

Package ‘bear’

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Title Average bioequivalence and bioavailability data analysis tool

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Depends R (>= 2.12.0), reshape, nlme, gdata

Imports ICSNP, sciplot, plotrix, ggplot2, png, grid

Suggests plyr

Description An average bioequivalence (ABE) and bioavailability data analysis tool including sample size estimation, noncompartmental analysis (NCA), ANOVA (lm) for a standard RT/TR 2x2x2 crossover design or a parallel study. And linear mixed effect model (lme of nlme) for a 2-treatment, 2-sequence with 2 periods or more (i.e. 2x2x3/2x2x4) replicate crossover design.

License GPL (>= 2)

NeedsCompilation no

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about.bear

*about.bear***Description**

function to show more information about package 'bear'.

aic

Akaike information criterion (AIC) method

Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

AICdemo

Akaike information criterion (AIC) method for demo function

Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

AICoutput

Output for Adjusted R squared (ARS) method

Description

We provides several txt outputs. 1. NCA PK.txt: $\rightarrow C_{max}, T_{max}, AUC_{0t}, AUC_{0inf}, AUC_{0t}/AUC_{0inf}, \ln(C_{max}), \ln(AUC_{0t}), \ln(AUC_{0inf}), MRT_{0inf}, T_{1/2}, V_d/F, \lambda z,$ and $Cl/F \rightarrow$ PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

AIC_BANOVA

*Akaike information criterion (AIC) method and ANOVA***Description**

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

ARS

*Adjusted R squared (ARS) method***Description**

This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

ARS.BANOVA

*Adjusted R squared (ARS) method and ANOVA***Description**

Adjusted R squared (ARS) method: This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

ARSdemo

*Adjusted R squared (ARS) method for demo function***Description**

This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

ARSdemo.BANOVA

*Adjusted R squared (ARS) method and ANOVA for demo function***Description**

Adjusted R squared (ARS) method: This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

ARSoutput

*Output for Adjusted R squared (ARS) method***Description**

We provides several txt outputs. 1. NCA PK.txt: $\rightarrow C_{max}, T_{max}, AUC_{0t}, AUC_{0inf}, AUC_{0t}/AUC_{0inf}, \ln(C_{max}), \ln(AUC_{0t}), \ln(AUC_{0inf}), MRT_{0inf}, T_{1/2}, V_d/F, \lambda z,$ and $CI/F \rightarrow$ PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

From: NCAoutput

 BANOVA

Statistical analysis (ANOVA(lm), 90CI...)

Description

With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

We investigate the assessment of equivalence in intra-subject variabilities of bioavailability between formulations. Point and interval estimates for the inter-subject and intra-subject variabilities are also provided.

Moreover, a normal distribution test procedure based on Spearman's rank and Pearson's correlation coefficient and Pitman-Morgan's adjusted F test are provided.

Finally, several tests for assumptions using the inter-subject and intra-subject residuals are discussed. Statistical tests for detection of outlying subjects such as Hotelling T2 are presented.

References

1. Chow SC and Liu JP. Design and analysis of bioavailability- bioequivalence studies. Chapman & Hall/CRC, New York (2009).
2. Liu JP and Weng CS. Detection of outlying data in bioavailability- bioequivalence studies. Statist. Med. 10, 1375-1389 (1991).

 BANOVAanalyze

ANOVA function

Description

Data for ANOVA

References

Guidance for Industry. Statistical approaches to establishing Bioequivalence.

 BANOVAcsv

choose separator and decimal type

Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

BANOVAdata *Input/Edit data for ANOVA function*

Description

->subject no.(subj) ->drug 1:Reference 2:Test ->sequence (seq) Sequence 1:Reference->Test sequence Sequence 2:Test->Reference sequence ->period (prd) Period 1: first treatment period Period 2: second treatment period ->Cmax ->AUC0t: area under the predicted plasma concentration time curve for test data. (time = 0 to t) ->AUC0INF: area under the predicted plasma concentration time curve for test data. (time = 0 to infinity) ->LnCmax: Log-transformed Cmax ->LnAUC0t: Log-transformed AUC0t ->LnAUC0INF: Log-transformed AUC0INF

BANOVAmenu *List of ANOVA Menu*

Description

You can use the functions as follows: 1.Statistical analysis (ANOVA(lm), 90CI...) 2.Demo for Statistical analysis (ANOVA(lm), 90CI...)

BANOVAoutput *Output of ANOVA function*

Description

We provides several txt outputs. 1.ANOVA stat.txt ->ANOVA:Cmax, AUC0t, AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf) ->90CI: ln(Cmax), ln(AUC0t), and ln(AUC0inf) ->plus ln(pAUC) if partial AUC is applied.

BANOVApplot *BANOVApplot*

Description

We provides several pdf. outputs about BANOVA plots for outlier detections. 1.Normal Probability Plot of lnCmax (intrasubj) 2.Normal Probability Plot of lnCmax (intersubj) 3.lnCmax(expected value) vs. studentized residuals(intrasubj) 4.lnCmax(expected value) vs. studentized residuals(intersubj) 5.Normal Probability Plot of lnAUC0t (intrasubj) 6.Normal Probability Plot of lnAUC0t (intersubj) 7.lnAUC0t(expected value) vs. studentized residuals(intrasubj) 8.lnAUC0t(expected value) vs. studentized residuals(intersubj) 9.Normal Probability Plot of lnAUC0INF (intrasubj) 10.Normal Probability Plot of lnAUC0INF (intersubj) 11.lnAUC0INF(expected value) vs. studentized residuals(intrasubj) 12.lnAUC0INF(expected value) vs. studentized residuals(intersubj)

bear.setup	<i>Setup module for bear</i>
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Description

You can setup the method/value for: 1. lambda_z estimation, 2. AUC calculation, 3. BE criterion (LL) 4. Dose, 5. Dosing Interval, 6. Tlast, and 7. x-axis & y-axis labels for plots.

bye	<i>The final step Menu</i>
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Description

try again or leave bear package.

create.products_sum	<i>create.products_sum</i>
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Description

this function is to create two temporary .csv files for the list of the section containing the means (SD) for each formulation (by time point) in NCA output file. These two .csv files will be deleted after nca_outputs file is done.

demoBANOVA	<i>Statistical analysis (ANOVA(lm), 90CI...)for demo file</i>
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Description

With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

demomenu	<i>menu for NCA demo file</i>
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Description

lambda z est. from the exact 3 data points, lambda z est. with adjusted R sq. (ARS), lambda z est. with Akaike information criterion (AIC), lambda z est. with Two-Times-Tmax method (TTT), lambda z est. with TTT and ARS, lambda z est. with TTT and AIC

demomenu1	<i>menu for NCA demo file</i>
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Description

lambda z est. from the exact 3 data points-> Statistical analysis, lambda z est. with adjusted R sq. (ARS)-> Statistical analysis, lambda z est. with Akaike information criterion (AIC)-> Statistical analysis, lambda z est. with Two-Times-Tmax method (TTT)-> Statistical analysis, lambda z est. with TTT and ARS-> Statistical analysis, lambda z est. with TTT and AIC-> Statistical analysis,

demopara	<i>Demo for sample size estimation</i>
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Description

Demo file for sample size estimation (crossover and replicated study)function

demosize	<i>Demo for sample size estimation</i>
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Description

Demo file for sample size estimation (crossover and replicated study)function

demo_datasets_gen	<i>To generate all demo datasets for testing purposes</i>
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Description

To generate all demo datasets for testing purposes On the top menu, enter '99' (no quote) to run this.

description_AIC *Description for Akaike information criterion (AIC) method*

Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

description_ARS *Description for Adjusted R squared (ARS) method*

Description

This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

description_BANOVA *Description for ANOVA*

Description

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

description_BE_criteria
Display BE criteria for Two One-Sided Test for all pivotal parameters

Description

Display BE criteria for Two One-Sided Test for all pivotal parameters in the output file.

description_drug *Description for drug*

Description

drug 1: Ref. drug 2: Test

description_drugcode *Description for drug code*

Description

Data Codes: Drug: 1: Ref. 2: Test Sequence: 1: Ref. -> Test 2: Test -> Ref. Period: 1: 1st-treatment period 2: 2nd-treatment period

description_import *Description for import csv*

Description

Description for import csv file

description_load *Description for load Rdata*

Description

Description for load Rdata file

description_Multipliedrugcode
Description for drug code for multiple study

Description

Data Codes: Drug: 1: Ref. 2: Test Sequence: 1: Ref. -> Test 2: Test -> Ref. Period: 1: 1st-treatment period 2: 2nd-treatment period

description_NCA *Description for Noncompartmental analysis (NCA)*

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λz) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable C_p). The extrapolated AUC (from time of the last measurable C_p to time infinity) is equal to the last measurable C_p divided by λz .

description_NCAcsv *Description for NCA csv file*

Description

Data file should consist of row1: column title, such as subj, seq, prd, time, conc & etc. column1: subject no.(subj) column2: sequence (seq) -> Sequence = 1 if Ref.->Test -> Sequence = 2 if Test->Ref. column3: period (prd) -> Period = 1: the 1st-treatment period -> Period = 2: the 2nd-treatment period column4: sampling time column5: drug plasma/serum/blood concentration (conc)

description_NCAinput *Description for NCA input data*

Description

Input/Edit Data -> subject no.(subj) -> sequence (seq) 1:Ref.->Test 2:Test->Ref. -> period (prd) 1: 1st-treatment period 2: 2nd-treatment period -> sampling time -> drug plasma/serum/blood concentration (conc)

description_ParamIX *Description for lme for parallel study*

Description

With a two-treatment, two-sequence, one-period, parallel design, lme deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

description_ParaNCAcsv

Description for NCA csv file for parallel study

Description

Data file should consist of row1: column title, such as subj, drug, time, conc & etc. column1: subject no.(subj) column2: treatment (drug) column3: sampling time column4: drug plasma/serum/blood concentration (conc)

description_ParaNCAinput

Description for NCA input data for parallel study

Description

Input/Edit Data -> subject no.(subj) -> treatment (drug) 1: Ref. 2: Test -> sampling time -> drug plasma/serum/blood concentration (conc)

description_plot

Description for plot

Description

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description_pointselect

description_pointselect

Description

Explain to users about how to make data point manual selection for lambda_z estimation.

description_Repdrugcode

Description of drug code for replicated study

Description

Data Codes: Drug: 1: Ref. 2: Test

description_RepMIX

Description for lme for replicated study

Description

With a two-treatment, more than two period, two-sequence randomized crossover design, linear mixed-effects model may be used. The lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

description_RepNCAcsv *Description of NCA csv file for replicated study*

Description

Data file should consist of row1: column title, such as subj, seq, prd, time, conc & etc. column1: subject no.(subj) column2: sequence (seq) -> Sequence = 1 if Ref.->Test -> Sequence = 2 if Test->Ref. column3: period (prd) -> Period = 1: the 1st-treatment period -> Period = 2: the 2nd-treatment period

column4: treatment (drug) column5: sampling time column6: drug plasma/serum/blood concentration (conc)

description_RepNCAinput

Description for NCA input data for replicated study

Description

Input/Edit Data -> subject no.(subj) -> sequence (seq) ex. 4 periods 1:Ref.->Test->Ref.->Test 2:Test->Ref.->Test->Ref. or ex. 3 periods 1:Ref.->Test->Test 2:Test->Ref.->Ref. -> period (prd) 1: 1st-treatment period 2: 2nd-treatment period 3: 3rd-treatment period 4: 4th-treatment period -> treatment (drug) 1: Ref. 2: Test -> sampling time -> drug plasma/serum/blood concentration (conc)

description_size *Description for sample size input for crossover and replicated study*

Description

Required data 1. Theta is the ratio in average BA between the two formulations expressed in percentage of the average reference BA. 2. $\text{Theta} = U_t/U_r$, where U_t and U_r denote the median BA for the Test and the Reference products. 3. CV stands for the intra-subject coefficient of variation.

description_size_para *Description for sample size input for parallel study*

Description

Required data 1. Theta is the ratio in average BA between the two formulations expressed in percentage of the average reference BA. 2. $\text{Theta} = U_t/U_r$, where U_t and U_r denote the median BA for the Test and the Reference products. 3. CV stands for the inter-subject coefficient of variation.

description_TOST1_lnAUC0INF
Description for Two One-Sided Test for lnAUC0INF

Description

Interpretation: $H_0: \text{MEAN-test/MEAN-ref} \leq \ln(\text{lower acceptance})$ or $\text{MEAN-test/MEAN-ref} \geq \ln(\text{Upper acceptance})$
 $H_a: \ln(\text{lower acceptance}) < \text{MEAN-test/MEAN-ref} < \ln(\text{Upper acceptance})$
 Because all P values are less than 0.05, we will reject the null hypothesis (H_0).

References

1. Chow SC and Liu JP. Design and Analysis of Bioavailability- Bioequivalence Studies. 3rd ed., Chapman & Hall/CRC, New York (2009).
2. Schuirmann DJ. On hypothesis testing to determine if the mean of a normal distribution is contained in a known interval. *Biometrics*, 37, 617(1981).
3. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *Journal of Pharmacokinetics and Biopharmaceutics*, 15, 657-680 (1987).
4. Anderson S and Hauck WW. A new procedure for testing equivalence in comparative bioavailability and other clinical trials. *Communications in Statistics-Theory and Methods*, 12, 2663-2692 (1983).

description_TOST1_InAUC0t

Description for Two One-Sided Test for lnAUC0t

Description

Interpretation: H_0 : $\text{MEAN-test/MEAN-ref} \leq \ln(\text{lower acceptance})$ or $\text{MEAN-test/MEAN-ref} \geq \ln(\text{Upper acceptance})$
 H_a : $\ln(\text{lower acceptance}) < \text{MEAN-test/MEAN-ref} < \ln(\text{Upper acceptance})$
Because all P values are less than 0.05, we will reject the null hypothesis (H_0).

References

1. Chow SC and Liu JP. Design and Analysis of Bioavailability- Bioequivalence Studies. 3rd ed., Chapman & Hall/CRC, New York (2009). 2. Schuirmann DJ. On hypothesis testing to determine if the mean of a normal distribution is contained in a known interval. *Biometrics*, 37, 617(1981). 3. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *Journal of Pharmacokinetics and Biopharmaceutics*, 15, 657-680 (1987). 4. Anderson S and Hauck WW. A new procedure for testing equivalence in comparative bioavailability and other clinical trials. *Communications in Statistics-Theory and Methods*, 12, 2663-2692 (1983).

description_TOST1_InCmax

Description for Two One-Sided Test for lnCmax

Description

Interpretation: H_0 : $\text{MEAN-test/MEAN-ref} \leq \ln(\text{lower acceptance})$ or $\text{MEAN-test/MEAN-ref} \geq \ln(\text{Upper acceptance})$
 H_a : $\ln(\text{lower acceptance}) < \text{MEAN-test/MEAN-ref} < \ln(\text{Upper acceptance})$
Because all P values are less than 0.05, we will reject the null hypothesis (H_0).

References

1. Chow SC and Liu JP. Design and Analysis of Bioavailability- Bioequivalence Studies. 3rd ed., Chapman & Hall/CRC, New York (2009). 2. Schuirmann DJ. On hypothesis testing to determine if the mean of a normal distribution is contained in a known interval. *Biometrics*, 37, 617(1981). 3. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *Journal of Pharmacokinetics and Biopharmaceutics*, 15, 657-680 (1987). 4. Anderson S and Hauck WW. A new procedure for testing equivalence in comparative bioavailability and other clinical trials. *Communications in Statistics-Theory and Methods*, 12, 2663-2692 (1983).

description_TOST_InAUC0INF

Description for Two One-Sided Test for lnAUC0INF

Description

Interpretation: $H_0: \text{MEAN-test/MEAN-ref} \leq \ln(\text{lower acceptance})$ or $\text{MEAN-test/MEAN-ref} \geq \ln(\text{Upper acceptance})$
 $H_a: \ln(\text{lower acceptance}) < \text{MEAN-test/MEAN-ref} < \ln(\text{Upper acceptance})$
If at least one of P value is more than 0.05, we will not reject the null hypothesis (H_0).

References

1. Chow SC and Liu JP. Design and Analysis of Bioavailability- Bioequivalence Studies. 3rd ed., Chapman & Hall/CRC, New York (2009). 2. Schuirmann DJ. On hypothesis testing to determine if the mean of a normal distribution is contained in a known interval. *Biometrics*, 37, 617(1981). 3. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *Journal of Pharmacokinetics and Biopharmaceutics*, 15, 657-680 (1987). 4. Anderson S and Hauck WW. A new procedure for testing equivalence in comparative bioavailability and other clinical trials. *Communications in Statistics-Theory and Methods*, 12, 2663-2692 (1983).

description_TOST_InAUC0t

Description for Two One-Sided Test for lnAUC0t

Description

Interpretation: $H_0: \text{MEAN-test/MEAN-ref} \leq \ln(\text{lower acceptance})$ or $\text{MEAN-test/MEAN-ref} \geq \ln(\text{Upper acceptance})$
 $H_a: \ln(\text{lower acceptance}) < \text{MEAN-test/MEAN-ref} < \ln(\text{Upper acceptance})$
If at least one of P value is more than 0.05, we will not reject the null hypothesis (H_0).

References

1. Chow SC and Liu JP. Design and Analysis of Bioavailability- Bioequivalence Studies. 3rd ed., Chapman & Hall/CRC, New York (2009). 2. Schuirmann DJ. On hypothesis testing to determine if the mean of a normal distribution is contained in a known interval. *Biometrics*, 37, 617(1981). 3. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *Journal of Pharmacokinetics and Biopharmaceutics*, 15, 657-680 (1987). 4. Anderson S and Hauck WW. A new procedure for testing equivalence in comparative bioavailability and other clinical trials. *Communications in Statistics-Theory and Methods*, 12, 2663-2692 (1983).

 description_TOST_InCmax

Description for Two One-Sided Test for InCmax

Description

Interpretation: $H_0: \text{MEAN-test/MEAN-ref} \leq \ln(\text{lower acceptance})$ or $\text{MEAN-test/MEAN-ref} \geq \ln(\text{Upper acceptance})$
 $H_a: \ln(\text{lower acceptance}) < \text{MEAN-test/MEAN-ref} < \ln(\text{Upper acceptance})$
 If at least one of P value is more than 0.05, we will not reject the null hypothesis (H_0).

References

1. Chow SC and Liu JP. Design and Analysis of Bioavailability- Bioequivalence Studies. 3rd ed., Chapman & Hall/CRC, New York (2009). 2. Schuirmann DJ. On hypothesis testing to determine if the mean of a normal distribution is contained in a known interval. *Biometrics*, 37, 617(1981). 3. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *Journal of Pharmacokinetics and Biopharmaceutics*, 15, 657-680 (1987). 4. Anderson S and Hauck WW. A new procedure for testing equivalence in comparative bioavailability and other clinical trials. *Communications in Statistics-Theory and Methods*, 12, 2663-2692 (1983).

 description_TTT

Description for Two Times Tmax (TTT) method

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$.

 description_TTTAIC

Description for Two-Times-Tmax (TTT) and Akaike information criterion (AIC)

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

description_TTTARS *Description for Two Times T_{max} (TTT) and Adjusted R squared (ARS)*

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

description_version *Description for version*

Description

Authors: Hsin-ya Lee, Yung-jin Lee Kaohsiung Veterans General Hospital (HY) & ptpc inc. (YJ), Kaoshiung, Taiwan 80794 E-mail: mobilepk@gmail.com website: <http://pkpd.kmu.edu.tw/bear>

entertitle *enter Dose, xaxis and yaxis*

Description

enter Dose, xaxis and yaxis

entertitle.demo	<i>enter Dose, xaxis and yaxis for demo file</i>
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Description

enter Dose, xaxis and yaxis

go	<i>List of bear Menu</i>
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Description

You can use the functions as follows: 1.Single dose study 2.Multiple dose study

go2menu	<i>List of bear Menu</i>
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Description

You can use the functions as follows: 1. Single dose study 2. Multiple dose study 3. *Single dose study (with ODA) 4. *Multiple dose study (with ODA) 5. Quit

helper.func	<i>helper.func</i>
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Description

some helper functions from: Cookbook for R, http://www.cookbook-r.com/Graphs/Plotting_means_and_error_bars_ used to help ggplot()

Author(s)

Winston Chang

icd.check	<i>icd.check</i>
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Description

function to check if it is an incomplete dataset, if yes, then stop bear.

indiv_dp.output	<i>to generate list of individual data points as .csv format</i>
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Description

to generate list of individual data points as .csv format

lm.mod	<i>module to run both lm() and aov()</i>
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Description

module to run both lm() and aov(); called by BANOVA()

lme_lm.mod	<i>module to run both lme() or lm()</i>
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Description

module to run both lme() or lm() for replicated or parallel study; called by RepMIX()

logdata	<i>Sample size estimation for log transformation data for crossover and replicated study</i>
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Description

This function will help you to choose appropriate sample size.

References

R-code based on SAS-code by (1) B. Jones and M.G. Kenward Design and Analysis of Cross-Over Trials Chapman & Hall/CRC, Boca Raton (2nd Edition 2000) (2) S. Patterson and B. Jones Bioequivalence and Statistics in Clinical Pharmacology Chapman & Hall/CRC, Boca Raton (2006) /*** WARNING : PROGRAM OFFERED FOR USE WITHOUT ANY GUARANTEES ***/ /*** NO LIABILITY IS ACCEPTED FOR ANY LOSS RESULTING FROM USE OF ***/ /*** THIS SET OF SAS INTRUCTIONS ***/ Modification of degrees of freedom according to a personal message by D. Hauschke (E-mail 2006-01-05) Tested in R-versions 2.6.2 / 2.5.1 / 1.9.1 / 1.9.0 2008-04-04 Sample size R-code was referred from Helmut Schuetz BEBAC - Consultancy services for Bioequivalence and Bioavailability Studies 1070 Vienna, Austria

Hauschke D, Steinijs VW, Diletti E and Burke M. Sample size determination for bioequivalence assessment using a multiplicative model. J. Pharmacokin. Biopharm. 20:557-561 (1992).

logo_plot_desc	<i>Description for NCA/ODA plots version</i>
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Description

Authors: Hsin-ya Lee, Yung-jin Lee Kaohsiung Veterans General Hospital (HY) & ptpc inc. (YJ), Kaoshiung, Taiwan 80794 E-mail: mobilepk@gmail.com website: <http://pkpd.kmu.edu.tw/bear>

Multiple1menu	<i>List of NCA non-replicated and replicated study</i>
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Description

You can use the functions as follows: 1. NCA for non-replicated crossover study, 2. NCA for replicated crossover study,

Multipleaic	<i>Akaike information criterion (AIC) method for multiple study</i>
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Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

MultipleAICdemo	<i>Akaike information criterion (AIC) method for demo function</i>
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Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

MultipleAICoutput	<i>Output for Adjusted R squared (ARS) method for multiple dose</i>
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Description

We provides several txt outputs. 1. NCA PK.txt: -> Cmax, Tmax, AUC0t, AUC0inf, AUC0t/AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf), MRT0inf, T1/2, Vd/F, lambda z, and CI/F -> PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

MultipleAIC_BANOVA	<i>Akaike information criterion (AIC) method and ANOVA for multiple dose</i>
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Description

This method selects data points to estimate lambda(z) based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

MultipleARS	<i>Adjusted R squared (ARS) method for multiple dose</i>
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Description

This method selects data points to estimate lambda(z) based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of Cmax. Thus, this method may exclude the data point of (Tmax, Cmax). WNL v6. has the similar algorithms like this.

MultipleARS.BANOVA *Adjusted R squared (ARS) method and ANOVA for multiple dose*

Description

Adjusted R squared (ARS) method: This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

MultipleARSDemo *Adjusted R squared (ARS) method for demo function for multiple dose*

Description

This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

MultipleARSoutput *Output for Adjusted R squared (ARS) method for multiple dose*

Description

We provides several txt outputs. 1. NCA PK.txt: $\rightarrow C_{max}, T_{max}, AUC_{0t}, AUC_{0inf}, AUC_{0t}/AUC_{0inf}, \ln(C_{max}), \ln(AUC_{0t}), \ln(AUC_{0inf}), MRT_{0inf}, T_{1/2}, V_d/F, \lambda z,$ and $Cl/F \rightarrow$ PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

MultipleBANOVA

Statistical analysis (ANOVA(lm), 90CI...)

Description

With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

We investigate the assessment of equivalence in intra-subject variabilities of bioavailability between formulations. Point and interval estimates for the inter-subject and intra-subject variabilities are also provided.

Moreover, a normal distribution test procedure based on Spearman's rank and Pearson's correlation coefficient and Pitman-Morgan's adjusted F test are provided.

Finally, several tests for assumptions using the inter-subject and intra-subject residuals are discussed. Statistical tests for detection of outlying subjects such as Hotelling T2 are presented.

References

1. Chow SC and Liu JP. Design and analysis of bioavailability- bioequivalence studies. Chapman & Hall/CRC, New York (2009).
2. Liu JP and Weng CS. Detection of outlying data in bioavailability- bioequivalence studies. Statist. Med. 10, 1375-1389 (1991).

MultipleBANOVAanalyze *ANOVA function for multiple dose*

Description

Data for ANOVA

References

Guidance for Industry. Statistical approaches to establishing Bioequivalence.

MultipleBANOVAcsv

choose separator and decimal type for multiple dose

Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

MultipleBANOVAdata *Input/Edit data for ANOVA function for multiple dose*

Description

->subject no.(subj) ->drug 1:Reference 2:Test ->sequence (seq) Sequence 1:Reference->Test sequence Sequence 2:Test->Reference sequence ->period (prd) Period 1: first treatment period Period 2: second treatment period ->C_{ss_max} ->AUC_{ss(tau)}: area under the predicted plasma concentration time curve (time = tau) ->LnC_{ss_max}: Log-transformed C_{max} ->LnAUC_{0ss(tau)}: Log-transformed AUC_{0ss(tau)}

MultipleBANOVAMenu *List of ANOVA Menu for multiple dose*

Description

You can use the functions as follows: 1.Statistical analysis (ANOVA(lm), 90CI...) 2.Demo for Statistical analysis (ANOVA(lm), 90CI...)

MultipleBANOVAoutput *Output of ANOVA function for multiple dose*

Description

We provides several txt outputs. 1.ANOVA stat.txt ->ANOVA:C_{ss_max}, AUC_{ss(tau)}, lnC_{ss_max}, lnAUC_{ss(tau)} ->90CI: lnC_{ss_max}, lnAUC_{ss(tau)}

MultipleBANOVApLot *BANOVApLot for multiple dose*

Description

We provides several pdf. outputs about BANOVA plots for outlier detections. 1.Normal Probability Plot of lnC_{ss_max} (intrasubj) 2.Normal Probability Plot of lnC_{ss_max} (intersubj) 3.lnC_{ss_max}(expected value) vs. studentized residuals(intrasubj) 4.lnC_{ss_max}(expected value) vs. studentized residuals(intersubj) 5.Normal Probability Plot of lnAUC_{ss(tau)} (intrasubj) 6.Normal Probability Plot of lnAUC_{ss(tau)} (intersubj) 7.lnAUC_{ss(tau)}(expected value) vs. studentized residuals(intrasubj) 8.lnAUC_{ss(tau)}(expected value) vs. studentized residuals(intersubj)

Multipladata	<i>Data for NCA analyze for multiple dose</i>
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Description

The data give the data of subjects, drug, sequence, period, time, and concentration.

MultipldemoBANOVA	<i>Statistical analysis (ANOVA(lm), 90CI...)for demo file</i>
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Description

With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

Multipldemomenu	<i>menu for NCA demo file</i>
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Description

lambda z est. from the exact 3 data points, lambda z est. with adjusted R sq. (ARS), lambda z est. with Akaike information criterion (AIC), lambda z est. with Two-Times-Tmax method (TTT), lambda z est. with TTT and ARS, lambda z est. with TTT and AIC

Multipldemomenu1	<i>menu for NCA demo file</i>
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Description

lambda z est. from the exact 3 data points-> Statistical analysis, lambda z est. with adjusted R sq. (ARS)-> Statistical analysis, lambda z est. with Akaike information criterion (AIC)-> Statistical analysis, lambda z est. with Two-Times-Tmax method (TTT)-> Statistical analysis, lambda z est. with TTT and ARS-> Statistical analysis, lambda z est. with TTT and AIC-> Statistical analysis,

 Multiplego

List of bear Menu

Description

You can use the functions as follows: 1.Sample size estimation for average BE 2.Noncompartment Analysis (NCA) 3.ANOVA 4.NCA->ANOVA

 Multiplemenu

List of NCA non-replicated and replicated study

Description

You can use the functions as follows: 1. NCA for non-replicated crossover study, 2. NCA for replicated crossover study,

 MultipleNCA

Noncompartmental analysis (NCA) for multiple dose

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable Cp). The extrapolated AUC (from time of the last measurable Cp to time infinity) is equal to the last measurable Cp divided by λ_z .

 MultipleNCA.BANOVA

NCA and ANOVA for multiple dose

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable Cp). The extrapolated AUC (from time of the last measurable Cp to time infinity) is equal to the last measurable Cp divided by λ_z .

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

MultipleNCA.BANOVAanalyze

NCA and ANOVA function for multiple dose

Description

This function includes both NCAanalyze and BANOVAanalyze functions.

MultipleNCA.BANOVAcsv *choose separator and decimal type for multiple dose*

Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

MultipleNCA.BANOVAdata

Input/Edit data for NCA and ANOVA function for multiple dose

Description

Input/Edit Data ->subject no.(subj) ->sequence (seq) Sequence 1:Reference->Test sequence Sequence 2:Test->Reference sequence ->period (prd) Period 1: first treatment period Period 2: second treatment period ->time ->concentration (conc)

MultipleNCA.BANOVAmenu

List of NCA and ANOVA Menu for multiple dose

Description

You can use the functions as follows: 1.NCA->ANOVA 2.Run demo for NCA -> Statistical analysis

MultipleNCAanalyze

NCA analyze function for multiple dose

Description

We provide noncompartmental analysis (NCA) approach to compute AUCs and terminal elimination rate constant (kel) for plasma concentration. Here we provide six methods, exact 3 data points, ARS, TTT, AIC, TTT and ARS, and TTT and AIC.

MultipleNCAcsv *choose separator and decimal type for multiple dose*

Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

MultipleNCAdata *Input/Edit data for NCA function for multiple dose*

Description

Input/Edit Data ->subject no.(subj) ->sequence (seq) Sequence 1:Reference->Test sequence Sequence 2:Test->Reference sequence ->period (prd) Period 1: first treatment period Period 2: second treatment period ->time ->concentration (conc)

MultipleNCAdemo *Select the exact 3 data points(NCA) for demo function for multiple dose*

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable Cp). The extrapolated AUC (from time of the last measurable Cp to time infinity) is equal to the last measurable Cp divided by λ_z .

MultipleNCAdemo.BANOVA

Select the exact 3 data points(NCA) and ANOVA for demo function for multiple dose

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable Cp). The extrapolated AUC (from time of the last measurable Cp to time infinity) is equal to the last measurable Cp divided by λ_z .

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

MultipleNCAmenu *List of NCA 2x2x2 Menu for multiple dose*

Description

You can use the functions as follows: 1.multiple Dose 2.Demo for multiple Dose

MultipleNCAoutput *Output of NCA for multiple dose*

Description

We provides several txt outputs. 1. NCA PK.txt: →Css_max, Tss_max, AUCss(tau), ln(Css_max), ln(AUCss(tau)), MRTss(tau), T1/2(z), Vd/F, lambda, Clss/F, Cav and Fluctuation → PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

MultipleNCAplot *NCAplot for multiple dose*

Description

We provides several pdf. outputs about NCA plots. 1.Conc. vs. Time for individual subjects 2.Log10(Conc.) vs. Time for individual subjects 3.Test (.Conc. vs. Time) for all subjects 4.Reference (.Conc. vs. Time) for all subjects 5.Conc.(mean+-sd) vs Time for test and reference

MultipleNCAsave *Save NCA outputs for multiple dose*

Description

This function can save the results after NCA.

MultipleNCAselect *Select the exact 3 points in NCA for multiple dose*

Description

This function can help users select the exact 3 points for NCA function.

MultipleNCAselct.BANOVA

Select the exact 3 points in NCA and ANOVA for multiple dose

Description

This function can help users select the exact 3 points for NCA function.

MultipleNCAselctdemo *Select the exact 3 points in NCA for demo function for multiple dose*

Description

This function can help users select the exact 3 points for NCA function.

MultipleNCAselctdemo.BANOVA

Select the exact 3 points in NCA and ANOVA for demo function for multiple dose

Description

This function can help users select the exact 3 points for NCA function.

MultipleNCAselctsave *Select the exact 3 points in NCA and Save the data for multiple dose*

Description

This function can save the exact 3 points.

MultipleNCAselctsave.BANOVA

Select the exact 3 points in NCA and Save the data for multiple dose

Description

This function can save the exact 3 points.

Multiplentertitle *enter Dose, tau, time of last dose, xaxis and yaxis for multiple dose*

Description

enter Dose, tau, time of last dose, xaxis and yaxis

Multiplentertitle.demo
enter Dose, tau, time of last dose, xaxis and yaxis for multiple dose for demo file

Description

enter Dose, tau, time of last dose, xaxis and yaxis

MultipleParaAIC *Akaike information criterion (AIC) method for parallel with multiple dose study*

Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

MultipleParaAIC.MIX *Akaike information criterion (AIC) method->statistics for parallel with multiple dose study*

Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

MultipleParaAICdemo *Akaike information criterion (AIC) method for demo function for parallel with multiple dose study*

Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

MultipleParaAICoutput *Output for Adjusted R squared (ARS) method for parallel with multiple dose study*

Description

We provides several txt outputs. 1. NCA PK.txt: $\rightarrow C_{ss_max}, T_{ss_max}, AUC_{ss}(\tau), \ln(C_{ss_max}), \ln(AUC_{ss}(\tau)), MRT_{ss}(\tau), T_{1/2}(z), V_d/F, \lambda, Cl_{ss}/F, C_{av}$ and Fluctuation \rightarrow PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

MultipleParaARS *Adjusted R squared (ARS) method for parallel with multiple dose study*

Description

This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

MultipleParaARS.MIX *Adjusted R squared (ARS) method and lme for parallel with multiple dose study*

Description

Adjusted R squared (ARS) method: This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

With a two-treatment, two-sequence, one-period, parallel design, bear deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

MultipleParaARSDemo *Adjusted R squared (ARS) method for demo function for parallel with multiple dose study*

Description

This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

MultipleParaARSoutput *Output for Adjusted R squared (ARS) method for parallel study*

Description

We provides several txt outputs. 1. NCA PK.txt: $\rightarrow C_{ss_max}, T_{ss_max}, AUC_{ss}(\tau), \ln(C_{ss_max}), \ln(AUC_{ss}(\tau)), MRT_{ss}(\tau), T_{1/2}(z), V_d/F, \lambda, Cl_{ss}/F, C_{av}$ and Fluctuation \rightarrow PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

MultipleParadata *Data for NCA analyze for parallel with multiple dose study*

Description

The data give the data of subjects, drug, time, and concentration.

MultipleParademomenu *menu for NCA demo file for parallel with multiple dose study*

Description

lambda z est. from the exact 3 data points, lambda z est. with adjusted R sq. (ARS), lambda z est. with Akaike information criterion (AIC), lambda z est. with Two-Times-Tmax method (TTT), lambda z est. with TTT and ARS, lambda z est. with TTT and AIC

MultipleParademomenu1 *menu for NCA->Statistical analysis demo file for parallel with multiple dose study*

Description

lambda z est. from the exact 3 data points-> Statistical analysis, lambda z est. with adjusted R sq. (ARS)-> Statistical analysis, lambda z est. with Akaike information criterion (AIC)-> Statistical analysis, lambda z est. with Two-Times-Tmax method (TTT)-> Statistical analysis, lambda z est. with TTT and ARS-> Statistical analysis, lambda z est. with TTT and AIC-> Statistical analysis,

MultipleParademoMIX *Statistical analysis (lme, 90CI...)for demo file for parallel with multiple dose study*

Description

Statistical analysis (lme, 90CI...): With a two-treatment, two-sequence, one-period, parallel design, bear deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

MultipleParamenu *List of NCA 2x2x1 Menu for multiple dose*

Description

You can use the functions as follows: 1.run NCA 2.Demo for NCA

MultipleParaMIX *Statistical analysis (lme, 90CI...) for parallel with multiple dose study*

Description

With a two-treatment, two-sequence, one-period, parallel design, bear deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

MultipleParaMIXanalyze *Split data to perform lme function for parallel with multiple dose study*

Description

Split data for lme function

References

Guidance for Industry. Statistical approaches to establishing Bioequivalence.

MultipleParaMIXcsv *choose separator and decimal type for multiple dose*

Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

MultipleParaMIXdata *Input/Edit data for lme function for parallel with multiple dose study*

Description

->subject no.(subj) ->drug 1:Reference 2:Test ->Css_max ->AUCss(tau): area under the predicted plasma concentration time curve (time = tau) ->LnCss_max: Log-transformed Cmax ->LnAUC0ss(tau): Log-transformed AUC0ss(tau)

MultipleParaMIXmenu *List of lme Menu for multiple dose*

Description

You can use the functions as follows: 1.Statistical analysis (lme, 90CI...) 2.Demo for Statistical analysis (lme, 90CI...)

MultipleParaMIXoutput *Output of lme function for multiple dose*

Description

We provides several txt outputs. 1.lme stat.txt ->lme: Css_max, AUCss(tau), lnCss_max, lnAUCss(tau) ->90CI: lnCss_max, lnAUCss(tau)

MultipleParaNCA *Noncompartmental analysis (NCA) for parallel with multiple dose study*

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable C_p). The extrapolated AUC (from time of the last measurable C_p to time infinity) is equal to the last measurable C_p divided by λ_z .

MultipleParaNCA.MIX *NCA and lme for parallel study for multiple dose*

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λz) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable Cp). The extrapolated AUC (from time of the last measurable Cp to time infinity) is equal to the last measurable Cp divided by λz .

Statistical analysis (lme, 90CI...): With a two-treatment, two-sequence, one-period, parallel design, bear deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

MultipleParaNCA.MIXanalyze
NCA and lme function for multiple dose

Description

This function includes both NCA and lme functions.

MultipleParaNCA.MIXcsv
choose separator and decimal type for multiple dose

Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

MultipleParaNCA.MIXdata
Input/Edit data for NCA and lme function for parallel with multiple dose study

Description

Input/Edit Data ->subject no.(subj) ->drug ref.: 1 test: 2 ->time ->concentration (conc)

MultipleParaNCA.MIXmenu

List of NCA and lme Menu for multiple dose

Description

You can use the functions as follows: 1.NCA->lme 2.Run demo for NCA -> Statistical analysis

MultipleParaNCAanalyze

NCA analyze function for parallel with multiple dose study

Description

We provide noncompartmental analysis (NCA) approach to compute AUCs and terminal elimination rate constant (k_{el}) for plasma concentration. Here we provide six methods, exact 3 data points, ARS, TTT, AIC, TTT and ARS, and TTT and AIC.

MultipleParaNCAcsv

choose separator and decimal type

Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

MultipleParaNCAdata

Input/Edit data for NCA function for parallel study

Description

Input/Edit Data ->subject no.(subj) ->drug ->time ->concentration (conc)

MultipleParaNCAdemo

Select the exact 3 data points(NCA) for demo function for parallel study

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable C_p). The extrapolated AUC (from time of the last measurable C_p to time infinity) is equal to the last measurable C_p divided by λ_z .

MultipleParaNCAdemo.MIX

Select the exact 3 data points(NCA) and lme for demo function

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λz) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable Cp). The extrapolated AUC (from time of the last measurable Cp to time infinity) is equal to the last measurable Cp divided by λz .

Statistical analysis (lme, 90CI...): With a two-treatment, two-sequence, one-period, parallel design, bear deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

MultipleParaNCAoutput *Output of NCA for parallel study*

Description

We provides several txt outputs. 1. NCA PK.txt: \rightarrow Css_max, Tss_max, AUCss(tau), \ln (Css_max), \ln (AUCss(tau)), MRTss(tau), $T_{1/2}(z)$, Vd/F, λ , Clss/F, Cav and Fluctuation \rightarrow PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

MultipleParaNCAplot *NCAplot for parallel study*

Description

We provides several pdf. outputs about NCA plots. 1.Conc. vs. Time for individual subjects 2.Log10(Conc.) vs. Time for individual subjects 3.Test (.Conc. vs. Time) for all subjects 4.Reference (.Conc. vs. Time) for all subjects 5.Conc.(mean+-sd) vs Time for test and reference

MultipleParaNCAsave *Save NCA outputs for parallel study*

Description

This function can save the results after NCA.

MultipleParaNCAselct *Select the exact 3 points in NCA for parallel study*

Description

This function can help users select the exact 3 points for NCA function.

MultipleParaNCAselct.MIX
Select the exact 3 points in NCA and lme for parallel study

Description

This function can help users select the exact 3 points for NCA function.

MultipleParaNCAselctdemo
Select the exact 3 points in NCA for demo function for parallel study

Description

This function can help users select the exact 3 points for NCA function.

MultipleParaNCAselctdemo.MIX
Select the exact 3 points in NCA and lme for demo function (parallel study)

Description

This function can help users select the exact 3 points for NCA function.

MultipleParaNCAselctsave
Select the exact 3 points in NCA and Save the data for parallel study

Description

This function can save data of the exact 3 points.

 MultipleParaNCAselctsave.MIX

Select the exact 3 points in NCA and Save the data

Description

This function can save the exact 3 points.

 MultipleParaTTT

Two Times Tmax (TTT) method for parallel study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max}. Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of lambda(z).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

 MultipleParaTTT.MIX

TTT and lme for parallel study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max}. Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of lambda(z).

Statistical analysis (lme, 90CI...): With a two-treatment, two-sequence, one-period, parallel design, bear deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

MultipleParaTTTAIC *TTT and AIC for parallel study*

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

MultipleParaTTTAIC.MIX
TTT ,AIC and lme for parallel study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

Statistical analysis (lme, 90CI...): With a two-treatment, two-sequence, one-period, parallel design, bear deploys the linear mixed effect model (lme). The statistical model includes a factor regarding

only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

MultipleParaTTTAICdemo

TTT and AIC for demo function for parallel study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

MultipleParaTTTAICoutput

Output for TTT and AIC for parallel study

Description

We provides several txt outputs. 1. NCA PK.txt: $\rightarrow C_{ss_max}$, T_{ss_max} , $AUC_{ss}(\tau)$, $\ln(C_{ss_max})$, $\ln(AUC_{ss}(\tau))$, $MRT_{ss}(\tau)$, $T_{1/2}(z)$, V_d/F , λ , Cl_{ss}/F , C_{av} and Fluctuation \rightarrow PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

MultipleParaTTTARS *TTT and ARS for parallel study*

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

MultipleParaTTTARS.MIX
TTT ,ARS and lme for parallel study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

Statistical analysis (lme, 90CI...): With a two-treatment, two-sequence, one-period, parallel design, R deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

MultipleParaTTTARSDemo

TTT and ARS for demo function for parallel study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

MultipleParaTTTARSDemo

Output for TTT and ARS for parallel study

Description

We provides several txt outputs. 1. NCA PK.txt: $\rightarrow C_{max}$, T_{max} , AUC_{0t} , AUC_{0inf} , AUC_{0t}/AUC_{0inf} , $\ln(C_{max})$, $\ln(AUC_{0t})$, $\ln(AUC_{0inf})$, MRT_{0inf} , $T_{1/2}$, V_d/F , λz , and $Cl/F \rightarrow$ PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

MultipleParaTTTdemo *Two Times Tmax (TTT) method for demo function for parallel study*

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z).

MultipleParaTTToutput *Output for Two Times Tmax (TTT) method for parallel study*

Description

We provides several txt outputs. 1. NCA PK.txt: ->Css_max, Tss_max, AUCss(tau), ln(Css_max), ln(AUCss(tau)), MRTss(tau), T1/2(z), Vd/F, lambda, Clss/F, Cav and Fluctuation -> PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.
3. Statistical summaries.txt

Multiplestat1menu *List of Statistical analysis non-replicated and replicated study*

Description

You can use the functions as follows: 1. Statistical analysis for non-replicated crossover study, 2. Statistical analysis for replicated crossover study,

Multiplestatmenu *List of NCA->statistics non-replicated and replicated study*

Description

You can use the functions as follows: 1. NCA for non-replicated crossover study, 2. NCA for replicated crossover study,

MultipleTTT

Two Times Tmax (TTT) method

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

MultipleTTT.BANOVA

TTT and ANOVA

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z).

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

MultipleTTTAIC

*TTT and AIC***Description**

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

MultipleTTTAIC.BANOVA *TTT ,AIC and ANOVA***Description**

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

MultipleTTTAICdemo *TTT and AIC for demo function*

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

MultipleTTTAICoutput *Output for TTT and AIC*

Description

We provides several txt outputs. 1. NCA PK.txt: $\rightarrow C_{ss_max}$, T_{ss_max} , $AUC_{ss}(\tau)$, $\ln(C_{ss_max})$, $\ln(AUC_{ss}(\tau))$, $MRT_{ss}(\tau)$, $T_{1/2}(z)$, Vd/F , λ , Cl_{ss}/F , C_{av} and Fluctuation \rightarrow PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

MultipleTTTARS

TTT and ARS

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

MultipleTTTARS.BANOVA *TTT,ARS and ANOVA*

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

MultipleTTTARSDemo *TTT and ARS for demo function*

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

MultipleTTTARSoutput *Output for TTT and ARS*

Description

We provides several txt outputs. 1. NCA PK.txt: $\rightarrow C_{ss_max}$, T_{ss_max} , $AUC_{ss}(\tau)$, $\ln(C_{ss_max})$, $\ln(AUC_{ss}(\tau))$, $MRT_{ss}(\tau)$, $T_{1/2}(z)$, V_d/F , λ , Cl_{ss}/F , C_{av} and Fluctuation \rightarrow PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

MultipleTTTdemo

Two Times Tmax (TTT) method for demo function

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$.

MultipleTTToutput

Output for Two Times Tmax (TTT) method

Description

We provides several txt outputs. 1. NCA PK.txt: $\rightarrow C_{ss_max}$, T_{ss_max} , $AUC_{ss}(\tau)$, $\ln(C_{ss_max})$, $\ln(AUC_{ss}(\tau))$, $MRT_{ss}(\tau)$, $T_{1/2}(z)$, V_d/F , λ , Cl_{ss}/F , C_{av} and Fluctuation \rightarrow PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

NCA

Noncompartmental analysis (NCA)

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λz) for drug plasma concentration. The linear trapezoidal method is applied to calculate $AUC(\text{time } 0 \text{ to the last measurable } C_p)$. The extrapolated AUC (from time of the last measurable C_p to time infinity) is equal to the last measurable C_p divided by λz .

 NCA.BANOVA

NCA and ANOVA

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable C_p). The extrapolated AUC (from time of the last measurable C_p to time infinity) is equal to the last measurable C_p divided by λ_z .

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

 NCA.BANOVAanalyze

NCA and ANOVA function

Description

This function includes both NCAanalyze and BANOVAanalyze functions.

 NCA.BANOVAcsv

choose separator and decimal type

Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

 NCA.BANOVAdata

Input/Edit data for NCA and ANOVA function

Description

Input/Edit Data ->subject no.(subj) ->sequence (seq) Sequence 1:Reference->Test sequence Sequence 2:Test->Reference sequence ->period (prd) Period 1: first treatment period Period 2: second treatment period ->time ->concentration (conc)

NCA.BANOVAmenu *List of NCA and ANOVA Menu*

Description

You can use the functions as follows: 1.NCA→ANOVA 2.Run demo for NCA → Statistical analysis

NCAanalyze *NCA analyze function*

Description

We provide noncompartmental analysis (NCA) approach to compute AUCs and terminal elimination rate constant (k_{el}) for plasma concentration. Here we provide six methods, exact 3 data points, ARS, TTT, AIC, TTT and ARS, and TTT and AIC.

NCAcsv *choose separator and decimal type*

Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

NCAdata *Input/Edit data for NCA function*

Description

Input/Edit Data ->subject no.(subj) ->sequence (seq) Sequence 1:Reference→Test sequence Sequence 2:Test→Reference sequence ->period (prd) Period 1: first treatment period Period 2: second treatment period ->time ->concentration (conc)

NCAdemo *Select the exact 3 data points(NCA) for demo function*

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable C_p). The extrapolated AUC (from time of the last measurable C_p to time infinity) is equal to the last measurable C_p divided by λ_z .

NCAdemo.BANOVA *Select the exact 3 data points(NCA) and ANOVA for demo function*

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable C_p). The extrapolated AUC (from time of the last measurable C_p to time infinity) is equal to the last measurable C_p divided by λ_z .

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

NCAmenu *List of NCA 2x2x2 Menu*

Description

You can use the functions as follows: 1.Single Dose 2.Demo for Single Dose

NCAoutput *Output of NCA*

Description

We provides several txt outputs. 1. NCA PK.txt: \rightarrow C_{max} , T_{max} , AUC_{0t} , AUC_{0inf} , AUC_{0t}/AUC_{0inf} , $\ln(C_{max})$, $\ln(AUC_{0t})$, $\ln(AUC_{0inf})$, MRT_{0inf} , $T_{1/2}$, V_d/F , λ_z , and $Cl/F \rightarrow$ PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

NCAplot *NCAplot*

Description

We provides several pdf. outputs about NCA plots. 1.Conc. vs. Time for individual subjects 2.Log10(Conc.) vs. Time for individual subjects 3.Test (.Conc. vs. Time) for all subjects 4.Reference (.Conc. vs. Time) for all subjects 5.Conc.(mean+sd) vs Time for test and reference

NCAreglplot	<i>Plot regression lines and save all these plots in a .pdf in NCA</i>
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Description

This function is for plotting regression lines of data manual selection for λ_z , from previously saved data point selection file (.RData).

NCAsave	<i>Save NCA outputs</i>
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Description

This function can save the results after NCA.

NCAselect	<i>Select 2-6 data points for $\lambda(z)$ estimation in NCA</i>
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Description

This function can help users to select 2-6 data points for $\lambda(z)$ estimation in NCA

NCAselect.BANOVA	<i>Select the exact 3 points in NCA and ANOVA</i>
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Description

This function can help users select the exact 3 points for NCA function.

NCAselectdemo	<i>Select the exact 3 points in NCA for demo function</i>
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Description

This function can help users select the exact 3 points for NCA function.

NCAselectdemo.BANOVA *Select the exact 3 points in NCA and ANOVA for demo function*

Description

This function can help users select the exact 3 points for NCA function.

NCAselectsave *Select the exact 3 points in NCA and Save the data*

Description

This function can save the exact 3 points.

NCAselectsave.BANOVA *Select the exact 3 points in NCA and Save the data*

Description

This function can save the exact 3 points.

normDataWithin *normDataWithin*

Description

normDataWithin():- helper functions from: Cookbook for R, http://www.cookbook-r.com/Graphs/Plotting_means_and_error
used to help ggplot()

Author(s)

Winston Chang

OutputFilez *OutputFilez*

Description

function to automatically setup default output files.

ParaAIC	<i>Akaike information criterion (AIC) method for parallel study</i>
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Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

ParaAIC.MIX	<i>Akaike information criterion (AIC) method->statistics for parallel study</i>
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Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

ParaAICdemo	<i>Akaike information criterion (AIC) method for demo function for parallel study</i>
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Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

ParaAICoutput	<i>Output for Adjusted R squared (ARS) method for parallel study</i>
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Description

We provides several txt outputs. 1. NCA PK.txt: $\rightarrow C_{max}, T_{max}, AUC_{0t}, AUC_{0inf}, AUC_{0t}/AUC_{0inf}, \ln(C_{max}), \ln(AUC_{0t}), \ln(AUC_{0inf}), MRT_{0inf}, T_{1/2}, V_d/F, \lambda z,$ and $Cl/F \rightarrow$ PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.
3. Statistical summaries.txt

 ParaARS

Adjusted R squared (ARS) method for parallel study

Description

This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

 ParaARS.MIX

Adjusted R squared (ARS) method and lme for parallel study

Description

Adjusted R squared (ARS) method: This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

With a two-treatment, two-sequence, one-period, parallel design, R uses the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

 ParaARSDemo

Adjusted R squared (ARS) method for demo function for parallel study

Description

This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

 ParaARSoutput

Output for Adjusted R squared (ARS) method for parallel study

Description

We provides several txt outputs. 1. NCA PK.txt: → Cmax, Tmax, AUC0t, AUC0inf, AUC0t/AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf), MRT0inf, T1/2, Vd/F, lambda z, and Cl/F → PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

 Paradata

Sample size estimation for log transformation data for parallel study

Description

This function will help you to choose appropriate sample size.

References

1. Hauschke D, Steinijs VW, Diletti E and Burke M. Sample size determination for bioequivalence assessment using a multiplicative model. J. Pharmacokin. Biopharm. 20:557-561 (1992).
2. Julious SA. Tutorial in biostatistics: Sample sizes for clinical trials with normal data. Statist. Med. 23:1921-1986 (2004)

 Parademomenu

menu for NCA demo file for parallel study

Description

lambda z est. from the exact 3 data points, lambda z est. with adjusted R sq. (ARS), lambda z est. with Akaike information criterion (AIC), lambda z est. with Two-Times-Tmax method (TTT), lambda z est. with TTT and ARS, lambda z est. with TTT and AIC

 Parademomenu1

menu for NCA->Statistical analysis demo file for parallel study

Description

lambda z est. from the exact 3 data points→ Statistical analysis, lambda z est. with adjusted R sq. (ARS)→ Statistical analysis, lambda z est. with Akaike information criterion (AIC)→ Statistical analysis, lambda z est. with Two-Times-Tmax method (TTT)→ Statistical analysis, lambda z est. with TTT and ARS→ Statistical analysis, lambda z est. with TTT and AIC→ Statistical analysis,

 ParademoMIX

Statistical analysis (lme, 90CI...)for demo file for parallel study

Description

Statistical analysis (lme, 90CI...): With a two-treatment, two-sequence, one-period, parallel design, bear deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

 Paralleldata

Data for NCA analyze for parallel study

Description

The data give the data of subjects, drug, time, and concentration.

 Paramenu

List of NCA 2x2x1 Menu

Description

You can use the functions as follows: 1.run NCA 2.Demo for NCA

 ParaMIX

Statistical analysis (lme, 90CI...) for parallel study

Description

With a two-treatment, two-sequence, one-period, parallel design, bear deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

ParaMIXanalyze	<i>Split data to perform lme function for parallel study</i>
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Description

Split data for lme function

References

Guidance for Industry. Statistical approaches to establishing Bioequivalence.

ParaMIXcsv	<i>choose separator and decimal type</i>
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Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

ParaMIXdata	<i>Input/Edit data for lme function for parallel study</i>
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Description

->subject no.(subj) ->drug 1:Reference 2:Test ->Cmax ->AUC0t: area under the predicted plasma concentration time curve for test data. (time = 0 to t) ->AUC0INF: area under the predicted plasma concentration time curve for test data. (time = 0 to infinity) ->LnCmax: Log-transformed Cmax ->LnAUC0t: Log-transformed AUC0t ->LnAUC0INF: Log-transformed AUC0INF

ParaMIXmenu	<i>List of lme Menu</i>
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Description

You can use the functions as follows: 1.Statistical analysis (lme, 90CI...) 2.Demo for Statistical analysis (lme, 90CI...)

ParaMIXoutput	<i>Output of lme function</i>
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Description

We provides several txt outputs. 1.lme stat.txt ->lme:Cmax, AUC0t, AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf) ->90CI: ln(Cmax), ln(AUC0t), and ln(AUC0inf)

ParaNCA	<i>Noncompartmental analysis (NCA) for parallel study</i>
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Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable Cp). The extrapolated AUC (from time of the last measurable Cp to time infinity) is equal to the last measurable Cp divided by λ_z .

ParaNCA.MIX	<i>NCA and lme for parallel study</i>
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Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable Cp). The extrapolated AUC (from time of the last measurable Cp to time infinity) is equal to the last measurable Cp divided by λ_z .

Statistical analysis (lme, 90CI...): With a two-treatment, two-sequence, one-period, parallel design, bear deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

ParaNCA.MIXanalyze	<i>NCA and lme function</i>
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Description

This function includes both NCA and lme functions.

ParaNCA.MIXcsv *choose separator and decimal type*

Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

ParaNCA.MIXdata *Input/Edit data for NCA and lme function for parallel study*

Description

Input/Edit Data ->subject no.(subj) ->drug ref.: 1 test: 2 ->time ->concentration (conc)

ParaNCA.MIXmenu *List of NCA and lme Menu*

Description

You can use the functions as follows: 1.NCA->lme 2.Run demo for NCA -> Statistical analysis

ParaNCAanalyze *NCA analyze function for parallel study*

Description

We provide noncompartmental analysis (NCA) approach to compute AUCs and terminal elimination rate constant (kel) for plasma concentration. Here we provide six methods, exact 3 data points, ARS, TTT, AIC, TTT and ARS, and TTT and AIC.

ParaNCAcsv *choose separator and decimal type*

Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

ParaNCAdata	<i>Input/Edit data for NCA function for parallel study</i>
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Description

Input/Edit Data ->subject no.(subj) ->drug ->time ->concentration (conc)

ParaNCAdemo	<i>Select the exact 3 data points(NCA) for demo function for parallel study</i>
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Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable Cp). The extrapolated AUC (from time of the last measurable Cp to time infinity) is equal to the last measurable Cp divided by λ_z .

ParaNCAdemo.MIX	<i>Select the exact 3 data points(NCA) and lme for demo function</i>
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Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable Cp). The extrapolated AUC (from time of the last measurable Cp to time infinity) is equal to the last measurable Cp divided by λ_z .

Statistical analysis (lme, 90CI...): With a two-treatment, two-sequence, one-period, parallel design, bear deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

ParaNCAoutput	<i>Output of NCA for parallel study</i>
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Description

We provides several txt outputs. 1. NCA PK.txt: -> Cmax, Tmax, AUC0t, AUC0inf, AUC0t/AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf), MRT0inf, T1/2, Vd/F, λ_z , and Cl/F -> PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

ParaNCAsplot	<i>NCAplot for parallel study</i>
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Description

We provides several pdf. outputs about NCA plots. 1.Conc. vs. Time for individual subjects 2.Log10(Conc.) vs. Time for individual subjects 3.Test (.Conc. vs. Time) for all subjects 4.Reference (.Conc. vs. Time) for all subjects 5.Conc.(mean+-sd) vs Time for test and reference

ParaNCAsave	<i>Save NCA outputs for parallel study</i>
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Description

This function can save the results after NCA.

ParaNCAselct	<i>Select the exact 3 points in NCA for parallel study</i>
--------------	--

Description

This function can help users select the exact 3 points for NCA function.

ParaNCAselct.MIX	<i>Select the exact 3 points in NCA and lme for parallel study</i>
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Description

This function can help users select the exact 3 points for NCA function.

ParaNCAselctdemo	<i>Select the exact 3 points in NCA for demo function for parallel study</i>
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Description

This function can help users select the exact 3 points for NCA function.

ParaNCAselctdemo.MIX *Select the exact 3 points in NCA and lme for demo function (parallel study)*

Description

This function can help users select the exact 3 points for NCA function.

ParaNCAselctsave *Select the exact 3 points in NCA and Save the data for parallel study*

Description

This function can save data of the exact 3 points.

ParaNCAselctsave.MIX *Select the exact 3 points in NCA and Save the data*

Description

This function can save the exact 3 points.

ParaTTT *Two Times Tmax (TTT) method for parallel study*

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max}. Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of lambda(z).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

 ParaTTT.MIX

TTT and lme for parallel study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$.

Statistical analysis (lme, 90CI...): With a two-treatment, two-sequence, one-period, parallel design, bear deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

 ParaTTTAIC

TTT and AIC for parallel study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

 ParaTTTAIC.MIX

TTT, AIC and lme for parallel study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

Statistical analysis (lme, 90CI...): With a two-treatment, two-sequence, one-period, parallel design, bear deploys the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

 ParaTTTAICdemo

TTT and AIC for demo function for parallel study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

ParaTTTAICoutput

Output for TTT and AIC for parallel study

Description

We provides several txt outputs. 1. NCA PK.txt: → Cmax, Tmax, AUC0t, AUC0inf, AUC0t/AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf), MRT0inf, T1/2, Vd/F, lambda z, and Cl/F → PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

ParaTTTARS

TTT and ARS for parallel study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

 ParaTTTARS.MIX

TTT ,ARS and lme for parallel study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

Statistical analysis (lme, 90CI...): With a two-treatment, two-sequence, one-period, parallel design, we deploy the linear mixed effect model (lme). The statistical model includes a factor regarding only one source of variation - treatment. There are no sources of variation associated with sequence or period because there are no sequences or periods in a parallel design. Moreover, lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error. Log-transformed BA measures will also be analyzed.

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

 ParaTTTARSdemo

TTT and ARS for demo function for parallel study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

ParaTTARSoutput *Output for TTT and ARS for parallel study*

Description

We provides several txt outputs. 1. NCA PK.txt: → Cmax, Tmax, AUC0t, AUC0inf, AUC0t/AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf), MRT0inf, T1/2, Vd/F, lambda z, and Cl/F → PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

ParaTTTdemo *Two Times Tmax (TTT) method for demo function for parallel study*

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z).

ParaTTToutput *Output for Two Times Tmax (TTT) method for parallel study*

Description

We provides several txt outputs. 1. NCA PK.txt: → Cmax, Tmax, AUC0t, AUC0inf, AUC0t/AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf), MRT0inf, T1/2, Vd/F, lambda, and Cl/F → PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

prdcoun	<i>legends for plots</i>
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Description

The legend description for replicated study

Repaic	<i>Akaike information criterion (AIC) method for replicated study</i>
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Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

RepAIC.MIX	<i>Akaike information criterion (AIC) method->statistics for replicated study</i>
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Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

RepAICdemo	<i>Akaike information criterion (AIC) method for demo function for replicated study</i>
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Description

This method selects data points to estimate $\lambda(z)$ based on the minimum AIC values. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max}, C_{max}) .

 RepAICoutput

Output for Adjusted R squared (ARS) method for replicated study

Description

We provides several txt outputs. 1. NCA PK.txt: → Cmax, Tmax, AUC0t, AUC0inf, AUC0t/AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf), MRT0inf, T1/2, Vd/F, lambda z, and CI/F → PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

 RepARS

Adjusted R squared (ARS) method for replicated study

Description

This method selects data points to estimate lambda(z) based on the maximum adjustedR squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of Cmax. Thus, this method may exclude the data point of (Tmax, Cmax). WNL v6. has the similar algorithms like this.

 RepARS.MIX

Adjusted R squared (ARS) method and lme for replicated study

Description

Adjusted R squared (ARS) method: This method selects data points to estimate lambda(z) based on the maximum adjustedR squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of Cmax. Thus, this method may exclude the data point of (Tmax, Cmax). WNL v6. has the similar algorithms like this.

Statistical analysis (lme, 90CI...): With a two-treatment, more than two period, two-sequence randomized crossover design, linear mixed-effects model may be used. The lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

RepARSDemo	<i>Adjusted R squared (ARS) method for demo function for replicated study</i>
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Description

This method selects data points to estimate $\lambda(z)$ based on the maximum adjusted R squared values. It starts with the last three data points from the concentration-time course, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it excludes the data points of C_{max} . Thus, this method may exclude the data point of (T_{max}, C_{max}) . WNL v6. has the similar algorithms like this.

RepARSDoutput	<i>Output for Adjusted R squared (ARS) method for replicated study</i>
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Description

We provides several txt outputs. 1. NCA PK.txt: $\rightarrow C_{max}, T_{max}, AUC_{0t}, AUC_{0inf}, AUC_{0t}/AUC_{0inf}, \ln(C_{max}), \ln(AUC_{0t}), \ln(AUC_{0inf}), MRT_{0inf}, T_{1/2}, V_d/F, \lambda z,$ and $CI/F \rightarrow$ PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.
3. Statistical summaries.txt

Repdemomenu	<i>menu for NCA demo file for replicated study</i>
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Description

λz est. from the exact 3 data points, λz est. with adjusted R sq. (ARS), λz est. with Akaike information criterion (AIC), λz est. with Two-Times- T_{max} method (TTT), λz est. with TTT and ARS, λz est. with TTT and AIC

Repdemomenu1	<i>menu for NCA-\rightarrowStatistical analysis demo file for replicated study</i>
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Description

λz est. from the exact 3 data points \rightarrow Statistical analysis, λz est. with adjusted R sq. (ARS) \rightarrow Statistical analysis, λz est. with Akaike information criterion (AIC) \rightarrow Statistical analysis, λz est. with Two-Times- T_{max} method (TTT) \rightarrow Statistical analysis, λz est. with TTT and ARS \rightarrow Statistical analysis, λz est. with TTT and AIC \rightarrow Statistical analysis,

 RepdemoMIX

Statistical analysis (lme, 90CI...)for demo file for replicated study

Description

Statistical analysis (lme, 90CI...): With a two-treatment, more than two period, two-sequence randomized crossover design, linear mixed-effects model may be used. The lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

 Replicateddata

Data for NCA analyze for replicated study

Description

The data give the data of subjects, drug, sequence, period, time, and concentration.

 Repmenu

List of NCA 2x2xn Menu

Description

You can use the functions as follows: 1.run NCA 2.Demo for NCAe

 RepMIX

Statistical analysis (lme, 90CI...) for replicated study

Description

With a two-treatment, more than two period, two-sequence randomized crossover design, linear mixed-effects model may be used. The lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

RepMIXanalyze	<i>Split data to perform lme function for replicated study</i>
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Description

Split data for lme function

References

Guidance for Industry. Statistical approaches to establishing Bioequivalence.

RepMIXcsv	<i>choose separator and decimal type</i>
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Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

RepMIXdata	<i>Input/Edit data for lme function for replicated study</i>
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Description

->subject no.(subj) ->drug 1:Reference 2:Test ->sequence (seq) Sequence 1:Reference->Test sequence Sequence 2:Test->Reference sequence ->period (prd) Period 1: first treatment period Period 2: second treatment period ->Cmax ->AUC0t: area under the predicted plasma concentration time curve for test data. (time = 0 to t) ->AUC0INF: area under the predicted plasma concentration time curve for test data. (time = 0 to infinity) ->LnCmax: Log-transformed Cmax ->LnAUC0t: Log-transformed AUC0t ->LnAUC0INF: Log-transformed AUC0INF

RepMIXmenu	<i>List of lme Menu</i>
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Description

You can use the functions as follows: 1.Statistical analysis (lme, 90CI...) 2.Demo for Statistical analysis (lme, 90CI...)

 RepMIXoutput

Output of lme function

Description

We provides several txt outputs. 1.lme stat.txt →lme:Cmax, AUC0t, AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf) →90CI: ln(Cmax), ln(AUC0t), and ln(AUC0inf)

 RepNCA

Noncompartmental analysis (NCA) for replicated study

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable Cp). The extrapolated AUC (from time of the last measurable Cp to time infinity) is equal to the last measurable Cp divided by λ_z .

 RepNCA.MIX

NCA and lme for replicated study

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable Cp). The extrapolated AUC (from time of the last measurable Cp to time infinity) is equal to the last measurable Cp divided by λ_z .

Statistical analysis (lme, 90CI...): With a two-treatment, more than two period, two-sequence randomized crossover design, linear mixed-effects model may be used. The lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

 RepNCA.MIXanalyze

NCA and lme function

Description

This function includes both NCA and lme functions.

RepNCA.MIXcsv *choose separator and decimal type*

Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

RepNCA.MIXdata *Input/Edit data for NCA and lme function for replicated study*

Description

Input/Edit Data ->subject no.(subj) ->sequence (seq) ->period (prd) Period 1: first treatment period
Period 2: second treatment period ->drug ->time ->concentration (conc)

RepNCA.MIXmenu *List of NCA and lme Menu*

Description

You can use the functions as follows: 1.NCA->lme 2.Run demo for NCA -> Statistical analysis

RepNCAanalyze *NCA analyze function for replicated study*

Description

We provide noncompartmental analysis (NCA) approach to compute AUCs and terminal elimination rate constant (kel) for plasma concentration. Here we provide six methods, exact 3 data points, ARS, TTT, AIC, TTT and ARS, and TTT and AIC.

RepNCAcsv *choose separator and decimal type*

Description

Separator : comma, semicolon ,white space. Decimal: comma, point.

RepNCAdata	<i>Input/Edit data for NCA function for replicated study</i>
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Description

Input/Edit Data ->subject no.(subj) ->sequence (seq) Sequence 1:Reference->Test sequence Sequence 2:Test->Reference sequence ->period (prd) Period 1: first treatment period Period 2: second treatment period ->drug ->time ->concentration (conc)

RepNCAdemo	<i>Select the exact 3 data points(NCA) for demo function for replicated study</i>
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Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable C_p). The extrapolated AUC (from time of the last measurable C_p to time infinity) is equal to the last measurable C_p divided by λ_z .

RepNCAdemo.MIX	<i>Select the exact 3 data points(NCA) and lme for demo function</i>
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Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (λ_z) for drug plasma concentration. The linear trapezoidal method is applied to calculate AUC(time 0 to the last measurable C_p). The extrapolated AUC (from time of the last measurable C_p to time infinity) is equal to the last measurable C_p divided by λ_z .

Statistical analysis (lme, 90CI...): With a two-treatment, more than two period, two-sequence randomized crossover design, linear mixed-effects model may be used. The lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

RepNCAoutput	<i>Output of NCA for replicated study</i>
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Description

We provides several txt outputs. 1. NCA PK.txt: -> C_{max} , T_{max} , AUC_{0t} , AUC_{0inf} , AUC_{0t}/AUC_{0inf} , $\ln(C_{max})$, $\ln(AUC_{0t})$, $\ln(AUC_{0inf})$, MRT_{0inf} , $T_{1/2}$, V_d/F , λ_z , and Cl/F -> PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

RepNCAPlot	<i>NCAplot for replicated study</i>
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Description

We provides several pdf. outputs about NCA plots. 1.Conc. vs. Time for individual subjects 2.Log10(Conc.) vs. Time for individual subjects 3.Test (.Conc. vs. Time) for all subjects 4.Reference (.Conc. vs. Time) for all subjects 5.Conc.(mean+-sd) vs Time for test and reference

RepNCAsave	<i>Save NCA outputs for replicated study</i>
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Description

This function can save the results after NCA.

RepNCAsselect	<i>Select the exact 3 points in NCA for replicated study</i>
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Description

This function can help users select the exact 3 points for NCA function.

RepNCAsselect.MIX	<i>Select the exact 3 points in NCA and lme for replicated study</i>
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Description

This function can help users select the exact 3 points for NCA function.

RepNCAsselectdemo	<i>Select the exact 3 points in NCA for demo function for replicated study</i>
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Description

This function can help users select the exact 3 points for NCA function.

RepNCAselctdemo.MIX *Select the exact 3 points in NCA and lme for demo function (replicated study)*

Description

This function can help users select the exact 3 points for NCA function.

RepNCAselctsave *Select the exact 3 points in NCA and Save the data for replicated study*

Description

This function can save data of the exact 3 points.

RepNCAselctsave.MIX *Select the exact 3 points in NCA and Save the data*

Description

This function can save the exact 3 points.

RepTTT *Two Times Tmax (TTT) method for replicated study*

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max}. Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of lambda(z).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

RepTTT.MIX

TTT and lme for replicated study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$.

With a two-treatment, more than two period, two-sequence randomized crossover design, linear mixed-effects model may be used. The lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

RepTTTAIC

TTT and AIC for replicated study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

RepTTTAIC.MIX

TTT ,AIC and lme for replicated study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

With a two-treatment, more than two period, two-sequence randomized crossover design, linear mixed-effects model may be used. The lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

RepTTTAICdemo

TTT and AIC for demo function for replicated study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

RepTTTAICoutput *Output for TTT and AIC for replicated study*

Description

We provides several txt outputs. 1. NCA PK.txt: → Cmax, Tmax, AUC0t, AUC0inf, AUC0t/AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf), MRT0inf, T1/2, Vd/F, lambda z, and Cl/F → PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

RepTTTARS *TTT and ARS for replicated study*

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

RepTTTARS.MIX

TTT ,ARS and lme for replicated study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

With a two-treatment, more than two period, two-sequence randomized crossover design, linear mixed-effects model may be used. The lme in nlme package is used to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

RepTTTARSDemo

TTT and ARS for demo function for replicated study

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

RepTTTARSoutput *Output for TTT and ARS for replicated study*

Description

We provides several txt outputs. 1. NCA PK.txt: → Cmax, Tmax, AUC0t, AUC0inf, AUC0t/AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf), MRT0inf, T1/2, Vd/F, lambda z, and Cl/F → PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

RepTTTdemo *Two Times Tmax (TTT) method for demo function for replicated study*

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z).

RepTTToutput *Output for Two Times Tmax (TTT) method for replicated study*

Description

We provides several txt outputs. 1. NCA PK.txt: → Cmax, Tmax, AUC0t, AUC0inf, AUC0t/AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf), MRT0inf, T1/2, Vd/F, lambda, and Cl/F → PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

 Singlego

List of bear Menu

Description

You can use the functions as follows: 1.Sample size estimation for average BE 2.Noncompartment Analysis (NCA) 3.ANOVA 4.NCA->ANOVA

sizemenu

List of Sample size estimation Menu

Description

You can use the functions as follows: 1.Sample size estimation (Raw data) 2.Sample size estimation (Log transformation) 3.Demo for sample size estimation (Raw data)

stat1menu

List of Statistical analysis non-replicated and replicated study

Description

You can use the functions as follows: 1. Statistical analysis for non-replicated crossover study, 2. Statistical analysis for replicated crossover study,

statmenu

List of Statistical analysis non-replicated and replicated study

Description

You can use the functions as follows: 1. Statistical analysis for non-replicated crossover study, 2. Statistical analysis for replicated crossover study,

summarySE

summarySE

Description

summarySE():- helper functions from: Cookbook for R, http://www.cookbook-r.com/Graphs/Plotting_means_and_error_bars used to help ggplot()

Author(s)

Winston Chang

summarySEwithin	<i>summarySEwithin</i>
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Description

summarySEwithin():- helper functions from: Cookbook for R, http://www.cookbook-r.com/Graphs/Plotting_means_and_error_bars/ used to help ggplot()

Author(s)

Winston Chang

test.nca_stat	<i>demo for NCA-anova demo file</i>
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Description

lambda z est. from the exact 3 data points-> Statistical analysis, lambda z est. with adjusted R sq. (ARS)-> Statistical analysis, lambda z est. with Akaike information criterion (AIC)-> Statistical analysis, lambda z est. with Two-Times-Tmax method (TTT)-> Statistical analysis, lambda z est. with TTT and ARS-> Statistical analysis, lambda z est. with TTT and AIC-> Statistical analysis,

TotalSingledata	<i>Data for NCA analyze</i>
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Description

The data give the data of subjects, drug, sequence, period, time, and concentration.

TTT	<i>Two Times Tmax (TTT) method</i>
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Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$.

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (C_{max} at T_{max}) and secondly, the inflection point of the curve (C_{inpt} at T_{inpt}). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. T_{inpt} is equal to two times T_{max} . Thus, The twofold of the observed T_{max} value can be used as a threshold of time points to be included in the calculation of $\lambda(z)$. Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after C_{max} . Thus, this method will not include the data point of (T_{max} , C_{max}).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

TTTAIC.BANOVA

*TTT, AIC and ANOVA***Description**

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

TTTAICdemo

*TTT and AIC for demo function***Description**

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply minimum AIC values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration-time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

References

Scheerans C, Derendorf H and Kloft C. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

TTTAICoutput

Output for TTT and AIC

Description

We provides several txt outputs. 1. NCA PK.txt: → Cmax, Tmax, AUC0t, AUC0inf, AUC0t/AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf), MRT0inf, T1/2, Vd/F, lambda z, and Cl/F → PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

TTTARS

TTT and ARS

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

TTTARS.BANOVA

*TTT ,ARS and ANOVA***Description**

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. Biopharm Drug Dispos 29, 145-157 (2008).

TTTARSdemo

*TTT and ARS for demo function***Description**

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z). Then, within that range, we apply maximum ARS values to get best fit. It starts with the last three data points from the concentration-time profile, performing log-linear regression to calculate the slope of that tail portion of the concentration- time curve. And then the last 4 data points, the last 5 data points, on and on until it reaches the data point right after Cmax. Thus, this method will not include the data point of (Tmax, Cmax).

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

TTTARsOutput

Output for TTT and ARS

Description

We provides several txt outputs. 1. NCA PK.txt: \rightarrow Cmax, Tmax, AUC0t, AUC0inf, AUC0t/AUC0inf, $\ln(\text{Cmax})$, $\ln(\text{AUC0t})$, $\ln(\text{AUC0inf})$, MRT0inf, T1/2, Vd/F, lambda z, and CI/F \rightarrow PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

References

Scheerans C, Derendorf H and C Kloft. Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs. *Biopharm Drug Dispos* 29, 145-157 (2008).

TTTdemo

Two Times Tmax (TTT) method for demo function

Description

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z).

TTTdemo.BANOVA

*Two Times Tmax (TTT) method and ANOVA for demo function***Description**

The TTT method is based on the Bateman function. The Bateman function has two outstanding points. First, the maximum of the curve (Cmax at Tmax) and secondly, the inflection point of the curve (Cinpt at Tinpt). The inflection point of the curve describes the point where the algebraic sign of the curvature changes. Tinpt is equal to two times Tmax. Thus, The twofold of the observed Tmax value can be used as a threshold of time points to be included in the calculation of lambda(z).

Statistical analysis (ANOVA(lm), 90CI...): With a two-treatment, two-period, two-sequence randomized crossover design, ANOVA statistical model includes factors of the following sources: sequence, subjects nested in sequences, period and treatment. ANOVA will be applied to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences. Log-transformed BA measures will also be analyzed.

TTToutput

*Output for Two Times Tmax (TTT) method***Description**

We provides several txt outputs. 1. NCA PK.txt: -> Cmax, Tmax, AUC0t, AUC0inf, AUC0t/AUC0inf, ln(Cmax), ln(AUC0t), ln(AUC0inf), MRT0inf, T1/2, Vd/F, lambda, and CI/F -> PK parameter summary (NCA outputs) 2. plots.pdf: individual linear and semilog plots, spaghetti plots, and mean conc. plots.

3. Statistical summaries.txt

xtick

*x-tick***Description**

Tick for plots.

ytick

*y-tick***Description**

Tick for plots.

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