A frailty model for quantifying the association between CompEx risk and variation in lung function

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Introduction

Random fluctuations in lung function have been shown to be associated with acute exacerbations in asthma (*1,2*).

These fluctuations may be quantified as a summary statistic of the peak expiratory flow (PEF), which can be collected using home-spirometry.

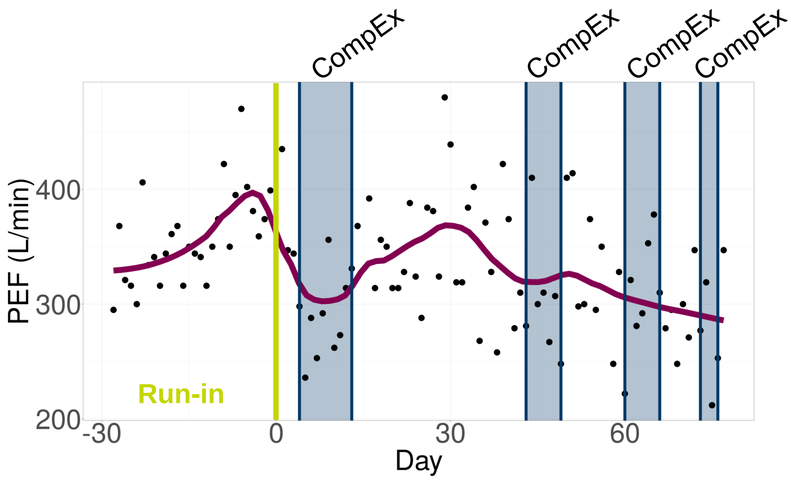
Further, it has been shown that using the endpoint CompEx in place of exacerbations allows for more efficient clinical trials *(3)*.

This work has focused on understanding how fluctuations are associated with CompEx risk as this knowledge may further improve clinical trial efficiency.

Clinical data

- The analysis was conducted using data from a Phase 2b dose-finding study of velsecorat, NCT03622112. (*4*).
- The clinical trial featured
  - a 3-to-4-week run-in period,
  - a 12-week treatment period,
  - 805 randomized patients,
  - 7 treatment arms.
- Twice daily spirometry measurements resulted in a large amount of PEF data. An example of an individual time-series is depicted in Figure 1.

Figure 1: Example data showing morning PEF measurements and CompEx events.



Methods

- Outliers in daily PEF were systematically removed by calculating an interval determined by the patient's interquartile range and removing data points outside of this interval.
- Multiple measures of variability in PEF during run-in were calculated per patient, including standard deviation (SD) and coefficient of variation.
- A frailty model for recurrent time to event data was developed to investigate the association between variability in PEF and CompEx risk.

$$\lambda_i(t) = Y_i(t)\lambda_0(t)\mu_i \exp\left(\beta^T X_{data,i}\right),$$

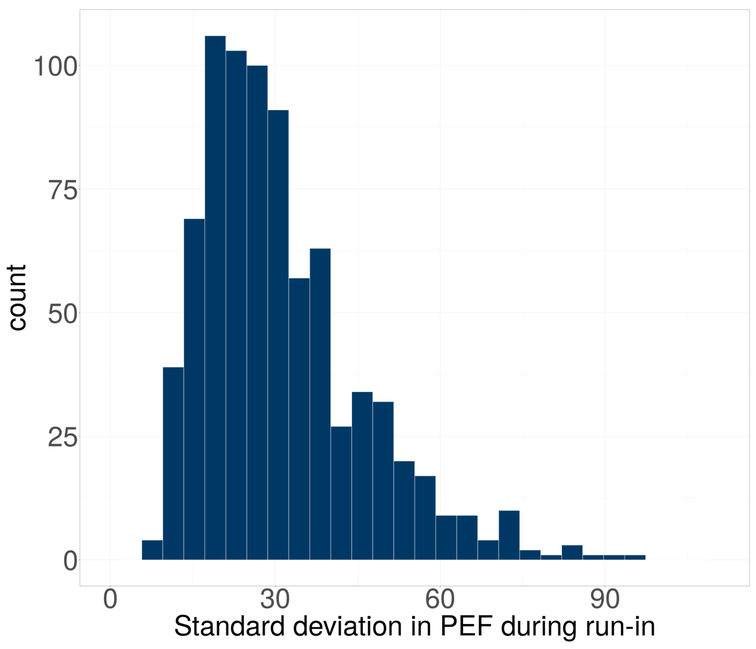
where Y – at-risk function
λ_0 – baseline hazard
μ – frailty parameter
β – vector of parameters

- Covariates included in the analysis were run-in variability in PEF, baseline PEF, and treatment arm.
- Multiple probability distributions were considered for the frailty parameter and the models were evaluated using the Akaike information criteria (AIC).

Results

- SD was chosen as the measure of variability in run-in PEF. The distribution of calculated SD-values can be seen in Figure 2.

Figure 2: Distribution of calculated standard deviation in run-in PEF (L/min).



- Run-in PEF SD was found to have a statistically significant ($p<0.01$) association with CompEx risk. All estimated parameters for the frailty model are reported in Table 1.

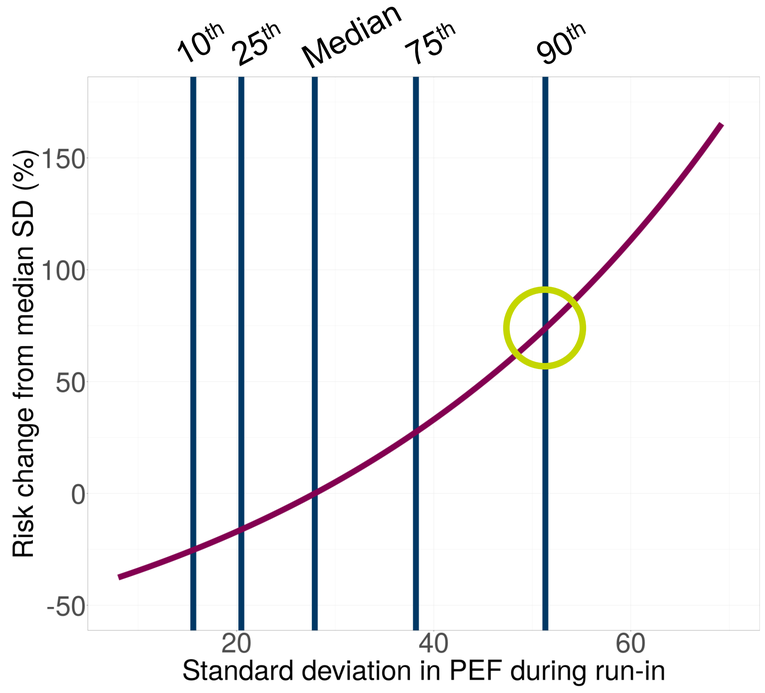
Table 1: Parameter estimates from the frailty model, exponentiated for ease of interpretation.

Parameter	Exp(estimate) (95% CI)	P-value
Baseline PEF	0.998 (0.996, 0.999)	<0.05
Run-in PEF SD	1.024 (1.008, 1.040)	<0.01
velsecorat 50 µg QD	0.405 (0.185, 0.886)	<0.05
velsecorat 90 µg QD	0.414 (0.191, 0.900)	<0.05
velsecorat 180 µg QD	0.404 (0.186, 0.878)	<0.05
velsecorat 360 µg QD	0.133 (0.055, 0.324)	<0.001
velsecorat 720 µg QD	0.087 (0.036, 0.206)	<0.001
FF 100 µg QD (open-label)	0.149 (0.064, 0.345)	<0.001

PEF peak expiratory flow; SD standard deviation; QD once daily; FF fluticasone furoate

- Using a gamma-distributed frailty parameter resulted in the smallest AIC and gave a significant likelihood increase over the no-frailty case.
- The estimated effect of a **one L/min increase in run-in PEF SD was a 2.4% increase in CompEx risk**.
- Given the distribution of SD-values (Figure 2), this effect resulted in a **74% increase in CompEx risk for a patient in the 90th percentile compared to the median**. This can be seen in Figure 3.

Figure 3. The estimated CompEx risk change from median as a function of standard deviation in run-in PEF. The vertical lines show several quantiles of the SD-distribution.



Conclusions

An association was found between run-in PEF variability and CompEx risk using the developed frailty model.

A strong heterogeneity in CompEx events was found, supporting the use of a frailty parameter in the model.

The findings suggest that standard deviation in PEF during run-in may be useful as a predictor of patient-level CompEx risk in clinical trials.

References

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