CLINICAL TRIALS

- ANOVA (ANDEVA)

- COVARIANCE

- POST CLINICAL INFORMATION

ANOVA

I. For Fasting blood glucose levels
Dose X time effect $p < 0.0001$
post hoc analysis Tukeys demonstrates
 all groups different at beginning of test $p < 0.001$.
 end test both V-411and Glibenclamida different from placebo $p < 0.001$
 at the end both V-411 and Glibenclamida differed from their initial level $p < 0.001$
 no difference between the placebo levels at beginning or end

Fasting blood glucose Beginning	Fasting blood glucose End
V-411= 12.55 SD= 3.14	9.6 SD=2.38
Glibenclamida= 11.27 SD= 2.18	9.7 SD=1.66
Placebo= 11.67 SD= 2.36	11.1 SD=5.66

II. For 2 hr glucose tolerance test
Dose X time effect $p < 0.0001$
post hoc analysis Tukeys demonstrates:

 at beginning no difference between V-411 and placebo or Glibenclamida and placebo but V 411> Glibenclamida $p < 0.001$

 at end V-411< Glibemcamida $p < 0.05$
 V-411 < placebo $p < 0.001$
 Glibenclamida < placebo $p < 0.001$
 both drug groups different at end compared to their starting level $p < 0.001$

2 hr. Glucose tolerance blood Beginning	2 hr. Glucose tolerance blood End
V-411= 17.99 SD=5.22	13.68 SD=4.44
Glibenclamida= 17.13 SD 3.21	14.26 SD=2.23
Placebo= 17.66 SD= 6.04	15.99 SD= 5.29

III. For 24 urine glucose test
dose X time effect $p < 0.0001$
post hoc analysis Tukeys demonstrates

at beginning V-411 < Glibenclamida and placebo $p < 0.001$ but Glibenclamida=placebo

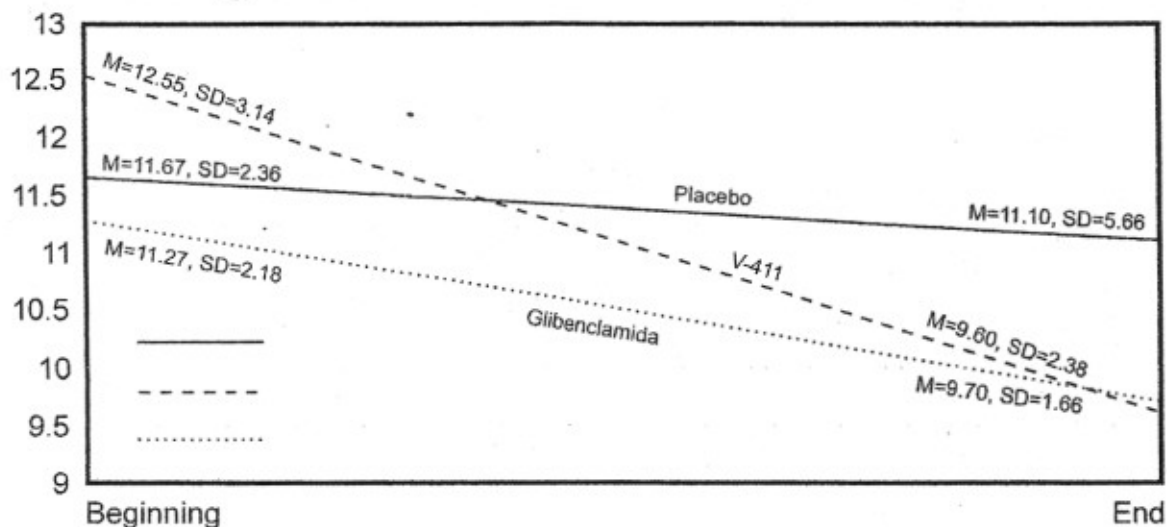at end both V-411 and Glibenclamida groups differed from their respective beginning levels
$p < 0.001$ but placebo did not change
V-411 < Glibenclamida < placebo $p < 0.001$
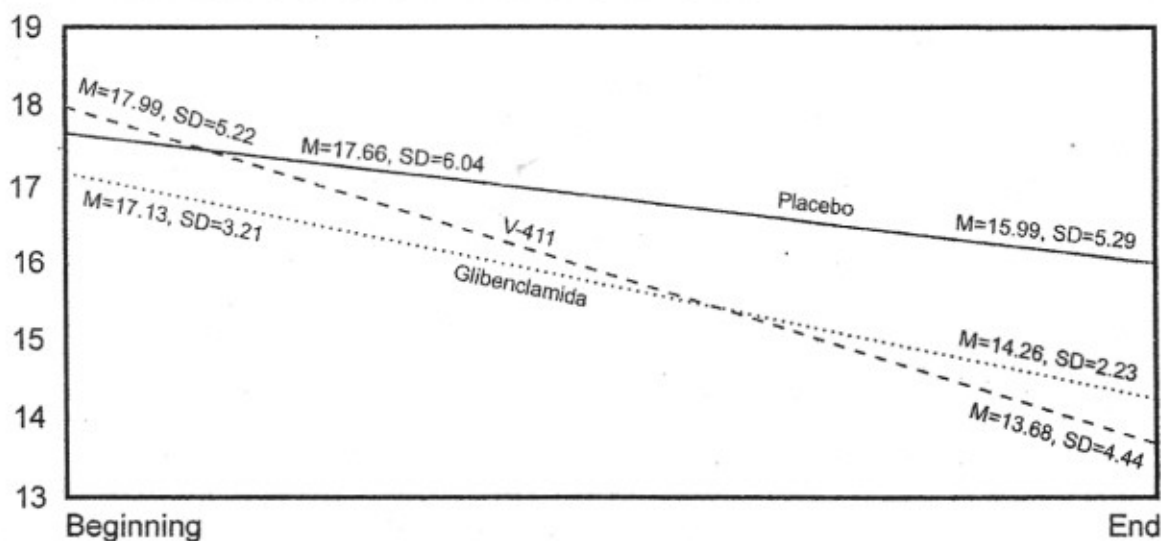
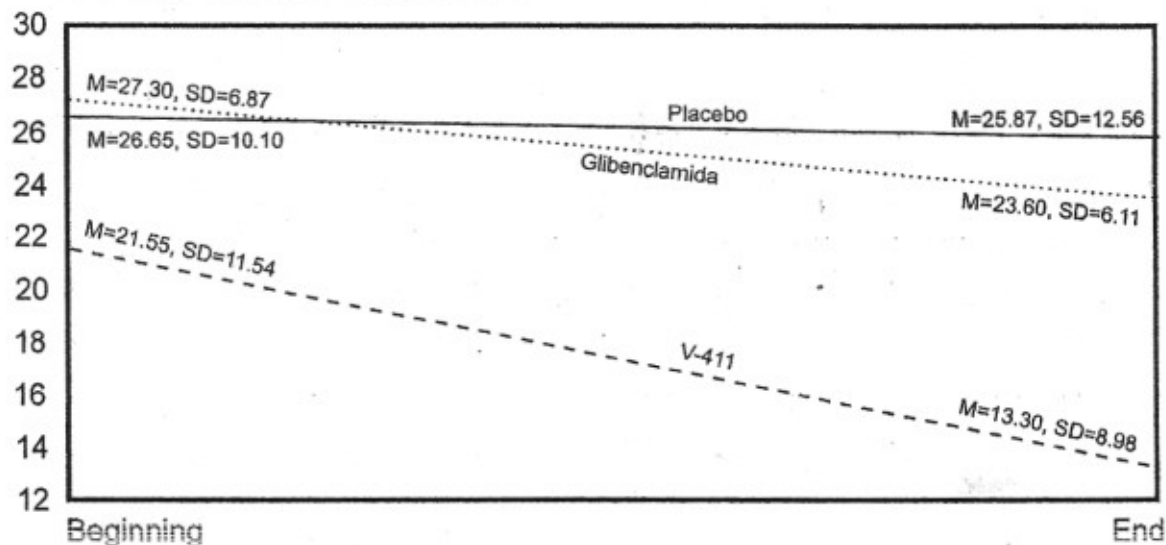| 24 hr urine glucose Beginning	24 hr urine glucose End
V-411= 21.55 SD=11.54	V-411 13.30 SD=8.98
Glibenclamida= 27.30 SD=6.87	Glibenclamida 23.60 SD=6.11
placebo= 26.65 SD=10.10	25.87 SD=12.56

Fasting Blood Glucose

M=12.55, SD=3.14
M=11.67, SD=2.36
M=11.27, SD=2.18
Placebo
V-411
Glibenclamida
M=11.10, SD=5.66
M=9.60, SD=2.38
M=9.70, SD=1.66
Beginning
End

2 hr. Glucose Tolerance Blood

M=17.99, SD=5.22
M=17.66, SD=6.04
M=17.13, SD=3.21
V-411
Glibenclamida
Placebo
M=15.99, SD=5.29
M=14.26, SD=2.23
M=13.68, SD=4.44
Beginning
End

24 hr. Urine Glucose

M=27.30, SD=6.87
Placebo
M=26.65, SD=10.10
Glibenclamida
M=21.55, SD=11.54
V-411
M=25.87, SD=12.56
M=23.60, SD=6.11
M=13.30, SD=8.98
Beginning
End

Analysis of Covariance

Analysis of Covariance of end values with the beginning values as covariates. In all cases the possibility of an interaction of treatment and beginning values was fitted. If the interaction is significative it is included in the model and the predicted values are reported in a graph.

Analysis of Covariance is equivalent to run tree regressions, of the end values as a linear function of the beginning values.. If there is interaction the tree lines are not parallel. Incase of not significant interaction these lines are parallel.

Response FBG end

Model · FBG end= Bo + Trat +B_1FBGbeg+ Trat*FBGbeg + E

Summary of Fit

RSquare   0.36824
RSquare Adj 0.359632
Root Mean Square Error   2.831377
Mean of Response   10.11129
Observations (or Sum Wgts)   373

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	5	1714.9026	342.981	42.7833
Error	367	2942.1279	8.017	Prob > F
C. Total	372	4657.0306		<.0001

Effect Tests

Source	DF	Sum of Squares	F Ratio	Prob > F
FBG beg	1	1439.4712	179.5591	<.0001
Treatment	2	264.2919	16.4838	<.0001
FBG beg*Treatment2		132.2680	8.2495	0.0003

Least Squares Means Table

Level	Least Sq Mean	Std Error	Mean
Glibencamide	10.143728	0.25568785	9.7863
Placebo	11.286617	0.26940514	11.0956
V-411	9.162118	0.25365164	9.6023

Mean is the raw Mean.
Lest Sq Mean is the adjusted by Least squares Mean. Fixed at the mean of FBGbeg
But since there is significant interaction it is not recommended to interpret these means. It is better to evaluate the graph of the predicted mean for FBGend for corresponding values of FBGbeg.
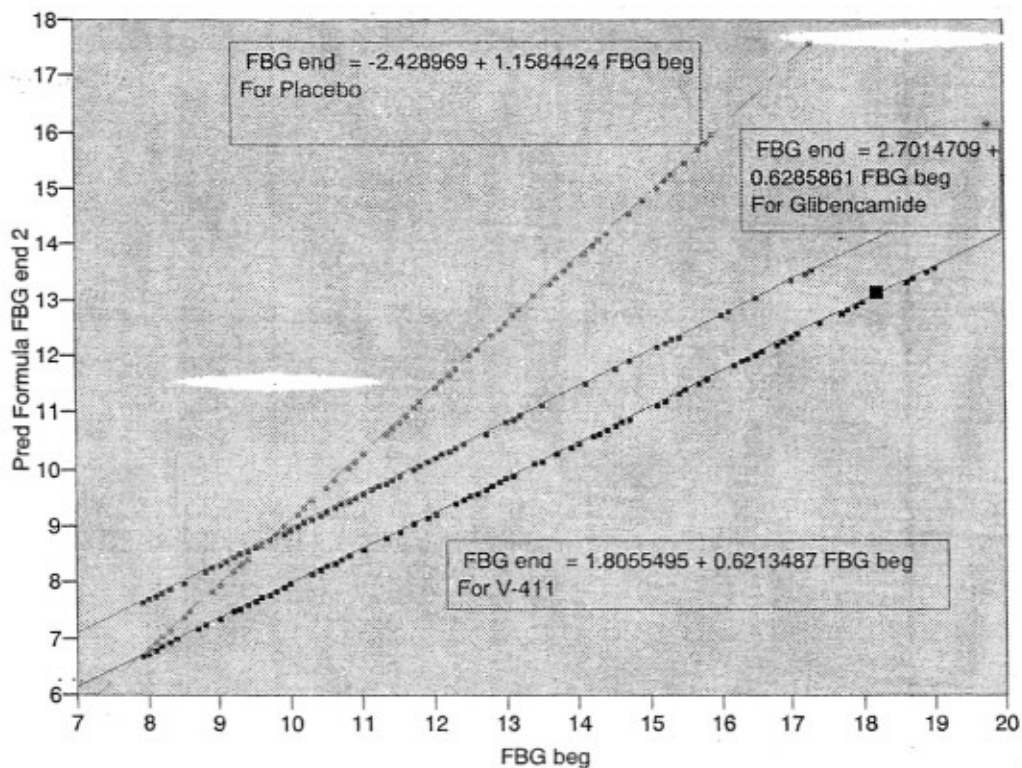
The expression for the predicted FBGend is:

FBGend= 0.692683767804871 + 0.80279240630886 * :FBG beg +

Match(:Treatment, "Glibencamide", -0.0537600067081076,
"Placebo", 1.08912922306211,
"V-411", -1.035369216354, .) +

(:FBG beg - 11.8396782841823) *
Match(:Treatment, "Glibencamide", -0.174206349184022,
"Placebo", 0.355650040727119,
"V-411", -0.18144300 :010097, .).

FBG end = -2.428969 + 1.1584424 FBG beg
For Placebo

FBG end = 2.7014709 + 0.6285861 FBG beg
For Glibencamide

FBG end = 1.8055495 + 0.6213487 FBG beg
For V-411

Notice that the increase in FBGend for each increase of one unit in FBG beg. Is bigger for Placebo 1.15. For Glibicamide and V-411 is almost identical 0.628 and 0.621 respectively. However the line of V-4-11 is lower.

Response 2hgtt end

Whole Model
Model   2hgtt end= Bo + Trat +$B_1$2hgtt beg + Trat*2hgtt beg + E

Summary of Fit

RSquare   0.786866
RSquare Adj   0.783962
Root Mean Square Error   1.962147
Mean of Response 14.57536
Observations (or Sum Wgts)   373

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	5	5216.4645	1043.29	270.9838
Error	367	1412.9572	3.85	Prob > F
C. Total	372	6629.4217		<.0001

Effect Tests

Source	DF	Sum of Squares	F Ratio	Prob > F
Treatment	2	386.4262	50.1850	<.0001
2hrgtt beg	1	3543.1954	920.3058	<.0001
2hrgtt beg*Treatment	2	32.7074	4.2477	**0.0150**

Treatment
Least Squares Means Table

Level	Least Sq Mean	Std Error	Mean
Glibencamide	14.550567	0.17322121	14.2679
Placebo	15.931797	0.18625321	15.9910
V-411	13.392318	0.17193910	13.6833

Same comments as above

The prediction equations is :
2hrgtt end=
2.1429020203101 *
Match(:Treatment, "Glibencamide", -0.0743265804097663,
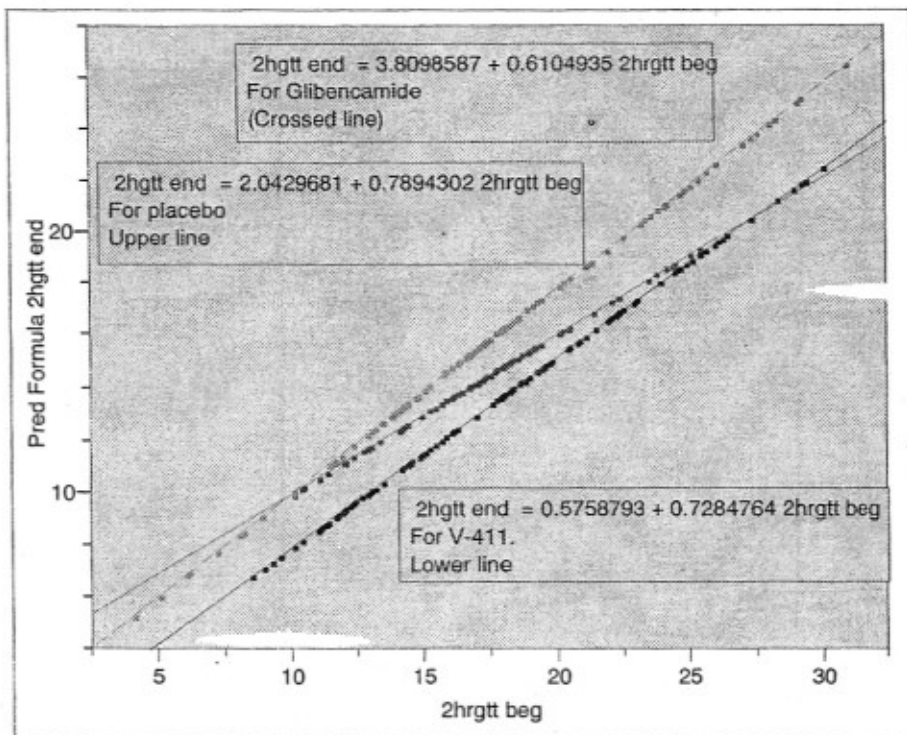"Placebo", 1.30690293857837,
"V-411", -1.2325763581686, .) +
0.709466705234857 * "2hrgtt beg" +
(:"2hrgtt beg" - 17.5934852546917) *
Match(:Treatment, "Glibencamide",
 -0.0989731870635621, "Placebo",
0.0799635135683293, "V-411", 0.0190096734952328, .)

The lowest values of 2hgtt end are for V-411 for all values of the initial or 2hgtt beg.

Response 24hr# U end

Whole Model
Model
24hr# U end = Bo , T... .C,24hr# U beg + Trat*24hr# U beg + E

Summary of Fit

RSquare	0.843475
RSquare Adj	0.841343
Root Mean Square Error	4.329243
Mean of Response	20.65536
Observations (or Sum Wgts)	373

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	5	37066.338	7413.27	395.5358
Error	367	6878.440	18.74	Prob > F
C. Total	372	43944.778		<.0001

Effect Tests

Source	DF	Sum of Squares	F Ratio	Prob > F
24 hr# U beg	1	22096.342	1178.953	<.0001
Treatment	2	4337.562	115.7156	<.0001
24 hr# U beg*Treatment	2	997.363	26.6072	<.0001

Least Squares Means Table

Level	Least Sq Mean	Std Error	Mean
Glibencamide	21.740398	0.39740923	23.5935
Placebo	21.179569	0.41588609	25.8739
V-411	15.759545	0.39575257	13.2954

Same comments as above for these means.

Prediction equation for 24 hr# U end

24 hr# U end =
(-1.30909947256565) +
0.871679259186529 * "24 hr# U beg" +
Match(:Treatment,
"Glibencamide", 1.1805606206871,
"Placebo", 3.6197315450951,
"V-411", -4.8002921657822, .) +
(24 hr# U beg" - 25.0882841823056) * Match(:Treatment,
"Glibencamide", -0.0321363226838728,
"Placebo", 0.207307226662005,
"V-411", -0.175170903978132, .)
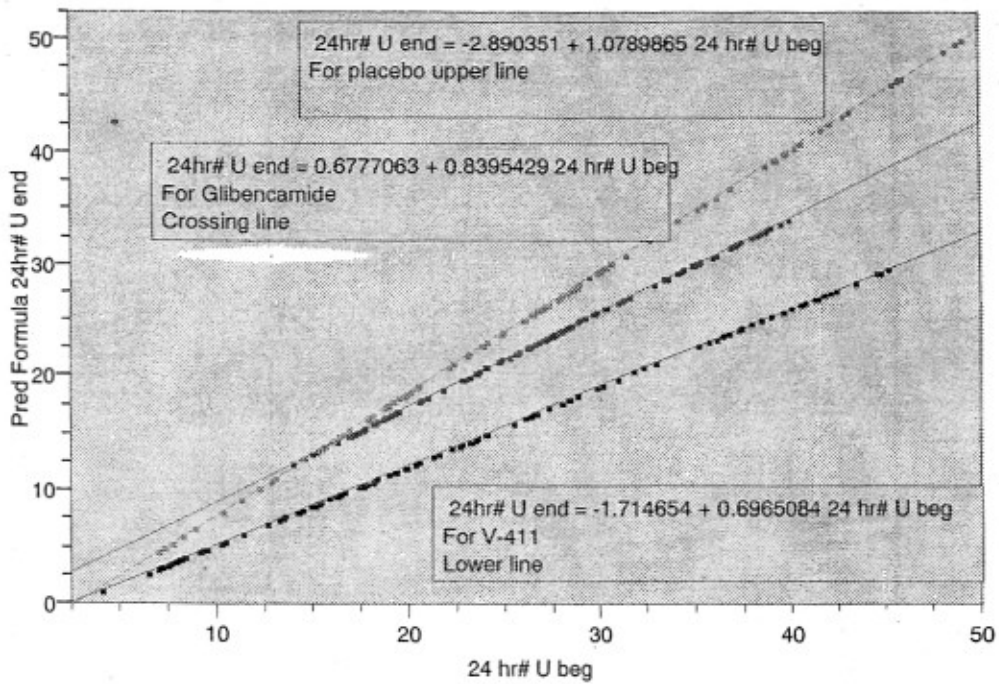
Again the end values of 24hrs#U is lower for all values of the beginning values for the treatment V-411.

CLINICAL TRIALS SUPPLEMENT

This supplement details the variance's analysis (ADV, ANOVA, ADEVA) that is mention on the second line of the first page, in the Tukey´s posthoc test.

This file was carried from the patient data base (RDP) by one of our maxim National Authorities on Statistics: Dr. Ignacio Mendez Ramirez.

- Former Director of the Institute in Mathematics Applies and Systems (IIMAS) at the UNAM.

- Titular Academic at the National Academic of Medicine.

- Ex President of the Society of Statistics

- Former Principal of the University Autonomy of Chapingo.

Clinic Assay to compare V-411 with Glibenclamide and Placebo.

Covariance's analysis.

With basal or initials values, there can be analyze the differences, but is preferable one covariance test that in essence consists in the adjust of rectos of regression of the final value on the initial per every treatment. If there's not interaction, the rectos are parallels.

ENSAYO CLINICO PARA COMPARAR V-411 CON GLIBENCAMIDE Y PLACEBO.
ANÁLISIS DE COVARIANZA.
Cuando se tienen valores basales o iniciales, se puede analizar las diferencias , pero es
preferible un análisis de covarianza que en esencia consiste en el ajuste de rectas de
regresión del valor final sobre el inicial para cada tratamiento. Si no hay interacción , las
rectas son paralelas.

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Response FBG end
Whole Model
Summary of Fit

RSquare	0.336815
RSquare Adj	0.325871
Root Mean Square Error	3.050316
Mean of Response	10.19777
Observations (or Sum Wgts)	309

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	5	1431.8228	286.365	30.7772
Error	303	2819.2418	9.304	Prob > F
C. Total	308	4251.0646		<.0001

Lack Of Fit

Source	DF	Sum of Squares	Mean Square	F Ratio
Lack Of Fit	163	1848.2975	11.3392	1.6350
Pure Error	140	970.9443	6.9353	Prob > F
Total Error	303	2819.2418		0.0015
				Max RSq
				0.7716

Parameter Estimates
Effect Tests

Term	Estimate	Std Error	t Ratio	Prob>|t
Intercept	0.7513783	0.858701	0.88	0.3823
FBG beg	0.8010265	0.071508	11.20	<.0001
Treatment[Glibencamide]	-0.05429	0.240388	-0.23	0.8215
Treatment[Placebo]	0.9741214	0.247879	3.93	0.0001
(FBG beg-11.6236)*Treatment[Glibencamide]	-0.17244	0.100568	-1.71	0.0874
(FBG beg-11.6236)*Treatment[Placebo]	0.3574159	0.100931	3.54	0.0005

Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
FBG beg	1	1	1167.5596	125.4843	<.0001
Treatment	2	2	154.2620	8.2897	0.0003
FBG beg*Treatment	2	2	116.6804	6.2702	0.0021

Press
2928.2498791

Bivariate Fit of Pred Formula FBG end By FBG beg

Relacion Valor inicial de FBG con el final predicho por el modelo de Covarianza. Notese que el qoe prouce la ineraccion es el Placebo. Para los dos medicamemnteso las lineas son paralelas con valores menores para V-411
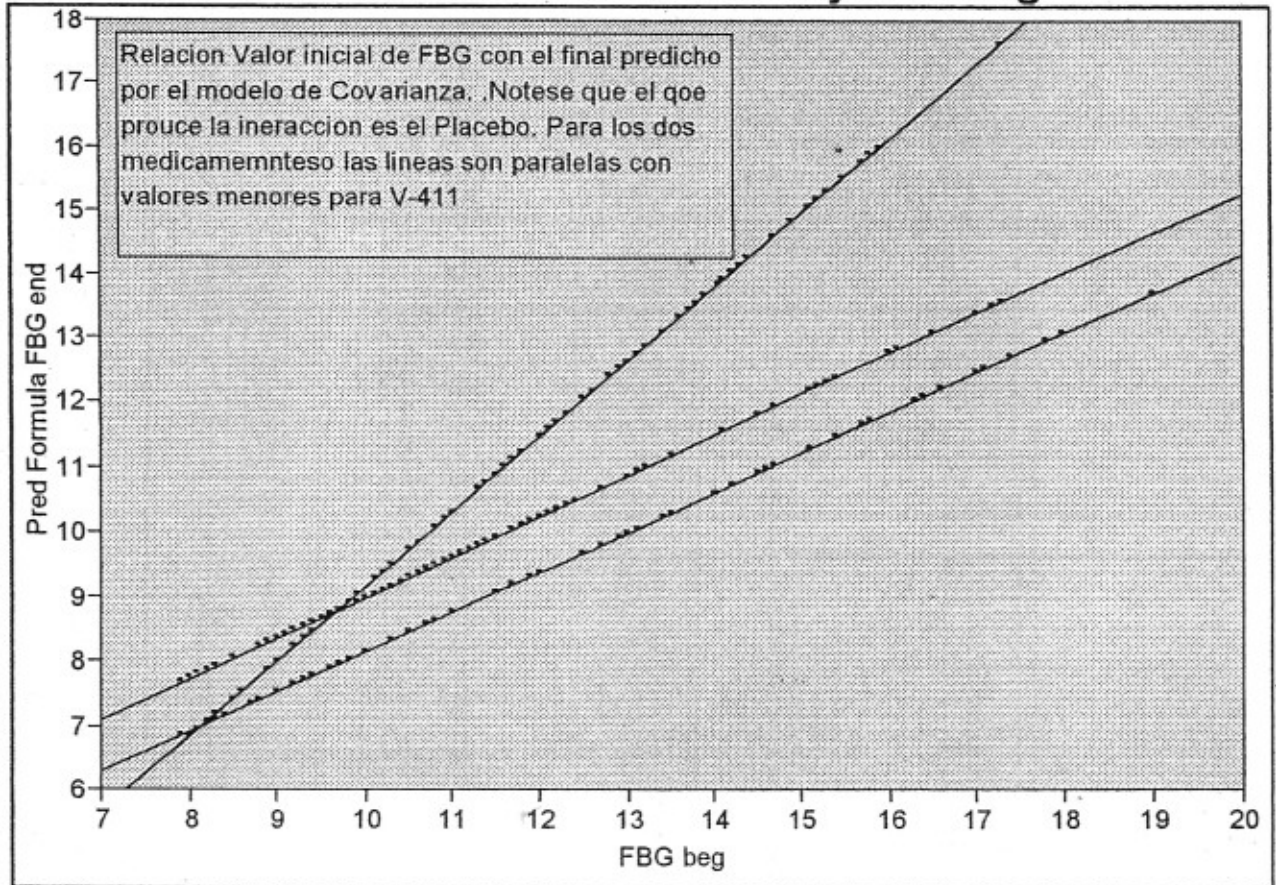
———Linear Fit Treatment=="Glibencamide
———Linear Fit Treatment=="Placebo"
———Linear Fit Treatment=="V_411"

Linear Fit Treatment=="Glibencamide"
Pred Formula FBG end = 2.7014709 + 0.6285861 FBG beg

Linear Fit Treatment=="Placebo"
Pred Formula FBG end = -2.428969 + 1.1584424 FBG beg

Linear Fit Treatment=="V_411"
Pred Formula FBG end = 1.9816332 + 0.616051 FBG beg

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Response 2hgtt end

Whole Model

Summary of Fit

RSquare	0.787731
RSquare Adj	0.784228
Root Mean Square Error	1.943915
Mean of Response	14.75764
Observations (or Sum Wgts)	309

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	5	4249.0214	849.804	224.8870
Error	303	1144.9782	3.779	Prob > F
C. Total	308	5393.9996		<.0001

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Pr
Intercept	1.8455137	0.471819	3.91	0.
Treatment[Glibencamide]	-0.056221	0.152024	-0.37	0.
Treatment[Placebo]	1.3099021	0.157216	8.33	<.
2hrgtt beg	0.7258947	0.026076	27.84	<.
(2hrgtt beg-17.5091)*Treatment[Glibencamide]	-0.115401	0.040255	-2.87	0.
(2hrgtt beg-17.5091)*Treatment[Placebo]	0.0635355	0.031526	2.02	0.

Effect Tests

Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
Treatment	2	2	285.2433	37.7425	<.0001
2hrgtt beg	1	1	2928.2432	774.9123	<.0001
2hrgtt beg*Treatment	2	2	33.5026	4.4330	0.0127

Press
1221.4795425