PKPD Single Ascending Dose User Manual

Document Version:00

Author(s): Pinyan Liu

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1. OVERALL DESCRIPTION

1.1 Description

The PKPD Single Ascending Dose is intended to allow the user to plot Exposure-Response relationship of summaries of PK/PD over time by different dose levels. This document contains exploratory plots for single ascending dose PK and PD data as well as the R code that generates these graphs. The plots presented here are based on simulated data.

1.2 Operating Environment

The function will be used with R Version 4.0.2 and RStudio.

1.3 Parameters

Parameters	Created	Usage
ID	N	Integer; unique subject ID
TIME	N	Numeric; time relative to first drug administration
NOMTIME	N	Numeric; nominal time
LIDV	N	Numeric; observation on a linear scale (observation type determined by CMT), units determined by EVENTU column
CMT	N	Integer; compartment number (determines observation type): CMT1 = Dosing event CMT2 = PK concentration CMT3 = Continuous response data
CENS	N	Integer; censored values (0 = not censored, 1 = censored)
TRTACT	N	Factor; treatment group label
PROFTIME	N	Numeric; time within PROFDAY
DOSE	N	Integer; Dose in mg
IPRED	N	Numeric; individual prediction
DAY_label	Y	Factor; label the day (Day 0 = Baseline)

TRTACT_low2high	Y	Factor; arrange TRTACT levels from low to high
TRTACT_high2low	Y	Factor; arrange TRTACT levels from high to low
LIDVNORM	Y	Numeric; dose normalization
CYCLE	N	Integer; count of drug administrations received
NAME	N	Factor; description of event
AUC_last	Y	Numeric; integral of TIME and LIDV
Cmax	Y	Numeric; maximum of LIDV

1.4 Datasets

Datasets	Derivation
pkpd_data	Derived from case1_pkpd (simulated dataset in R), arrange by dose, including newly created variables: TRTACT_low2high, TRTACT_high2low, DAY_label
pk_data	Derived from pkpd_data, filter when CMT==2, including new variable: LIDVNORM
pk_data_cycle1	Derived from pk_data, filter when CYCLE==1
pd_data	Derived from pkpd_data, filter when CMT==3
pd_data_baseline_day85	Derived from pkpd_data, filter when CMT==3 and DAT_label = “Baseline” and “Day 85”
event_data	Derived from pkpd_data, filter when CMT==1
pk_vs_pd_data	Derived from pkpd_data, filter when LIDV is not NA; rename concentration= ‘2’ and response= ‘3’
NCA	Derived from pk_data_cycle1, including new variable: AUC_last, Cmax
AUC_last	Derived from NCA, filter when param==”AUC_last”
pk_vs_pd_data_day85	Derived from pk_vs_pd_data. Filter when DAY_label==”Day 85”; concentration and response is not NA; left joined with AUC_last

1.5 Required Packages

Package	Usage
xgxr	Exploratory Graphics for Pharmacometrics. Supports a structured approach for exploring PKPD data
ggplot2	Create Graphics
dplyr	A fast, consistent tool for working with data frame like objects, both in memory and out of memory.
tidyr	Tools to help to create tidy data, where each column is a variable, each row is an observation, and each cell contains a single value.
caTools	Contains several basic utility functions including: fast calculation of AUC.
extrafont	Fonts that are imported into extrafont can be used with PDF or PostScript output files. On Windows, extrafont will also make system fonts available for bitmap output.

Packages should be installed in advance by **install.packages("package name")**

1.5 Constraints

NA

2. EXAMPLE

2.1 Sample Data Used in Following Examples

Sample data (part) is the pkpd_data.

	ID	TIME	NOMTIME	TIMEUNIT	AMT	LIDV	CMT	NAME	EVENTU	CENS	EVID	WEIGHTB
1	1	-0.01687	-0.1	Hours	0	61.543	3	PD - Continuous	kg	0	0	119.06
2	1	0.00000	0.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
3	1	23.81642	23.9	Hours	0	-35.811	3	PD - Continuous	kg	0	0	119.06
4	1	23.87617	24.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
5	1	47.76291	48.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
6	1	71.83392	72.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
7	1	95.85056	96.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
8	1	119.76342	120.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
9	1	143.88690	144.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
10	1	167.77789	168.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
11	1	191.76256	192.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
12	1	215.83221	216.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
13	1	239.95015	240.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
14	1	264.12673	264.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
15	1	288.22482	288.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
16	1	312.26797	312.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
17	1	336.26810	335.9	Hours	0	367.880	3	PD - Continuous	kg	0	0	119.06
18	1	336.39455	336.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
19	1	360.43004	360.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
20	1	384.39138	384.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
21	1	408.52288	408.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
22	1	432.71179	432.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06
23	1	456.76340	456.0	Hours	0	*NA*	1	Dosing	mg	0	1	119.06

Sample Data 1. pkpd_data (part)

Sample call**:**

```
#Load Datasets

#Simulate Datasets

pkpd_data<-case1_pkpd %>% arrange (DOSE) %>% select(-IPRED) %>%
    mutate (TRTACT_low2high=factor (TRTACT,levels=unique(TRTACT)),
    TRTACT_high2low=factor (TRTACT,levels=rev(unique(TRTACT))),
    DAY_label=paste ("Day", PROFDAY),
    DAY_label=ifelse (DAY_label=="Day 0","Baseline", DAY_label))
```

```
LOQ=0.05 #ng/ml
dose_max=as.numeric(max(pkpd_data$DOSE))
pk_data<-pkpd_data %>% filter (CMT==2) %>%
            mutate (LIDVNORM = LIDV / as.numeric(DOSE))

pk_data_cycle1<-pk_data %>% filter (CYCLE==1)

pd_data<-pkpd_data %>% filter (CMT==3)

pd_data_baseline_day85<-pkpd_data %>%
                              filter (CMT==3, DAY_label %in% c ("Baseline", "Day 85"))

event_data<-pkpd_data %>% filter (CMT==1)

pk_vs_pd_data<-pkpd_data %>% filter (!is.na (LIDV)) %>% select(-c(EVENTU,NAME)) %>%
                    spread (CMT, LIDV) %>% rename (Concentration='2', Response='3')

NCA<-pk_data_cycle1 %>% group_by(ID,DOSE) %>% filter(!is.na(LIDV)) %>%
      #Make Two New Variables: AUC_last & Cmax
       Summarize (AUC_last=caTools::trapz (TIME,LIDV), Cmax=max(LIDV)) %>%
      #Except for ID, DOSE, Transpose the Rest Variables
      tidyr::gather(PARAM,VALUE,-c(ID,DOSE)) %>%   ungroup() %>%
      mutate (VALUE_NORM=VALUE/DOSE)

AUC_last<-NCA %>% filter (PARAM=="AUC_last") %>%
            rename (AUC_last = VALUE) %>% select (-c (DOSE, PARAM, VALUE_NORM))

pk_vs_pd_data_day85 <- pk_vs_pd_data %>% filter (DAY_label=="Day 85",
                              !is.na (Concentration), !is.na(Response)) %>% left_join(AUC_last)

#Create Variables' Units
time_units_dataset <- "hours"
```

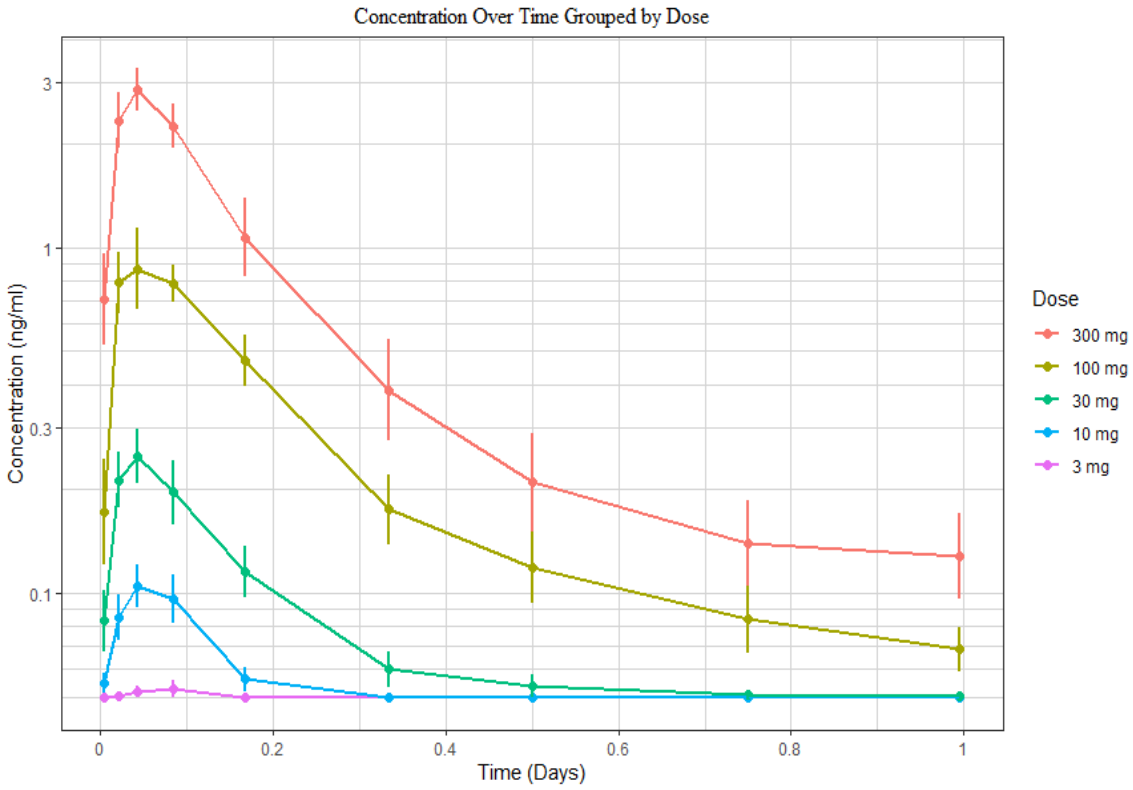
```
time_units_plot <- "days"
trtact_label <-"Dose"
dose_label <- "Dose (mg)"
conc_label <- "Concentration (ng/ml)"
auc_label <- "AUCtau (h.(bg/ml))"
concnorm_label <- "Normalized Concentration (ng/ml)/mg"
sex_label <- "Sex"
w100_label <- "WEIGHTB>100"
pd_label <- "FEV1 (ml)"
cens_label <- "Censored"
```

2.2 Example1: Summary of PK Over Time (Concentration Over Time Grouped by Dose)

Sample Call:

```
ggplot(data=pk_data_cycle1, aes(x = NOMTIME, y = LIDV, group = DOSE,
        color = TRTACT_high2low)) +
xgx_geom_ci(conf_level = 0.95)+
xgx_scale_y_log10()+
xgx_scale_x_time_units (units_dataset = time_units_dataset,units_plot = time_units_plot)+
labs(y=conc_label, color=trtact_label,title="Concentration Over Time Grouped by Dose") +
theme(plot.title=element_text(family="Times New Roman",size=(12),hjust = 0.5))
```

Sample Output:

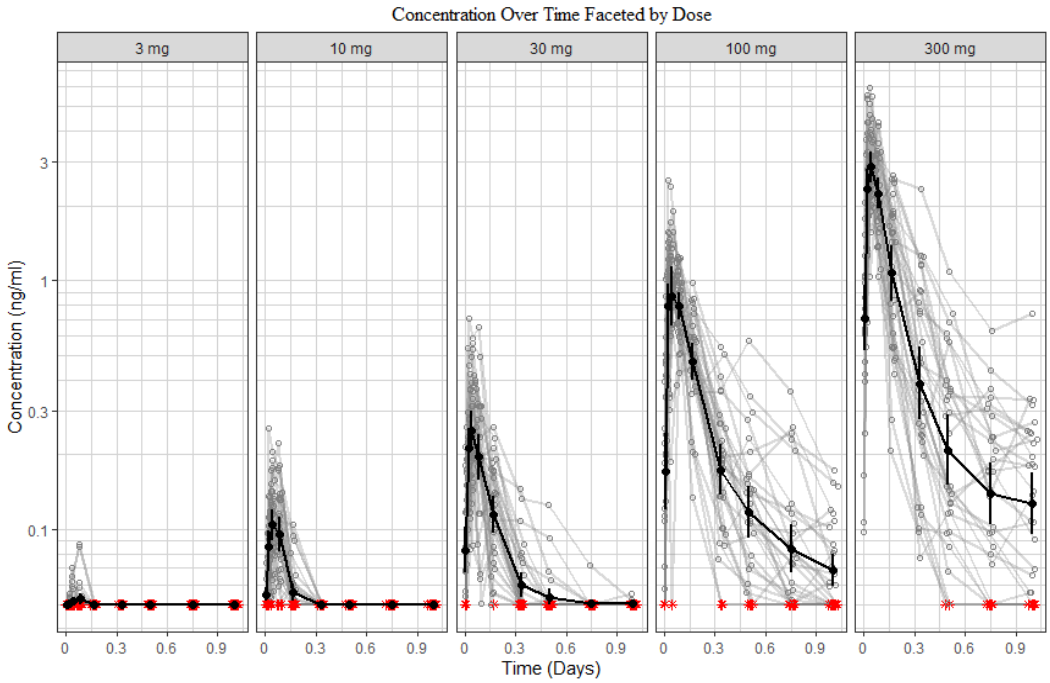


2.3 Example2: Summary of PK Over Time (Concentration Over Time Faceted by Dose)

Sample Call:

```
ggplot(data=pk_data_cycle1,aes (x=TIME,y=LIDV)) +
geom_line(aes(group=ID), color ="grey50", size =1, alpha=0.3) +
geom_point(aes(color=factor (CENS),shape=factor(CENS))) +
scale_shape_manual(values = c(1,8))+
scale_color_manual(values=c("grey50","red")) +
xgx_geom_ci(aes(x= NOMTIME, color=NULL, group= NULL,shape=NULL), conf_level=0.95)+
xgx_scale_y_log10()+
xgx_scale_x_time_units(units_dataset = time_units_dataset,units_plot = time_units_plot)+
labs (y=conc_label,color=trtact_label,title = "Concentration Over Time Faceted by Dose")+
theme (legend.position = "none",plot.title=element_text(family="Times New
        Roman",size=(12),hjust = 0.5))+
facet_grid(.~TRTACT_low2high)
```

Sample Output:

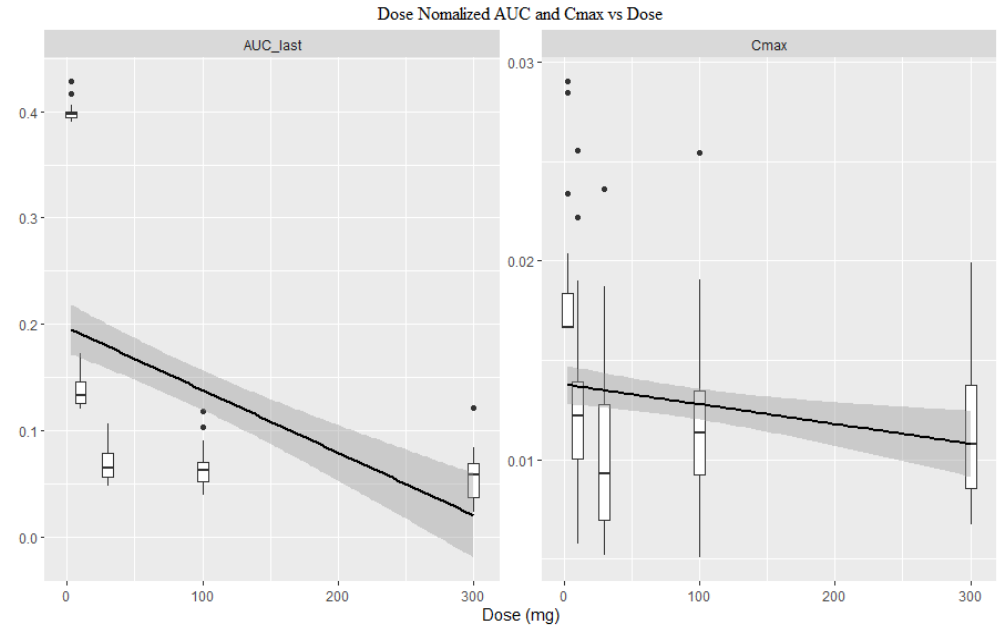


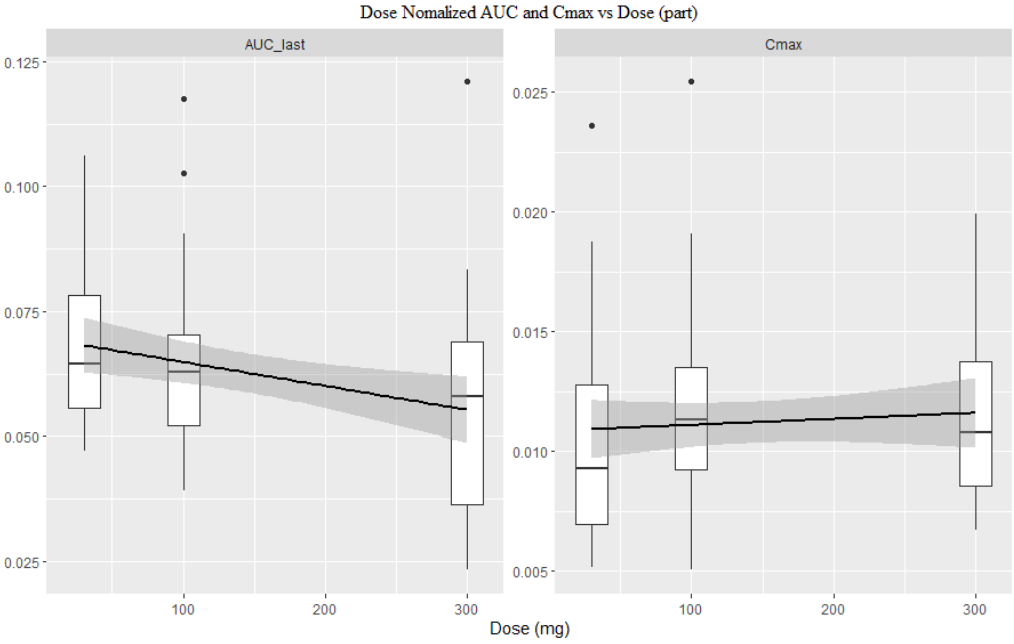
2.4 Example3: Summary of PK Over Time (Dose Normalized AUC and Cmax vs Dose)

Sample Call:

```
ggplot(data=NCA,aes(x=DOSE,y=VALUE_NORM))+
geom_boxplot(aes(group=DOSE),width=8)+
geom_smooth(method="lm",color="black")+
facet_wrap(~PARAM,scales="free_y")+
labs(x=dose_label,title="Dose Nomalized AUC and Cmax vs Dose")+
theme(legend.position = "none",plot.title=element_text(family="Times New
      Roman",size=(12),hjust = 0.5))+
theme(axis.title.y = element_blank())
#Choose Only 30,100 And 300 Sose
ggplot(data=NCA[!NCA$DOSE==3 & !NCA$DOSE ==10,],
aes(x=DOSE,y=VALUE_NORM))+
geom_boxplot(aes(group=DOSE))+
geom_smooth(method = "lm",color="black")+
facet_wrap(~PARAM,scales="free_y")+
labs(x=dose_label,title="Dose Nomalized AUC and Cmax vs Dose (part)")+
theme(plot.title=element_text(family="Times New Roman",size=(12),hjust = 0.5))+
theme(axis.title.y = element_blank())
```

Sample Output:



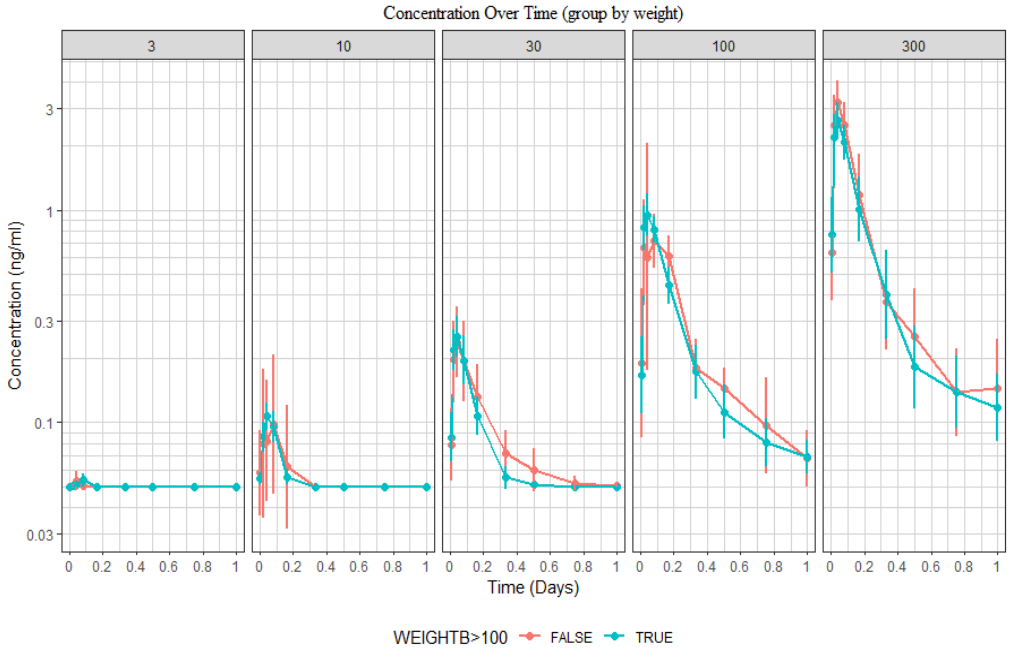


2.5 Example4: Summary of PK Over Time (Concentration Over Time Grouped by Weight)

Sample Call:

```
ggplot(data=pk_data_cycle1,aes(x=NOMTIME, y=LIDV, group=WEIGHTB>100,
       color=WEIGHTB>100))+
xgx_geom_ci(conf_level = 0.95)+
xgx_scale_y_log10()+
xgx_scale_x_time_units(units_dataset=time_units_dataset,units_plot = time_units_plot)+
facet_grid(.~DOSE)+
labs(y=conc_label,color=w100_label,title="Concentration Over Time (group by weight)")+
    theme(legend.position = "bottom",legend.direction = "horizontal",
    plot.title=element_text(family="Times New Roman",size=(12),hjust = 0.5))
```

Sample Output:

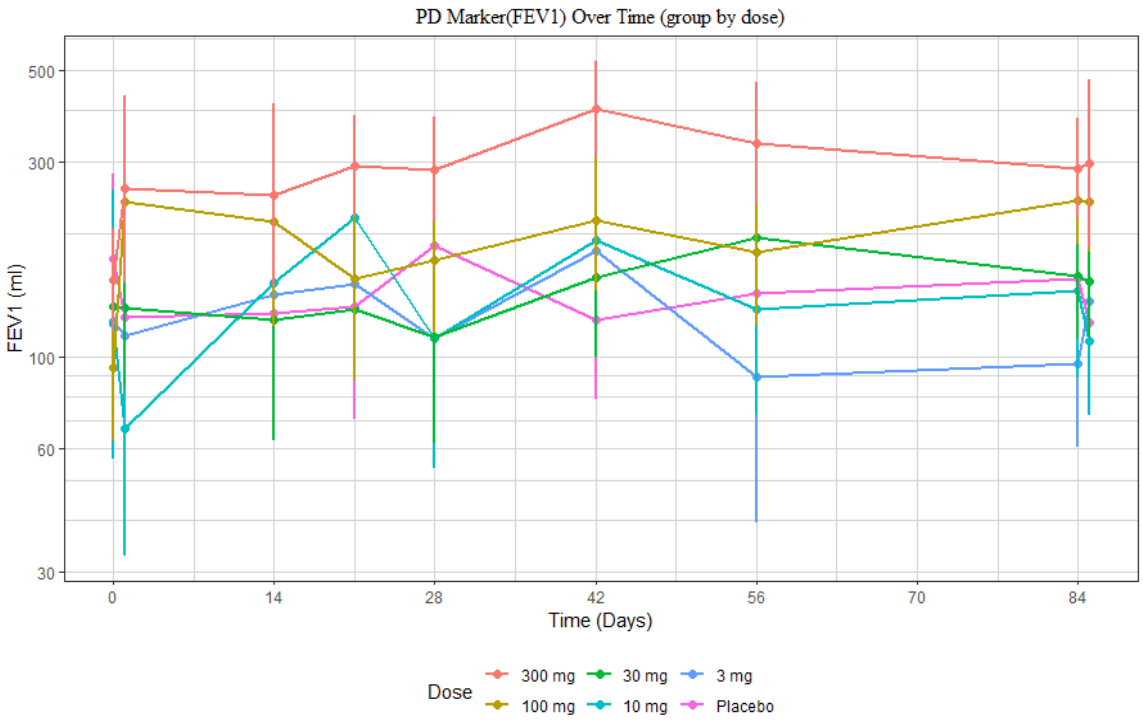


2.6 Example5: Summary of PD Over Time (Concentration Over Time Grouped by Weight)

Sample Call:

```
ggplot(data=pd_data,aes(x=NOMTIME, y=LIDV, group=DOSE, color=TRTACT_high2low))+
xgx_geom_ci(conf_level = 0.95)+
xgx_scale_y_log10()+
xgx_scale_x_time_units(units_dataset=time_units_dataset,units_plot = time_units_plot)+
labs (y=pd_label,color=trtact_label,title="PD Marker(FEV1) Over Time (group by dose)")+
theme (legend.position = "bottom",plot.title=element_text(family="Times New
      Roman",size=(12),hjust = 0.5))
```

Sample Output:

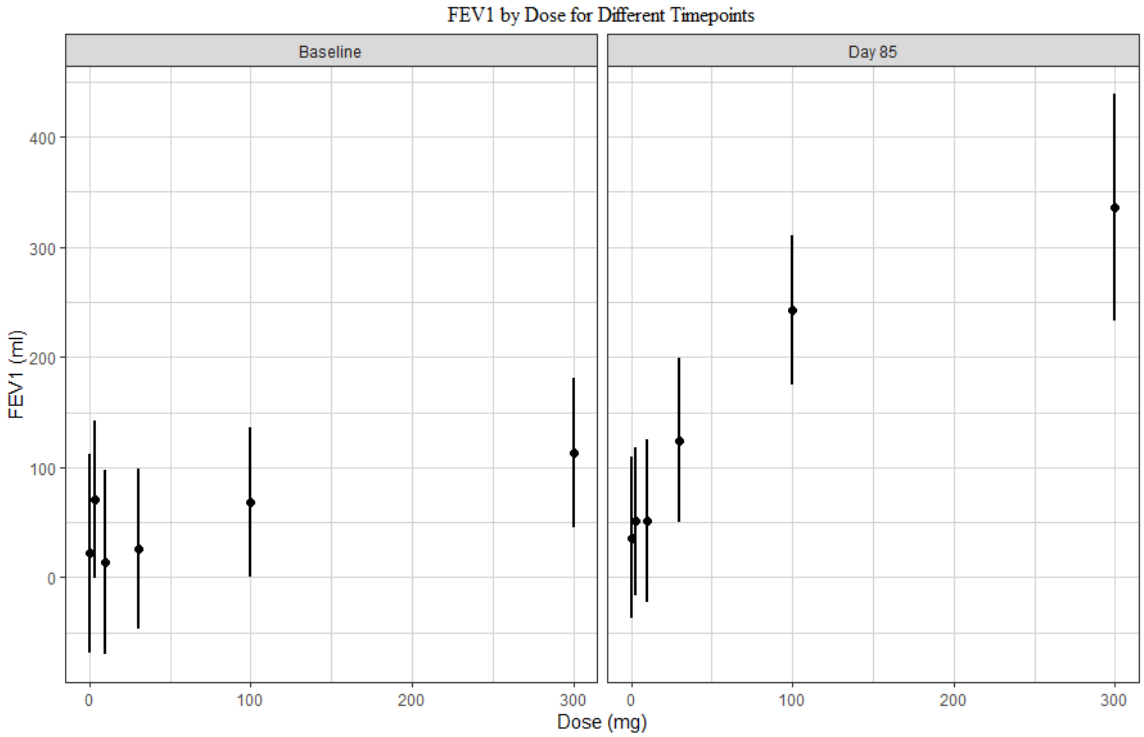


2.7 Example6: Summary of PD Over Time (Dose-Response Relationship on baseline and day 85)

Sample Call:

```
ggplot(data=pd_data_baseline_day85,aes(x=DOSE, y=LIDV, group=DOSE))+
    xgx_geom_ci(conf_level = 0.95)+
    facet_grid(~DAY_label)+
    labs (x=dose_label,y=pd_label,color=trtact_label,title="FEV1 by Dose for Different
        Timepoints")+
    theme(legend.position = "bottom",
    plot.title=element_text(family="Times New Roman",size=(12),hjust = 0.5))
```

Sample Output:

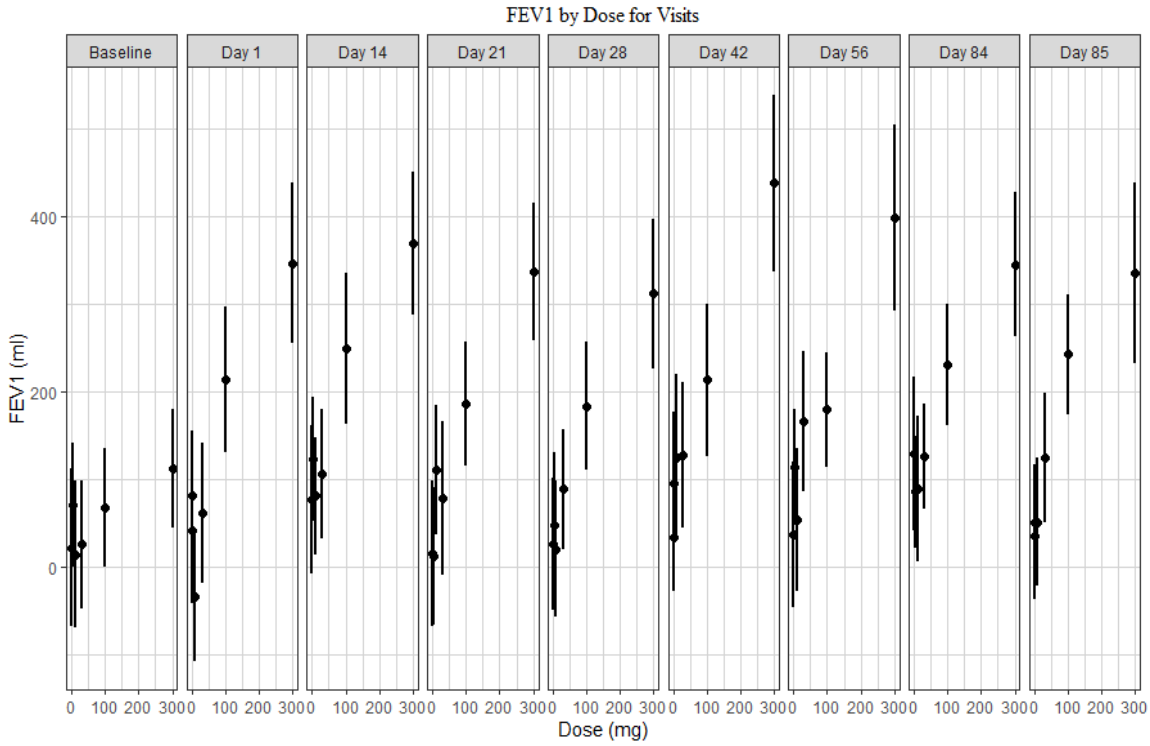


2.8 Example7: Summary of PD Over Time (Dose-Response Relationship on Different Day)

Sample Call:

```
ggplot(data=pd_data,aes(x=DOSE,y=LIDV,group=DOSE))+
xgx_geom_ci(conf_level = 0.95)+
facet_grid(~DAY_label)+
labs(x=dose_label,y=pd_label,color=trtact_label,title="FEV1 by Dose for Visits")+
theme(legend.position = "bottom",plot.title=element_text(family="Times New
      Roman",size=(12),hjust = 0.5))
```

Sample Output:

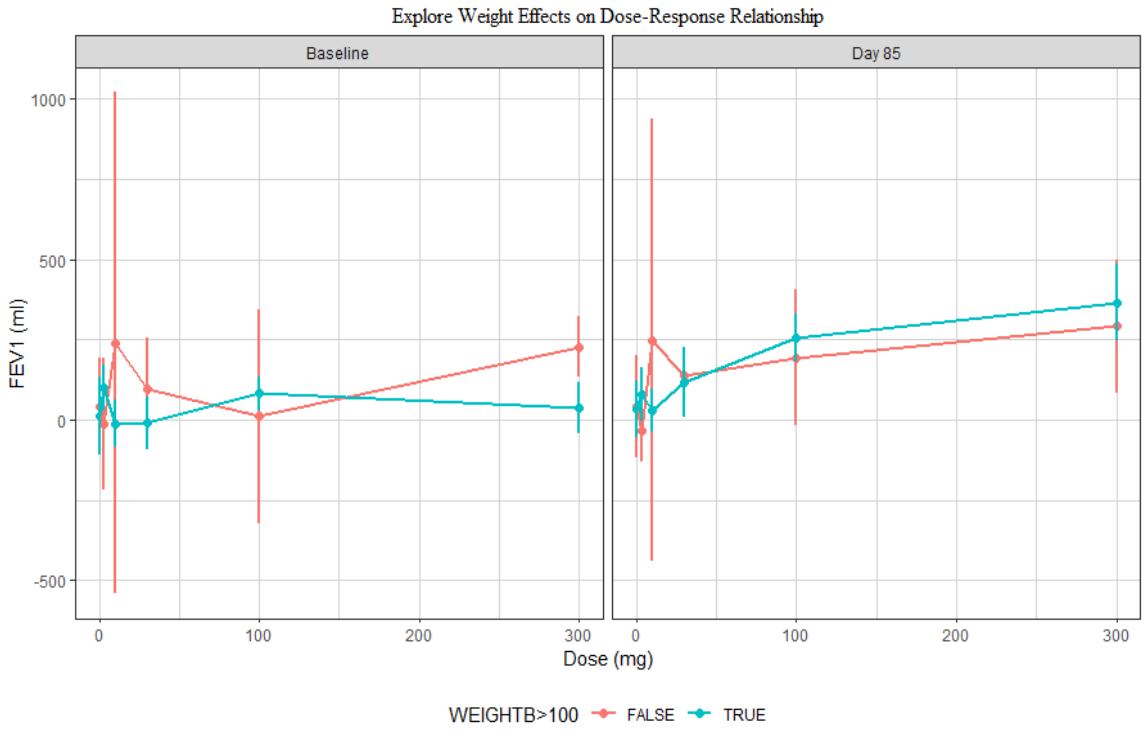


2.9 Example8: Summary of PD Over Time (Weight Effects on Dose-Response Relationship)

Sample Call:

```
ggplot(data=pd_data_baseline_day85,aes(x=DOSE, y=LIDV, group=WEIGHTB>100,
        color=WEIGHTB>100))+
xgx_geom_ci(conf_level = 0.95)+
facet_grid(~DAY_label) +
labs(x=dose_label,y=pd_label,color=w100_label,title="Explore Weight Effects on Dose-Response
    Relationship")+
theme(legend.position = "bottom",
plot.title=element_text(family="Times New Roman",size=(12),hjust = 0.5))
```

Sample Output:

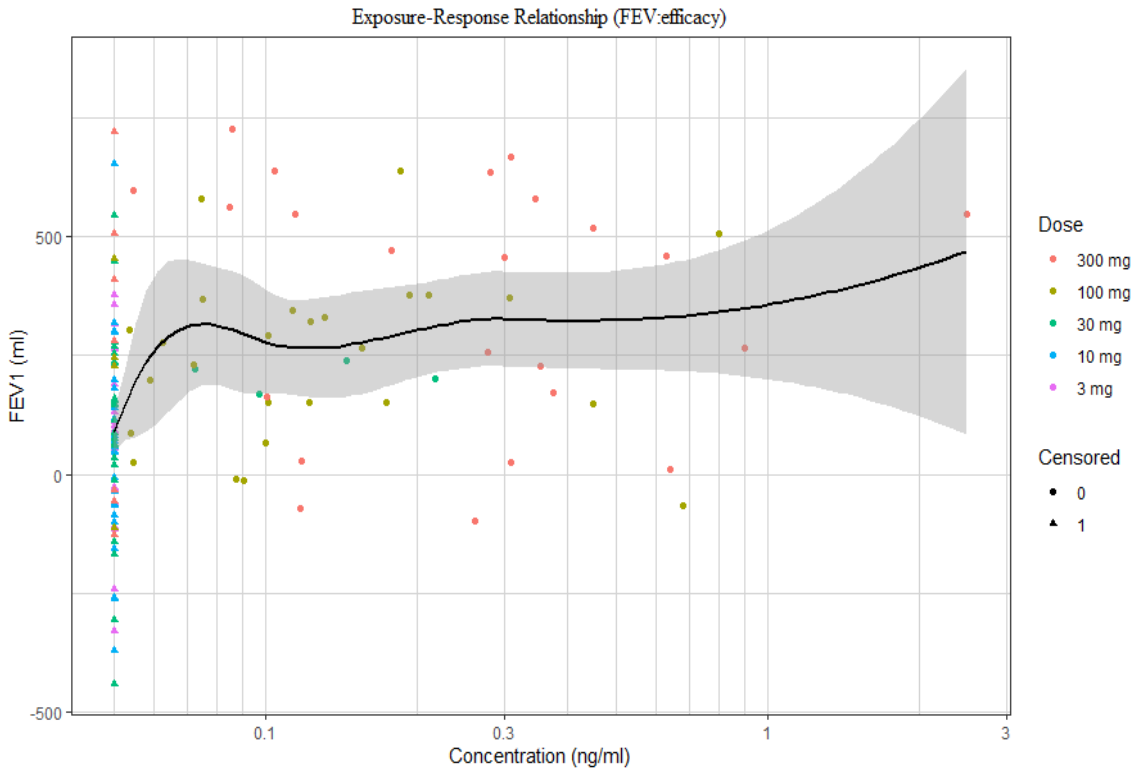


2.10 Example9: Summary of PD Over Time (Exposure-Response Relationship For Concentration)

Sample Call:

```
g=ggplot(data=pk_vs_pd_data_day85,aes(x=Concentration,y=Response))+
        geom_point(aes(color=TRTACT_high2low,shape=factor(CENS)))+
geom_smooth(color="black",shale=NULL)+
xgx_scale_x_log10()+
labs(x=conc_label,y=pd_label,color=trtact_label,shape=cens_label,title="Exposure-Response
    Relationship (FEV:efficacy)")+
theme(plot.title=element_text(family="Times New Roman",size=(12),hjust = 0.5))
print(g)
```

Sample Output:



2.11 Example10: Summary of PD Over Time (Exposure-Response Relationship For AUC)

Sample Call:

```
gAUC=g + aes(x=AUC_last)+xlab(auc_label)
print(gAUC)
```

Sample Output: