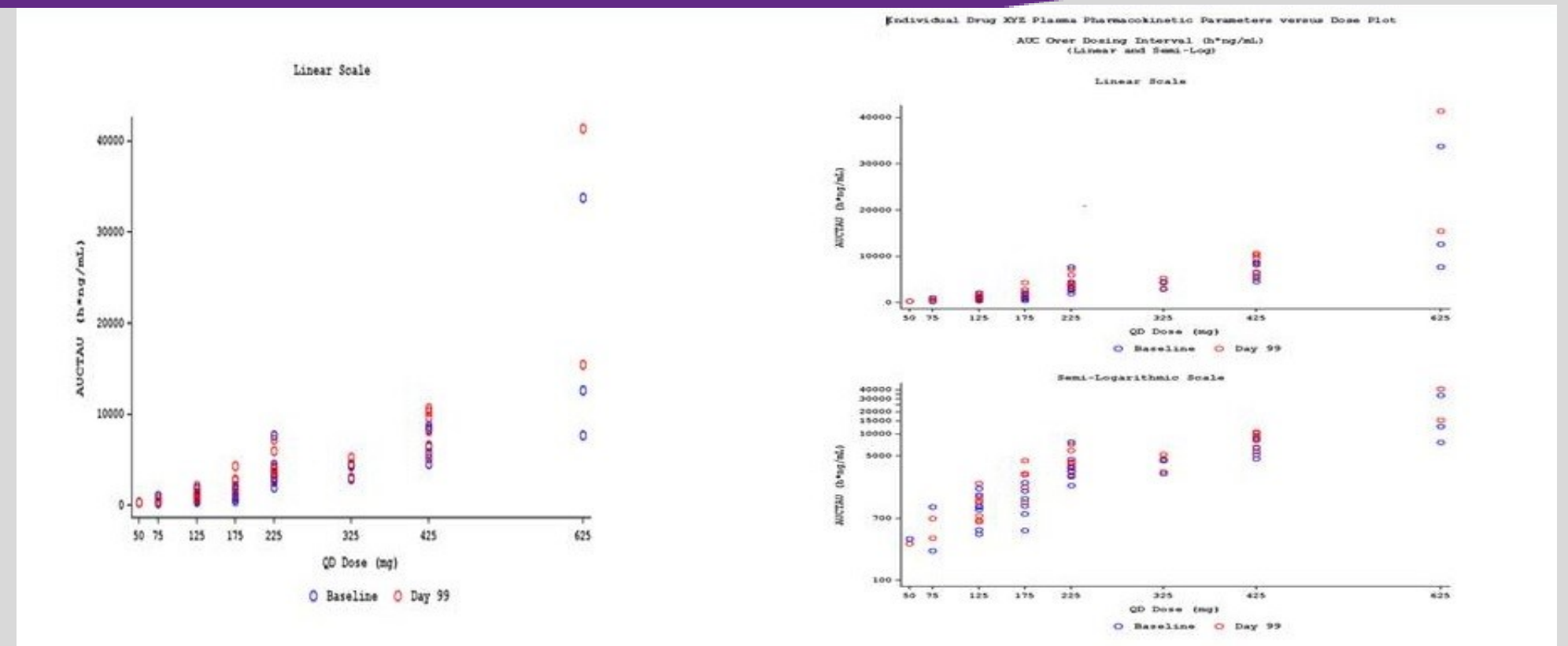


INTRODUCTION

- The purpose 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.
- A visual examination of PK parameters plotted against dose levels is the first step for the PK-dose relationship
- A dose-proportionality analysis evaluates the relationship between pharmacokinetic parameters and dose levels

PK PARAMETERS VS DOSE LEVEL

- PK parameters Cmax (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 (in linear scale or log scale) 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.
- Style template used for defining graph attributes in ODS RTF.



SAS GTL

1

- The LAYOUT LATTICE statement in PROC TEMPLATE is a handy tool for displaying multiple graphs on the same page.
- layout lattice / rows=2 rowweight=(0.05 0.45 0.05 0.45); ... endlayout;
- The LAYOUT OVERLAY statement in PROC TEMPATE can be used to generate the label and the actual graph display.

```
layout overlay / valdisplaynone axisopts=(displaynone) axisopts=(displaynone);
entry haligncenter textattr=(size=7 family="Courier New" weight=bold)
| haligncenter "Linear Scale"/valigntop;
endlayout;
```

2

- 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 / axisopts=(label="QD Dose (mg)" labelattrs=(size=7pt)
display=(line tickvalues ticks label) type=linear
lineopts=(tickvaluefitpolicy=stagger tickvalue=(dtrtl))
tickvalueattrs=(size=6pt family="Courier New" weight=bold))
yaxisopts=(label="AUC" labelattrs=(size=7pt)
display=(line tickvalues ticks label) type=linear
tickvalueattrs=(size=6pt family="Courier New" weight=bold));

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

scatterplot x=trtl 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;
```

4

- The XAXISOPTS option defines the X-axis of the graph. The macro variable TRT1 contains the x-axis values.
- The YAXISOPTS option defines the Y-axis of the graph. The macro variable P contains the label value of the parameter,
- The SCATTERPLOT statement creates a scatter plot of AUC value (variable TRT1) versus dose levels at two different time points
- The DISCRETELEGEND statement creates the legend for the graph

DOSE PROPORTANILITY

1

- 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).
- 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.

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

2

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

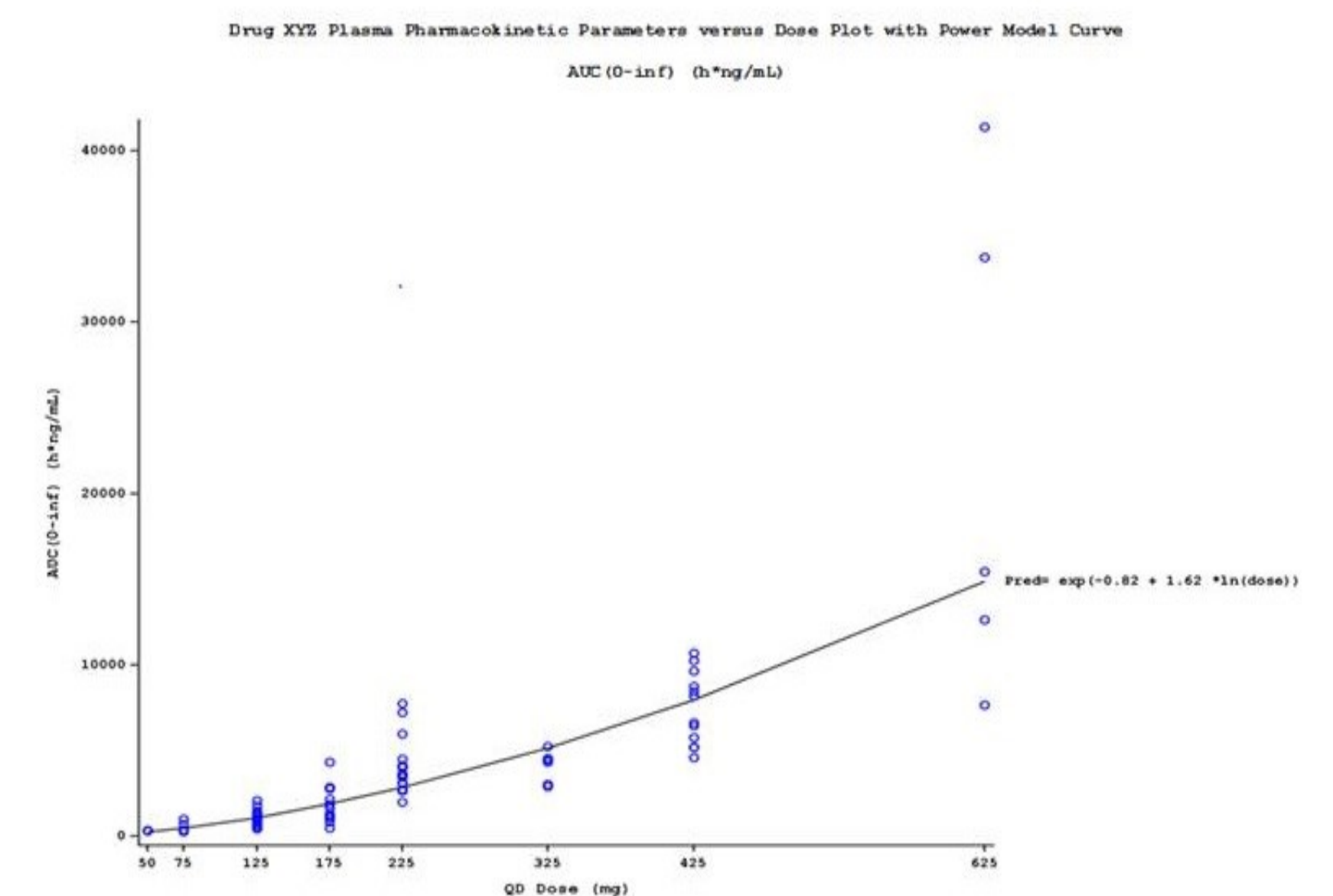
data final;
set rep;
by trtl;
slope=slope;
intercept=intercept;
if first.trtl then curve=exp(intercept + slope*ldose); **the power model curve;
run;
```

3

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

4



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.

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

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