Combined

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```
pkpara=function(ti,Ci)
{
Cmax=max(Ci)
Tmax=ti[which.max(Ci)]
nC=length(Ci)
AUCt=sum((Ci[2:nC]+Ci[1:(nC-1)])*(ti[2:nC]-ti[1:(nC-1)]))/2
tTemp=ti[(which.max(Ci)+1):nC]
LCTemp=log10(Ci[(which.max(Ci)+1):nC])
Ke=lm(LCTemp~tTemp)$coefficients[2]*(-2.303)
thalf=0.693/Ke
AUCinf=AUCt+Ci[nC]/Ke
Out=data.frame("Cmax"=Cmax,"Tmax"=Tmax,"AUCt"=AUCt,"AUCinf"=AUCinf,"Ke"=Ke,"thalf"=thalf)
row.names(Out)=""
return(Out)
}
```

```
crossanova=function(Y,Seq,Per,Sub)
{
data=data.frame(Y,Seq,Per,Sub)
Y11=data[data$Per==1&data$Seq==1,1];n1=length(Y11)
Y21=data[data$Per==2&data$Seq==1,1]
Y12=data[data$Per==1&data$Seq==2,1]
Y22=data[data$Per==2&data$Seq==2,1];n2=length(Y22)

df_temp=data.frame(c(Y11,Y12),c(Y21,Y22))

Chat=(mean(Y12)+mean(Y22))-(mean(Y11)+mean(Y21))
Fhat=(((mean(Y21)-mean(Y11))-(mean(Y22)-mean(Y12)))/2)
Phat=(((mean(Y21)-mean(Y11))-(mean(Y12)-mean(Y22)))/2)

SStotal=(2*(n1+n2)-1)*var(data$Y)

SSBetween=2*sum((apply(df_temp,1,mean)-mean(data$Y))^2)
SSwithin=sum(apply(df_temp,1,var))

SScarry=2*n1*n2/(n1+n2)*Chat^2/4
SSinter=SSBetween-SScarry

SSdrug=2*n1*n2/(n1+n2)*Fhat^2
SSperiod=2*n1*n2/(n1+n2)*Phat^2
SSintra=SSwithin-SSdrug-SSperiod

source1=c("Carry","Inter","Drug","Period","Intra","Total")
```

```
SS=round(c(SScarry,SSinter,SSdrug,SSperiod,SSintra,SStotal),3)
df=c(1,n1+n2-2,1,1,n1+n2-2,2*(n1+n2)-1)
MSq=round(SS/df,3)

Fcal=round(c(MSq[1]/MSq[2],MSq[2:4]/MSq[5],0,0),3)
Pval=rep(0,6)
Pval[1]=1-pf(Fcal[1],df[1],df[2])
Pval[2:4]=1-pf(Fcal[2:4],df[2:4],df[5])
Pval=round(Pval,3)
return(data.frame("Source"=source1,"DF"=df,SumofSq=SS,MSq,Fcal,Pval))
}
```

```
data<- read.csv("C:/Users/Hp/Dropbox/Clinical Trials using R software/BABEData22.csv");

crossanova("Y"=data$Y,"Seq"=data$Seq,"Per"=data$Per,"Sub"=data$Sub)
```

```
##   Source DF   SumofSq     MSq  Fcal  Pval
## 1  Carry  1   276.000 276.000 0.375 0.547
## 2  Inter 22 16211.489 736.886 4.406 0.000
## 3   Drug  1    62.792  62.792 0.375 0.547
## 4 Period  1    35.967  35.967 0.215 0.647
## 5  Intra 22  3679.430 167.247 0.000 0.000
## 6  Total 47 20265.677 431.185 0.000 0.000
```

```
df_temp=read.csv("C:/Users/Hp/Dropbox/Clinical Trials using R software/BABEData.csv",header=F)
tp=df_temp[1,5:ncol(df_temp)]
cp=df_temp[2:nrow(df_temp),5:ncol(df_temp)]
```

```
##    Sub seq treat Per   Cmax Tmax     AUCt   AUCinf        Ke    thalf
## 2    1   1     2   2 10.423 2.00 34.43512 35.35856 0.3530299 1.963006
## 3    3   1     2   2  8.016 1.75 26.55588 27.86808 0.2964480 2.337678
## 4    6   1     2   2 10.868 2.00 29.15875 30.43765 0.3409167 2.032755
## 5    8   1     2   2  8.120 2.25 24.65762 25.68948 0.3043059 2.277313
## 6   10   1     2   2  6.925 2.25 22.11113 23.73775 0.2797196 2.477481
## 7   12   1     2   2  8.795 2.25 29.35938 30.82531 0.2974213 2.330028
## 8   13   1     2   2 10.485 1.75 33.28162 34.53787 0.3383099 2.048418
## 9   15   1     2   2 10.279 2.25 27.65212 28.83582 0.3353895 2.066254
## 10  18   1     2   2  9.531 2.00 27.98450 28.86150 0.3489184 1.986138
## 11  20   1     2   2  8.238 1.75 26.18725 27.54316 0.3141796 2.205744
## 12  21   1     2   2  8.026 2.25 21.85450 22.60271 0.3394789 2.041364
## 13  23   1     2   2 10.553 2.00 29.18863 30.05290 0.3633083 1.907471
## 14   1   1     1   1  6.857 2.25 17.87250 18.33783 0.3459877 2.002962
## 15   3   1     1   1 11.547 2.00 34.27425 35.82114 0.3219364 2.152599
## 16   6   1     1   1  8.176 1.75 23.87463 25.32962 0.3024064 2.291618
## 17   8   1     1   1  6.926 1.75 18.97850 19.93447 0.3054483 2.268796
## 18  10   1     1   1  5.987 2.25 17.19537 17.90923 0.3221949 2.150872
## 19  12   1     1   1 10.166 2.00 34.37562 35.68934 0.3235107 2.142124
## 20  13   1     1   1  6.857 2.25 19.13000 19.57740 0.3598584 1.925757
## 21  15   1     1   1 11.547 2.00 33.82825 35.23362 0.3273157 2.117222
## 22  18   1     1   1  8.070 1.50 24.11212 25.57568 0.3006373 2.305103
## 23  20   1     1   1  7.776 2.25 19.36212 19.87008 0.3583010 1.934128
## 24  21   1     1   1 11.184 2.00 31.51225 32.84983 0.3476438 1.993420
## 25  23   1     1   1  8.235 1.75 23.90400 24.88222 0.3230350 2.145278
## 26   2   2     2   1  6.575 1.75 22.38650 23.45391 0.3016635 2.297261
## 27   4   2     2   1  6.119 2.25 20.37575 20.61233 0.4226871 1.639511
```

```
## 28   5   2     2   1  7.880 2.25 23.42512 24.37285 0.3344843 2.071846
## 29   7   2     2   1  9.884 1.75 30.37800 31.72263 0.3093781 2.239978
## 30   9   2     2   1  7.295 1.75 24.47087 25.65862 0.2988868 2.318604
## 31  11   2     2   1 10.820 2.00 33.78200 34.11396 0.4277651 1.620048
## 32  14   2     2   1  9.331 2.00 31.03337 32.12294 0.3175577 2.182280
## 33  16   2     2   1  7.236 1.75 21.54925 22.77152 0.2994432 2.314295
## 34  17   2     2   1  6.032 2.25 19.13125 20.11394 0.3174955 2.182708
## 35  19   2     2   1  7.582 2.25 26.94450 27.94725 0.2991782 2.316345
## 36  22   2     2   1  7.333 1.75 23.94487 25.50104 0.2968840 2.334245
## 37  24   2     2   1  8.351 1.75 26.25512 27.58973 0.3132003 2.212642
## 38   2   2     1   2  8.721 1.75 25.65962 26.73247 0.3327596 2.082584
## 39   4   2     1   2 10.018 2.25 27.85300 29.05957 0.3207450 2.160595
## 40   5   2     1   2  7.941 1.75 23.04812 24.20442 0.3139335 2.207474
## 41   7   2     1   2  7.531 2.00 23.50062 24.99897 0.2983283 2.322945
## 42   9   2     1   2  9.543 1.75 28.11875 29.11601 0.3399327 2.038639
## 43  11   2     1   2  8.125 2.00 19.17550 20.72421 0.2886277 2.401017
## 44  14   2     1   2  7.721 1.75 26.02587 27.31192 0.3102543 2.233652
## 45  16   2     1   2  7.741 1.75 25.26325 26.38210 0.3235467 2.141886
## 46  17   2     1   2  7.731 2.25 20.66437 22.23625 0.2811932 2.464498
## 47  19   2     1   2  8.886 1.75 24.80262 25.71471 0.3453623 2.006589
## 48  22   2     1   2  8.479 2.00 21.63837 22.10300 0.3895578 1.778940
## 49  24   2     1   2  9.136 1.50 28.44237 29.82778 0.3233717 2.143044
```

```
crossanova(df3$Cmax,df3$seq,df3$Per,df3$Sub)
```

```
##   Source DF SumofSq   MSq  Fcal  Pval
## 1  Carry  1   6.436 6.436 3.515 0.074
## 2  Inter 22  40.285 1.831 0.747 0.750
## 3   Drug  1   0.001 0.001 0.000 1.000
## 4 Period  1   4.122 4.122 1.682 0.208
## 5  Intra 22  53.932 2.451 0.000 0.000
## 6  Total 47 104.775 2.229 0.000 0.000
```

Anova for Tmax

```
crossanova(df3$Tmax,df3$seq,df3$Per,df3$Sub)
```

```
##   Source DF SumofSq   MSq  Fcal  Pval
## 1  Carry  1   0.105 0.105 1.780 0.196
## 2  Inter 22   1.299 0.059 1.255 0.299
## 3   Drug  1   0.064 0.064 1.362 0.256
## 4 Period  1   0.001 0.001 0.021 0.886
## 5  Intra 22   1.029 0.047 0.000 0.000
## 6  Total 47   2.499 0.053 0.000 0.000
```

Conclusion hiodshvoafdvoidfh bdnafip bn'odfi

```
crossanova(df3$AUCt,df3$seq,df3$Per,df3$Sub)
```

```
##   Source DF  SumofSq    MSq  Fcal  Pval
## 1  Carry  1   22.656 22.656 1.191 0.287
## 2  Inter 22  418.503 19.023 0.723 0.774
## 3   Drug  1   39.406 39.406 1.498 0.234
## 4 Period  1   12.528 12.528 0.476 0.497
## 5  Intra 22  578.674 26.303 0.000 0.000
```

```
## 6  Total 47 1071.767 22.804 0.000 0.000
```

```
crossanova(df3$AUCinf,df3$seq,df3$Per,df3$Sub)
```

```
##   Source DF  SumofSq    MSq  Fcal  Pval
## 1  Carry  1   22.645 22.645 1.128 0.300
## 2  Inter 22  441.763 20.080 0.731 0.766
## 3   Drug  1   38.359 38.359 1.397 0.250
## 4 Period  1   16.067 16.067 0.585 0.452
## 5  Intra 22  603.956 27.453 0.000 0.000
## 6  Total 47 1122.790 23.889 0.000 0.000
```

```
crossanova(df3$thalf,df3$seq,df3$Per,df3$Sub)
```

```
##   Source DF SumofSq   MSq  Fcal  Pval
## 1  Carry  1   0.008 0.008 0.296 0.592
## 2  Inter 22   0.603 0.027 0.587 0.890
## 3   Drug  1   0.000 0.000 0.000 1.000
## 4 Period  1   0.005 0.005 0.109 0.744
## 5  Intra 22   1.019 0.046 0.000 0.000
## 6  Total 47   1.635 0.035 0.000 0.000
```

```
crossanova(df3$Ke,df3$seq,df3$Per,df3$Sub)
```

```
##   Source DF SumofSq   MSq Fcal Pval
## 1  Carry  1   0.000 0.000    0  1.0
## 2  Inter 22   0.017 0.001    1  0.5
## 3   Drug  1   0.000 0.000    0  1.0
## 4 Period  1   0.000 0.000    0  1.0
## 5  Intra 22   0.028 0.001    0  0.0
## 6  Total 47   0.046 0.001    0  0.0
```