

Input File: Workbook - [parametrosfarmacocineticos_atenololSPH58_08_DD.pwo]

Date: 2/12/2010
Time: 16:06:41

WINNONLIN LINEAR MIXED EFFECTS MODELING / BIOEQUIVALENCE
Version 5.2.1 Build 2008033011
Core Version 17Oct2006

Model Specification and User Settings

Dependent variable : Cmax
Transform : LN
Fixed terms : int+sequence+form+period
Random/repeated terms : sequence*subject
Maximum iterations : 50
Convergence Criterion : 1e-010
Singularity tolerance : 1e-010
Denominator df option : residual

Class variables and their levels

form :	R	T							
subject :	12	18	20	21	28	31	35	37	
period :	1	2							
sequence :	RT	TR							

Using method of moments for starting values

Starting estimates of variance parameters:

Var(sequence*subject) 0.032944
Var(Residual) 0.014295

Diagnostics

Total Observations : 16
Observations Used : 16
Obs. Missing Model Terms : 0
Residual SS : 0.0857701
Residual df : 6
Residual Variance : 0.014295

Breakout of variance structure

Variance Index : 1
Source : Random
Type : Variance Components
Columns : sequence*subject
Parameters : Var(sequence*subject)

Variance Index : 2
Source : Assumed
Type : Identity
Columns : None
Parameters : Var(Residual)

Variance parameter estimation at each iteration:

Iteration	Objective	function	Var(sequence*subject)	Var(Residual)
0	-14.3139		0.032944	0.014295

Newton's algorithm converged.

Final variance parameter estimates:

Var(sequence*subject) 0.032944
Var(Residual) 0.014295
Intersubject CV 0.18301
Intrasubject CV 0.11999 (CV intra voluntarios do farmaco para o grupo analiso)

```

REML log(likelihood)      3.28659
-2* REML log(likelihood) -6.57318
Akaike Information Crit.  5.42682
Schwarz Bayesian Crit.   8.33626

```

Ordered Final Hessian Eigenvalues:

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15212.7
1801.19

```

Solution

Effect:Level	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
int	6.6459	0.145729	6	45.6044	0.0000	95	2.447
6.289 7.002							
sequence:RT	-0.0446895	0.163486	6	-0.273354	0.7937	95	2.447 -
0.4447 0.3553							
sequence:TR	Not estimable						
form:R	0.105694	0.069029	6	1.53116	0.1766	95	2.447 -
0.06321 0.2746							
form:T	Not estimable						
period:1	-0.011166	0.069029	6	-0.161758	0.8768	95	2.447 -
0.1801 0.1577							
period:2	Not estimable						

Sequential Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	6	8849.92	0.0000
sequence	1	6	0.0747222	0.7937
form	1	6	2.80442	0.1450
period	1	6	0.0261655	0.8768

Sequential Sum of Squares

Hypothesis	DF	SS	MS	F_stat
sequence	1	0.00599146	0.00599146	0.0747222
0.7937				
sequence*subject	6	0.481099	0.0801831	5.60916
0.0273				
form	1	0.0400892	0.0400892	2.80442
0.1450				
period	1	0.000374036	0.000374036	0.0261655
0.8768				
Error	6	0.0857701	0.014295	

Partial Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	6	6659.73	0.0000
sequence	1	6	0.0747222	0.7937
form	1	6	2.34445	0.1766
period	1	6	0.0261655	0.8768

Partial Sum of Squares

Hypothesis	DF	SS	MS	F_stat
sequence	1	0.00599146	0.00599146	0.0747222
0.7937				
sequence*subject	6	0.481099	0.0801831	5.60916
0.0273				
form	1	0.0335139	0.0335139	2.34445

0.1766
 0.8768 period 1 0.000374036 0.000374036 0.0261655
 Error 6 0.0857701 0.014295

Least squares means

	form	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
Lower_CI	Upper_CI							
6.551	6.896	R 6.72366	0.0887309	6	75.7759	0.0000	90	1.943
6.446	6.79	T 6.61797	0.0887309	6	74.5847	0.0000	90	1.943

Differences between means

	form	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
Lower_CI	Upper_CI							
0.02844	0.2398	R - T 0.105694	0.069029	6	1.53116	0.1766	90	1.943

Bioequivalence Statistics

User-Specified Confidence Level for CI's and Power = 90.0000
 Percent of Reference to Detect for 2-1 Tests and Power = 20.0%
 A.H.Lower = 0.800 A.H.Upper = 1.250

Formulation variable: form

Reference: R LSMean= 6.723665 SE= 0.088731 GeoLSM= 831.860682

Test: T LSMean= 6.617971 SE= 0.088731 GeoLSM= 748.424672

Difference = -0.1057, Diff_SE= 0.0690, df= 6.0
 Ratio(%Ref) = 89.9700 (razao das medias geometricas T/R)

	Classical	Westlake
CI 80% = (81.4570, 99.3725)	(84.3856, 115.6144)
CI 90% = (78.6734, 102.8885)	(81.3105, 118.6895)
CI 95% = (75.9841, 106.5301)	(78.4837, 121.5163)

Failed to show average bioequivalence for confidence=90.00 and percent=20.0.
 (fora do intervalo de bioequivalencia de 80%-125%)

(intervalo de confianca de 90% para a razao das medias geometricas T/R)

Two One-Sided T-tests

Prob(< 80%)=0.0699 Prob(> 125%)=0.0016 Max=0.0699 Total=0.0714

Anderson-Hauck Procedure

A.H. p-value = 0.068323

Power of ANOVA for Confidence Level 90.00

Power at 20% = 0.878588

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WINNONLIN LINEAR MIXED EFFECTS MODELING / BIOEQUIVALENCE
Version 5.2.1 Build 2008033011
Core Version 17Oct2006

Model Specification and User Settings

Dependent variable : AUClast
Transform : LN
Fixed terms : int+sequence+form+period
Random/repeated terms : sequence*subject
Maximum iterations : 50
Convergence Criterion : 1e-010
Singularity tolerance : 1e-010
Denominator df option : residual

Class variables and their levels

form :	R	T						
subject :	12	18	20	21	28	31	35	37
period :	1	2						
sequence :	RT	TR						

Using method of moments for starting values

Starting estimates of variance parameters:

Var(sequence*subject) 0.00911946
Var(Residual) 0.0204185

Diagnostics

Total Observations : 16
Observations Used : 16
Obs. Missing Model Terms : 0
Residual SS : 0.122511
Residual df : 6
Residual Variance : 0.0204185

Breakout of variance structure

Variance Index : 1
Source : Random
Type : Variance Components
Columns : sequence*subject
Parameters : Var(sequence*subject)

Variance Index : 2
Source : Assumed
Type : Identity
Columns : None
Parameters : Var(Residual)

Variance parameter estimation at each iteration:

Iteration	Objective function	Var(sequence*subject)	Var(Residual)
0	-15.433	0.00911946	0.0204185

Newton's algorithm converged.

Final variance parameter estimates:

Var(sequence*subject) 0.00911946
Var(Residual) 0.0204185
Intersubject CV 0.095714
Intrasubject CV 0.143626

```

REML log(likelihood)      4.40572
-2* REML log(likelihood) -8.81143
Akaike Information Crit.  3.18857
Schwarz Bayesian Crit.   6.09801

```

Ordered Final Hessian Eigenvalues:

```

12674.2
4558.97

```

Solution

Effect:Level	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
int	8.57108	0.106611	6	80.3959	0.0000	95	2.447
8.31 8.832							
sequence:RT	0.0555183	0.113516	6	0.48908	0.6421	95	2.447 -
0.2222 0.3333							
sequence:TR	Not estimable						
form:R	0.0492487	0.0824995	6	0.596957	0.5724	95	2.447 -
0.1526 0.2511							
form:T	Not estimable						
period:1	0.0807383	0.0824995	6	0.978651	0.3655	95	2.447 -
0.1211 0.2826							
period:2	Not estimable						

Sequential Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	6	31167.2	0.0000
sequence	1	6	0.2392	0.6421
form	1	6	1.57335	0.2564
period	1	6	0.957758	0.3655

Sequential Sum of Squares

Hypothesis	DF	SS	MS	F_stat
sequence	1	0.00924685	0.00924685	0.2392
0.6421				
sequence*subject	6	0.231945	0.0386575	1.89325
0.2284				
form	1	0.0321254	0.0321254	1.57335
0.2564				
period	1	0.019556	0.019556	0.957758
0.3655				
Error	6	0.122511	0.0204185	

Partial Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	6	23300.7	0.0000
sequence	1	6	0.2392	0.6421
form	1	6	0.356358	0.5724
period	1	6	0.957758	0.3655

Partial Sum of Squares

Hypothesis	DF	SS	MS	F_stat
sequence	1	0.00924685	0.00924685	0.2392
0.6421				
sequence*subject	6	0.231945	0.0386575	1.89325
0.2284				
form	1	0.0072763	0.0072763	0.356358

0.5724								
	period	1	0.019556	0.019556	0.957758			
0.3655	Error	6	0.122511	0.0204185				

Least squares means

	form	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
8.552	R	8.68846	0.0701641	6	123.831	0.0000	90	1.943
8.503	T	8.63921	0.0701641	6	123.129	0.0000	90	1.943

Differences between means

	form	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
0.1111	R - T	0.0492487	0.0824995	6	0.596957	0.5724	90	1.943

Bioequivalence Statistics

User-Specified Confidence Level for CI's and Power = 90.0000
Percent of Reference to Detect for 2-1 Tests and Power = 20.0%
A.H.Lower = 0.800 A.H.Upper = 1.250

Formulation variable: form

Reference: R LSMean= 8.688461 SE= 0.070164 GeoLSM= 5934.041659

Test: T LSMean= 8.639212 SE= 0.070164 GeoLSM= 5648.877559

Difference = -0.0492, Diff_SE= 0.0825, df= 6.0
Ratio(%Ref) = 95.1944

	Classical	Westlake
CI 80% = (84.5315, 107.2024)	(86.9997, 113.0003)
CI 90% = (81.0907, 111.7511)	(83.1583, 116.8417)
CI 95% = (77.7890, 116.4944)	(79.4689, 120.5311)

Average bioequivalence shown for confidence=90.00 and percent=20.0.

Two One-Sided T-tests

Prob(< 80%)=0.0398 Prob(> 125%)=0.0082 Max=0.0398 Total=0.0480

Anderson-Hauck Procedure

A.H. p-value = 0.031620

Power of ANOVA for Confidence Level 90.00

Power at 20% = 0.764037

Input File: Workbook - [parametrosfarmacocineticos_atenololSPH58_08_DD.pwo]

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WINNONLIN LINEAR MIXED EFFECTS MODELING / BIOEQUIVALENCE
Version 5.2.1 Build 2008033011
Core Version 17Oct2006

Model Specification and User Settings

Dependent variable : AUCINF_obs
Transform : LN
Fixed terms : int+sequence+form+period
Random/repeated terms : sequence*subject
Maximum iterations : 50
Convergence Criterion : 1e-010
Singularity tolerance : 1e-010
Denominator df option : residual

Class variables and their levels

form :	R	T						
subject :	12	18	20	21	28	31	35	37
period :	1	2						
sequence :	RT	TR						

Using method of moments for starting values

Starting estimates of variance parameters:

Var(sequence*subject) 0.0122068
Var(Residual) 0.0166405

Diagnostics

Total Observations :	16
Observations Used :	16
Obs. Missing Model Terms :	0
Residual SS :	0.0998427
Residual df :	6
Residual Variance :	0.0166405

Breakout of variance structure

Variance Index : 1
Source : Random
Type : Variance Components
Columns : sequence*subject
Parameters : Var(sequence*subject)

Variance Index : 2
Source : Assumed
Type : Identity
Columns : None
Parameters : Var(Residual)

Variance parameter estimation at each iteration:

Iteration	Objective function	Var(sequence*subject)	Var(Residual)
0	-15.8664	0.0122068	0.0166405

Newton's algorithm converged.

Final variance parameter estimates:

Var(sequence*subject)	0.0122068
Var(Residual)	0.0166405
Intersubject CV	0.110822
Intrasubject CV	0.129536

```

REML log(likelihood)      4.83908
-2* REML log(likelihood) -9.67817
Akaike Information Crit.  2.32183
Schwarz Bayesian Crit.   5.23127

```

Ordered Final Hessian Eigenvalues:

```

14363.5
5370.3

```

Solution

Effect:Level	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
int	8.62263	0.107936	6	79.8863	0.0000	95	2.447
sequence:RT	0.0658912	0.116982	6	0.563261	0.5937	95	2.447
sequence:TR	Not estimable						
form:R	0.0438031	0.074477	6	0.588143	0.5779	95	2.447
form:T	Not estimable						
period:1	0.0694321	0.074477	6	0.932262	0.3872	95	2.447
period:2	Not estimable						

Sequential Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	6	29693.3	0.0000
sequence	1	6	0.317263	0.5937
form	1	6	1.48199	0.2692
period	1	6	0.869113	0.3872

Sequential Sum of Squares

Hypothesis	DF	SS	MS	F_stat
sequence	1	0.0130249	0.0130249	0.317263
sequence*subject	6	0.246325	0.0410541	2.46713
form	1	0.024661	0.024661	1.48199
period	1	0.0144624	0.0144624	0.869113
Error	6	0.0998427	0.0166405	

Partial Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	6	22186	0.0000
sequence	1	6	0.317263	0.5937
form	1	6	0.345912	0.5779
period	1	6	0.869113	0.3872

Partial Sum of Squares

Hypothesis	DF	SS	MS	F_stat
sequence	1	0.0130249	0.0130249	0.317263
sequence*subject	6	0.246325	0.0410541	2.46713
form	1	0.00575614	0.00575614	0.345912

0.5779								
	period		1	0.0144624	0.0144624		0.869113	
0.3872								
	Error		6	0.0998427	0.0166405			

Least squares means

	form	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
Lower_CI	Upper_CI							

	R	8.73409	0.0693389	6	125.962	0.0000	90	1.943
8.599	8.869							
	T	8.69029	0.0693389	6	125.331	0.0000	90	1.943
8.556	8.825							

Differences between means

	form	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
Lower_CI	Upper_CI							

	R - T	0.0438031	0.074477	6	0.588143	0.5779	90	1.943
0.1009	0.1885							

Bioequivalence Statistics

User-Specified Confidence Level for CI's and Power = 90.0000
Percent of Reference to Detect for 2-1 Tests and Power = 20.0%
A.H.Lower = 0.800 A.H.Upper = 1.250

Formulation variable: form

Reference: R LSMean= 8.734092 SE= 0.069339 GeoLSM= 6211.094519

Test: T LSMean= 8.690289 SE= 0.069339 GeoLSM= 5944.901856

Difference = -0.0438, Diff_SE= 0.0745, df= 6.0
Ratio(%Ref) = 95.7142

	Classical	Westlake
CI 80% = (85.9806, 106.5498)	(88.2470, 111.7530)
CI 90% = (82.8149, 110.6229)	(84.7405, 115.2595)
CI 95% = (79.7647, 114.8530)	(81.3678, 118.6322)

Average bioequivalence shown for confidence=90.00 and percent=20.0.

Two One-Sided T-tests

Prob(< 80%)=0.0264 Prob(> 125%)=0.0058 Max=0.0264 Total=0.0322

Anderson-Hauck Procedure

A.H. p-value = 0.020567

Power of ANOVA for Confidence Level 90.00

Power at 20% = 0.834744