

Input File: Workbook - [parametrosfarmacocineticos\_atenololSPH58\_08\_ID.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 : 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 : 1 3 4 6 9 10 14 16 17 19 22  
24 25 27 30 34  
period : 1 2  
sequence : RT TR

Using method of moments for starting values

Starting estimates of variance parameters:  
Var(sequence\*subject) 0.131534  
Var(Residual) 0.0552627

Diagnostics

Total Observations : 32  
Observations Used : 32  
Obs. Missing Model Terms : 0  
Residual SS : 0.773677  
Residual df : 14  
Residual Variance : 0.0552627

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:

Objective  
Iteration function Var(sequence\*subject) Var(Residual)  
0 -14.2823 0.131534 0.0552627

Newton's algorithm converged.

Final variance parameter estimates:

Var(sequence\*subject) 0.131534  
Var(Residual) 0.0552627  
Intersubject CV 0.374935  
Intrasubject CV 0.238366

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REML log(likelihood)      -11.448
-2* REML log(likelihood) 22.8961
Akaike Information Crit.  34.8961
Schwarz Bayesian Crit.   42.8893

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Ordered Final Hessian Eigenvalues:

```

2370.3
267.198

```

Solution

Effect:Level	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
int	6.5602	0.143254	14	45.7942	0.0000	95	2.145
sequence:RT	-0.139069	0.20602	14	-0.67503	0.5107	95	2.145
sequence:TR	Not estimable						
form:R	0.0143156	0.0858391	14	0.166773	0.8699	95	2.145
form:T	Not estimable						
period:1	0.10131	0.0858391	14	1.18023	0.2576	95	2.145
period:2	Not estimable						

Sequential Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	14	4333.67	0.0000
sequence	1	14	0.455665	0.5107
form	1	14	0.0175538	0.8965
period	1	14	1.39293	0.2576

Sequential Sum of Squares

Hypothesis	DF	SS	MS	F_stat
sequence	1	0.145052	0.145052	0.455665
sequence*subject	14	4.45663	0.31833	5.76031
form	1	0.000970071	0.000970071	0.0175538
period	1	0.0769772	0.0769772	1.39293
Error	14	0.773677	0.0552627	

Partial Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	14	4041.33	0.0000
sequence	1	14	0.455665	0.5107
form	1	14	0.0278131	0.8699
period	1	14	1.39293	0.2576

Partial Sum of Squares

Hypothesis	DF	SS	MS	F_stat
sequence	1	0.145052	0.145052	0.455665
sequence*subject	14	4.45663	0.31833	5.76031
form	1	0.00153703	0.00153703	0.0278131

0.8699								
	period	1	0.0769772	0.0769772	1.39293			
0.2576	Error	14	0.773677	0.0552627				

Least squares means

	form	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
Lower_CI	Upper_CI							
-----								
	R	6.55564	0.111593	14	58.7457	0.0000	90	1.761
6.359	6.752							
	T	6.54132	0.111593	14	58.6174	0.0000	90	1.761
6.345	6.738							

Differences between means

	form	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
Lower_CI	Upper_CI							
-----								
	R - T	0.0143156	0.0858391	14	0.166773	0.8699	90	1.761
0.1369	0.1655							

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= 6.555638 SE= 0.111593 GeoLSM= 703.197624

Test: T LSMean= 6.541322 SE= 0.111593 GeoLSM= 693.202624

Difference = -0.0143, Diff\_SE= 0.0858, df= 14.0  
Ratio(%Ref) = 98.5786

	Classical	Westlake
CI 80% = (	87.8281, 110.6451)	( 88.4629, 111.5371)
CI 90% = (	84.7435, 114.6725)	( 84.9877, 115.0123)
CI 95% = (	81.9986, 118.5112)	( 81.7882, 118.2118)

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

Two One-Sided T-tests

Prob(< 80%)=0.0145 Prob(> 125%)=0.0076 Max=0.0145 Total=0.0221

Anderson-Hauck Procedure

A.H. p-value = 0.006918

Power of ANOVA for Confidence Level 90.00

Power at 20% = 0.792223



REML log(likelihood) -4.28666  
 -2\* REML log(likelihood) 8.57332  
 Akaike Information Crit. 20.5733  
 Schwarz Bayesian Crit. 28.5665

Ordered Final Hessian Eigenvalues:

14485.4  
 338.311

Solution

Effect:Level	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
Lower_CI	Upper_CI						
int	8.62617	0.127195	14	67.8187	0.0000	95	2.145
8.353	8.899						
sequence:RT	-0.0262531	0.195558	14	-0.134247	0.8951	95	2.145 -
0.4457	0.3932						
sequence:TR	Not estimable						
form:R	0.0605059	0.0542208	14	1.11592	0.2832	95	2.145 -
0.05579	0.1768						
form:T	Not estimable						
period:1	0.0202652	0.0542208	14	0.373754	0.7142	95	2.145 -
0.09603	0.1366						
period:2	Not estimable						

Sequential Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	14	8360.75	0.0000
sequence	1	14	0.0180223	0.8951
form	1	14	1.11516	0.3088
period	1	14	0.139692	0.7142

Sequential Sum of Squares

Hypothesis	DF	SS	MS	F_stat
sequence	1	0.00516917	0.00516917	0.0180223
sequence*subject	14	4.01549	0.286821	13.0082
form	1	0.0245884	0.0245884	1.11516
period	1	0.0030801	0.0030801	0.139692
Error	14	0.308689	0.0220492	

Partial Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	14	7832.26	0.0000
sequence	1	14	0.0180223	0.8951
form	1	14	1.24527	0.2832
period	1	14	0.139692	0.7142

Partial Sum of Squares

Hypothesis	DF	SS	MS	F_stat
sequence	1	0.00516917	0.00516917	0.0180223
sequence*subject	14	4.01549	0.286821	13.0082

0.2832	form	1	0.0274572	0.0274572	1.24527
0.7142	period	1	0.0030801	0.0030801	0.139692
	Error	14	0.308689	0.0220492	

Least squares means

	form	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
Lower_CI	Upper_CI							
-----								
8.505	R	8.68368	0.101468	14	85.5809	0.0000	90	1.761
8.444	T	8.62317	0.101468	14	84.9845	0.0000	90	1.761

Differences between means

	form	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
Lower_CI	Upper_CI							
-----								
0.03499	R - T	0.0605059	0.0542208	14	1.11592	0.2832	90	1.761
		0.156						

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= 8.683680 SE= 0.101468 GeoLSM= 5905.739690

Test: T LSMean= 8.623174 SE= 0.101468 GeoLSM= 5559.003095

Difference = -0.0605, Diff\_SE= 0.0542, df= 14.0  
Ratio(%Ref) = 94.1288

	Classical	Westlake
CI 80% = (	87.5075, 101.2511)	( 89.6981, 110.3019)
CI 90% = (	85.5535, 103.5637)	( 87.4284, 112.5716)
CI 95% = (	83.7925, 105.7402)	( 85.4800, 114.5200)

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

Two One-Sided T-tests

Prob(< 80%)=0.0048 Prob(> 125%)=0.0001 Max=0.0048 Total=0.0048

Anderson-Hauck Procedure

A.H. p-value = 0.004717

Power of ANOVA for Confidence Level 90.00

Power at 20% = 0.983159



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REML log(likelihood)      -3.11128
-2* REML log(likelihood)  6.22257
Akaike Information Crit.  18.2226
Schwarz Bayesian Crit.   26.2158

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Ordered Final Hessian Eigenvalues:

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16869.5
406.436

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Solution

Effect:Level	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
Lower_CI	Upper_CI						
int	8.6843	0.121596	14	71.4192	0.0000	95	2.145
8.423	8.945						
sequence:RT	-0.0293221	0.186782	14	-0.156986	0.8775	95	2.145 -
0.4299	0.3713						
sequence:TR	Not estimable						
form:R	0.0565018	0.0521969	14	1.08247	0.2973	95	2.145 -
0.05545	0.1685						
form:T	Not estimable						
period:1	0.0157005	0.0521969	14	0.300794	0.7680	95	2.145 -
0.09625	0.1277						
period:2	Not estimable						

Sequential Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	14	9276.76	0.0000
sequence	1	14	0.0246446	0.8775
form	1	14	1.08224	0.3158
period	1	14	0.0904768	0.7680

Sequential Sum of Squares

Hypothesis	DF	SS	MS	F_stat
sequence	1	0.00644839	0.00644839	0.0246446
sequence*subject	14	3.66318	0.261656	12.805
form	1	0.0221144	0.0221144	1.08224
period	1	0.00184879	0.00184879	0.0904768
Error	14	0.286074	0.0204339	

Partial Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	14	8689.65	0.0000
sequence	1	14	0.0246446	0.8775
form	1	14	1.17175	0.2973
period	1	14	0.0904768	0.7680

Partial Sum of Squares

Hypothesis	DF	SS	MS	F_stat
sequence	1	0.00644839	0.00644839	0.0246446
sequence*subject	14	3.66318	0.261656	12.805

0.2973	form	1	0.0239434	0.0239434	1.17175
0.7680	period	1	0.00184879	0.00184879	0.0904768
	Error	14	0.286074	0.0204339	

Least squares means

	form	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
Lower_CI	Upper_CI							
-----								
8.563	R	8.73399	0.096969	14	90.0699	0.0000	90	1.761
	T	8.67749	0.096969	14	89.4872	0.0000	90	1.761
8.507								

Differences between means

	form	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit
Lower_CI	Upper_CI							
-----								
0.03543	R - T	0.0565018	0.0521969	14	1.08247	0.2973	90	1.761
		0.1484						

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= 8.733987 SE= 0.096969 GeoLSM= 6210.438391

Test: T LSMean= 8.677485 SE= 0.096969 GeoLSM= 5869.266875

Difference = -0.0565, Diff\_SE= 0.0522, df= 14.0  
Ratio(%Ref) = 94.5065

	Classical	Westlake
CI 80% = (	88.0982, 101.3809)	( 90.2092, 109.7908)
CI 90% = (	86.2036, 103.6091)	( 88.0135, 111.9865)
CI 95% = (	84.4947, 105.7045)	( 86.1254, 113.8746)

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

Two One-Sided T-tests

Prob(< 80%)=0.0033 Prob(> 125%)=0.0001 Max=0.0033 Total=0.0033

Anderson-Hauck Procedure

A.H. p-value = 0.003208

Power of ANOVA for Confidence Level 90.00

Power at 20% = 0.987605