

Graphical Examination of Pharmacokinetic Parameters versus Dose in Early Phase Dose Escalation Trials Using SAS® Graph Template Language (GTL)

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ABSTRACT

An important primary objective of early phase dose escalation trials is to determine the safety, tolerability, and maximally tolerated dose (MTD) or recommended phase 2 dose (RP2D) of the study drug. As a secondary objective, a dose-proportionality analysis may be conducted to evaluate the relationship between pharmacokinetic parameters and dose levels. These PK parameters may include C_{max} (maximum observed plasma concentration) and AUC (area under the plasma concentration-time curve) derived based on the study drug plasma concentrations of individual subjects. A visual examination of these PK parameters plotted against administered dose levels is therefore the first step for understanding the PK-dose relationship. SAS GTL is a powerful tool to generate graphical display for examining PK parameters versus dose.

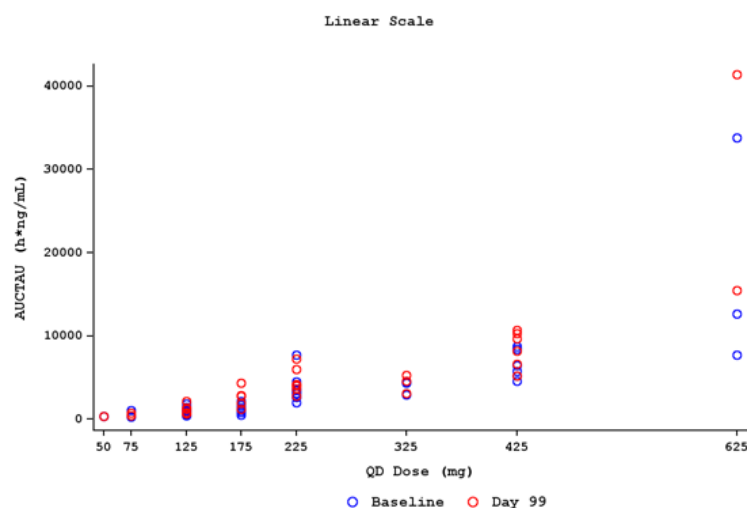
INTRODUCTION

In early phase dose escalation trials, safety endpoints such as adverse events, deaths due to AE, dose limiting toxicities, and hepatobiliary laboratory events are regularly monitored for each dose cohort to help make decisions for escalating, de-escalating, staying at the same dose, or stopping the study. Pharmacokinetic profile and the dose proportionality of PK parameters and dose levels may provide insight of the dose exposure relationship.

This paper will first illustrate how to display a graph of C_{max} and AUC versus dose level in linear and semi-log scales on the same page using SAS GTL. A Dose proportionality analysis using SAS PROC MIX with the associated graphical display will also be shown.

PK PARAMETERS VERSUS DOSE LEVELS

PK parameters C_{max} (maximum observed plasma concentration) and AUC (area under the plasma concentration-time curve) are derived based on the study drug plasma concentrations of individual subjects in the trial. These parameters are usually plotted against different administered dose levels to examine the drug exposure and dose relationship. In the example plot below, AUC over dosing interval in linear scale is plotted against the different QD dose levels at two time points.

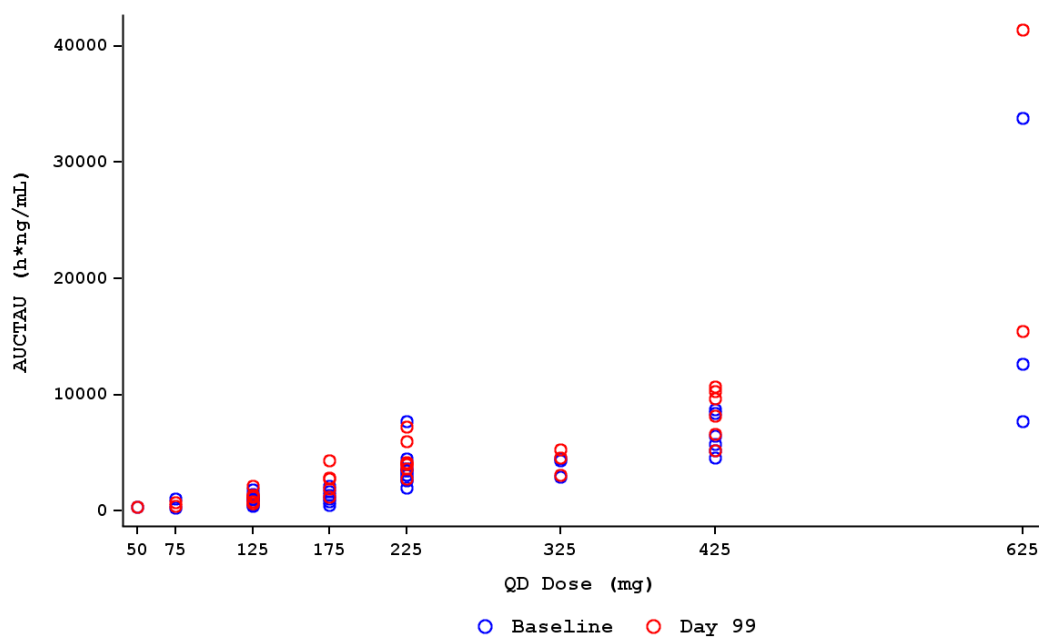


In addition, we may also want to display AUC in a log scale versus dose levels on the same page as shown below. This can be easily accomplished using SAS GTL PROC TEMPLATE and SGRENDER.

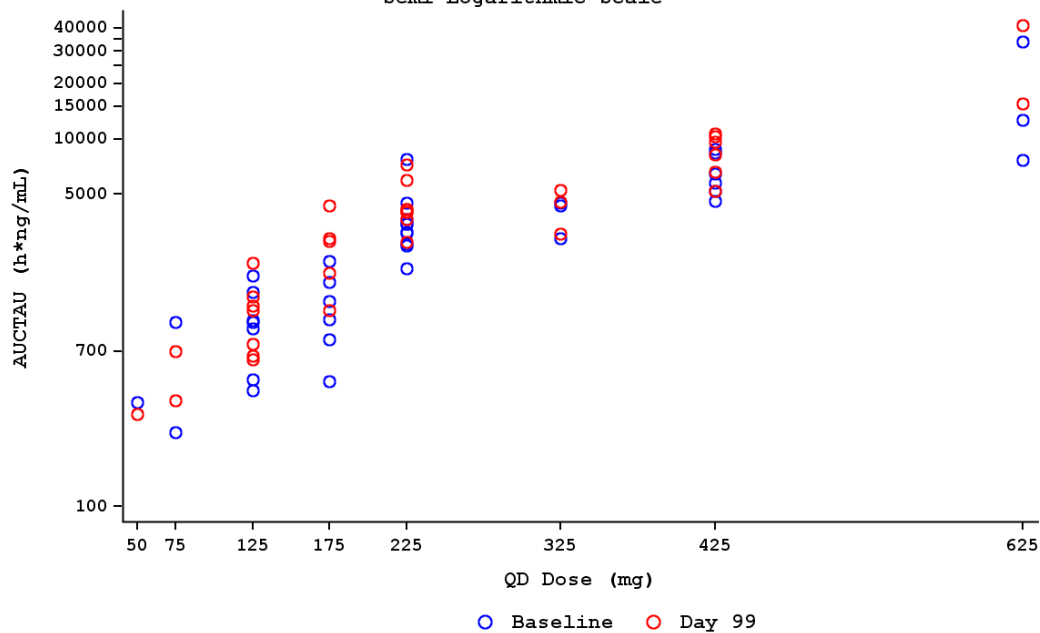
Individual Drug XYZ Plasma Pharmacokinetic Parameters versus Dose Plot

AUC Over Dosing Interval (h*ng/mL) (Linear and Semi-Log)

Linear Scale



Semi-Logarithmic Scale



SAS GTL:

The LAYOUT LATTICE statement in PROC TEMPLATE is a handy tool for displaying multiple graphs on the same page. The following example divides a graph into 4 different rows, with two graphs stacked on top of each other, in a portrait orientation. We have 4 rows because we want two narrow bands for the labels of each plot.

```
layout lattice / rows=2 rowweight=(0.05 0.45 0.005 0.45);  
...  
...  
endlayout;
```

The LAYOUT OVERLAY statement in PROC TEMPLATE can be used to generate the label and the actual graph display. The following example creates the label "Linear Scale". The same code can be repeated to create the label for "Semi-Logarithmic Scale".

```
layout overlay / walldisplay=none xaxisopts=(display=none) yaxisopts=(display=none);  
                entry halign=center textattrs=(size=7 family="Courier New" weight=bold)  
                halign=center "Linear Scale"/valign=top;  
  
endlayout;
```

The following LAYOUT OVERLAY statement creates a scatter plot for AUC in linear scale versus dose levels in linear scale. Note that the same code can be repeated to generate a scatter plot for AUC in log scale versus dose, by simply replacing "**type=linear**" with "**type=log logopts=(base=10 minorticks=true)**" in the YAXISOPTS option.

```
layout overlay / xaxisopts=(label="QD Dose (mg)" labelattrs=(size=7pt)  
                        display=(line tickvalues ticks label) type=linear  
                        linearopts=(tickvaluefitpolicy=stagger tickvaluelist=(&trt1))  
                        tickvalueattrs=(size=6pt family="Courier New" weight=bold))  
                yaxisopts=(label="&p" labelattrs=(size=7pt)  
                        display=(line tickvalues ticks label) type=linear  
                        tickvalueattrs=(size=6pt family="Courier New" weight=bold));  
  
                scatterplot x=trt1 y=d1 /markerattrs=(color=blue symbol=circle size=7px)  
                legendlabel="Baseline" name="a";  
  
                scatterplot x=trt1 y=d15 /markerattrs=(color=red symbol=circle size=7px)  
                legendlabel="Day 99" name="b";  
  
                discretelegend "a" "b" /location=outside across=2 autoalign=(right)  
                title=" " border=false valueattrs=(size=7pt);  
  
endlayout;
```

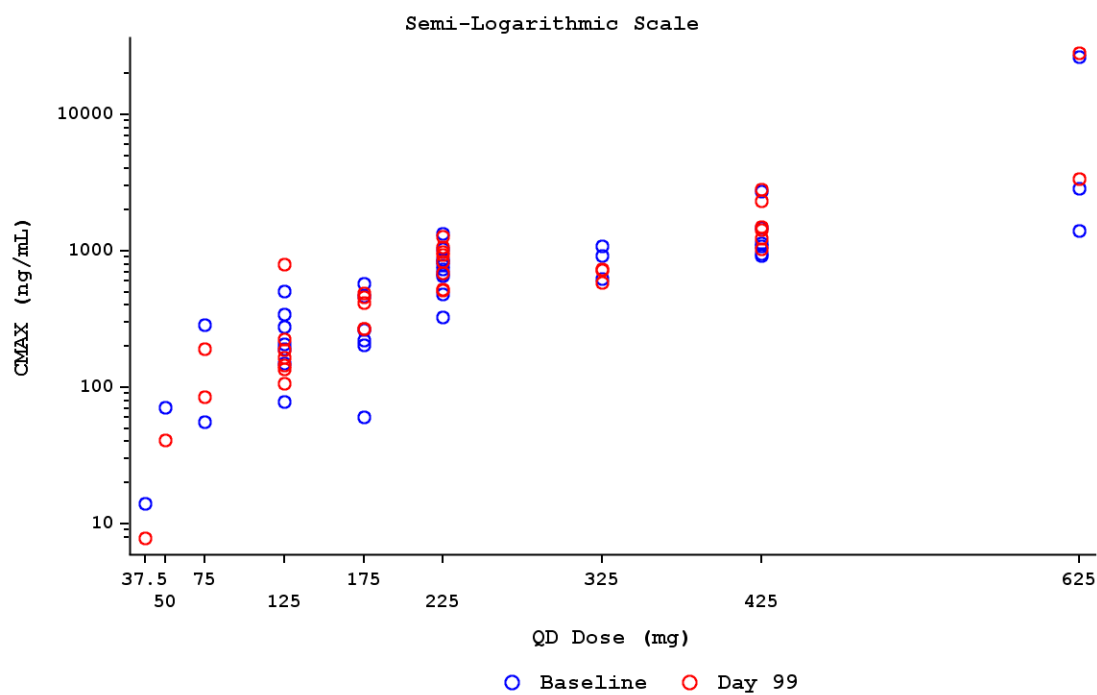
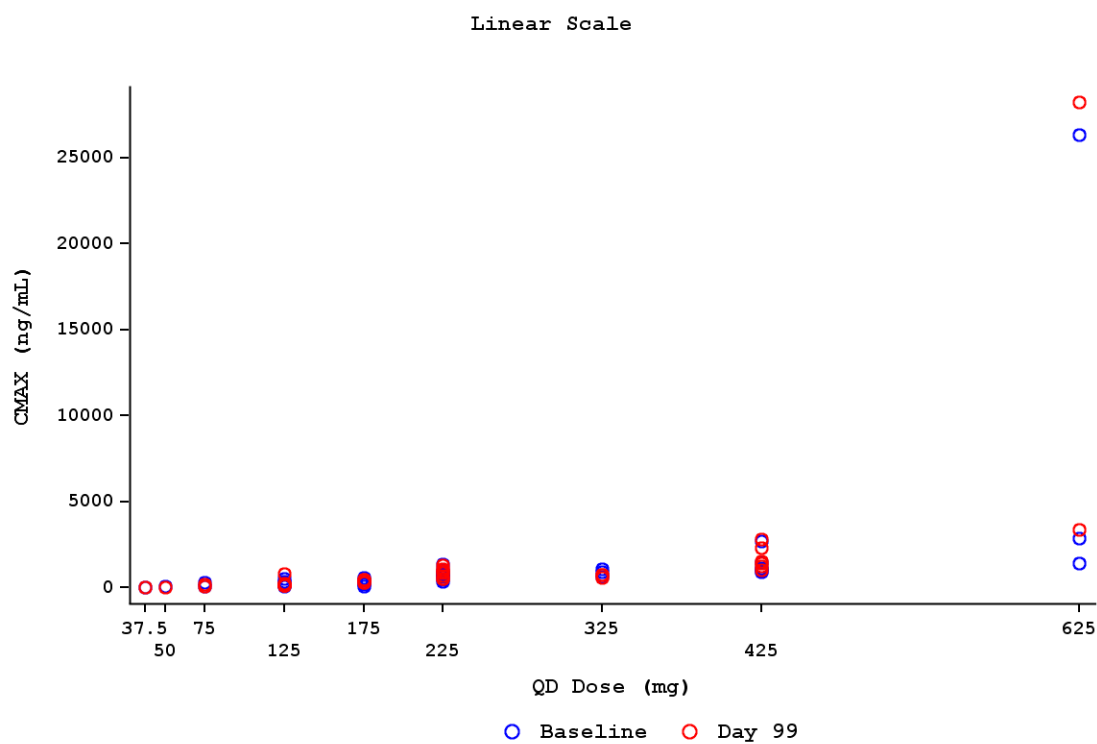
A few additional notes:

- i. The XAXISOPTS option defines the X-axis of the graph. The macro variable TRT1 contains the x-axis values, e.g. 50, 75, 125, 175.
- ii. The YAXISOPTS option defines the Y-axis of the graph. The macro variable P contains the label value of the parameter, e.g. AUCTAU (h*ng/mL).
- iii. The SCATTERPLOT statement creates a scatter plot of AUC value (variable TRT1) versus dose levels at two different time points: baseline in blue (variable D1) and day 99 in red (variable D15).
- iv. The DISCRETELEGEND statement creates the legend for the graph.

The following graph shows the PK parameter Cmax in linear and log scale plotted against the administered dose levels on one page using SAS GTL. PK parameters, not limiting to AUC or Cmax, can be generated dynamically and efficiently in a SAS macro using GTL. Appendix 1 provides the SAS program on how this can be accomplished.

Individual Drug XYZ Plasma Pharmacokinetic Parameters versus Dose Plot

Max Conc (ng/mL)
(Linear and Semi-Log)



DOSE PROPORTIONALITY:

A common approach to test dose proportionality is by using power model, regression of log transformed data. The modeling assumption is that the logarithm of the PK variable is linearly related to logarithm of dose (Smith et al., 2000):

$$\ln(\text{PK}) = \beta_0 + \beta_1 \cdot \ln(\text{dose})$$

The analysis can be performed using PROC MIXED in SAS/STAT after transforming the PK and dose variables to log scale in the DATA STEP as in the following example.

```
data rep;
  set rep;
  laval=log(aval);
  ldose=log(trt1);
run;

ods output SolutionF = sf0 ;
proc mixed data = rep method = ML;
  class subjid;
  model laval = ldose / alpha = 0.10 cl solution ddfm = kr ;
  random subjid; **subject as random effect;
run;
ods output close;

proc sql noprint;
  select round(estimate,.01) into: slope from sf0 where effect='ldose';
  select round(estimate,.01) into: intercept from sf0 where effect='Intercept';
quit;

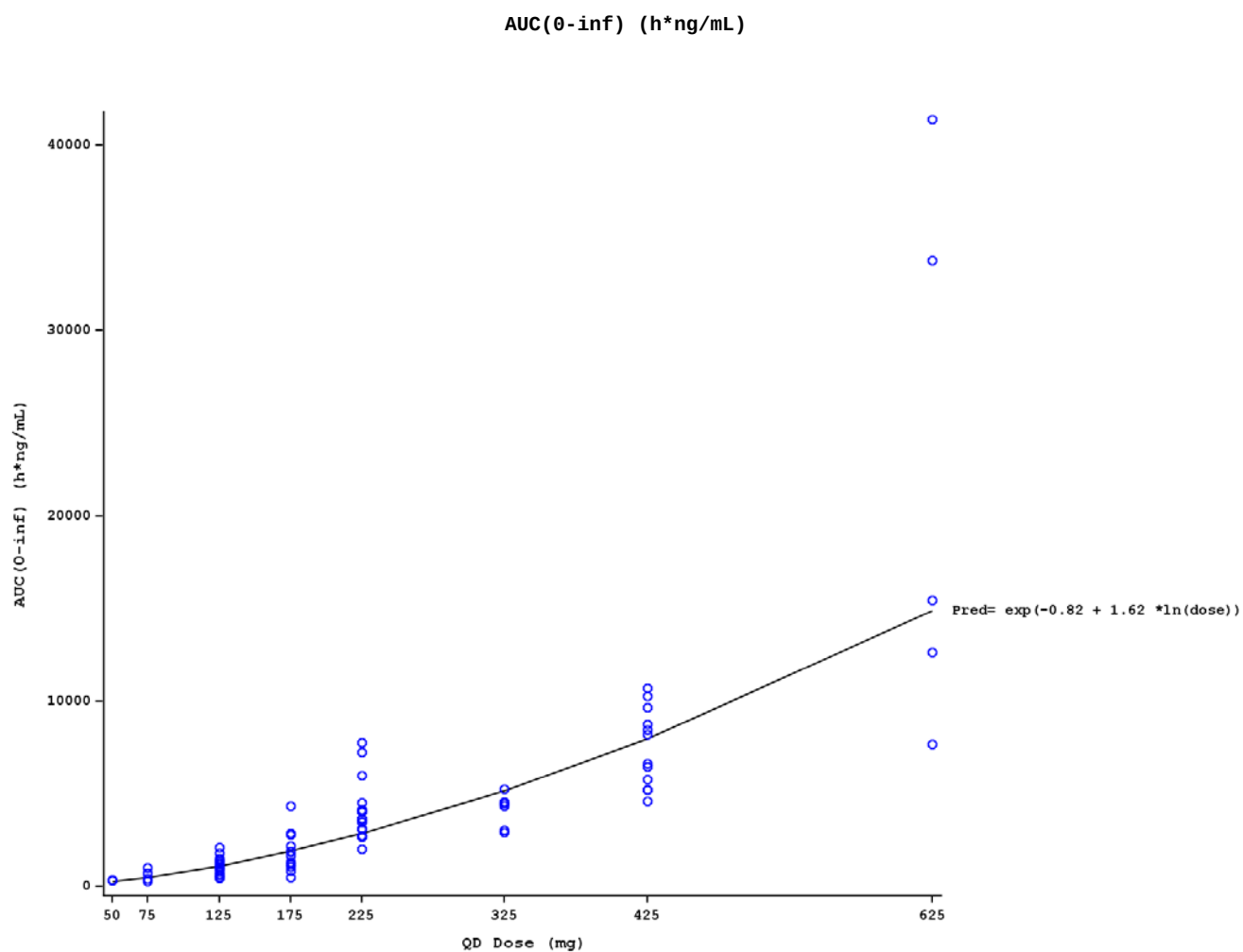
proc sort data=rep;
  by trt1;
run;

data final;
  set rep;
  by trt1;
  slope=&slope;
  intercept=&intercept;
  if first.trt1 then curve=exp(intercept + slope*ldose); **the power model curve;
run;
```

Using the SERIESPLOT statement in PROC TEMPLATE, the power model curve can be displayed on the same plot AUC(0-inf) versus dose as shown in the next graph.

```
seriesplot x=trt1 y=curve/curvelabel="Pred= exp(%cmpres(&intercept) + %cmpres(&slope)
*ln(dose))" curvelabellocation=outside curvelabelattrs=(size=6pt family="Courier New");
```

Drug XYZ Plasma Pharmacokinetic Parameters versus Dose Plot with Power Model Curve



CONCLUSION

SAS GTL is a flexible and versatile tool for visual examination of PK parameters in early phase dose escalation trials. GTL can further be used for graphing multiple safety endpoints such as adverse events, deaths due to AE, dose limiting toxicities, and hepatobiliary laboratory events for individual patient profile. This will be an important topic for another paper.

REFERENCES

Newlands, A. (2006), "Statistics and Pharmacokinetics in Clinical Pharmacology Studies", PhUSE 2006

SAS Institute Inc. (2014), "SAS 9.4 Graph Template Language: User's Guide, Third Edition", Cary, NC, USA

Smith et al. (2000), "Confidence Interval Criteria for Assessment of Dose Proportionality", Pharmaceutical Research, Vol. 17, No. 10, Plenum Publishing Corporation, NY, USA

CONTACT INFORMATION

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APPENDIX 1

```
%macro pp;
libname libanal "C:\Users\tsangc\pk plot";

**REP is a temporary data set derived from ADaM ADPP where derived PK parameters are stored;
**Save PK parameters in a macro variable PARM;
proc sql noprint;
  select distinct parm into: parm separated by '|' from rep;
quit;

options orientation= portrait;

ODS RTF file="C:\Users\tsangc\pk plot\pkplot.rtf" bodytitle style=PR0128pt1 nogtitle
nogfootnote;

ods graphics / reset=all border=off width=6 in height=8in;

%macro temp(p);
proc template;
  define statgraph sgplot;
    begingraph;
      layout lattice / rows=2 rowweight=(0.05 0.45 0.005 0.45);

      layout overlay / walldisplay=none xaxisopts=(display=none) yaxisopts=(display=none);
        entry halign=center textattrs=(size=7 family="Courier New" weight=bold)
        halign=center "Linear Scale"/valign=top;
      endlayout;
      layout overlay / xaxisopts=(label="QD Dose (mg)" labelattrs=(size=7pt)
        display=(line tickvalues ticks label) type=linear
        linearopts=(tickvaluefitpolicy=stagger tickvaluelist=&trt1))
        tickvalueattrs=(size=6pt family="Courier New" weight=bold))
        yaxisopts=(label="&p" labelattrs=(size=7pt)
        display=(line tickvalues ticks label) type=linear
        tickvalueattrs=(size=6pt family="Courier New" weight=bold));

        scatterplot x=trt1 y=d1 /markerattrs=(color=blue symbol=circle size=7px)
        legendlabel="Baseline" name="a";

        scatterplot x=trt1 y=d15 /markerattrs=(color=red symbol=circle size=7px)
        legendlabel="Day 99" name="b";

        discretelegend "a" "b" /location=outside across=2 autoalign=(right)
        title=" " border=false valueattrs=(size=7pt);
      endlayout;

      layout overlay / walldisplay=none xaxisopts=(display=none) yaxisopts=(display=none);
        entry halign=center textattrs=(size=7 family="Courier New" weight=bold)
        halign=center "Semi-Logarithmic Scale"/valign=bottom;
      endlayout;
      layout overlay / xaxisopts=(label="QD Dose (mg)" labelattrs=(size=7pt)
        display=(line tickvalues ticks label) type=linear
        linearopts=(tickvaluefitpolicy=stagger tickvaluelist=&trt1))
        tickvalueattrs=(size=6pt family="Courier New" weight=bold))
        yaxisopts=(label="&p" labelattrs=(size=7pt)
        display=(line tickvalues ticks label) type=log logopts=(base=10
        minorticks=true) tickvalueattrs=(size=6pt family="Courier New"
        weight=bold));

        scatterplot x=trt1 y=d1 /markerattrs=(color=blue symbol=circle size=7px)
        legendlabel="Baseline" name="a";
```



```

scatterplot x=trt1 y=d15 /markerattrs=(color=red symbol=circle size=7px)
legendlabel="Day 99" name="b";

discretelegend "a" "b" /location=outside across=2 autoalign=(right)
title=" " border=false valueattrs=(size=7pt);

    endlayout;
    endlayout;
endgraph;
end;
run;
%mend;

**Count number of PK parameters for display;
proc sql noprint;
    select count(distinct parm) into: checkp from rep;
quit;

**Loop through each PK parameter to generate title, value range and create graph using PROC
TEMPLATE and SGRENDER in a dynamic fashion;
%do xx=1 %to &checkp;
    proc sql noprint;
        create table temp as select trt1 from rep where parm="%scan(&parm,&xx,|)" and trt1>.;
        select param into: title from rep where parm="%scan(&parm,&xx,|)";
        select distinct trt1 into: trt1 separated by ' ' from temp order by trt1;
    quit;

    title1 j=c "Individual Drug XYZ Plasma Pharmacokinetic Parameters versus Dose Plot" ;
    title3 j=c "&title";
    title4 j=c "(Linear and Semi-Log)" ;

    %temp(%scan(&parm,&xx,|));
    proc sgrender data=rep template=sgplot;
        where parm="%scan(&parm,&xx,|)" ;
    run;
%end;

ods rtf close;

%mend pp;
%pp;

```