

# Population concentration-QT-modelling of CHF6001 following dry powder inhalation in healthy volunteers

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Background & objectives

CHF6001 is a potent and selective phosphodiesterase-4 (PDE-4) inhibitor currently under development for treatment of chronic obstructive pulmonary disease (COPD). CHF6001 is being developed for inhalation to help overcome the well-known gastrointestinal side effects associated with this therapeutic class when given orally [1]. Plasma concentrations and Fridericia corrected QT interval (QTcF) data from 2 phase I studies in healthy volunteers at different dose levels were used to assess potential QT prolongation liability. The exposure-response relationship was investigated using observed QtcF as well as placebo- and baseline adjusted QTcF ( $\Delta$ QTcF,  $\Delta\Delta$ QTcF), respectively [2-4].

Methods

**Patients & Data:** CHF6001 plasma concentrations and QTcF data (12-lead ECGs extracted from 24-hour holter recordings just before the scheduled blood sampling in triplicate) from 2 phase I (FIH and Extension) double-blind, randomized, placebo-controlled studies with single (SAD) and repeated ascending doses (MAD).

- **FIH:** 61 subjects with once daily administration via the Aerolizer® inhaler (20 - 2000 µg).
- **Extension:** 39 subjects with twice daily administration via the NEXThaler® inhaler (2400 - 4800 µg/day)

In total, CHF6001 plasma concentrations and QTcF data (12-lead ECGs extracted from 24-hour holter recordings just before the scheduled blood sampling in triplicate), collected in 100 healthy volunteers on active treatment and 22 on placebo, were subject to modelling.

Results

**Approach 1 (QTcF as DV):** Using only data from the subjects receiving placebo, a model describing the diurnal changes of QTcF was first developed. A function with three cosine terms described the data best. Next, using all data, a linear slope model was found to best describe the weak concentration-QTcF relationship. The model equation is shown below. Including sex as a covariate on the baseline significantly improved the fit indicating that male subjects had a about 3.3% lower QTcF at baseline than females. It was also found that subjects in the SAD part of the extension study had a 3.8% higher baseline. Parameter estimates of the model are presented in table 1.

$$QTcF = BASE \times (1 + SEX) \times (1 - STUPART) \times \left(1 + AMP \times \cos\left(\frac{2\pi(time - PIK)}{24}\right) + AMP2 \times \cos\left(\frac{2\pi(time - PIK2)}{12}\right) + AMP3 \times \cos\left(\frac{2\pi(time - PIK3)}{6}\right)\right) + SL \times Conc + \epsilon$$

where BASE is the overall average baseline, AMP, AM2, AMP3 are the amplitudes of the cosine functions PIK, PIK2 and PIK3 the time shift parameters; SEX is the covariate effect for male subjects (0 for females), STUPART is the covariate effect for the SAD part of the Extension study (otherwise 0); SL is the slope of the linear relationship, Conc is the observed plasma concentration,  $\epsilon$  is the additive residual error

**Approach 2 ( $\Delta\Delta$ QTcF as DV):** A simple linear model with additive residual error provided the best fit to the data. Inclusion of an intercept did not improve the model fit significantly.

A slope of -0.23 (90% CI: -0.71 - 0.25) ms per ng/ml was estimated for this model.

**Approach 3 ( $\Delta$ QTcF as DV):** A linear mixed-effects model as proposed by Garnet et al. [4] was applied to the data. Time-after-dose, observed baseline QTcF and treatment (active/placebo) were added as categorical covariates on the intercept. Random effects were included on slope and intercept. ‘Study’ was included as a covariate on the additive residual error.

$$\Delta QTcF = (INT + \eta_0) + TRT + (SL + \eta_1) \times Conc + TIME + BL.effect \times (QTcF_0 - \overline{QTcF_0}) + \epsilon$$

Where INT is the intercept, associated with a normally distributed random effect variable  $\eta_0$ , TRT is a parameter accounting for potential imbalance between placebo and active treatment groups, SL is the slope of the concentration-QT relationship associated with the random effect variable  $\eta_1$ , TIME accounts for the natural time variation of QTcF throughout the day, treating scheduled time-after-dose as a categorical covariate. BL.effect adjusts for the deviation of the individual baseline measurement  $QTcF_0$  from the overall mean baseline;  $\epsilon$  is the additive residual error with a different magnitude (standard deviation) for each study.

A slope of -0.58 (CI90%: -1.4 to -0.058) ms per ng/ml was estimated for this model.

Three approaches were used in the modelling:

1. using the observed QTcF measurements (mean of triplicate measurements) as dependent variable (DV), and estimation of baseline parameters including modeling of the circadian rhythm of QTcF over time,
2. using the placebo adjusted change from baseline QTcF ( $\Delta\Delta$ QTcF) as DV and
3. using the change from baseline QTc ( $\Delta$ QTcF) as DV.

**Software:** NONMEM V7.3.0 was used for data analysis, Simulo v7.1 was used for the simulations.

Table 1: Parameter estimates for approach 1 (QTcF as DV)

| Parameter                        | Estimate  | SE*     | 90% CP <sup>b</sup> | Bootstrap <sup>a</sup> |                    |         |
|----------------------------------|-----------|---------|---------------------|------------------------|--------------------|---------|
|                                  |           |         |                     | Median                 | 90% CI             | Shr.(%) |
| <b>Fixed effects parameters</b>  |           |         |                     |                        |                    |         |
| BASE                             | 409       | 3.28    | 404 - 415           | 409                    | 403 - 415          | -       |
| AMP                              | 0.00401   | 0.00106 | 0.00226 - 0.00575   | 0.004                  | 0.00308 - 0.00495  | -       |
| PIK (h)                          | 0 (fixed) | -       | -                   | -                      | -                  | -       |
| AMP2                             | 0.0137    | 0.00591 | 0.00398 - 0.0234    | 0.0138                 | 0.0109 - 0.0168    | -       |
| PIK2 (h)                         | 10.6      | 0.273   | 10.2 - 11.1         | 10.6                   | 10.4 - 10.8        | -       |
| AMP3                             | 0.00641   | 0.00588 | -0.00327 - 0.0161   | 0.00645                | 0.00376 - 0.00905  | -       |
| PIK3 (h)                         | 21.3      | 0.0976  | 21.1 - 21.4         | 21.3                   | 21.1 - 21.5        | -       |
| SL (mms/μg/mL)                   | 0.191     | 0.228   | -0.184 - 0.567      | 0.176                  | -0.192 - 0.544     | -       |
| SEX                              | -0.0333   | 0.00848 | -0.0473 to -0.0194  | -0.0325                | -0.0469 to -0.0174 | -       |
| STUPART                          | -0.0383   | 0.0112  | -0.0568 to -0.0198  | -0.0394                | -0.0582 to -0.019  | -       |
| <b>Random effects parameters</b> |           |         |                     |                        |                    |         |
| IV BL (CV%) <sup>c</sup>         | 3.28      | 0.0019  | 2.95 - 3.58         | 3.24                   | 2.94 - 3.52        | 0.453   |
| IV AMP (CV%) <sup>d</sup>        | 78.1      | 0.14    | 41.4 - 110          | 76.8                   | 58.1 - 103         | 35.9    |
| IV AMP2 (CV%) <sup>d</sup>       | 20.3      | 0.113   | 0 - 34.9            | 18.2                   | 0.201 - 34.5       | 68.9    |
| <b>Residual variability</b>      |           |         |                     |                        |                    |         |
| Residual error additive (msec)   | 5.65      | 0.149   | 5.4 - 5.9           | 5.64                   | 5.39 - 5.88        | 4.8     |

BASE: baseline QTc before dose; AMP, AMP2, AMP3: amplitudes of the baseline QTc, the second, and the third post-dose QTc, respectively; PIK, time from QTc before dose to AMP, AMP2, AMP3; SEX: fractional difference in QT for male subjects; STUPART: fractional difference in QT for SAD part of the extension study; IV: inter-individual variability; CV: coefficient of variation; \*SE on SD scale for variability estimates

<sup>a</sup>Asymptotic confidence interval derived from NONMEM standard errors

<sup>b</sup>90% CI for 90% of the population

<sup>c</sup>CV = 100 \* (sigma<sup>2</sup>/lambda<sup>2</sup>) (lambda = lambda<sub>0</sub>)

BASE: baseline QTcF before dose; AMP, AMP2, AMP3: amplitudes of the baseline QTcF; PIK, PIK2, PIK3: times when maximum amplitudes occurs; SL: slope of QTcF-concentration relationship; SEX: fractional difference in QT for male subjects; STUPART: fractional difference in QT for SAD part of the extension study; IV: inter-individual variability

\* SE on SD scale for variability estimates

<sup>b</sup> Asymptotic confidence interval derived from NONMEM standard errors

<sup>c</sup> 1000 runs out of 1000

<sup>d</sup> CV = 100\*sqrt(variance)-1

Figure 1: Visual predictive check for approach 1. Solid lines are the 10th and 90th (blue lines) and 50th (median; red line) percentiles of the observed data (open circles) and the colored areas are the 95%CI of the simulated quantiles. STU48 is the FIH study and STU8 is the extension study.

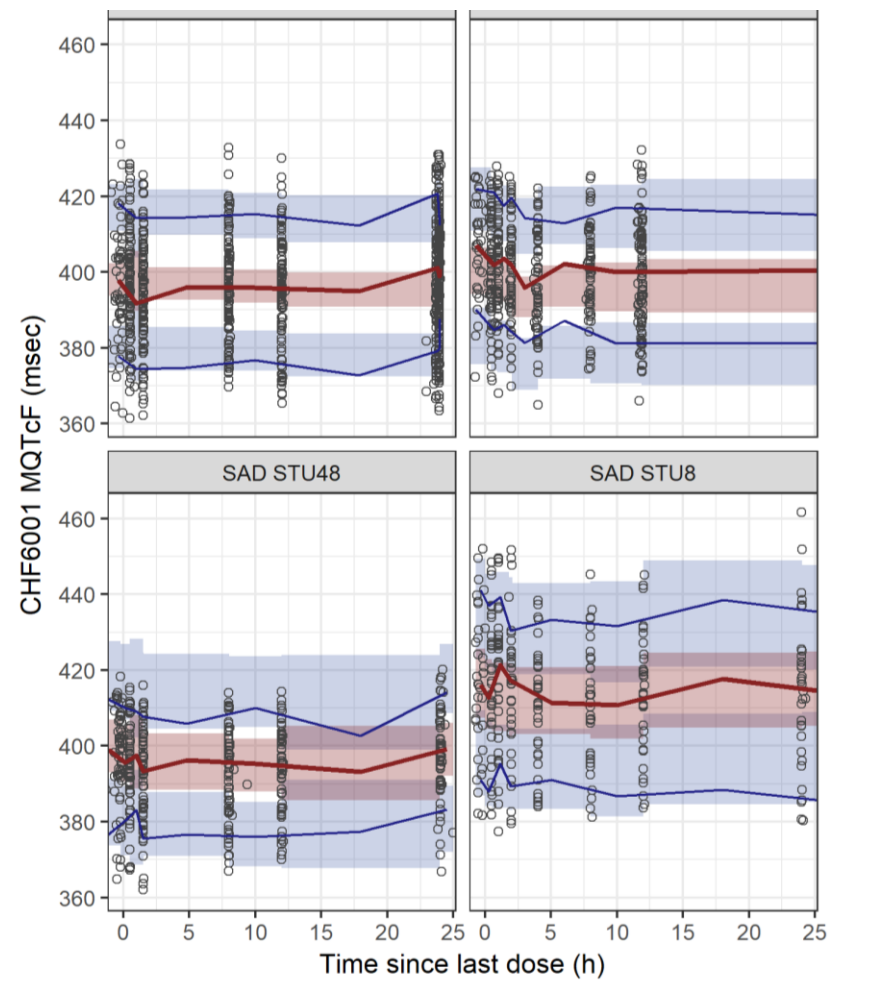
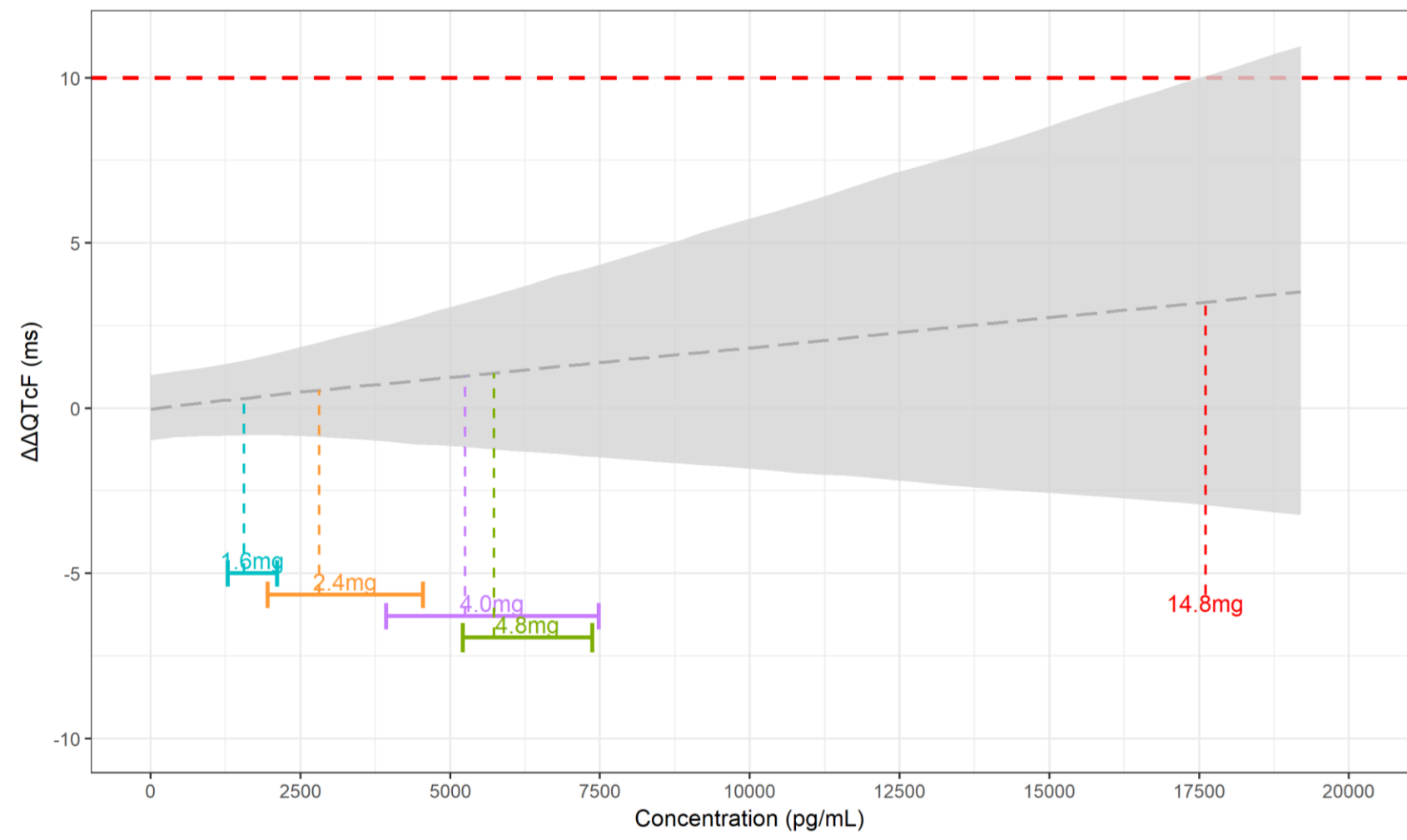


Figure 2: Simulated  $\Delta\Delta$ QTcF response as a function of plasma concentration of CHF6001.

The grey area encompasses the 90% confidence interval around the simulations. The geometric mean and range of Cmax values in several dose groups are indicated. For the purpose of illustration, the response was extrapolated beyond the range of observed concentrations – 14.8 mg would be a hypothetical dose where the upper limit of the 90% confidence interval of the predicted  $\Delta\Delta$ QTcF may exceed 10ms.



Conclusions

The developed models adequately described the data of FIH and Extension studies, using QTcF,  $\Delta\Delta$ QTcF and  $\Delta$ QTcF as dependent variables. Similar slope estimates were obtained using the three approaches and in none the slope was not significantly positive.

Method 1) gave the most precise estimate of slope (narrowest confidence interval). Given the available data, CHF6001 is unlikely to show an increase of QTcF of >10ms in the dose range studied.

References

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