Introduction
Chronic Obstructive Pulmonary Disease (COPD) is characterized by significant airflow obstruction due to structural alteration of the small airways and bronchocoonstriction due to inflammation. It is observed that patients with COPD are worse during the night or in the early morning. The circadian variation has been reported in COPD.1

Calverley et al2 discussed the circadian variation in FEV1 in patients with COPD. However, their analysis focuses on the difference between the highest and lowest values divided by the mean of the values during 24 hours periods. The change of FEV1 vs time was not discussed. In this paper, we use nonlinear mixed effects model to analyze the relationship between lung function and time in patients with COPD.

Data
Lung function (FEV1 and FVC) was measured at –1 hour pre-time zero, at 1, 1.5, 3, 5, 10, 15, 20, 25, 30 minutes and 1 hour, and at 1, 2, 3, 4, 5, 6, 8, 12 and 18 hours post-time zero on day -1 and day 9. Time zero was around 8:00AM. A total of 448 FEV1 observations were used in the analysis. The change in lung function within 24 hours was analyzed by a nonlinear mixed-effects modeling program.

Methods of Analysis
Values of FEV1 and FVC were obtained from the same spirometry recording. Three valid spirometry results were assessed at each specified time point. Of the three assessments performed at each time point, the recording was either 1) the highest FEV1 value, 2) the highest value of FEV1+FVC, or 3) the highest value of FEV1+FVC performed earliest in time was used. Baseline values were the values at pre-time zero on Day –1.

A population pharmacodynamic approach was used to analyze the data using NONMEM version V level 1.1. In order to model the lung function change during 24 hours period, the following approaches were attempted:

1. Expressing lung function as the difference of two exponential functions.

These methods were evaluated by examining the objective function and goodness of fit plots.

Result
Demographic Data
Patient baseline features are summarized as below. The mean (Standard Deviation) age was 63 (10) years, 64% were men and the mean FEV1 was 1.49 L (49% predicted). The mean smoking history was 64 pack years, with 19% of the total population being smokers.

Spirometric Parameters
Forced expiratory volume in 1 second (FEV1)
The mean plot of FEV1 vs. time is presented in figure 1. It showed that the relationship of FEV1 and time could be described by difference of two exponential functions or a cosine function.

(Data)

Though cosine function had a slightly higher objective function, cosine function had a better fit than bi-exponential function by population DV/PRED vs. time plot and individual DV/IPRED/PRED vs. time plots.

Forced vital capacity (FVC)
The pattern of FVC was similar to the FEV1 response, and a similar approach was used to model the data. The first model was to express FVC as the the bi-exponential functions. The typical FVC is 2.86(exp0.0037(t1-1.1*exp(-0.2)). The precision of the estimators was relative good and the IV was smaller than 2% of FEV1. The magnitude of residual variability was 5.0%. The model fitted the data well by the diagnostic plots.

A cosine function was used to describe the circadian variation of FVC. The typical rhythm-adjusted 24-hr mean baseline effect was related to gender, height and age. The typical amplitude for the cosine terms, which expressed as a change from the mean, was 139 mL. The typical time shift for the cosine terms was 7.6 hour. The relationship between FEV1, gender, height and age could be estimated by the data. The estimated coefficients were close to the values from literature.

Discussion
FEV1 and FVC were highest around 2-3PM, then decreased to the lowest value at 2-3AM, by the cosine function approach. The circadian effect may be attributed to the normal circadian variation in airway caliber. Airway caliber exhibits a circadian variation during the 24 hour day, with maximum values occurring around noon and the minimum values in the early morning. Studies of spirometric tests in normal subjects whose FEV1 was measured on different occasions between 9AM and 9PM confirm that the peak values occurred around midnight. The lowest spirometric test values occurred during the circadian trough in the early morning.1 By comparing the diagnostic plots of lung function, cosine function approach can better describe the declining phase of the data. These observations support that cosine function is a good choice to describe the circadian variation of lung function in COPD . Previous reports had some limitations. These authors only analyzed the maximum change during a 24 hour period and have not described FEV1 and FVC changes with time during a 24 hour period.

Conclusion
Lung function can be modeled with a cosine function to describe the circadian effect in patients with COPD. It is important to consider this effect when calculating the post-dose drug effect for any drug to treat patients with COPD.

References

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