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

URL http://pkpd.kmu.edu.tw/bear

Repository CRAN

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R topics documented:

`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 minimun 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).

AICdemo *Akaike information criterion (AIC) method for demo function*

Description

This method selects data points to estimate lambda(z) based on the minimun 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).

AICoutput *Output for Adjusted R squared (ARS) 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 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

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

Description

This method selects data points to estimate lambda(z) based on the minimun 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.

ARS *Adjusted R squared (ARS) method*

Description

This method selects data points to estimate lambda(z) based on the maximun adjustedR squred 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 algoirthms 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 maximun adjustedR squred 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 algoirthms 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 maximun adjustedR squred 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 algoirthms 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 maximun adjustedR squred 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 algoirthms 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: –> 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

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 treatmetn period Period 2: second treatmetn 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.

BANOVAplot *BANOVAplot*

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` *Setup module for bear*

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` *The final step Menu*

Description

try again or leave bear package.

`create.products_sum` *create.products_sum*

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` *Statistical analysis (ANOVA(lm), 90CI...)for demo file*

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 *menu for NCA demo file*

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 *menu for NCA demo file*

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 *Demo for sample size estimation*

Description

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

demosize *Demo for sample size estimation*

Description

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

demo_datasets_gen *To generate all demo datasets for testing purposes*

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 minimun 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).

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

Description

This method selects data points to estimate lambda(z) based on the maximun adjustedR squred 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 algoirthms 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 criteia for Two One-Sided Test for all pivotal parameters

Description

Display BE criteia 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_Multipledrugcode *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 (lambda 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 lambda z.

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, 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.

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. Theta=Ut/Ur, where Ut and Ur 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. Theta=Ut/Ur, where Ut and Ur 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: Ho: MEAN-test/MEAN-ref =< ln(lower acceptance) or MEAN-test/MEAN-ref >= ln(Upper acceptance) Ha: ln(lower acceptance) < MEAN-test/MEAN-ref < ln(Upper acceptance) Because all P values are less than 0.05, we will reject the null hypothesis (Ho).

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 continued 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_lnAUC0t`

Description for Two One-Sided Test for lnAUC0t

Description

Interpretation: Ho: MEAN-test/MEAN-ref =< ln(lower acceptance) or MEAN-test/MEAN-ref >= ln(Upper acceptance) Ha: ln(lower acceptance) < MEAN-test/MEAN-ref < ln(Upper acceptance) Because all P values are less than 0.05, we will reject the null hypothesis (Ho).

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 continued 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_lnCmax`

Description for Two One-Sided Test for lnCmax

Description

Interpretation: Ho: MEAN-test/MEAN-ref =< ln(lower acceptance) or MEAN-test/MEAN-ref >= ln(Upper acceptance) Ha: ln(lower acceptance) < MEAN-test/MEAN-ref < ln(Upper acceptance) Because all P values are less than 0.05, we will reject the null hypothesis (Ho).

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 continued 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_lnAUC0INF

Description for Two One-Sided Test for lnAUC0INF

Description

Interpretation: Ho: MEAN-test/MEAN-ref =< ln(lower acceptance) or MEAN-test/MEAN-ref >= ln(Upper acceptance) Ha: ln(lower acceptance) < MEAN-test/MEAN-ref < ln(Upper acceptance) If at least one of P value is more than 0.05, we will not reject the null hypothesis (Ho).

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 continued 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_lnAUC0t

Description for Two One-Sided Test for lnAUC0t

Description

Interpretation: Ho: MEAN-test/MEAN-ref =< ln(lower acceptance) or MEAN-test/MEAN-ref >= ln(Upper acceptance) Ha: ln(lower acceptance) < MEAN-test/MEAN-ref < ln(Upper acceptance) If at least one of P value is more than 0.05, we will not reject the null hypothesis (Ho).

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 continued 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_lnCmax

Description for Two One-Sided Test for lnCmax

Description

Interpretation: Ho: MEAN-test/MEAN-ref =< ln(lower acceptance) or MEAN-test/MEAN-ref >= ln(Upper acceptance) Ha: ln(lower acceptance) < MEAN-test/MEAN-ref < ln(Upper acceptance) If at least one of P value is more than 0.05, we will not reject the null hypothesis (Ho).

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 continued 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 (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).

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 (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 minimun 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).

`description_TTTARS` *Description for Two Times Tmax (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 (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 maximun 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).

`description_version` *Description for version*

Description

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`entertitle` *enter Dose, xaxis and yaxis*

Description

enter Dose, xaxis and yaxis

`entertitle.demo` *enter Dose, xaxis and yaxis for demo file*

Description

enter Dose, xaxis and yaxis

`go` *List of bear Menu*

Description

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

`go2menu` *List of bear Menu*

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` *helper.func*

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` *icd.check*

Description

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

`indiv_dp.output` *to generate list of individual data points as .csv format*

Description

to generate list of individual data points as .csv format

`lm.mod` *module to run both lm() and aov()*

Description

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

`lme_lm.mod` *module to run both lme() or lm()*

Description

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

`logdata` *Sample size estimation for log transformation data for crossover and replicated study*

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, Steinijans 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` *Description for NCA/ODA plots version*

Description

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`Multiple1menu` *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,

`Multipleaic` *Akaike information criterion (AIC) method for multiple study*

Description

This method selects data points to estimate lambda(z) based on the minimun 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).

`MultipleAICdemo` *Akaike information criterion (AIC) method for demo function*

Description

This method selects data points to estimate lambda(z) based on the minimun 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).

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

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

MultipleAIC_BANOVA *Akaike information criterion (AIC) method and ANOVA for multiple dose*

Description

This method selects data points to estimate lambda(z) based on the minimun 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 *Adjusted R squared (ARS) method for multiple dose*

Description

This method selects data points to estimate lambda(z) based on the maximun adjustedR squred 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 algoirthms 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 maximun adjustedR squred 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 algoirthms 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 maximun adjustedR squred 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 algoirthms like this.

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

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

`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 treatmetn period Period 2: second treatmetn period ->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)

`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:Css_max, AUCss(tau), lnCss_max, lnAUCss(tau) –>90CI: lnCss_max, lnAUCss(tau)

`MultipleBANOVAplot` *BANOVAplot for multiple dose*

Description

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

Multipledata *Data for NCA analyze for multiple dose*

Description

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

MultipledemoBANOVA *Statistical analysis (ANOVA(lm), 90CI...)for demo file*

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.

Multipledemomenu *menu for NCA demo file*

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

Multipledemomenu1 *menu for NCA demo file*

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 (lambda 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 lambda 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 (lambda 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 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.

`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 treatmetn period Period 2: second treatmetn 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 treatmetn period Period 2: second treatmetn 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 (lambda 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 lambda 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 (lambda 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 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.

`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.

`MultipleNCAselect.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.

`MultipleNCAselectdemo` *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.

`MultipleNCAselectdemo.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.

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

Description

This function can save the exact 3 points.

`MultipleNCAselectsave.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 minimun 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).

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

Description

This method selects data points to estimate lambda(z) based on the minimun 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).

`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 minimun 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).

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

`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 maximun adjustedR squred 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 algoirthms 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 maximun adjustedR squred 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 algoirthms 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 maximun adjustedR squred 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 algoirthms like this.

`MultipleParaARSoutput` *Output for Adjusted R squared (ARS) 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

`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 (lambda 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 lambda 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 (lambda 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 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.

`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 (kel) 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 (lambda 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 lambda 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 (lambda 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 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.

MultipleParaNCAoutput *Output of NCA 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

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.

`MultipleParaNCAselect` *Select the exact 3 points in NCA for parallel study*

Description

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

`MultipleParaNCAselect.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.

`MultipleParaNCAselectdemo`
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.

`MultipleParaNCAselectdemo.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.

`MultipleParaNCAselectsave`
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.

`MultipleParaNCAselectsave.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 (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).

`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 (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 (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 minimun 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 minimun 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 (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 minimun 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).

`MultipleParaTTTAICoutput`

Output for TTT and AIC 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

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 (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 maximun 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).

`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 (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 maximun 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, 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).

`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 (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 maximun 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).

`MultipleParaTTTARSoutput`

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).

`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 (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 minimun 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).

`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 (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 minimun 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.

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 (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 minimun 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).

MultipleTTTAICoutput *Output for TTT and AIC*

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

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 (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 maximun 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).

`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 (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 maximun 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).

`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 (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 maximun 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).

`MultipleTTTARSoutput` *Output for TTT and ARS*

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

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 (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).

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

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

NCA *Noncompartmental analysis (NCA)*

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (lambda 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 lambda z.

NCA.BANOVA *NCA and ANOVA*

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (lambda 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 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.

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 treatmetn period Period 2: second treatmetn 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 (kel) 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 treatmetn period Period 2: second treatmetn 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 (lambda 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 lambda 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 (lambda 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 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.

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: –> 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

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 *Plot regression lines and save all these plots in a .pdf in NCA*

Description

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

NCAsave *Save NCA outputs*

Description

This function can save the results after NCA.

NCAselect *Select 2-6 data points for lambda(z) estimation in NCA*

Description

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

NCAselect.BANOVA *Select the exact 3 points in NCA and ANOVA*

Description

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

NCAselectdemo *Select the exact 3 points in NCA for demo function*

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 *Akaike information criterion (AIC) method for parallel study*

Description

This method selects data points to estimate lambda(z) based on the minimun 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).

ParaAIC.MIX *Akaike information criterion (AIC) method->statictics for parallel study*

Description

This method selects data points to estimate lambda(z) based on the minimun 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).

ParaAICdemo *Akaike information criterion (AIC) method for demo function for parallel study*

Description

This method selects data points to estimate lambda(z) based on the minimun 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).

ParaAICoutput *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

ParaARS *Adjusted R squared (ARS) method for parallel study*

Description

This method selects data points to estimate lambda(z) based on the maximun adjustedR squred 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 algoirthms 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 maximun adjustedR squred 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 algoirthms 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.

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 maximun adjustedR squred 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 algoirthms 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, Steinijans 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` *Split data to perform lme function for parallel study*

Description

Split data for lme function

References

Guidance for Industry. Statistical approaches to establishing Bioequivalence.

`ParaMIXcsv` *choose separator and decimal type*

Description

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

`ParaMIXdata` *Input/Edit data for lme function for parallel study*

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` *List of lme Menu*

Description

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

ParaMIXoutput *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)

ParaNCA *Noncompartmental analysis (NCA) for parallel study*

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (lambda 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 lambda z.

ParaNCA.MIX *NCA and lme for parallel study*

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (lambda 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 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.

ParaNCA.MIXanalyze *NCA and lme function*

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 — *Input/Edit data for NCA function for parallel study*

Description

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

ParaNCAdemo — *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 (lambda 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 lambda z.

ParaNCAdemo.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 (lambda 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 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.

ParaNCAoutput — *Output of NCA 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

ParaNCAplot *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

ParaNCAsave *Save NCA outputs for parallel study*

Description

This function can save the results after NCA.

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

Description

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

ParaNCAselect.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.

ParaNCAselectdemo *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.

ParaNCAselectdemo.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.

ParaNCAselectsave *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.

ParaNCAselectsave.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 (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).

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 (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 (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 (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 minimun 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).

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 (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 minimun 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.

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 (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 minimun 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).

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 maximun 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 maximun 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, 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).

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 maximun 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).

`ParaTTTARSoutput` *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

prdcount *legends for plots*

Description

The legend description for replicated study

Repaic *Akaike information criterion (AIC) method for replicated study*

Description

This method selects data points to estimate lambda(z) based on the minimun 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).

RepAIC.MIX *Akaike information criterion (AIC) method->statictics for replicated study*

Description

This method selects data points to estimate lambda(z) based on the minimun 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).

RepAICdemo *Akaike information criterion (AIC) method for demo function for replicated study*

Description

This method selects data points to estimate lambda(z) based on the minimun 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).

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 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

RepARS *Adjusted R squared (ARS) method for replicated study*

Description

This method selects data points to estimate lambda(z) based on the maximun adjustedR squred 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 algoirthms 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 maximun adjustedR squred 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 algoirthms 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 *Adjusted R squared (ARS) method for demo function for replicated study*

Description

This method selects data points to estimate lambda(z) based on the maximun adjustedR squred 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 algoirthms like this.

RepARSoutput *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 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

Repdemomenu *menu for NCA demo file for replicated 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

Repdemomenu1 *menu for NCA->Statistical analysis demo file for replicated 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,

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` *Split data to perform lme function for replicated study*

Description

Split data for lme function

References

Guidance for Industry. Statistical approaches to establishing Bioequivalence.

`RepMIXcsv` *choose separator and decimal type*

Description

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

`RepMIXdata` *Input/Edit data for lme function for replicated study*

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 treatmetn period Period 2: second treatmetn 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` *List of lme Menu*

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 (lambda 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 lambda 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 (lambda 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 lambda 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 treatmetn period Period 2: second treatmetn 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 *Input/Edit data for NCA function for replicated study*

Description

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

RepNCAdemo *Select the exact 3 data points(NCA) for demo function for replicated study*

Description

Noncompartmental analysis (NCA) approach is used to compute AUCs and the terminal elimination rate constants (lambda 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 lambda z.

RepNCAdemo.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 (lambda 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 lambda 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 *Output of NCA 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

RepNCAplot *NCAplot for replicated 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

RepNCAsave *Save NCA outputs for replicated study*

Description

This function can save the results after NCA.

RepNCAselect *Select the exact 3 points in NCA for replicated study*

Description

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

RepNCAselect.MIX *Select the exact 3 points in NCA and lme for replicated study*

Description

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

RepNCAselectdemo *Select the exact 3 points in NCA for demo function for replicated study*

Description

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

RepNCAselectdemo.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.

RepNCAselectsave *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.

RepNCAselectsave.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 (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).

`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 (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).

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 (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 minimun 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).

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 minimun 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 minimun 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 maximun 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 maximun 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 maximun 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 *summarySEwithin*

Description

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

Author(s)

Winston Chang

test.nca_stat *demo for NCA-anova demo file*

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 *Data for NCA analyze*

Description

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

TTT *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).

TTT.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).

TTTAIC *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 (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 minimun 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).

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 minimun 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 minimun 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).

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 maximun 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 maximun 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 maximun 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: –> 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).

`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 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

xtick *x-tick*

Description

Tick for plots.

ytick *y-tick*

Description

Tick for plots.

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