

PHUSE US Connect 2021 - Presentation No: DV03

Visualization of Sparse PK Concentration Sampling Data, Step by Step (Improvement by Improvement)

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Pharmacokinetic (PK) data:

- – Rich (intense) concentration sampling. Routinely collected in early stages of drug development. The collected PK characteristics aid in the selection of promising molecules and help to make a go/no-go decision and to select a right dosage. Rich PK information implies that complete concentration–time profiles were determined.
- – Sparse concentration sampling is very common in late phase (Phase II and III) studies. Sparse PK information implies that few samples are collected during each study or study day from each patient. Because of ethical and medical concerns, only a limited number of samples are taken from any given patient. Sparse PK sampling is also very common in pediatric studies to minimize the total volume of blood sampled.

As usual, results of PK sampling might need visual representation. The anticipated graph will have a combination of timepoint boxplots overlaid with scatterplots. This type of overlay became compatible with the PROC SGPLOT starting from version 9.4M3. Starting with this version of SAS, bar charts can be done over a linear category axis.

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According to study protocol, each patient received daily administration of oral study drug ABCD.

PK blood samples are drawn on:

- Cycle 1 Day 1 (1 - 4 hours postdose)
- Cycle 1 Day 15 (predose; 1 - 4 hours postdose; 6 - 9 hours postdose)
- Cycle 2 Day 1 (predose; 2 - 6 hours postdose)
- Cycle 3 Day 1 (predose)

Collected PK data were mapped into SDTM domain PC. Analysis data set ADPC was created.

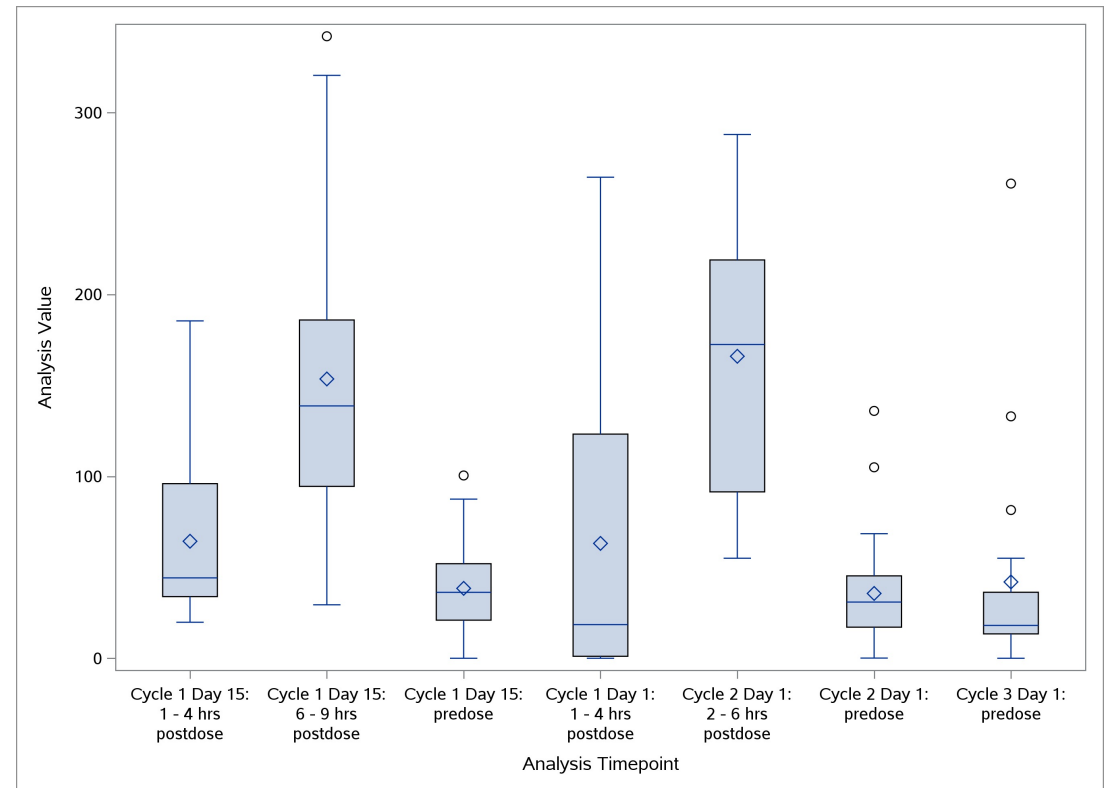
SUBJID	VISIT	VISITNUM	PCTPT	PCTPTNUM	ATPT	AVAL	ARRLT (Actual Relative Time (hrs))
1001	Cycle 1 Day 1	1.01	1 – 4 hrs postdose	2	Cycle 1 Day 1: 1 - 4 hrs postdose	44.6	0.5
1001	Cycle 1 Day 15	1.15	predose	0	Cycle 1 Day 15: predose	41.8	
1001	Cycle 1 Day 15	1.15	1 – 4 hrs postdose	2	Cycle 1 Day 15: 1 - 4 hrs postdose	40.9	0.66677

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STEP 1: STARTING BOXPLOT

```
proc sgplot data = from_adpc;  
  vbox aval / category = atpt;  
run;
```



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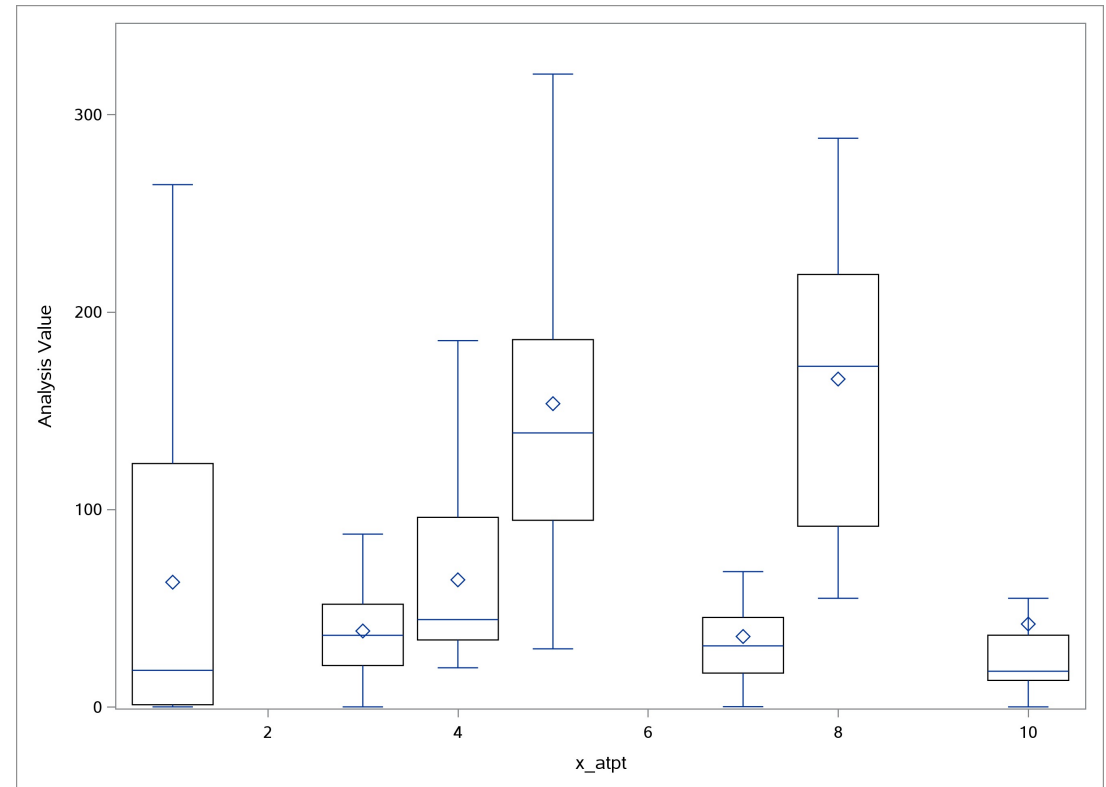
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STEP 2: ORDERING BOXPLOTS AND ARRANGING THEIR LOCATIONS; REMOVING OUTLIERS AND FILLINGS

New variable X_ATPT:

- 1 for Cycle 1 Day 1: 1 - 4 hrs postdose
- 3 for Cycle 1 Day 15: predose
- 4 for Cycle 1 Day 15: 1 - 4 hrs postdose
- 5 for Cycle 1 Day 15: 6 - 9 hrs postdose
- 7 for Cycle 2 Day 1: predose
- 8 for Cycle 2 Day 1: 2 - 6 hrs postdose
- 10 for Cycle 3 Day 1: predose

```
vbox aval / category = x_atpt  
  nooutliers nofill;  
xaxis type = linear;
```



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STEP 3: ADJUSTING HORIZONTAL AXIS; KEEPING ONLY NEEDED TICKS IN NEEDED FORMAT

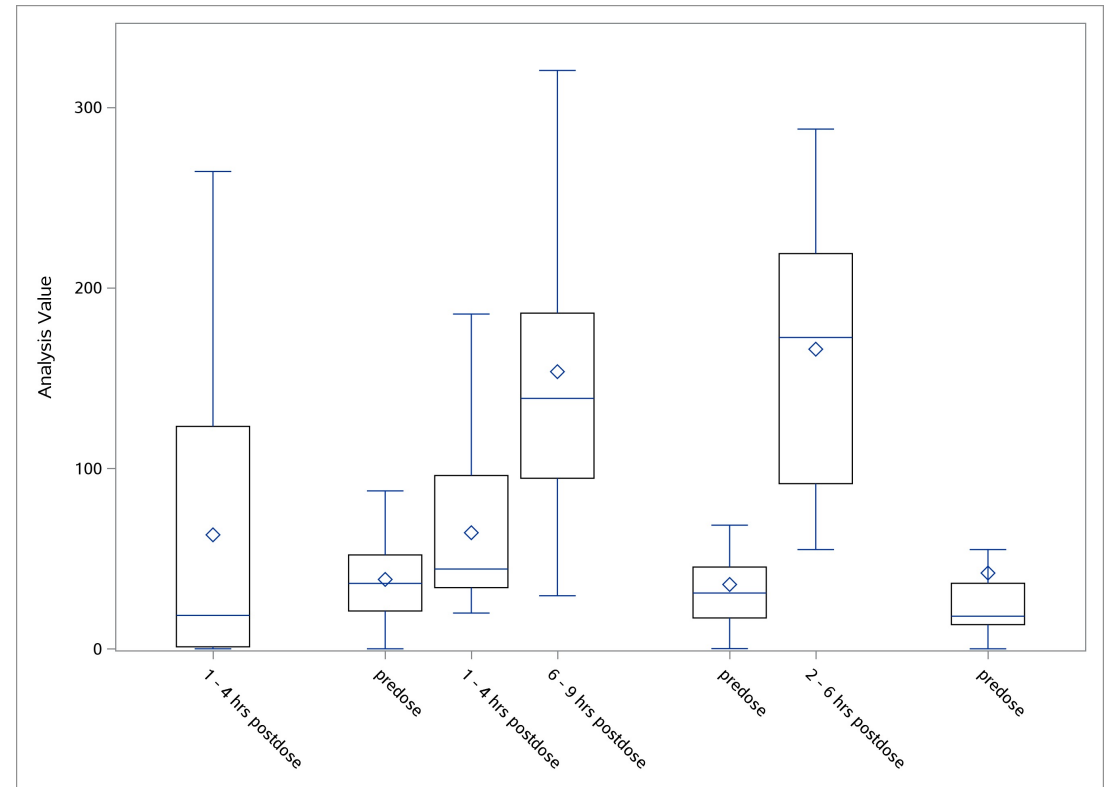
Value of macro variable

needed_hor_values:

1 3 4 5 7 8 10

New format tpt_values. for displaying
needed horizontal ticks.

```
xaxis type = linear display =  
  nolabel) values =  
  &needed_hor_values)  
valuesformat = tpt_values.  
fitpolicy = rotate  
offsetmin = 0.1 offsetmax =  
0.1;
```

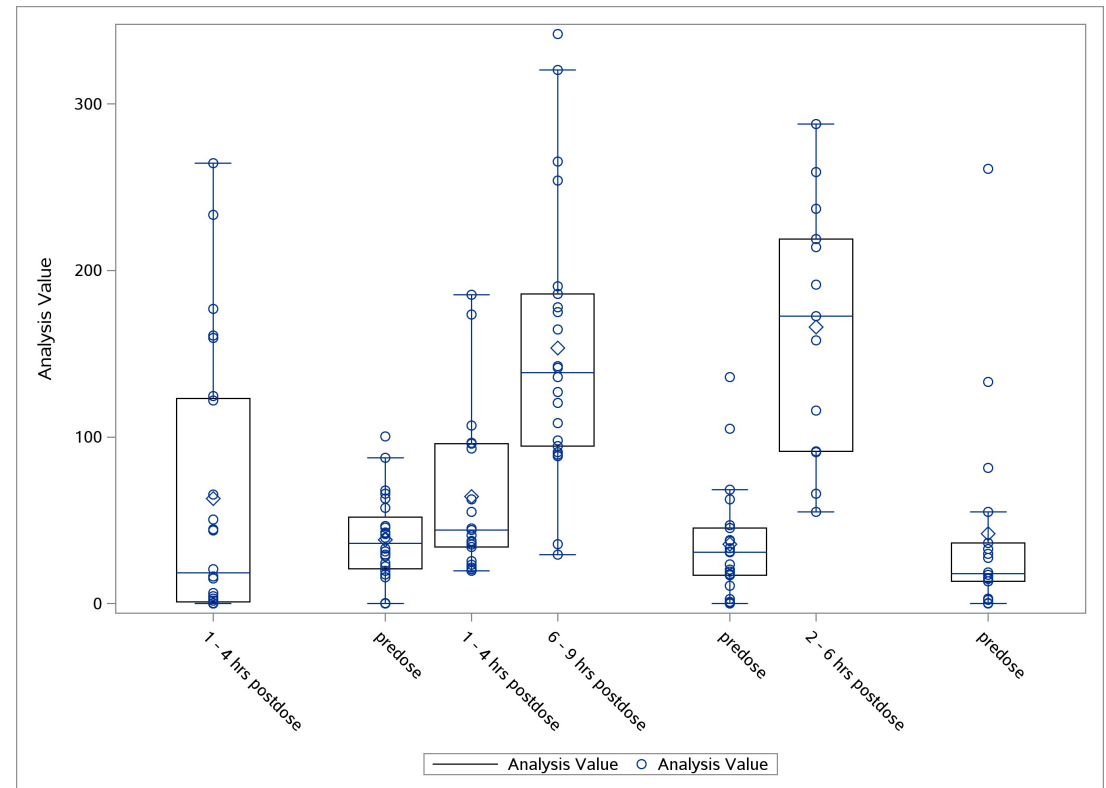


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STEP 4: ADDING SCATTERPLOT (DISPLAYING RESULTS OF INDIVIDUAL SAMPLINGS BY TIMEPOINTS)

```
scatter x = x_atpt y = aval;
```



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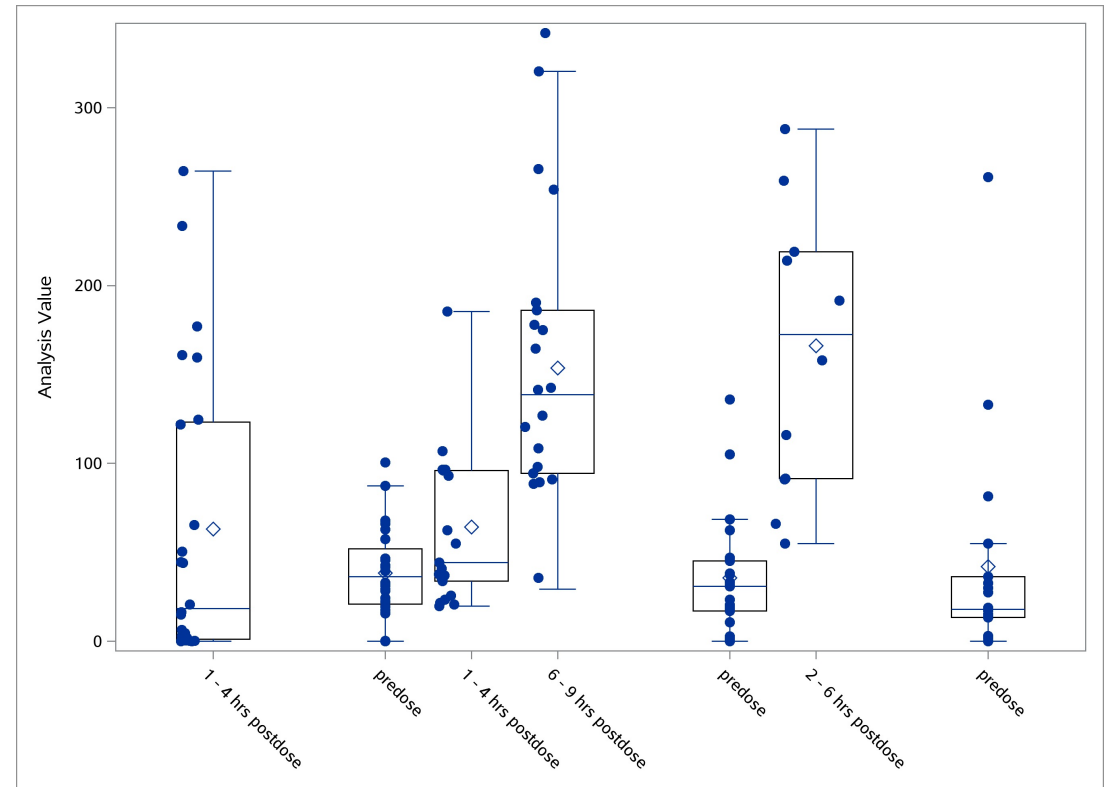
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STEP 5: ADJUSTING SCATTERPLOT; SHIFTING VALUES OF INDIVIDUAL SAMPLING RESULTS USING ELAPSED TIME INFORMATION; ELIMINATING AUTOMATICALLY CREATED LEGEND

Option `noautolegend` in `PROC SGPLOT`

Additional variable `x_scatter` gives us the value of the horizontal coordinates of each dot for the results of individual sampling (the value this variable is based on actual reference (elapsed) time).

```
scatter x = x_scatter  
       y = aval / jitter  
markerattrs =  
       (symbol = circlefilled);
```



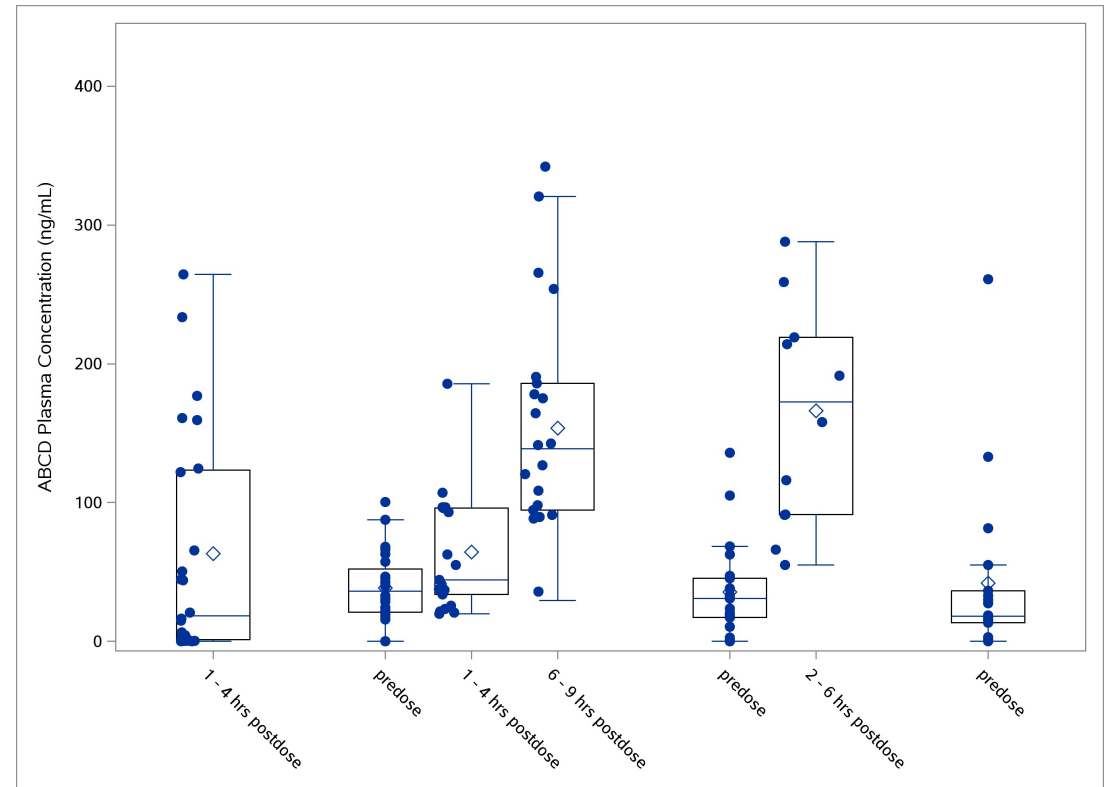
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STEP 6: ADJUSTING VERTICAL AXIS

- Reserving top 10% for future annotation
(offsetmax = 0.1)
- Options thresholdmin = 1 and thresholdmax = 1 in yaxis statement ensures that the data range is bounded by tick marks.

```
yaxis  
  type = linear  
  label = 'ABCD Plasma  
    Concentration (ng/mL)'  
  thresholdmin = 1  
  thresholdmax = 1  
  offsetmax = 0.1;
```

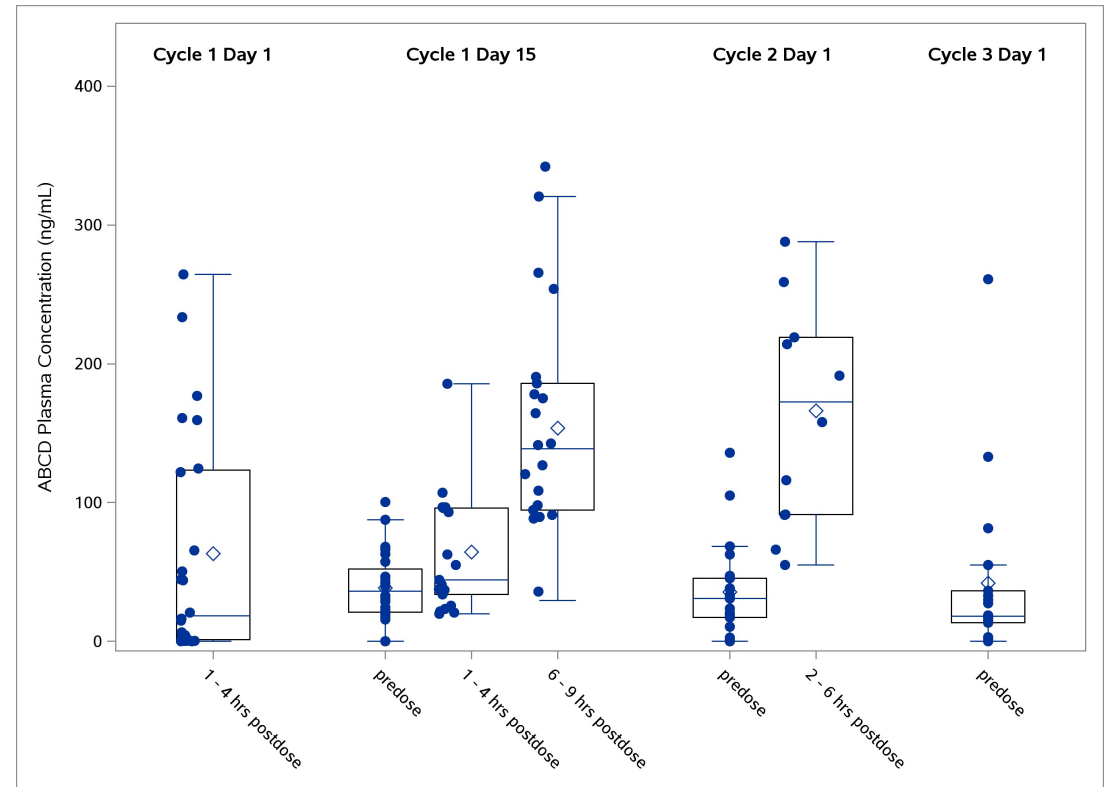


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STEP 7: ADDING INFORMATION ABOUT VISITS AS AN ANNOTATION

- It makes sense to display the visit information in the center, above the timepoints related to each visit.
 - The specially created data set `for_visit_annotation` will be applied in `PROC SGPLOT` statement
- ```
proc sgplot
 data = from_adpc
 sganno = for_visit_annotation
 noautolegend;
```

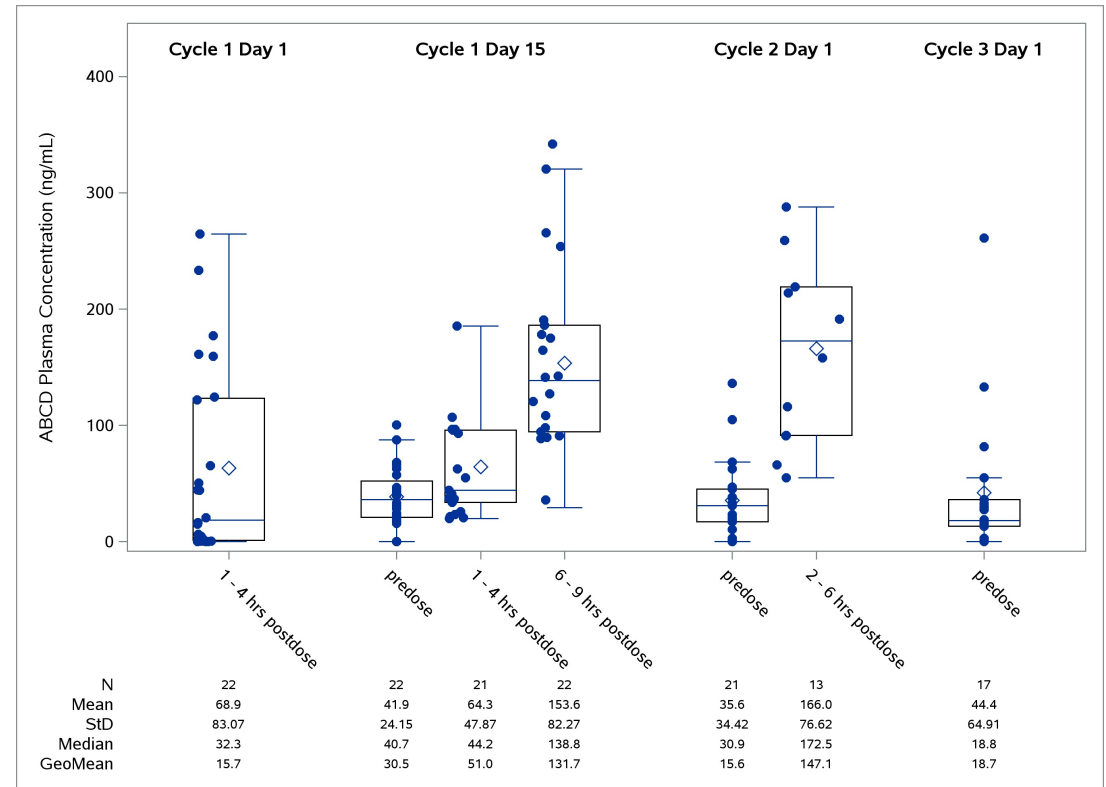


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### STEP 8: ADDING NECESSARY STATISTICS

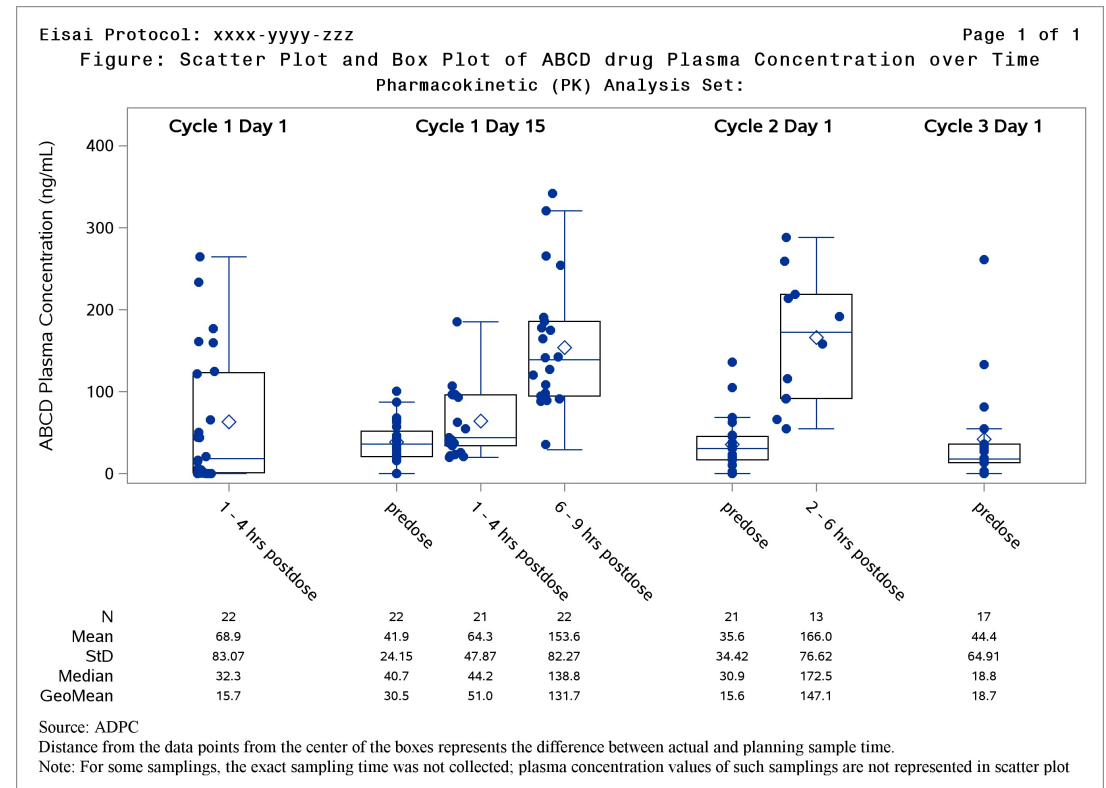
- Check with Study Pharmacological Director how to handle concentration values Below Level of Quantification (BLQ) in derivation of geometric mean.
  - Use `proc univariate` for obtaining needed statistics; output in separate data set `stats`
  - Concatenate data sets from `adpc` and `stats` into data set `final` (will be used in `PROC SGPLOT`)
- ```
label n = 'N' mean = 'Mean'  
      std = 'StD' median = 'Median'  
      geomean = 'GeoMean';  
xaxistable n mean std median  
           geomean / location = outside;
```



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STEP 9: TITLES / FOOTNOTES



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POSSIBLE FURTHER STEPS (FURTHER IMPROVEMENTS)

- applying different colors,
- applying different fonts,
- applying attribute map(s)
- other features

This is not the subject of the presentation. For more details, please see SAS® 9.4 ODS Graphics: Procedures Guide.

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CONCLUSIONS

By applying the techniques described in this paper, the reader can successfully visualize results of sparse Pharmacokinetic sampling. We suggest creating this type of graph, a combination of boxplot and scatterplots that also displays the required statistics.

Similar graphs (a combination of boxplots and scatterplots with displaying required statistics) can be used in visualizing results of other discrete measurements, such as Vital Signs, ECG, or Laboratory Data. This is one of the first articles to demonstrate that the combination of a boxplot and scatterplot in the same graph can be easily achieved by using PROC SGPLOT without using more complicated Graph Template Language.

This article can be used as methodological guidance, with the main idea: **Do not try to create complicated figures all at once, do it step by step (improvement by improvement).**

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CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the authors at:

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**ANY
QUESTIONS?**

