# Pharmacokinetic Modeling and Simulation of Naltrexone for Extended-Release Intramuscular Injectable Suspension to Derive Alternative Bioequivalence Metrics

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## Introduction

Vivitrol® (naltrexone) 380mg/vial for extended-release (ER) intramuscular injectable suspension (NDA # 21897) by Alkermes is a long-acting injectable (LAI) approved for the treatment of alcohol and opioid dependence. Literature and clinical pharmacology data suggest that Vivitrol is therapeutically effective when plasma concentrations are sustained above a threshold of 1 ng/ml during the desired ER phase. The pharmacokinetics (PK) of Vivitrol is characterized by three peaks, which occur immediately after injection (i.e., 2 hours), after 2-3 days, and after 2 weeks. These peaks are correlated with the different phases of drug release associated with Vivitrol's microsphere formulation – initial release in aqueous environment, the hydration phase, and the sustained-release phase governed by polymer erosion, respectively[1].

The objective of the current study is to utilize the population pharmacokinetic (popPK) model (developed and validated by Alkermes)[2] to simulate the PK profiles of hypothetical naltrexone for ER suspension formulations, and, thereafter, to evaluate the performance of alternative bioequivalence (BE) metrics for the in vivo study to ensure therapeutic equivalence (using the target concentration of 1 ng/ml as the efficacy surrogate). This study was conducted to determine whether BE metrics beside the typical overall AUCs and $C_{max}$ would be necessary in the evaluation of the recommended in vivo two-treatment, parallel BE study to ensure that Q1/Q2 (qualitatively and quantitatively the same to the reference product) generic products are therapeutically equivalent to Vivitrol and to re-assess the modified $f_2$ (i.e., similarity factor) *in vitro* comparative dissolution test.

## Methods

**Vivitrol popPK model:**

Alkermes provided a NONMEM®-based popPK model[2] for Vivitrol developed from a single-center, double-blind, placebo-controlled clinical study where 24 subjects received single or multiple doses the 380 mg strength intramuscularly. Covariates included age, BMI, and weight. Drug absorption was modeled after the different phases of drug release from the microsphere implant as different transit compartments entering into the central component. A two-compartment model describes the clearance and distribution of naltrexone in systemic circulation. For this study, the NONMEM model was translated into R.

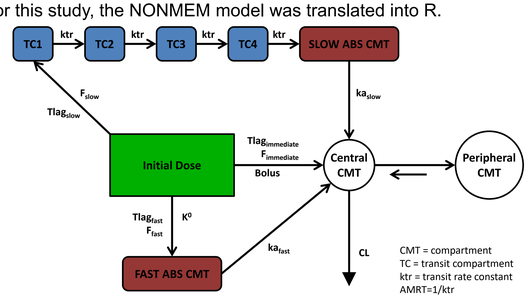



**Figure 1:** Structural model for Vivitrol administrated intramuscularly.

**PK simulation and virtual BE trials:**

Consistent with the recommended BE study for Vivitrol generics, 1000 virtual parallel studies were conducted with both treatment arms receiving the reference product (i.e., Vivitrol 380 mg) with various number of subjects per arms. With numerous BE evaluation metrics (partial AUCs [pAUCs], trough concentration, AUMC, profile comparison tests, and areas above therapeutic threshold,…), the percentage of studies passing BE criteria were determined to determine study power. 1000 subjects were simulated to determine the residual coefficient of variation (CV) for each metric, as well.

A series of hypothetic test formulations' PK profiles were generated by varying the formulation-associated parameters of the popPK model which intends to cover the broad formulation design space. Alternative BE metrics were assessed for these test formulations against reference. The percentage of simulated trials to conclude BE based on the alternative BE metrics were compared to determine the appropriateness of the tested metrics.

## Alternative BE Metrics

Alternative BE metrics were considered to determine which would be appropriate to ensuring that generic formulations could achieve therapeutic threshold plasma concentrations of 1 ng/ml for 28 days[3]. In all, BE metrics evaluated included: the traditional BE metrics, pAUCs ($AUC_{1\text{-}10}$ and $AUC_{10\text{-}28}$), $C_{28}$, area above 1 ng/ml between 10-28 days ($AUC_{above}$), area below 1 ng/ml between 10-28 days ($AUC_{below}$), ratio of $AUC_{above}$ to $AUC_{below}$ ($AUC_{ratio}$), $AUMC_{10\text{-}28}$, and the $f_1$ (difference factor) and the $f_2$ test for PK profile comparison. PK profiles were also evaluated by an efficacy surrogate - the maintenance of plasma concentrations above 1 ng/ml for 28 days.

In addition, we established an inverse in vitro-in vivo relationship between Vivitrol dissolution and PK profile based upon the similarity in cumulative *in vitro* drug release (using the real-time method) and the *in vivo* cumulative AUC. This relationship allowed for the prediction of the *in vitro* dissolution profile associated with the PK profiles simulated and for an evaluation of whether passing of the modified $f_2$ test ensures BE.

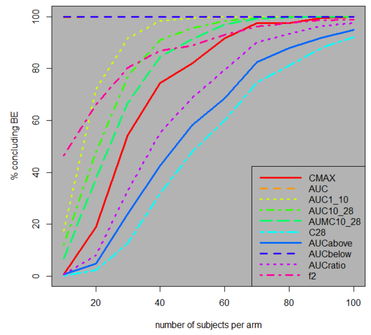
*profile comparison metric equations:*

$$f_1 = 100\frac{\sum_{i=1}^{n}|R_i - T_i|}{\sum_{i=1}^{n} R_i} \qquad f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{i=1}^{n}(R_i - T_i)^2\right]^{-1/2}\times 100\right\} \qquad f_2(\text{mod}) = 50\log_{10}\left\{\left[1+\frac{1}{n}\sum_{i=1}^{n}((R_i - T_i) - X_i)^2\right]^{-0.5} 100\right\}$$

## Results

### Power analysis

**Figure 2:** Probability of concluding BE for Vivitrol 380 mg against itself (reference vs. reference). 'f2' refers to the plasma concentration-based profile comparison test.




| Metric | $C_{28}$ | $AUC_{above}$ | $AUC_{ratio}$ | $C_{max}$ | $AUMC_{10\text{-}28}$ |
|---|---|---|---|---|---|
| CV (%) | 78.60 | 71.02 | 64.31 | 55.43 | 48.65 |
| **Metric** | **$AUC_{10\text{-}28}$** | **$AUC_{1\text{-}10}$** | **$AUC_{0\text{-}t}$** | **$AUC_{below}$** | |
| CV (%) | 44.31 | 38.05 | 13.53 | 6.95 | |

**Table 1.** Residual CV of relevant PK metrics from power analysis calculated from parallel BE analysis of 500 reference profiles against 500 other reference profiles

### E.g. AMRT parameter sensitivity analysis

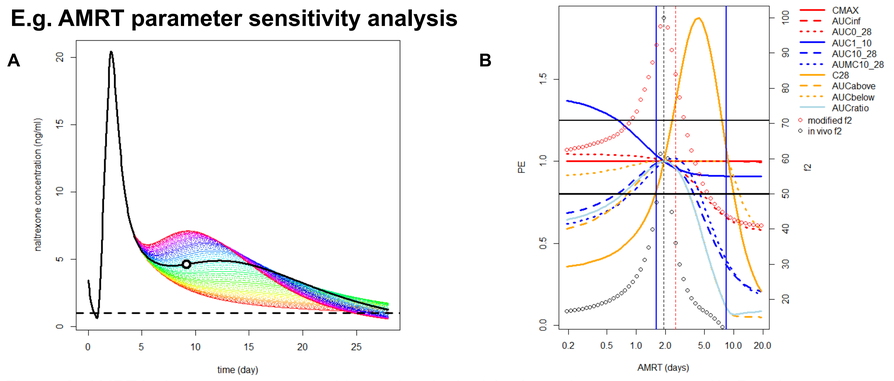



**Figure 3:** AMRT is the average mean residence time in the 'slow' transit compartments. (A) Resultant naltrexone PK profiles from PSA on AMRT. The baseline simulation at AMRT = 1.93 days is emphasized with the black solid curve. Coloration of the curves from lower to higher values of AMRT progress from red to violet, according to the colors of the rainbow – ROYGBIV. The dashed horizontal line represents the 1 ng/ml therapeutic threshold. (B) Sensitivity of PK metrics to AMRT. Point estimate (PE) on the left axis represents the ratio of the resultant PK metric at a specific formulation parameter value to the value of the same PK metric at the baseline value of AMRT (vertical black dashed line). The horizontal black lines represent the BE limits of 0.8 and 1.25. The passing $f_2$ value of 50 overlaps with the PE=0.8 horizontal line. The values of AMRT between the vertical blue lines represent the profiles that stay above 1 ng/ml for 28 days.

## Results (con't.)

Metric combinations:

- 'Traditional': $C_{max}$, $AUC_{0\text{-}\infty}$, and $AUC_{0\text{-}t}$
- 'trad_mf2': 'traditional' + modified $f_2$test
- 'trad_10_28': 'traditional' + $AUC_{10\text{-}28}$
- 'trad_1_28': 'traditional' + $AUC_{1\text{-}10}$ + $AUC_{10\text{-}28}$
- 'minusAUCt': remove $AUC_{0\text{-}t}$ from 'trad_1_28'

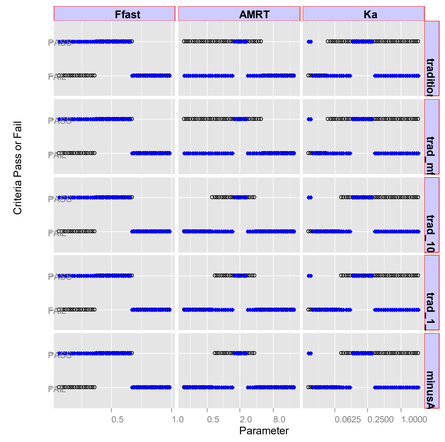



**Figure 4:** The ability of each metric combination (represented by unfilled black diamonds in each panel) to pass or fail each theoretical formulation (passing determined as PEs between 0.8 and 1.25). The blue diamonds represent whether a formulation would be expected to be therapeutically equivalent to Vivitrol based upon sustaining plasma levels above the therapeutic threshold.

## Conclusions

- In September 2015, the BE recommendation was revised to include the pAUCs, while removing $AUC_{0\text{-}t}$ and the modified $f_2$ test as BE evaluation criteria[4]. Our current analysis provided supportive evidence as follows:
- Traditional BE metrics and the modified $f_2$ test resulted in a high false positive rate: several formulations concluded BE but would fail to sustain plasma concentrations above 1 ng/ml for 28 days.
- The inclusion of $AUC_{1\text{-}10}$ and $AUC_{10\text{-}28}$ in the BE evaluation criteria reduces this false positive rate and provides greater assurance that generic formulations are therapeutically equivalent.
- The pAUCs have less intersubject variability than $C_{max}$, thus not expected to increase the study sample size and regulatory burden.
- OGD is currently sponsoring research into the high intersubject variability, study length, and expenditure associated with parallel BE studies with LAI products[5].

## References

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