Evaluation of Partial AUC in Bioequivalence Studies Using Destructive Sampling Design

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Background

Traditional Bioequivalence (BE) Study Design

- All study subjects provide a blood sample at each of the scheduled sampling times
- Therefore, each subject has a complete blood concentration-time profile
- Accordingly, pharmacokinetic (PK) parameters, such as AUC and Cmax, can be estimated for each subject

Background

BE Study with Destructive Sampling Design

- Each subject is sampled only once (i.e., at only one of the scheduled sampling times) throughout the study

- Therefore, only one "composite" profile can be obtained for each treatment group (Test or Reference)

- Accordingly, treatment comparisons of PK parameters are based on estimates derived from the single "composite" profile for each treatment group

Background

PK Metrics to Evaluate BE

- Traditional BE Study Design
  - Cmax – peak exposure (reflecting product differences in rate of absorption)
  - AUC – extent of absorption

- BE Study with Destructive Sampling Design
  - Partial AUC – early exposure (reflecting product differences in rate of absorption)
  - AUC – extent of absorption

Method

Confidence Interval (CI) for T/R Ratio of Partial AUC

Our approach: Bailer-Satterthwaite-Filler

- Bailer (1988): Linear combinations of mean concentrations at sampling times to estimate AUC and its variances, but did not consider CI for T/R ratio.

- Nedelman etc. (1995): Bailer-Satterthwaite method, extending the Bailer approach to improve the precision of the variance estimate and then estimate the CI for AUC differences.

- Wolfsegger (2007): Fieller type approach to construct CI of the mean T/R ratio, the Satterthwaite approximation of the DF and Nedelman's critical value from the t-distribution

Method

Estimate Partial AUC and Its Variance

- Let X_{ijk} be the measured drug concentration from the ith subject at time t_j receiving the treatment *k*, k=T, R for test and reference treatment

$$\bar{X}_{jk} = \frac{1}{n_{jk}} \sum_{i=1}^{n_{jk}} X_{ijk}$$

Method

Estimate Partial AUC and Its Variance

- Using the trapezoidal rule, estimate partial AUC from 0 to the sampling time t_j for treatment *k*

$$\widehat{AUC_{jk}} = \sum_{l=1}^{j} w_l \bar{X}_{lk}, \qquad \text{k=T or R}$$

where $w_1 = \frac{1}{2}(t_1)$ *if j=1*

$$w_l = \frac{1}{2}(t_{l+1} - t_{l-1}) \ \ if\ 2 \le l \le j-1$$

$$w_j = \frac{1}{2}\left(t_j - t_{j-1}\right)$$

Method

Estimate Partial AUC and Its Variance

- The variance of $\widehat{AUC}_{\text{jk}}$ can be estimated by

$$Var(\widehat{AUC}_{\text{jk}}) = S^2_{\text{jk}} = \sum_{l=1}^{j} \frac{1}{n_{lk}} w_l^2 s_{lk}^2$$

where $s_{lk}^2 = \frac{1}{n_{lk}-1} \sum_{i=1}^{n_{lk}} (X_{ilk} - \bar{X}_{lk})^2$

Method

Estimate T/R Ratio of Partial AUC

- The T/R ratio of partial AUC from 0 to the sampling time t_j, $\widehat{Rj}$, can be estimated as

$$\widehat{Rj} = \frac{\widehat{AUC}_{jT}}{\widehat{AUC}_{jR}}$$

Method

90% Confidence Interval for the Ratio of Partial AUC

- $\widehat{AUC}_{jT} = M_{jT}$, variance ($\widehat{AUC}_{jT}$)=$S^2{}_{jT}$
- $\widehat{AUC}_{jR} = M_{jR}$, variance ($\widehat{AUC}_{jR}$)=$S^2{}_{jR}$

- 90% CI of T/R ratio of partial AUC from 0 to the sampling time t_j

$$\frac{(M_{jT}M_{jR}) \pm \sqrt{(M_{jT}M_{jR})^2 - (M^2{}_{jT} - t^2 S^2{}_{jT})(M^2{}_{jR} - t^2 S^2{}_{jR})}}{M^2{}_{jR} - t^2 S^2{}_{jR}}$$

where, t=$t_{95,df}$, $df = \sum_{l=1}^{j}(n_{lT} + n_{lR} - 2)$

Simulation

Impact of Study Design on Partial AUC Approach to Compare Rate of Absorption

- Partial AUC cutoff sampling time
- Blood sampling schedule
- Number of subjects at each sampling time

Simulation

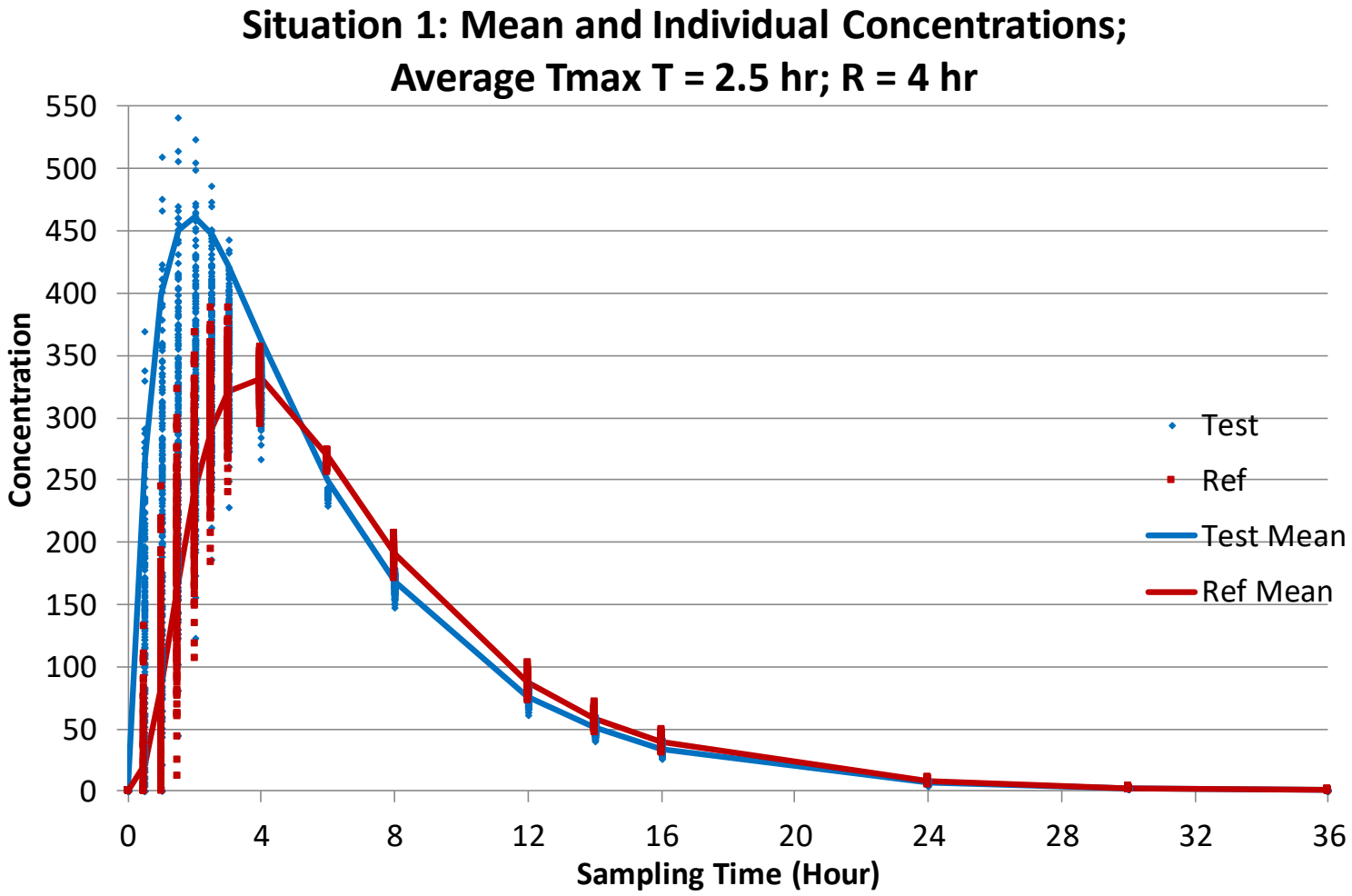
Impact of Study Design on Partial AUC Approach to Compare Rate of Absorption

- Two situations were simulated following a two-compartment model
  - Situation 1: Different absorption rates with low inter-subject variability
  - Situation 2: Same absorption rates with high inter-subject variability

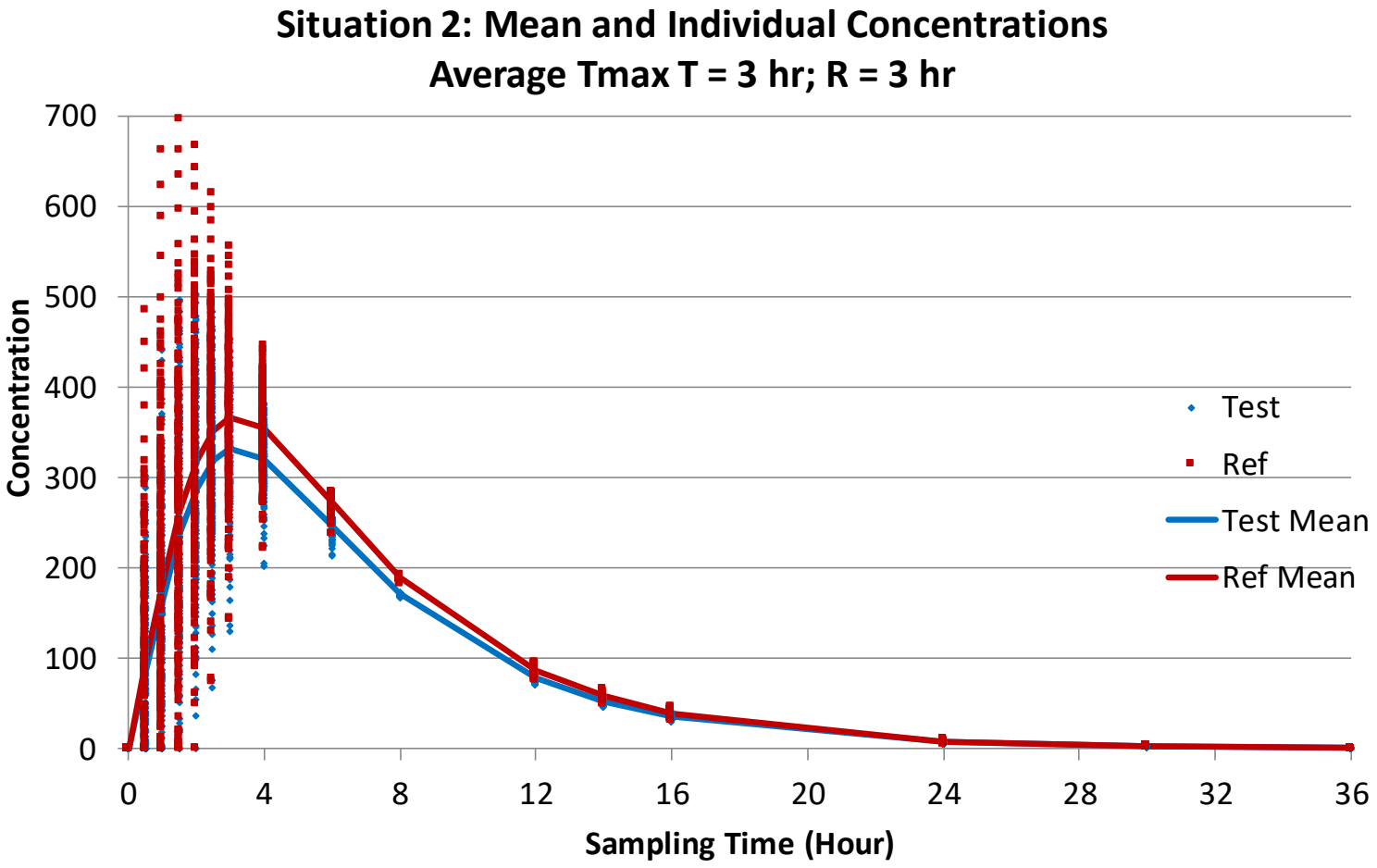
- In addition, a shift in the onset of drug absorption was introduced into the simulated profiles of the test and reference formulations

- Each simulated data set contains 376 subjects (188 in Test, 188 in Reference) with 15 sampling times

Simulation


Situation 1: Mean and Individual Concentrations;
Average Tmax T = 2.5 hr; R = 4 hr
Concentration
550
500
450
400
350
300
250
200
150
100
50
0
0
4
8
12
16
20
24
28
32
36
Sampling Time (Hour)
Test
Ref
Test Mean
Ref Mean

Simulation


Situation 2: Mean and Individual Concentrations
Average Tmax T = 3 hr; R = 3 hr
Concentration
700
600
500
400
300
200
100
0
0
4
8
12
16
20
24
28
32
36
Sampling Time (Hour)
Test
Ref
Test Mean
Ref Mean

Simulation

Impact of Study Design on Partial AUC Approach to Compare Rate of Absorption

- Varying cutoff sampling times for partial AUC
  - $AUC_{0\text{-}0.5\ hour}$
  - $AUC_{0\text{-}1\ hour}$
  - …
  - $AUC_{0\text{-}36\ hour}$

Simulation

Impact of Study Design on Partial AUC Approach to Compare Rate of Absorption

- Varying the sampling schedule
  - Sampling Schedule 1: All (15 sampling times: hours 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 14, 16, 24, 30, and 36)
  - Sampling Schedule 2: Early (12 sampling times: hours 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 36).
  - Sampling Schedule 3: Late (10 sampling times: hours 1, 2, 4, 8, 12, 14, 16, 24, 30, and 36).
  - Sampling Schedule 4: Few (9 sampling times: hours 0.5, 1, 2, 4, 8, 12, 16, 24, and 36).

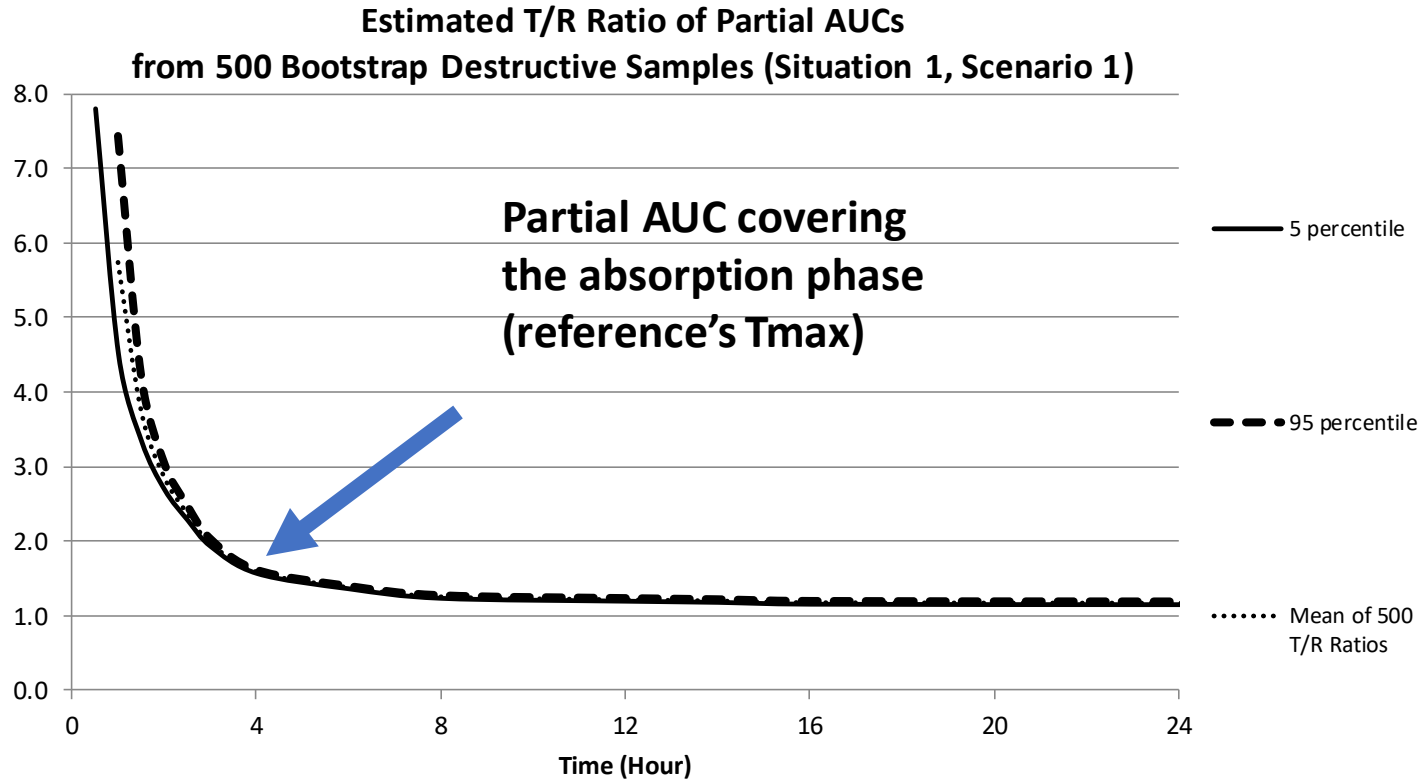
Simulation

Impact of Study Design on Partial AUC Approach to Compare Rate of Absorption

- Varying the number of subjects per sampling time
  - Scenario 1: 20 subjects for sampling times occurring from hours 0.5 to 4, and 5 subjects for sampling times from hours 6 to 36.
  - Scenario 2: 16 subjects for sampling times occurring from hours 0.5 to 4, and 8 subjects for sampling times from hours 6 to 36.
  - Scenario 3: 8 subjects for every sampling time.
  - Scenario 4: 4 subjects for every sampling time

Results

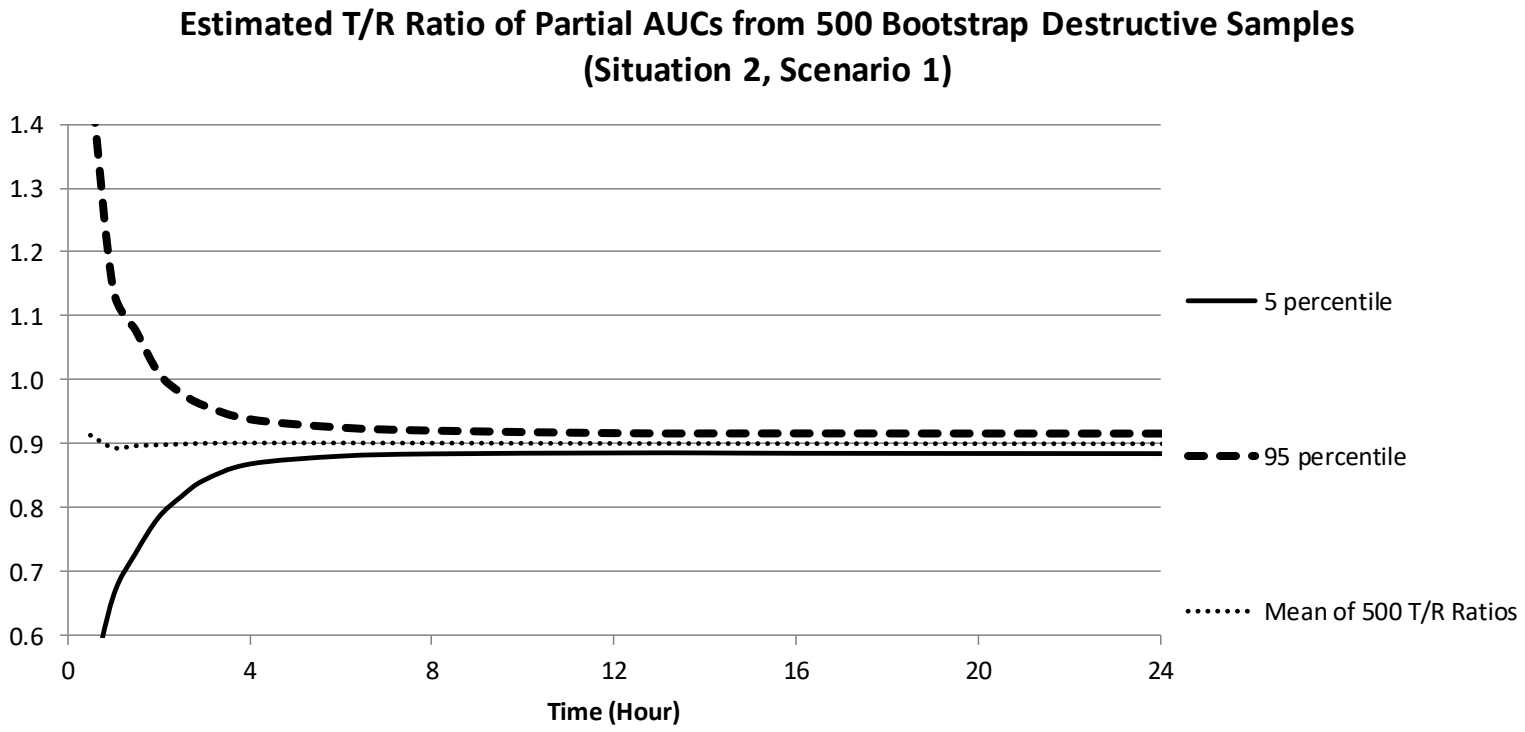
Impact of Cutoff Sampling Time on the Estimated T/R Ratio of Partial AUC



Situation 1: Different absorption rates, low between-subject variability
Scenario 1: n=20 per sampling time for up to hour 4, and n=5 per sampling time after hour 4

Results

Impact of Cutoff Sampling Time on the Estimated T/R Ratio of Partial AUC



Situation 2: Same product absorption rate, high between-subject variability
Scenario 1: n=20/timepoint up to hr 4, and n=5/timepoint after hr 4

Results

Impact of Cutoff Sampling Time on the Estimated T/R Ratio of Partial AUC

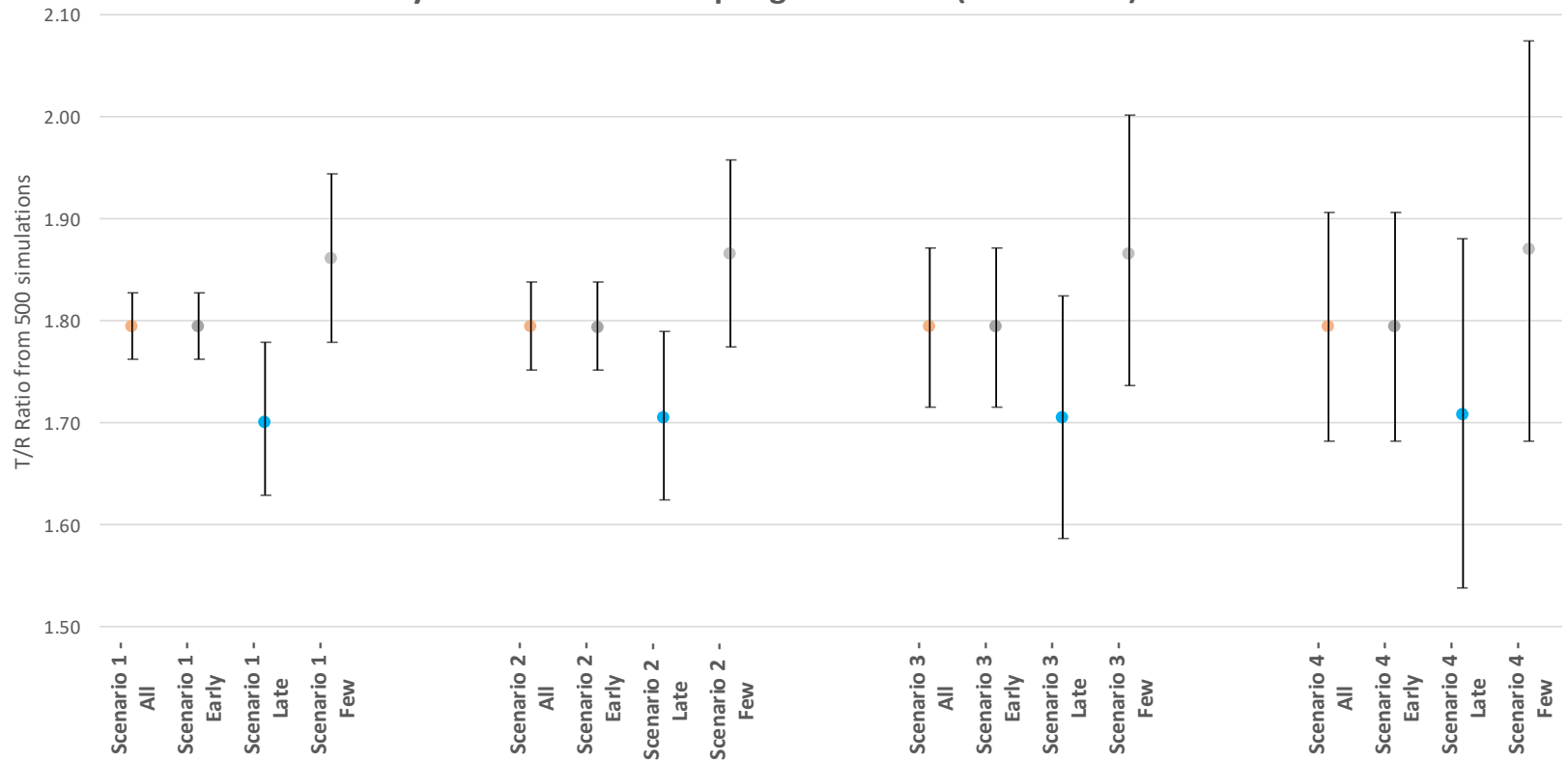
- The partial AUC covering the portion of the profile where absorption is the predominant kinetic process provides a sensitive surrogate for comparing product absorption rates.

- The cutoff sampling time is approximately defined by the composite curve Tmax of the test and/or reference product.

Results

Impact of Sampling Schedule and Number of Subjects on the Estimated T/R Ratio of Partial AUC

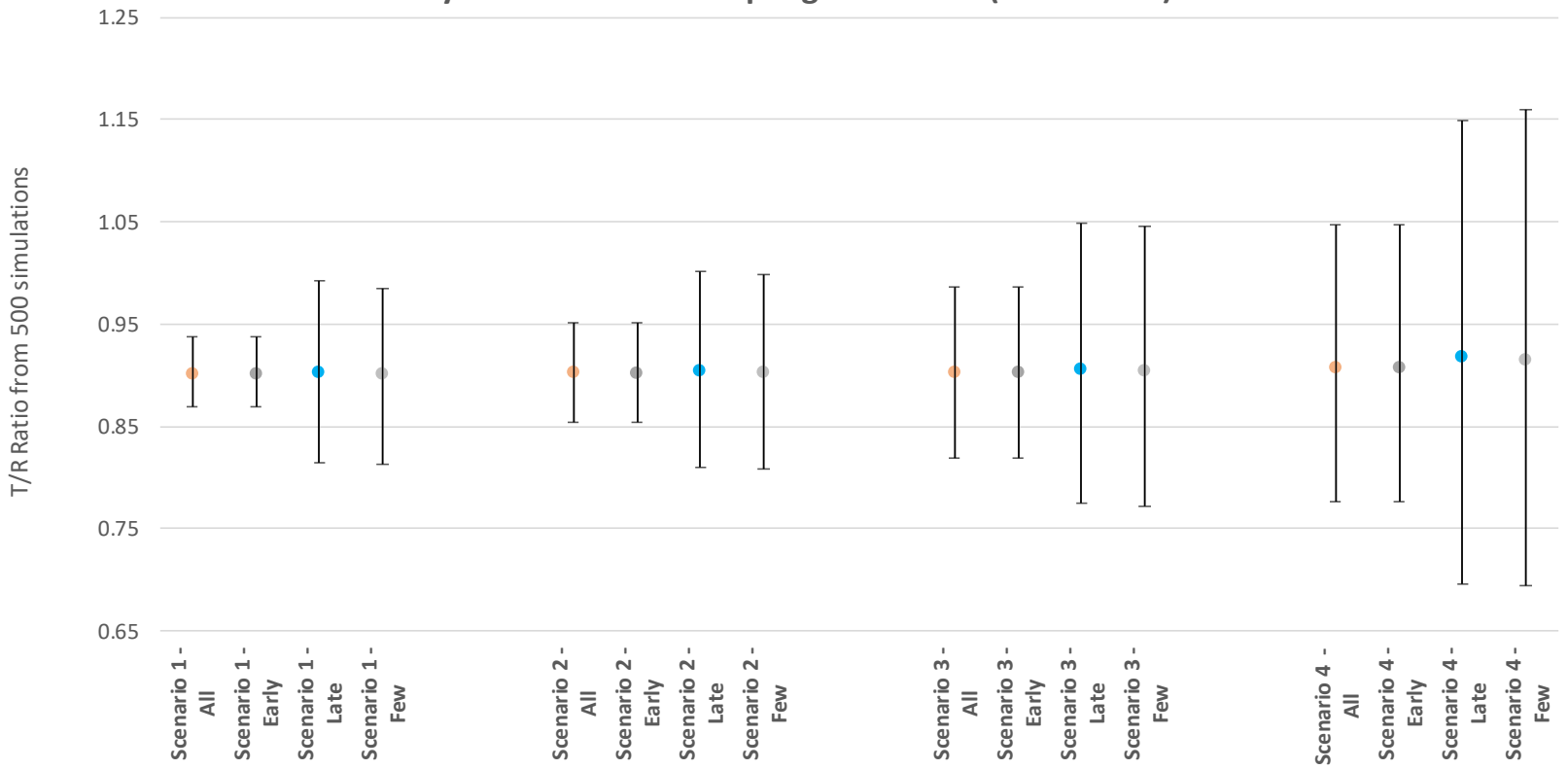
Figure 4a. Estimated T/R Ratio of $AUC_{0\text{-}4\ Hour}$ by Scenarios and Sampling Schedules (Situation 1)



Results

Impact of Sampling Schedule and Number of Subjects on the Estimated T/R Ratio of Partial AUC

Figure 4b. Estimated T/R Ratio of $AUC_{0\text{-}4\ Hour}$ by Scenarios and Sampling Schedules (Situation 2)



Results

Impact of Sampling Schedule and Number of Subjects on the Estimated T/R Ratio of Partial AUC

- Impact on T/R ratio of $AUC_{0\text{-}4\ hour}$
  - Omitting earlier sampling times -> less likely to capture the difference in product rates of absorption, if it exists.
  - The fewer the sampling times included in the estimate, the wider the 95^{th}-5^{th} percentile range.
  - The fewer the number of subjects included at the sampling times covered by the partial area, the wider the 95^{th}-5^{th} percentile range.

Conclusions

- **To evaluate product BE using studies with destructive sampling design, Partial AUC covering the absorption phase of the test/reference products provides a reliable surrogate to compare rate of absorption.**

- **Bailer-Satterthwaite-Fieller CI approach may be applied in the studies with destructive sampling design for assessing BE by constructing 90% CI for the T/R ratio of partial AUCs.**

Discussion

Points to consider in designing a BE study using destructive sampling design

- When comparing product rates of absorption, the partial area should not extend beyond composite Tmax of the test and/or the reference product.

- To improve our ability to describe the most rapidly changing portion of the composite curves, it is important to focus on capturing drug concentrations during those sampling times up to the estimated Tmax of the test and/or reference formulations.

- If there is a constraint on the study sample size, allocating more animals to the sampling times prior to the composite Tmax reduces the variability associated with the partial AUC estimate.

Discussion

Why we choose partial AUC instead of composite Cmax to compare the rate of absorption

- It reduces the risk of biasing the equivalence decision based upon the sampling schedule.

- The greater the variability in time to peak between subjects, the less likely the composite Cmax will be well-defined from a composite curve.

- Partial AUC estimates include a greater number of subjects in the calculation of the 90% CI of estimated T/R ratio.

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Thank you !!!