The impact of late-runner participants on PK variability in healthy volunteer, single-ascending dose trials

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Introduction

- Clinical Pharmacology trials are normally conducted in participant cohorts with all participants dosed in staggered fashion on the same day, with the exception of studies where sentinel dosing is necessary.
- Pharmacokinetic (PK) variability is minimized as much as possible through certain study design aspects, including the enrollment of healthy participants, restrictive enrollment criteria, and procedural controls.
- Occasionally, due to recruitment challenges or other external factors (e.g. the COVID-19 pandemic, high screen fail frequencies), complete cohorts cannot be enrolled as planned, with remaining participants dosed on different date(s) to complete a full panel.
- This analysis was aimed to assess the impact of late-runner participants on PK data outcomes, as determined by changes in PK variability.

Methods

- A late-runner was defined as a study participant dosed four or more days apart from the cohort remainder.
- A review of 275 healthy volunteer studies with late-runners conducted at Fortrea Clinical Research Units (CRUs) from 2013 to 2023 was performed, to determine the study type with the highest late-runner frequency.
- Single ascending dose (SAD) trials and SAD components of single/multiple ascending dose (SAD/MAD) trials were most late-runner frequent and thus selected for this analysis, to control for potential other sources of variability.
- Large molecule trials, multi-site trials, metabolites, and cohorts dosed in the fed state were excluded to further limit PK variability sources.
- The resultant analysis sample included 22 studies comprising of 134 participant cohorts, 52 of which were cohorts with late-runners (from a total of 1,062 SAD cohorts enrolled during the observation period).
- PK parameters evaluated were $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and C_{max}, where the geometric CV% served as the measure of variability.
- Primary analysis (study level analysis):
  - For each study, the geometric CV% was calculated for all study cohorts (including both cohorts with and without late-runner participants).
  - These values, after log-transformation, were analyzed using a mixed effects analysis of variance (ANOVA), with a fixed effect for late-runner status (cohorts including late-runners versus cohorts without late-runners) and a random effect of study.

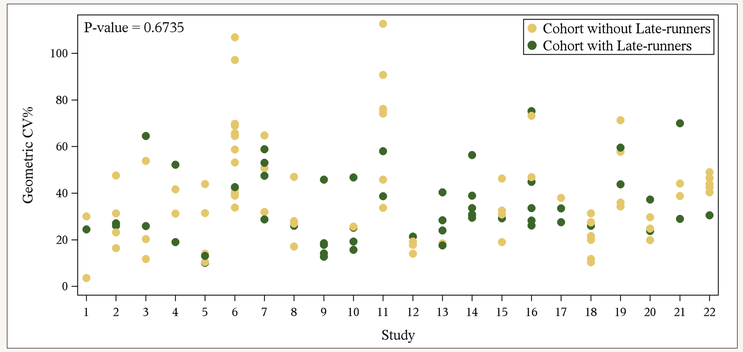

Figure 1. Geometric coefficient of variation (CV%) of $AUC_{0\text{-}tlast}$ by study: cohorts with late-runners compared to cohorts without late-runner participants.

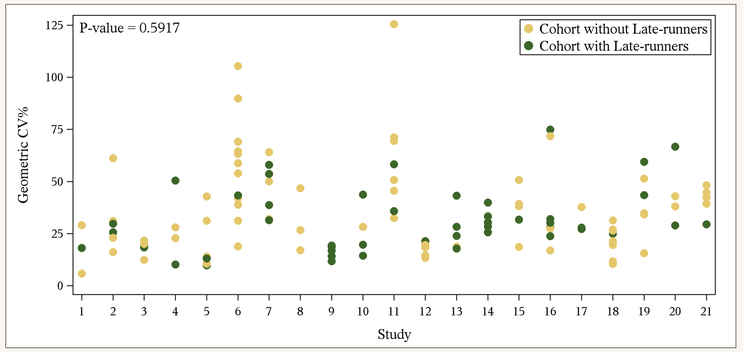

Figure 2. Geometric coefficient of variation (CV%) of $AUC_{0\text{-}\infty}$ by study: cohorts with late-runners compared to cohorts without late-runner participants.

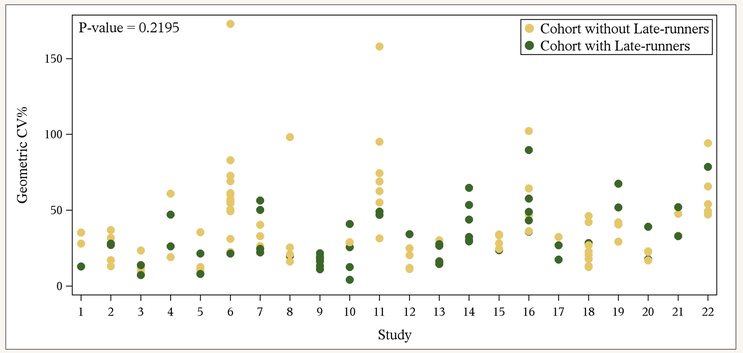

Figure 3. Geometric coefficient of variation (CV%) of C_{max} by study: cohorts with late-runners compared to cohorts without late-runner participants.

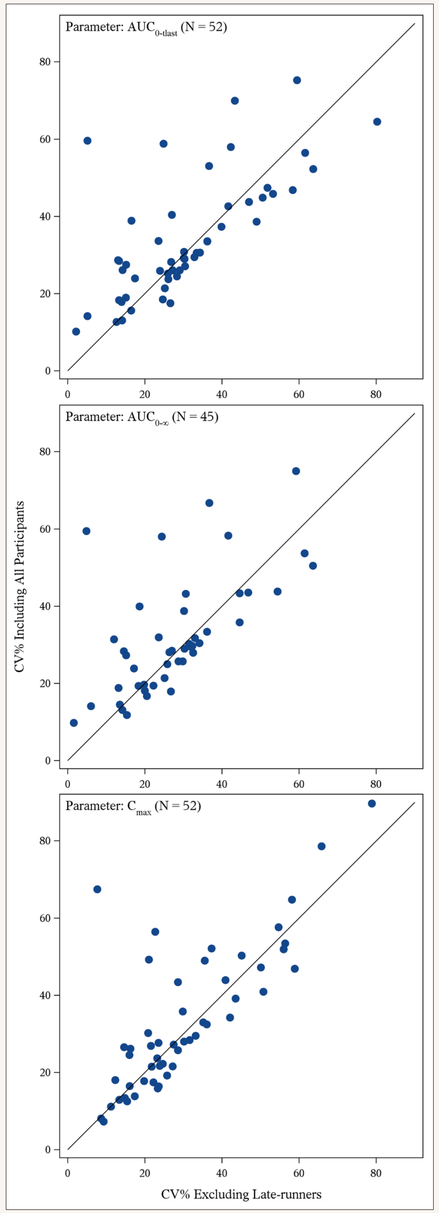

Figure 4. Geometric coefficient of variation (CV%) of $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, and C_{max} by cohort: all subjects included compared to excluding late-runners; N = number of cohorts.

Methods (cont'd)

- Secondary analysis (cohort level analysis):
  - The geometric CV% was calculated for cohorts with late-runners only, once with all participants included, and again after excluding the late-runner participants.
  - The corresponding values were then compared to assess the effect of including the late-runners on PK variability of that cohort.

Results

- The primary analysis revealed that there was no significant difference in the geometric CV% of $AUC_{0\text{-}tlast}$ (P-value = 0.6735), $AUC_{0\text{-}\infty}$ (P-value = 0.5917) and C_{max} (P-value = 0.2195), when comparing cohorts with late-runners and those without, across all studies included in the analysis. (See Figures 1 to 3)
- The secondary analysis showed that there was no consistent effect of late-runner inclusion on cohort PK variability, as exhibited by $AUC_{0\text{-}tlast}$ (variability increased in 46.2% and decreased in 53.8% of cohorts), $AUC_{0\text{-}\infty}$ (variability increased in 44.4% and decreased in 55.6% of cohorts) and C_{max} (variability increased in 42.3% and decreased in 57.7% of cohorts), compared to when calculated excluding the late-runner participants. (See Figure 4)
  - In that comparison, late-runner induced CV% increases were of greater magnitude compared to CV% decreases. Since the lower bound for variability decreases can never drop below zero, and in practice values <5% are very rare, these decreases are expected to be generally smaller than the variability increases. (See Figure 4)

Conclusions

- Although late-runner participants are commonly avoided owing to operational and financial adversities, incomplete panel enrollment cannot always be mitigated.
- This analysis demonstrated that resulting late-runner participants have no meaningful impact on the variability (CV%) of the PK parameters $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and C_{max}.
- PK exposure data derived from late-runner participant studies conducted at Fortrea CRUs are therefore valid to include in drug development decisions.

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