How Much PK Data Do We Really Need in Phase 3? A Milvexian Case Study

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BACKGROUND AND OBJECTIVE

- In large clinical trials, optimizing the collection of pharmacokinetic (PK) samples could significantly reduce patient burden, improve study feasibility, and conserve resources
- Using milvexian, a selective factor XIa inhibitor, as an example, we leveraged a model-based approach to assess the proportion of patients from which PK samples should be collected to allow for robust characterization of the relationship between exposure and safety or efficacy outcomes
  — This helped to inform the PK sampling strategy of the 3 large, ongoing clinical trials of the milvexian phase 3 program (ClinicalTrials.gov Identifiers: NCT05702034, NCT05754957, and NCT05757869)

METHODS

- **Two key scenarios** were evaluated pertaining to whether an underlying relationship exists between milvexian exposure and event outcomes (safety or efficacy):
  1. Event outcomes occur stochastically irrespective of milvexian systemic exposure
  2. Milvexian systemic exposure drives safety and/or efficacy; a logistic regression–based approach describes the relationship between milvexian exposure and event outcomes
- The percentage of trials that accurately approximate underlying event rates was estimated. In addition, the ability to detect the presence or absence of a relationship between milvexian exposure and event outcomes and to adequately estimate the potential relationship was also characterized

Model Assumptions

- Drug exposure: area under the curve (AUC; dose/clearance) drives safety/efficacy
- A total of 15,000 patients (planned study size) randomized 1:1
- Event rates (safety/efficacy) of 1% to 5% based on historical data
- Presumed between-patient variability in exposure of 30% to 50%

RESULTS

Table 1. Scenario 1: Estimation of Underlying Outcome Event Rates

	Population sampled		
N = 2000 trials	100%	50%	33%
Trials with event rate accurately estimated (≥80%), %	100	95	91
Event rate estimated, %	1.0 (1.0-1.0)	1.0 (0.8-1.2)	1.0 (0.7-1.2)
Number of events	75 (75-75)	38 (30-45)	25 (17-30)
AUC mean ratio*	1.06 (1.06-1.06)	1.06 (0.96-1.17)	1.06 (0.91-1.22)

CI, confidence interval.
Assuming a 1% event rate. Values are median (90% CI) unless otherwise stated.
*AUC mean ratio = mean AUC for patients with/without event.

Table 2. Scenario 2: Characterizing the Underlying Relationship Between Milvexian Exposure and Event Outcomes

	Population sampled		
N = 2000 trials	100%	50%	33%
Number of events	77 (77-77)	39 (32-46)	25 (19-32)
Trials with β1 ≠ 0 (P <0.05), %	100	94	77
Trials with slope within ±35% of true slope, %	100	91	78
AUC mean ratio*	1.32 (1.32-1.32)	1.32 (1.16-1.47)	1.32 (1.11-1.53)

Assuming an exposure-response relationship exists with a 1% event rate (0.5% baseline event rate) and 50% between-subject variability in exposure; β1 = 0.025. Values are median (90% CI) unless otherwise stated.
*AUC mean ratio = mean AUC for patients with/without event.

CONCLUSIONS

- PK sampling of only a subset (33% [5000/15,000]) of the study population provided sufficient data to:
  — **Estimate event rates ≥1% in ≥91% of trials**
  — **Estimate the absence or presence of the exposure-response relationship in ≥77% of trials**
  — **Characterize the underlying exposure-response relationship**
- **The modeling and simulation framework presented herein provided guidance on an optimal PK sampling strategy for the 3 large, ongoing clinical trials of the milvexian phase 3 program and can be applied to optimize PK sampling in other large clinical trials**

Figure 1. Logistic-regression simulations for 1 trial, with 100% of the population sampled and an event rate of 1% (Scenario 2).

Events	Q1	Q2	Q3	Q4
Number (% of total)	14 (18%)	12 (16%)	18 (23%)	33 (43%)

$$\text{Logit} = \beta_0 + \beta_1 \cdot AUC$$

$$P(event) = \frac{exp^{logit}}{1 + exp^{logit}}$$

0.5% baseline event rate

Q, quartile.
Tick marks at y = 0 and y = 0.10 represent individual patients without and with an event, respectively, at the corresponding milvexian exposure.
The blue shaded area represents the 95% CI, and the solid black line is the median.