only little bias vs. time and predicted concentration. The plot of CWRES vs. population predicted heart rate (upper right) further indicates that the additive structure of the model for residual variability is appropriate. Finally, the visual predictive check (VPC, Figure 3) confirmed the model's ability to describe the observed mean heart rate and inter-individual variability. The observed HR in both COPD and non-COPD subjects was reproduced very well with a slight tendency to under-predict the lowest 2.5% of the data. On the other hand, a VPC on the percentage of patients with an absolute heart rate of more than 100–120 beats min⁻¹ confirmed that this statistic was well captured by the model (result not shown).

HR simulations On the basis of the final model, the expected maximum change in heart rate was simulated for a range of clinically relevant doses of PF-00610355 following once daily administration for 43 days. Heart rate profiles were simulated in COPD patients using the CRC-749 inhalation device with an expected relative fine particle dose of 25% for the evaluated dose range. Table 4 shows the predicted maximum HR_{CFB} at steady-state on day 43. For each of the 250 replicated simulations, the (between subjects) median and 95% prediction interval of the maximum simulated change in HR was derived. The (between replicates) median of these 250 simulations is listed in Table 4. The maximum HR_{CFB} in COPD patients ranged from approximately 10.7 beats min⁻¹ in the placebo group to approximately 13.4 beats min⁻¹ in the highest evaluated daily dose of 280 µg, corresponding to a placebo-corrected increase in HR_{CFB} in the COPD popula-

tion of 2.7 (0.90, 4.82) beats min⁻¹. Table 4 also shows the fraction of (250) COPD patients experiencing a maximum HR_{CFB} of at least 5, 10, or 20 beats min⁻¹ on day 43 (see also Figure 4). While most placebo subjects experienced a maximum HR_{CFB} on day 43 of at least 10 beats min⁻¹ at one or more observation time points, only 8% of placebo subjects experienced maximum increases of at least 20 beats min⁻¹. For the highest dose of 280 µg, this fraction increased to 19% in the corresponding COPD population (135% higher incidence than placebo). For this dose, 89% and 68% of the COPD patients are expected to experience increases in heart rate of more than 5 and 10 beats min⁻¹, respectively (10% and 26% increase relative to placebo, respectively).

Discussion

COPD patients often suffer from various cardiovascular complications, such as ischaemic heart disease, right ventricular hypertrophy and arrhythmias [8–10]. Increase in heart rate as a result of the systemic use of LABAs such as salmeterol, formoterol and more recently, indicaterol [23] and PF-00610355, may result in an additional cardiovascular safety concern in this patient population. Furthermore, the concomitant use of LABAs with other drugs with intrinsic cardiovascular effects, such as corticosteroids, should also be considered [13]. Therefore, a systematic understanding of the factors that drive the extent of LABA-induced tachycardia, will help in establishing the cardiovascular safety profile of PF-00610355 and may support the identification of a treatment regimen with an optimal efficacy/safety profile.

The aim of the analysis presented here was to assess the cardiovascular effects of a new inhaled LABA PF-00610355 in COPD patients by including all available relevant PF-00610355 heart rate data with respect to drug exposure in plasma (pharmacokinetics) and key explanatory variables in various patients' settings (COPD, healthy volunteers and asthma). Model-based simulations allowed evaluation of the expected heart effects of PF-00610355 in the future population of COPD patients. The simulations indicated that the median expected placebo-corrected maximum increase in heart rate would be 2.7 beats min⁻¹ (95% confidence interval: 0.90, 4.82 beats min⁻¹) for a daily PF-00610355 dose of 280 µg (Table 4). In hypertensive patients, 5 beats min⁻¹ was associated with increased mortality [24]. For LABA stimulated heart rate increases in COPD patients it is unknown what increase translates into safety findings and whether maximum increase or average 24 h increase is the most relevant measure. However 5 beats min⁻¹ was also used for the placebo corrected change of mean 24 h heart rate of a newly developed LABA (indacaterol) in COPD patients [25]. For PF-00610355 we took a more conservative approach, by focusing on the placebo corrected change of the maximum change in

Figure 2

Goodness of fit plot for the final HR model. Population (A) and individual (C) predictions are scattered evenly around the line of unity. Epsilon shrinkage is 35%. Conditional weighted residuals of heart rate predictions (CWRES) vs. time after first dose (B), and CWRES vs. time since last dose (E, truncated to 0–24 h for clarity). CWRES vs. population predicted PF-00610355 concentration (D). CWRES in COPD patients and healthy volunteers are shown in red and black, respectively, and solid lines show loess smooth curves

Table 4

Median (over study replicates) of median (95% PI) individual maximum HR_{CFB} and fraction of patients with maximum change in heart rate of more than 5, 10, and 20 beats min⁻¹ on day 43 in COPD patients. The last column shows the maximum placebo-corrected HR_{CFB} on day 43 in COPD patients

Dose of PF-00610355 (μg)	Maximum HR _{CFB}	% with HR _{CFB} >5	% with HR _{CFB} >10	% with HR _{CFB} > 20	Maximum placebo-corrected HR _{CFB}
0	10.73 (–1.88, 23.65)	80.8 (75.6, 85.6)	54.2 (47.7, 61.1)	8.0 (4.8, 12.3)	0.00 (0.00, 0.00)
56	11.37 (–1.25, 24.50)	83.6 (78.4, 87.5)	58.0 (51.7, 64.7)	10.0 (6.4, 16.3)	0.63 (–0.80, 2.14)
112.4	11.95 (–0.91, 25.61)	85.2 (80.8, 89.5)	61.6 (55.2, 68.4)	12.4 (8.1, 18.7)	1.13 (–0.34, 2.97)
140	12.19 (–0.67, 26.07)	85.6 (80.5, 91.6)	63.2 (55.7, 70.7)	13.2 (8.4, 19.9)	1.44 (–0.01, 3.42)
200	12.78 (–0.24, 27.43)	86.8 (82.2, 91.9)	65.6 (58.0, 74.3)	16.0 (9.7, 25.8)	2.05 (0.44, 4.32)
280	13.37 (0.06, 28.64)	88.8 (84.0, 93.6)	68.2 (61.6, 76.7)	18.8 (11.8, 29.5)	2.70 (0.90, 4.82)

heart rate, rather than the mean change in heart rate over 24 h. However, both the between and within subject variability in HR may be quite substantial (see Figure 4). The model-based estimate of variability was used to calculate the probability of exceeding a maximum heart rate increase of more than 20 beats min⁻¹ (Table 4). For the

maximum evaluated PF-00610355 dose of 280 μg day⁻¹, this probability was around 19%.

The limited effect of PF-00610355 on heart rate in COPD patients as indicated by the model-based simulations may have been a result of desensitization (tolerance) of the β₂-adrenoreceptor upon prolonged exposure in

Figure 3

Visual predictive check of heart rate vs. dose (upper panels) based on 1000 datasets simulated using the PKPD model, corrected for model prediction and stratified by COPD status. The dark grey scatter and the solid lines show the observed data and the corresponding median and 95% percentile intervals. The light grey boxes indicate the 95% confidence interval of model-predicted median and 95% percentile intervals. Observed samples were sorted into six bins (lower panels) containing an approximately equal number of samples according to the administered dose

Figure 4

Black solid lines and grey area illustrates the median (between replicates) median and 95% percentile intervals within replicates maximum change in HR (A) and maximum absolute HR (B) vs. dose on day 43 in COPD patients. Error bars show the 95% percentile intervals of the medians between replicates. Dashed lines show 5, 10, and 20 beats min^{-1} change in HR (A) and 90, 100, and 110 beats min^{-1} absolute HR (B). Open circles show observed data

these patients. It has been demonstrated that tolerance may develop to the bronchoprotective effects of salmeterol as soon as after two to three doses [26]. In the data set used here, more pronounced increases in heart rate in

the relevant dose range have been observed in healthy volunteers (see Figure 1). This is partly explained by pharmacokinetic differences between healthy volunteers and COPD patients, seeing that the systemic exposure of

PF-00610355 is substantially lower in COPD than in healthy volunteers [14]. However, after correction for pharmacokinetic differences, COPD patients were still substantially less sensitive than healthy volunteers to the heart rate effects of PF-00610355, as indicated by a three-fold lower potency (EC_{50}) in the former population (Table 3). This difference may have resulted from previous, long-term use of inhaled β_2 -adrenoceptor agonists and use of short acting compounds as rescue medication during run-in and study period. This established desensitization in COPD patients may be further supported by the fact that no further (relevant) loss of sensitivity to the heart rate effects of PF-00610355 was observed during the time course evaluated in the data set, even after 42 days of dosing. The potential presence of tolerance was formally addressed in the model development process. This resulted in an estimated decrease of maximum response (E_{max}) of 13% in an intermediate model and insignificant changes in the final model. Conceptually, tolerance development in the data set could have been identified from the heart rate data in healthy volunteers who, in contrast to COPD patients, were not pre-exposed to β_2 -adrenoceptor agonists. However, the majority of the healthy volunteer data related to single dose data and as such, it was not feasible to identify tolerance development in response to chronic dosing in this population.

The effect of the use of relevant concomitant medication, such as corticosteroids on the heart rate effects of PF-00610355 was systematically evaluated in this analysis. The prior use of LAACs and both prior and concomitant use of corticosteroids did not have a significant effect on the heart rate effect of PF-00610355. Conflicting results have been reported of these drug interactions and this inconsistent pattern may therefore be in line with these observations in this current analysis. For instance, it has been shown that corticosteroids enhance the expression of β_2 -adrenoceptors [13], and may subsequently result in an increased effect of PF-00610355 on heart rate. On the other hand, a review of clinical literature concerning the safety of LABAs and inhaled corticosteroids, both as monotherapies and in combination, in patients with COPD, has suggested that cardiovascular effects may actually be reduced in combination with inhaled corticosteroids [12].

Similarly, variable results have been reported for the cardiovascular risk of LAACs. A meta-analysis by Singh *et al.* [27] indicated that inhaled anticholinergics significantly increased the risk of cardiovascular death, myocardial infarction or stroke. Conversely, studies with tiotropium by Celli *et al.* [28] did not demonstrate an increase in cardiovascular events and even showed a reduced risk of cardiovascular events, cardiovascular mortality and all-cause mortality in COPD patients.

In conclusion, the results of this safety analysis, on the basis of currently available phase I/II clinical data indicate, that only a limited effect on heart rate should be expected following administration of PF-00610355 in doses of up

to $280 \mu\text{g day}^{-1}$ in COPD patients. Although substantial increases in heart rate were observed in healthy volunteers, both pharmacokinetic as well as pharmacodynamic differences between healthy volunteers and COPD patients explain the modest effect of PF-00610355 on heart rate in the patient population.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare PMD and EC had support from Pfizer Inc for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, SM, AC and JR were employed by Pfizer Inc in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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