Statistical Analysis Report for A Placebo-Controlled Clinical Trial Evaluating the Effects of Medical Treatment on Patients with Alzheimer's Disease

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Contents

1 Introduction

This document comprises the statistical analysis report for a placebo-controlled clinical trial evaluating the effect of a medical treatment on patients with Alzheimer's disease.

This report contains a brief description of the statistical methods used for analysis. It presents results in the form of summary tables, graphs, and statistical analyses, with interpretations.

2 Objectives and Methods

2.1 Objectives

The objective of this clinical trial is to study the effects of a medical treatment on patients with Alzheimer's disease (AD). Two levels of treatment doses (High and Low) were given to randomized patients, in addition to a placebo treatment.

The severity of Alzheimer's disease is measured by ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale). It consists of 11 tasks measuring the disturbances of memory, language, praxis, attention and other cognitive abilities which are often referred to as the core symptoms of AD. A total score is calculated, ranging from $0-70$, with higher scores (≥ 18) indicating greater cognitive impairment.

Hence this statistical analysis focuses on the relationship between the medical treatment and ADAS-cog measurements.

2.2 Data Management Methods

The original data set was a comma separated value (csv) file. Each line of data corresponds to a patient number, the received treatment, and 7 bi-weekly ADAS-cog measurements starting from week 0 (Baseline) to week 12 (Endpoint). There were no missing values of baseline ADAS-cog measurements, however, there were some missing values at subsequent times of observation.

The original data set included measurements for a total number of 80 subjects. 90%

of the data (72 subjects) were selected randomly to perform subsequent analyses.

The original csv file was read into SAS. Random data selection and subsequent analyses were carried out in SAS. The original wide form of data is transformed into long form to fit statistical models. The results of the analyses (tables, graphs and statistical analyses) were transferred from SAS into this statistical report.

2.3 Statistical Methods

Standard acceptable statistical procedures were performed, with $p < 0.05$ being selected as the level of significance. The statistical methodology is described in detail below.

2.3.1 Handling of Missing Data

Two methods are used to handle missing data.

1. Last Observation Carried Forward (LOCF).

   For each subject, most recent available measurement is substituted for the missing value.

2. Baseline Observation Carried Forward (BOCF).

   For each subject, baseline measurement is substituted for the missing value.

2.3.2 Efficacy Analysis

Two approaches are used to analyze the data.

1. Endpoint Analysis. For each way (LOCF or BOCF) missing data is handled, subsequent analyses apply two statistical methods.

   (a) Using the last ADAS-cog measurement of each subject as dependent variable and treatment as factor, Analysis of Variance (ANOVA) is performed to test the hypothesis that the mean of last ADAS-cog measurements across three different treatments are equal.

   (b) For each subject, calculate the change from baseline to last measurement (week 12$-$week 0). Using the change as dependent variable,

baseline measurement as covariate and treatment as factor, Analysis of Covariance (ANCOVA) is performed to test the hypothesis that the mean of change in ADAS-cog measurements across three different treatments are equal after adjusting for the baseline measurements.

2. Longitudinal Analysis.

   Missing data need not be handled for longitudinal analysis since random intercept and random intercept and slope models utilize all the available data for analysis.

   Box-plot, line plot and covariance matrix scatter plot are used to examine raw data and possible correlation structure.

   Based on observation of the previous graphs, time has both random effect and quadratic fixed effect, therfore random intercept and slope model is applied for subsequent analyses. Possible interaction between treatment and time is examined. At last, time is considered as a factor and fit into a two-way ANOVA model.

3 Results and Conclusions

3.1 Preliminary Examination of Data

Box-plot of raw data (Figure 1) shows there is a trend of ADAS-cog measurements increasing over time regardless of treatment. There are some differences between the mean of ADAS-cog measurements of each treatment group suggesting the effectiveness of treatment to some degree, however further analysis is needed to determine whether the differences are statistically significant. There are several outliers of ADAS-cog measurements in placebo group, and two outliers in high dose group, suggesting the random effect of each individual.

Line plot of each subject (Figure 2) shows ADAS-cog measurements increase and then decrease over time across all treatments with different location of peaks, which suggests a fixed effect of quadratic time and possibly an interaction between time and treatment.

Scatter plot matrix of measurement covariance (Figure A.3.3,A.3.4,A.3.5) indicates that the correlations of pairs of measurements made at different times differ, hence a random slope and intercept model should be used for longitudinal analysis.

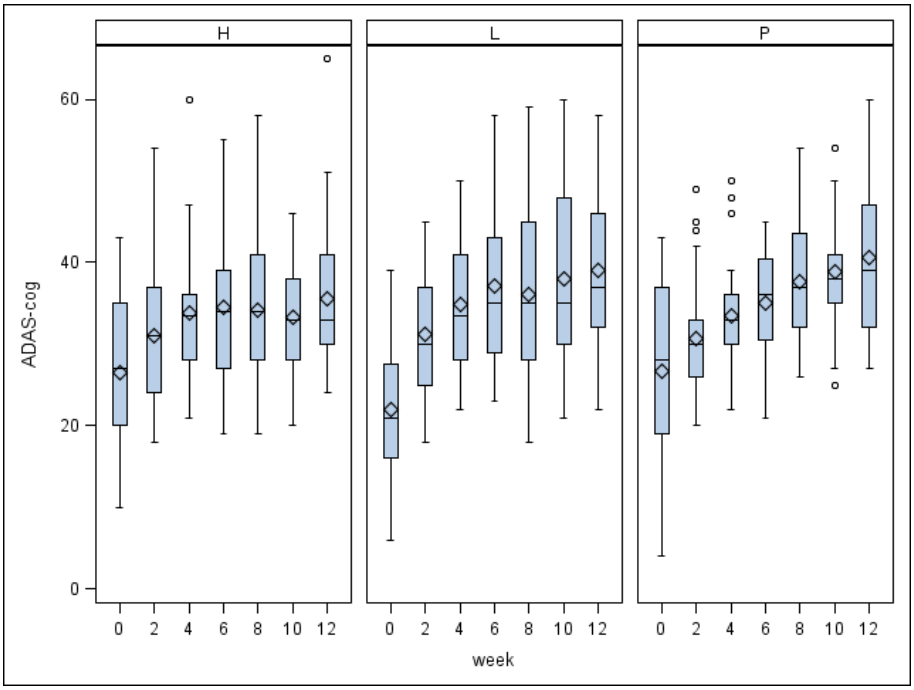

Figure 1: Boxplot

3.2 Endpoint Analysis

Using data set obtained by handling missing values by LOCF, perform ANOVA. Results are shown in Listing A.2.1, corresponding diagnostic plots are shown in Figure A.3.6.

Source	DF	Type I SS	Mean Square	F Value	Pr > F
trt	2	334.9420531	167.4710266	1.86	0.1632

Source	DF	Type III SS	Mean Square	F Value	Pr > F
trt	2	334.9420531	167.4710266	1.86	0.1632

Comparisons significant at the 0.05 level are indicated by ***.

trt Comparison	Difference Between Means	Simultaneous 95% Confidence Limits	
Placebo - Low	1.727	-4.767	8.220
Placebo - High	5.212	-1.353	11.777
Low - Placebo	-1.727	-8.220	4.767
Low - High	3.486	-3.145	10.116
High - Placebo	-5.212	-11.777	1.353
High - Low	-3.486	-10.116	3.145

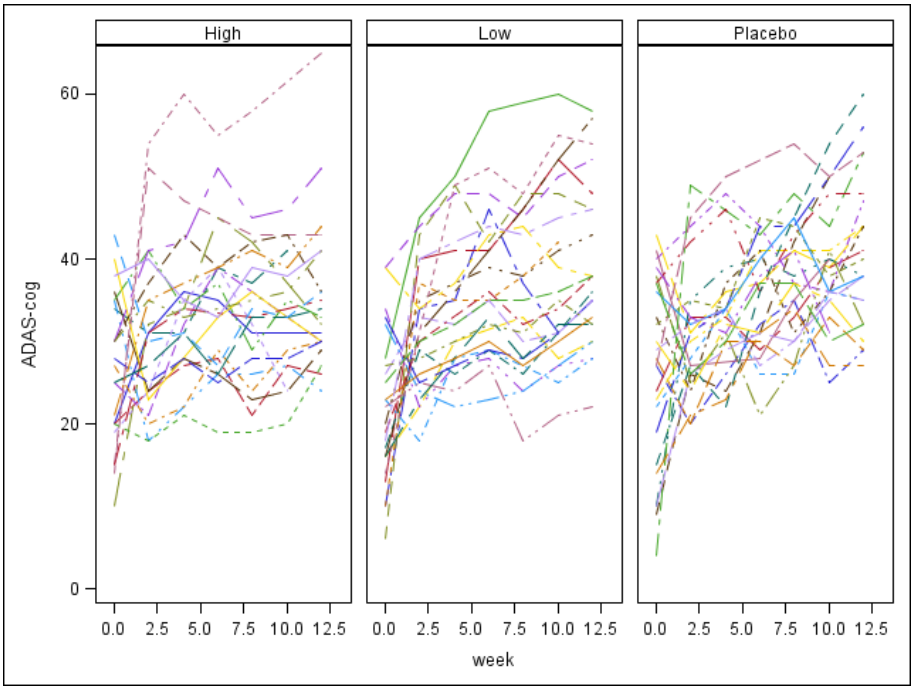

Figure 2: Line Plot

The p-value fortreatment is larger than 0.05 therefore it does not reject the hypothesis that the mean of last measurements across all treatments are equal. Means of placebo group is higher than both low dose group and high dose group, however the 95% confidence interval for each difference between means contains 0 therefore the differences between means are not statistically significant. The conclusion of this analysis is that the treatment is not effective in reducing AD symptoms.

Normal quantile plot of residuals shows there is some departure from normality.

ANCOVA is then performed using change as dependent variable, treatment as factor and baseline measurement as covariate. Results are shown in Listing A.2.2, corresponding diagnostic plots are shown in Figure A.3.7, A.3.8.

Source	DF	Type I SS	Mean Square	F Value	Pr > F
trt	2	782.666763	391.333382	4.48	0.0149
week0	1	9782.007661	9782.007661	111.99	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
trt	2	329.721769	164.860884	1.89	0.1593
week0	1	9782.007661	9782.007661	111.99	<.0001

Least Squares Means for Effect trt

i	j	Difference Between Means	Simultaneous 95% Confidence Limits for LSMean(i)-LSMean(j)	
1	2	-2.570159	-9.223126	4.082808
1	3	-5.243631	-11.713997	1.226735
2	3	-2.673473	-9.202399	3.855454

The p-value fo treatment using Type I SS is less than 0.05, however when using Type III SS the p-value is greater than 0.05 which does not provide a consistent conclusion. The least squares means for treatment effect table shows the 95% confidence intervals for difference between means include 0 for all comparisons which indicates the differences are not statistically significant. Therefore the conclusion is consistent with previous analysis, that there is not enough evidence to claim the treatment is effective.

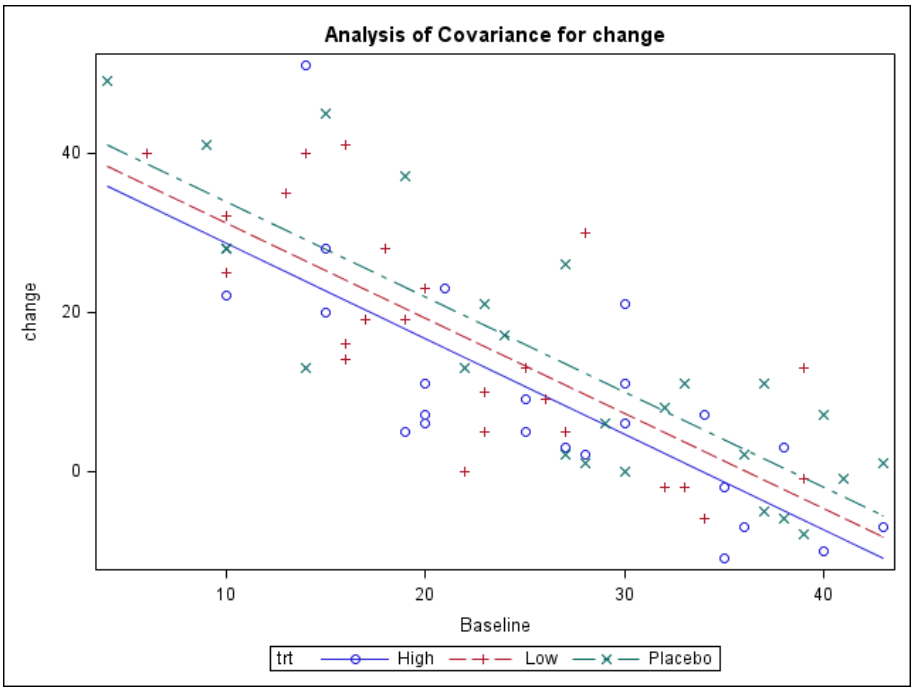

Figure 3: ANCOVA Plot (LOCF)

Diagnostic plots show the model satisfies the assumptions of ANCOVA except there is a slight departure from normality in the residuals. Figure 3 shows parellel regression line of change on baseline, which confirms the same slope assumption for ANCOVA.

Same analysis procedures are performed on the data set processed using BOCF and conclusions are unchanged. Results and corresponding diagnostic plots are

shown in Listing A.2.3, A.2.4, Figure A.3.9, A.3.10, A.3.11.

3.3 Longitudinal Analysis

Random intercept and slope model is used to fit the data. The dependent variable is ADAS-cog measurement, fixed effects include treatment, quadratic time and the interaction between treatment and time, and there is random intercept and random time effect. Results are shown in Listing A.2.5. Predicted values, normal quantile plot of residuals and plot of residuals against predicted values are given in Figure A.3.12, A.3.13, A.3.14.

Solution for Fixed Effects

Effect	Treatment	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		36.4558	1.3493	69	27.02	<.0001
trt	High	-1.8621	1.9026	69	-0.98	0.3311
trt	Low	-0.9713	1.8824	69	-0.52	0.6075
trt	Placebo	0	.	.	.	.
week		1.0958	0.1915	407	5.72	<.0001
week*week		-0.1064	0.01853	407	-5.74	<.0001
week*trt	High	-0.4805	0.2763	407	-1.74	0.0828
week*trt	Low	0.05979	0.2735	407	0.22	0.8270
week*trt	Placebo	0	.	.	.	.

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
trt	2	69	0.48	0.6208
week	1	407	71.72	<.0001
week*week	1	407	32.96	<.0001
week*trt	2	407	2.25	0.1068

The p-value associated with treatment is greater than 0.05, the p-value associated with the interaction of treatment and time variable is also greater than 0.05, indicating there is not enough evidence to indicate that treatment is effective. However p-values are less than 0.05 for both linear and quadratic terms of time, indicating time has a significant effect on AD.

As a comparison, model assuming independence of repeated measurements is fitted and results are shown in Listing A.2.6, corresponding diagnostic plots are shown in Figure A.3.15, A.3.16.

Again treatment and its interaction do not have a significant effect on ADAS-cog whereas time does have a significant effect on ADAS-cog. Given different correlation structure, the conclusion is consistent. Diagnostic plot Figure A.3.16

shows there is some degree of interaction between treatment and time.

When time is considered as a class variable, it can be seen as a factor, hence two-way ANOVA is appropriate for subsequent analysis. The model includes ADAS-cog as dependent variable, treatment and time as factors. Results are shown in Listing A.2.7, corresponding diagnostic plots are shown in Figure A.3.17 and A.3.18.

Source	DF	Type I SS	Mean Square	F Value	Pr > F
trt	2	309.188676	154.594338	1.98	0.1387
week	6	8686.901266	1447.816878	18.58	<.0001
trt*week	12	961.490008	80.124167	1.03	0.4211

Source	DF	Type III SS	Mean Square	F Value	Pr > F
trt	2	322.039001	161.019500	2.07	0.1278
week	6	8589.804122	1431.634020	18.37	<.0001
trt*week	12	961.490008	80.124167	1.03	0.4211

The p-values associated with treatment and its interaction with time are greater than 0.05, the p-value associated with time is less than 0.05. Previous conclusions still hold. Time has a significant effect on Alzheimer's disease.

Figure 4 shows residuals have constant variance and approximately normal distribution, which satisfies the assumptions for ANOVA.

In conclusion, statistical analysis shows the medical treatment does not have a significant effect on Alzheimer's disease. Time has a significant effect on Alzheimer's disease as it worsens over time.

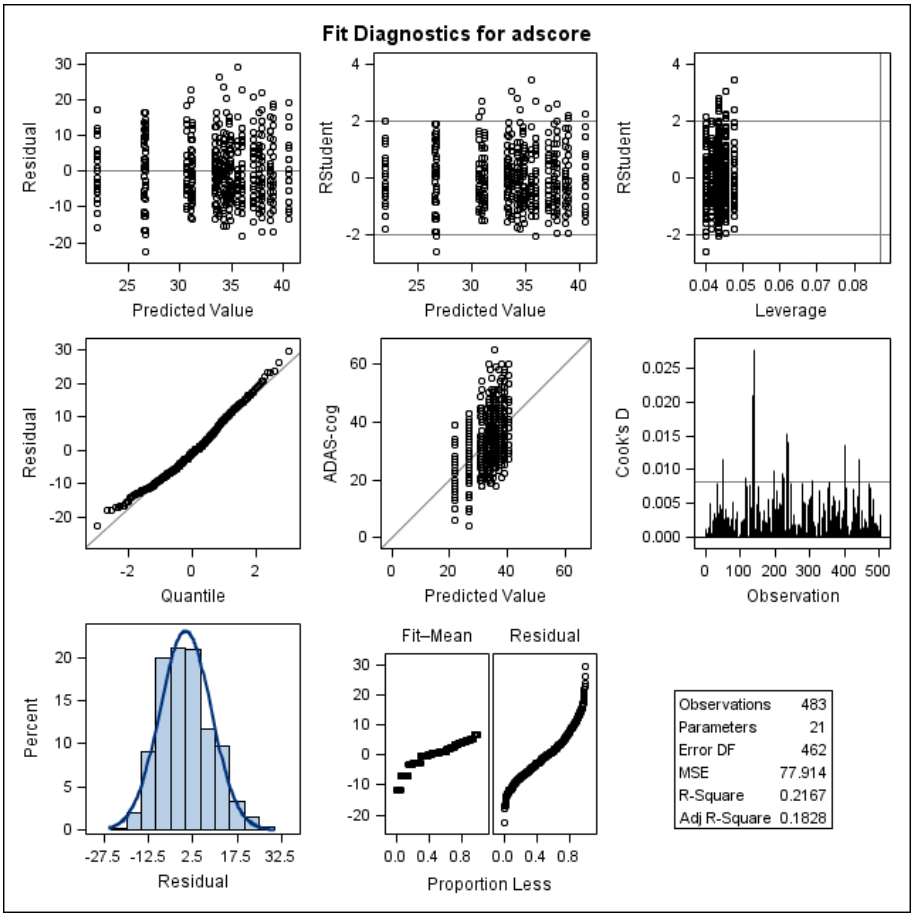

Figure 4: Two-way ANOVA Diagnostic Plot

A Appendix

A.1 SAS Code

```
options nodate nonumber ls=75;

/* Import data */
PROC IMPORT OUT= WORK.ad
            DATAFILE= "C:\Users\Ivy\Documents\ad.csv"
            DBMS=CSV REPLACE;
     GETNAMES=YES;
     DATAROW=2;
RUN;

/* Treatment format */
proc format;
  value $trt 'H'='High' 'L'='Low' 'P'='Placebo';
run;
```

```
/* Randomly select 90% of data */
data sample;
    set ad nobs=total;
    if _N_ = 1 then n=total;
    retain k 72 n;
    random = ranuni(2363);
    propn = k/n;
    if random le propn then
       do;
         output;
         k=k-1;
       end;
    n=n-1;
    if k=0 then stop;
  drop n k random propn;
  label trt='Treatment';
  format trt $trt.;
run;

/* Transform data into long form */
data samplel;
  set sample;
  array ad {*} ad0 ad2 ad4 ad6 ad8 ad10 ad12;
  array w{7} (0 2 4 6 8 10 12);
  do i = 1 to 7;
    adscore=ad{i};
    week=w{i};
  output;
  end;
  label adscore='ADAS-cog';
  keep trt pat week adscore;
run;

/* Boxplot */
proc sgpanel data=samplel;
  panelby trt /columns=3 spacing=10 novarname;
  vbox adscore/category=week;
run;

/* Line plot */
proc sgpanel data=samplel noautolegend;
  panelby trt /columns=3 spacing=10 novarname;
  series y=adscore x=week /group=pat;
run;

/* Covariance matrix */
proc sgscatter data=sample;
  matrix ad0 ad2 ad4 ad6 ad8 ad10 ad12;
  by trt notsorted;
run;

/* Handle missing values by LOCF */
data locf;
  retain adscore;
  set samplel (rename=(adscore=adscorem));
  if adscorem^=. then adscore=adscorem;
  drop adscorem;
  label adscore='ADAS-cog';
run;

/* Transform locf into wide form */
```

```
proc sort data=locf;
  by trt pat;
run;
proc transpose data=locf out=locfw(keep=trt pat week0-week12) prefix=week;
  by trt pat;
  id week;
  var adscore;
run;

/* Compute change from baseline to endpoint */
data locfw1;
  set locfw;
  change=week12-week0;
  label week0='Baseline';
  label week12='Endpoint';
run;

/* ANOVA: last ADAS-cog measurement as dependent variable, treatment as factor */
ods graphics on;
proc glm data=locfw1 plots=diagnostics;
  class trt;
  model week12=trt;
  means trt /tukey cldiff;
run;
ods graphics off;

/* ANCOVA: change as dependent variable, treatment as factor, baseline
    measurement as covariate */
ods graphics on;
proc glm data=locfw1 plots=diagnostics;
  class trt;
  model change=trt week0;
  lsmeans trt /adjust=tukey cl;
run;
ods graphics off;

/* Handle missing values by BOCF */
proc sort data=samplel;
  by trt pat week;
run;
data bocf;
  retain base;
  set samplel;
  by trt pat week;
  if first.pat=1 then base=adscore;
  if adscore=. then adscore=base;
  drop base;
run;

/* Transpose bocf into wide form */
proc sort data=bocf;
  by trt pat;
run;
proc transpose data=bocf out=bocfw(keep=trt pat week0-week12) prefix=week;
  by trt pat;
  id week;
  var adscore;
run;

/* Compute change from baseline to endpoint */
data bocfw1;
  set bocfw;
```

```
  change=week12-week0;
  label week0='Baseline';
  label week12='Endpoint';
run;

/* ANOVA: last ADAS-cog measurement as dependent variable, treatment as factor */
ods graphics on;
proc glm data=bocfw1 plots=diagnostics;
  class trt;
  model week12=trt;
  means trt /tukey cldiff;
run;
ods graphics off;

/* ANCOVA: change as dependent variable, treatment as factor, baseline
    measurement as covariate */
ods graphics on;
proc glm data=bocfw1 plots=diagnostics;
  class trt;
  model change=trt week0;
  lsmeans trt /adjust=tukey cl;
run;
ods graphics off;

/* Standardize time */
proc stdize data=samplel out=samplels method=mean;
  var week;
run;

/* Random intercept and slope model: fixed effect includes treatment,
quadratic time, interaction between treatment and time; random intercept and
    random time effect */
proc mixed data=samplels covtest noclprint;
  class trt pat;
  model adscore=trt week|week trt*week/s ddfm=bw;
  random int week /subject=pat type=un;
run;

/* Obtain conditional predicted value and residuals*/
proc mixed data=samplels covtest noclprint;
  class trt pat;
  model adscore=trt week|week trt*week/s ddfm=bw outp=mixout;
  random int week /subject=pat type=un;
run;

/* Predicted value plotted against time */
proc sgpanel data=mixout noautolegend;
  panelby trt /columns=3 spacing=10 novarname;
  series y=pred x=week /group=pat;
run;

/* Residuals plotted against predicted value and time */
proc sgscatter data=mixout;
  plot resid *(pred week)/group=trt loess=(clm);
run;

/* Normal quantile plot of residuals */
proc univariate data=mixout noprint;
  var resid;
  probplot resid /normal(mu=est sigma=est);
run;
```

```
/* Assume independence in repeated measurements */
ods graphics on;
proc glm data=samplels plots=diagnostics;
  class trt;
  model adscore=trt week|week trt*week/solution;
run;
ods graphics off;

/* Include time as a factor */
ods graphics on;
proc glm data=samplels plots=diagnostics;
  class trt week;
  model adscore=trt|week ;
  lsmeans trt week/adjust=tukey cl;
run;
ods graphics off;
```

A.2 Tables

Listing A.2.1: ANOVA using Endpoint (missing values handled by LOCF)

```
                            The SAS System

                          The GLM Procedure

                       Class Level Information

                Class         Levels    Values

                trt                3    High Low Placebo


                 Number of Observations Read          72
                 Number of Observations Used          72
                            The SAS System

                          The GLM Procedure

Dependent Variable: week12   Endpoint

                                    Sum of
 Source                     DF       Squares   Mean Square  F Value  Pr > F

 Model                       2    334.942053    167.471027     1.86  0.1632

 Error                      69   6208.710725     89.981315

 Corrected Total            71   6543.652778


            R-Square     Coeff Var      Root MSE    week12 Mean

            0.051186      24.75466      9.485848       38.31944


 Source                     DF     Type I SS   Mean Square  F Value  Pr > F

 trt                         2   334.9420531   167.4710266     1.86  0.1632
```

Source	DF	Type III SS	Mean Square	F Value	Pr > F
trt	2	334.9420531	167.4710266	1.86	0.1632

The SAS System

The GLM Procedure

Tukey's Studentized Range (HSD) Test for week12

NOTE: This test controls the Type I experimentwise error rate.

Alpha	0.05
Error Degrees of Freedom	69
Error Mean Square	89.98131
Critical Value of Studentized Range	3.38748

Comparisons significant at the 0.05 level are indicated by ***.

trt Comparison	Difference Between Means	Simultaneous 95% Confidence Limits	
Placebo - Low	1.727	-4.767	8.220
Placebo - High	5.212	-1.353	11.777
Low - Placebo	-1.727	-8.220	4.767
Low - High	3.486	-3.145	10.116
High - Placebo	-5.212	-11.777	1.353
High - Low	-3.486	-10.116	3.145

Listing A.2.2: ANCOVA using Change with baseline as covariate (missing values handled by LOCF)

The SAS System

The GLM Procedure

Class Level Information

Class	Levels	Values
trt	3	High Low Placebo

Number of Observations Read	72
Number of Observations Used	72

The SAS System

The GLM Procedure

Dependent Variable: change

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	10564.67442	3521.55814	40.32	<.0001
Error	68	5939.77002	87.34956		

Corrected Total	71	16504.44444	

R-Square	Coeff Var	Root MSE	change Mean
0.640111	70.38903	9.346099	13.27778

Source	DF	Type I SS	Mean Square	F Value	Pr > F
trt	2	782.666763	391.333382	4.48	0.0149
week0	1	9782.007661	9782.007661	111.99	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
trt	2	329.721769	164.860884	1.89	0.1593
week0	1	9782.007661	9782.007661	111.99	<.0001

The GLM Procedure
Least Squares Means
Adjustment for Multiple Comparisons: Tukey-Kramer

trt	change LSMEAN	LSMEAN Number
High	10.6003529	1
Low	13.1705116	2
Placebo	15.8439842	3

Least Squares Means for effect trt
Pr > |t| for H0: LSMean(i)=LSMean(j)

Dependent Variable: change

i/j	1	2	3
1		0.6261	0.1349
2	0.6261		0.5912
3	0.1349	0.5912	

trt	change LSMEAN	95% Confidence Limits	
High	10.600353	6.697225	14.503481
Low	13.170512	9.298643	17.042380
Placebo	15.843984	12.095674	19.592294

Least Squares Means for Effect trt

i	j	Difference Between Means	Simultaneous 95% Confidence Limits for LSMean(i)-LSMean(j)	
1	2	-2.570159	-9.223126	4.082808
1	3	-5.243631	-11.713997	1.226735
2	3	-2.673473	-9.202399	3.855454

Listing A.2.3: ANOVA using Endpoint (missing values handled by BOCF)

```
                              The SAS System

                            The GLM Procedure

                         Class Level Information

                 Class         Levels    Values

                 trt                3    High Low Placebo


                  Number of Observations Read          72
                  Number of Observations Used          72
                              The SAS System

                            The GLM Procedure

Dependent Variable: week12   Endpoint

                                      Sum of
 Source                     DF       Squares   Mean Square  F Value  Pr > F

 Model                       2    240.697319    120.348659     1.06  0.3525

 Error                      69   7844.177681    113.683735

 Corrected Total            71   8084.875000


            R-Square     Coeff Var      Root MSE    week12 Mean

            0.029771      28.59153      10.66226       37.29167


 Source                     DF     Type I SS   Mean Square  F Value  Pr > F

 trt                         2   240.6973188   120.3486594     1.06  0.3525


 Source                     DF   Type III SS   Mean Square  F Value  Pr > F

 trt                         2   240.6973188   120.3486594     1.06  0.3525
                              The SAS System

                            The GLM Procedure

              Tukey's Studentized Range (HSD) Test for week12

      NOTE: This test controls the Type I experimentwise error rate.


                Alpha                                      0.05
                Error Degrees of Freedom                     69
                Error Mean Square                       113.6837
                Critical Value of Studentized Range     3.38748


      Comparisons significant at the 0.05 level are indicated by ***.
```

trt Comparison	Difference Between Means	Simultaneous 95% Confidence Limits	
Placebo - Low	1.697	-5.602	8.995
Placebo - High	4.454	-2.925	11.833
Low - Placebo	-1.697	-8.995	5.602
Low - High	2.757	-4.695	10.210
High - Placebo	-4.454	-11.833	2.925
High - Low	-2.757	-10.210	4.695

Listing A.2.4: ANCOVA using Change with baseline as covariate (missing values handled by BOCF)

The SAS System

The GLM Procedure

Class Level Information

Class	Levels	Values
trt	3	High Low Placebo

Number of Observations Read	72
Number of Observations Used	72

The SAS System

The GLM Procedure

Dependent Variable: change

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	7703.67340	2567.89113	22.27	<.0001
Error	68	7841.82660	115.32098		
Corrected Total	71	15545.50000			

R-Square	Coeff Var	Root MSE	change Mean
0.495556	87.66335	10.73876	12.25000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
trt	2	641.297101	320.648551	2.78	0.0691
week0	1	7062.376302	7062.376302	61.24	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
trt	2	239.868677	119.934338	1.04	0.3590
week0	1	7062.376302	7062.376302	61.24	<.0001

The SAS System

The GLM Procedure

Least Squares Means
Adjustment for Multiple Comparisons: Tukey-Kramer

trt	change LSMEAN	LSMEAN Number
High	9.8119270	1
Low	12.4835894	2
Placebo	14.2687813	3

Least Squares Means for effect trt
Pr > |t| for H0: LSMean(i)=LSMean(j)

Dependent Variable: change

i/j	1	2	3
1		0.6812	0.3282
2	0.6812		0.8364
3	0.3282	0.8364	

trt	change LSMEAN	95% Confidence Limits	
High	9.811927	5.327194	14.296660
Low	12.483589	8.034774	16.932405
Placebo	14.268781	9.961936	18.575627

Least Squares Means for Effect trt

i	j	Difference Between Means	Simultaneous 95% Confidence Limits for LSMean(i)-LSMean(j)	
1	2	-2.671662	-10.315988	4.972663
1	3	-4.456854	-11.891369	2.977661
2	3	-1.785192	-9.286994	5.716610

Listing A.2.5: Mix model

The SAS System

The Mixed Procedure

Model Information

Data Set	WORK.SAMPLELS
Dependent Variable	adscore
Covariance Structure	Unstructured
Subject Effect	pat
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Between-Within

Dimensions

Covariance Parameters	4
Columns in X	9
Columns in Z Per Subject	2
Subjects	72
Max Obs Per Subject	7

Number of Observations

Number of Observations Read	504
Number of Observations Used	483
Number of Observations Not Used	21

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	3470.21454512	
1	2	3248.44467836	0.00000320
2	1	3248.44083027	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Subject	Estimate	Standard Error	Z Value	Pr Z
UN(1,1)	pat	38.7180	7.3958	5.24	<.0001
UN(2,1)	pat	3.0445	0.8430	3.61	0.0003
UN(2,2)	pat	0.6221	0.1597	3.90	<.0001
Residual		30.8868	2.3823	12.96	<.0001

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	3248.4
AIC (smaller is better)	3256.4
AICC (smaller is better)	3256.5
BIC (smaller is better)	3265.5

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	221.77	<.0001

Solution for Fixed Effects

Effect	Treatment	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		36.4558	1.3493	69	27.02	<.0001
trt	High	-1.8621	1.9026	69	-0.98	0.3311
trt	Low	-0.9713	1.8824	69	-0.52	0.6075

trt	Placebo	0	.	.	.	.
week		1.0958	0.1915	407	5.72	<.0001
week*week		-0.1064	0.01853	407	-5.74	<.0001
week*trt	High	-0.4805	0.2763	407	-1.74	0.0828
week*trt	Low	0.05979	0.2735	407	0.22	0.8270
week*trt	Placebo	0	.	.	.	.

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
trt	2	69	0.48	0.6208
week	1	407	71.72	<.0001
week*week	1	407	32.96	<.0001
week*trt	2	407	2.25	0.1068

Listing A.2.6: Independence model

The SAS System

The GLM Procedure

Class Level Information

Class	Levels	Values
trt	3	High Low Placebo

Number of Observations Read	504
Number of Observations Used	483

The SAS System

The GLM Procedure

Dependent Variable: adscore ADAS-cog

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	6	9186.15300	1531.02550	19.82	<.0001
Error	476	36767.77246	77.24322		
Corrected Total	482	45953.92547			

R-Square	Coeff Var	Root MSE	adscore Mean
0.199899	26.05891	8.788812	33.72671

Source	DF	Type I SS	Mean Square	F Value	Pr > F
trt	2	309.188676	154.594338	2.00	0.1363
week	1	7330.880602	7330.880602	94.91	<.0001
week*week	1	992.975371	992.975371	12.86	0.0004
week*trt	2	553.108355	276.554178	3.58	0.0286

Source	DF	Type III SS	Mean Square	F Value	Pr > F
trt	2	323.556524	161.778262	2.09	0.1243
week	1	7038.009836	7038.009836	91.11	<.0001
week*week	1	990.460920	990.460920	12.82	0.0004
week*trt	2	553.108355	276.554178	3.58	0.0286

Parameter		Estimate		Standard Error	t Value	Pr > |t|
Intercept		36.33917123	B	0.82081934	44.27	<.0001
trt	High	-1.98404680	B	0.97910411	-2.03	0.0433
trt	Low	-0.70798437	B	0.97105319	-0.73	0.4663
trt	Placebo	0.00000000	B	.	.	.
week		1.10259615	B	0.16987010	6.49	<.0001
week*week		-0.10385792		0.02900355	-3.58	0.0004
week*trt	High	-0.52679539	B	0.24485060	-2.15	0.0319
week*trt	Low	0.08413640	B	0.24265115	0.35	0.7289
week*trt	Placebo	0.00000000	B	.	.	.

NOTE: The X'X matrix has been found to be singular, and a generalized inverse was used to solve the normal equations. Terms whose estimates are followed by the letter 'B' are not uniquely estimable.

Listing A.2.7: Two-way ANOVA

The SAS System

The GLM Procedure

Class Level Information

Class	Levels	Values
trt	3	High Low Placebo
week	7	-6 -4 -2 0 2 4 6

Number of Observations Read	504
Number of Observations Used	483

The SAS System

The GLM Procedure

Dependent Variable: adscore ADAS-cog

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	20	9957.57995	497.87900	6.39	<.0001
Error	462	35996.34552	77.91417		
Corrected Total	482	45953.92547			

R-Square	Coeff Var	Root MSE	adscore Mean

```
          0.216686      26.17184      8.826900        33.72671


Source                     DF     Type I SS   Mean Square  F Value  Pr > F

trt                         2    309.188676    154.594338     1.98  0.1387
week                        6   8686.901266   1447.816878    18.58  <.0001
trt*week                   12    961.490008     80.124167     1.03  0.4211


Source                     DF   Type III SS   Mean Square  F Value  Pr > F

trt                         2    322.039001    161.019500     2.07  0.1278
week                        6   8589.804122   1431.634020    18.37  <.0001
trt*week                   12    961.490008     80.124167     1.03  0.4211
                          The SAS System

                        The GLM Procedure
                       Least Squares Means
            Adjustment for Multiple Comparisons: Tukey-Kramer

                               adscore      LSMEAN
                  trt           LSMEAN      Number

                  High       32.7101046           1
                  Low        33.9993883           2
                  Placebo    34.6877386           3


                  Least Squares Means for effect trt
                 Pr > |t| for H0: LSMean(i)=LSMean(j)

                     Dependent Variable: adscore

                i/j              1             2             3

                  1                       0.3985        0.1109
                  2         0.3985                      0.7604
                  3         0.1109        0.7604


                        adscore
               trt       LSMEAN      95% Confidence Limits

               High     32.710105       31.315855    34.104354
               Low      33.999388       32.627544    35.371233
               Placebo  34.687739       33.348103    36.027374


                   Least Squares Means for Effect trt

                      Difference          Simultaneous 95%
                         Between       Confidence Limits for
                i    j     Means        LSMean(i)-LSMean(j)

                1    2  -1.289284       -3.629657     1.051090
                1    3  -1.977634       -4.291142     0.335874
                2    3  -0.688350       -2.982602     1.605901
                          The SAS System

                        The GLM Procedure
                       Least Squares Means
```

Adjustment for Multiple Comparisons: Tukey-Kramer

week	adscore LSMEAN	LSMEAN Number
-6	25.0394686	1
-4	30.9524638	2
-2	34.0079051	3
0	35.5216529	4
2	35.9613527	5
4	36.6922266	6
6	38.4184704	7

Least Squares Means for effect week
Pr > |t| for H0: LSMean(i)=LSMean(j)

Dependent Variable: adscore

i/j	1	2	3	4	5	6	7
1		0.0014	<.0001	<.0001	<.0001	<.0001	<.0001
2	0.0014		0.3962	0.0390	0.0143	0.0025	<.0001
3	<.0001	0.3962		0.9549	0.8543	0.5637	0.0646
4	<.0001	0.0390	0.9549		0.9999	0.9870	0.4878
5	<.0001	0.0143	0.8543	0.9999		0.9990	0.6723
6	<.0001	0.0025	0.5637	0.9870	0.9990		0.9172
7	<.0001	<.0001	0.0646	0.4878	0.6723	0.9172	

week	adscore LSMEAN	95% Confidence Limits	
-6	25.039469	22.994056	27.084881
-4	30.952464	28.892300	33.012628
-2	34.007905	31.888307	36.127503
0	35.521653	33.414896	37.628410
2	35.961353	33.887710	38.034995
4	36.692227	34.616090	38.768364
6	38.418470	36.266465	40.570475

Least Squares Means for Effect week

i	j	Difference Between Means	Simultaneous 95% Confidence Limits for LSMean(i)-LSMean(j)	
1	2	-5.912995	-10.287910	-1.538080
1	3	-8.968437	-13.407360	-4.529513
1	4	-10.482184	-14.907203	-6.057165
1	5	-10.921884	-15.311237	-6.532531

The SAS System

The GLM Procedure
Least Squares Means
Adjustment for Multiple Comparisons: Tukey-Kramer

Least Squares Means for Effect week

Difference Between Means	Simultaneous 95% Confidence Limits for

i	j	Means	LSMean(i)-LSMean(j)	
1	6	-11.652758	-16.044788	-7.260728
1	7	-13.379002	-17.853196	-8.904807
2	3	-3.055441	-7.509830	1.398948
2	4	-4.569189	-9.009722	-0.128656
2	5	-5.008889	-9.413881	-0.603896
2	6	-5.739763	-10.147423	-1.332103
2	7	-7.466007	-11.955545	-2.976468
3	4	-1.513748	-6.017356	2.989861
3	5	-1.953448	-6.422017	2.515122
3	6	-2.684321	-7.155521	1.786878
3	7	-4.410565	-8.962500	0.141370
4	5	-0.439700	-4.894458	4.015058
4	6	-1.170574	-5.627969	3.286822
4	7	-2.896818	-7.435194	1.641559
5	6	-0.730874	-5.152865	3.691117
5	7	-2.457118	-6.960726	2.046491
6	7	-1.726244	-6.232461	2.779974

A.3 Figures

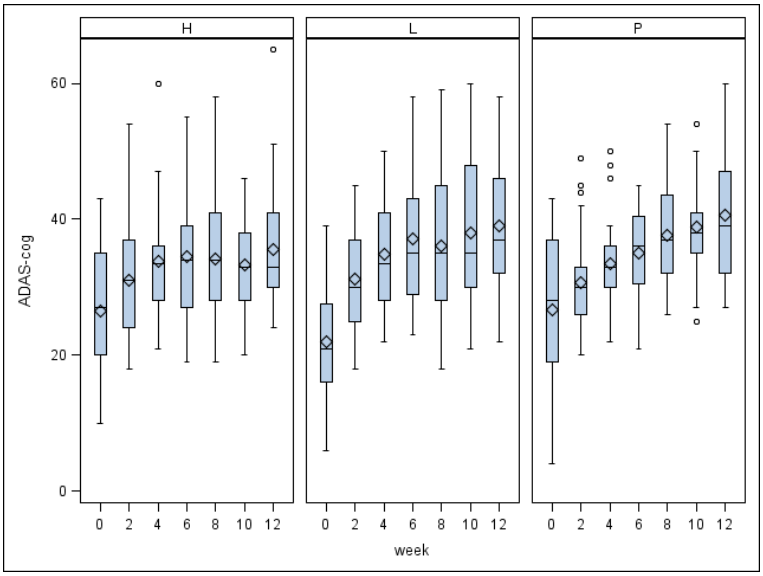

Figure A.3.1: Boxplot

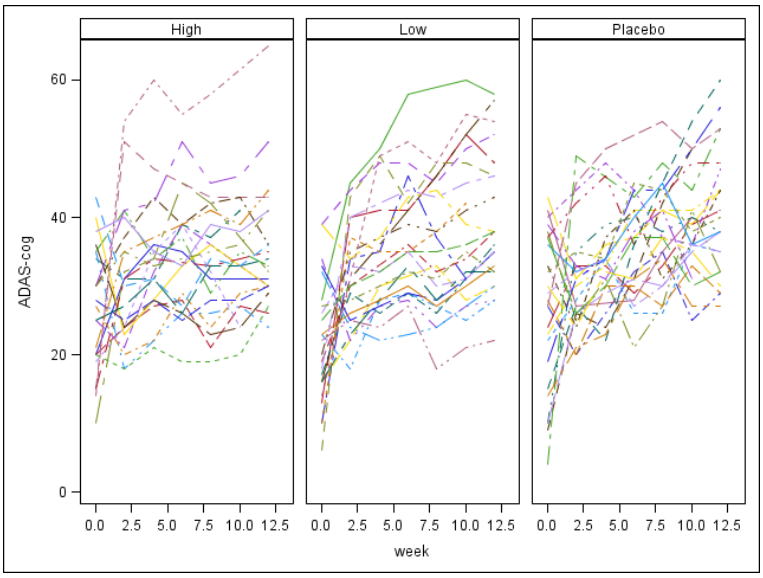

Figure A.3.2: Line Plot

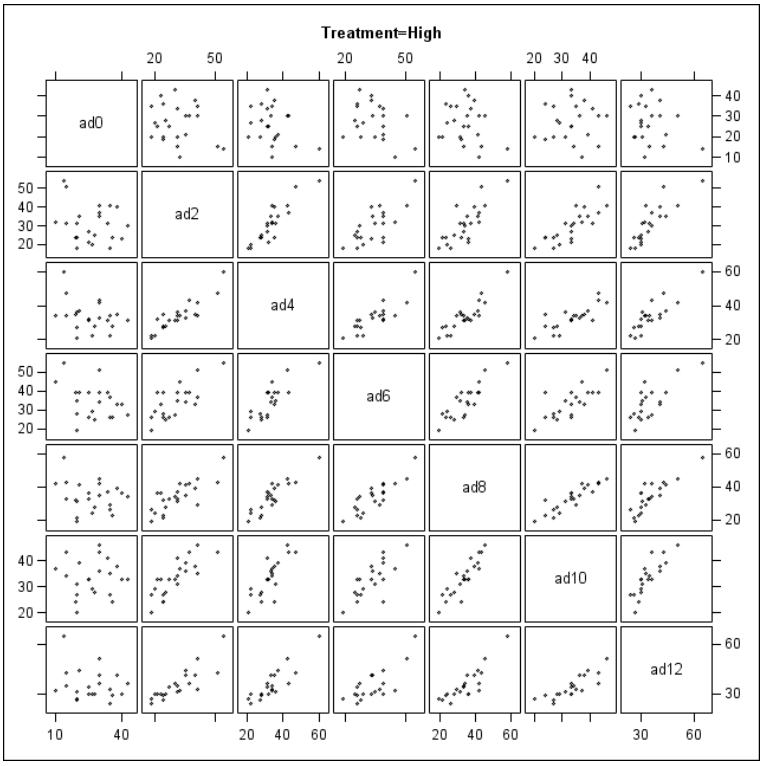

Figure A.3.3: Covariance Matrix High Dose

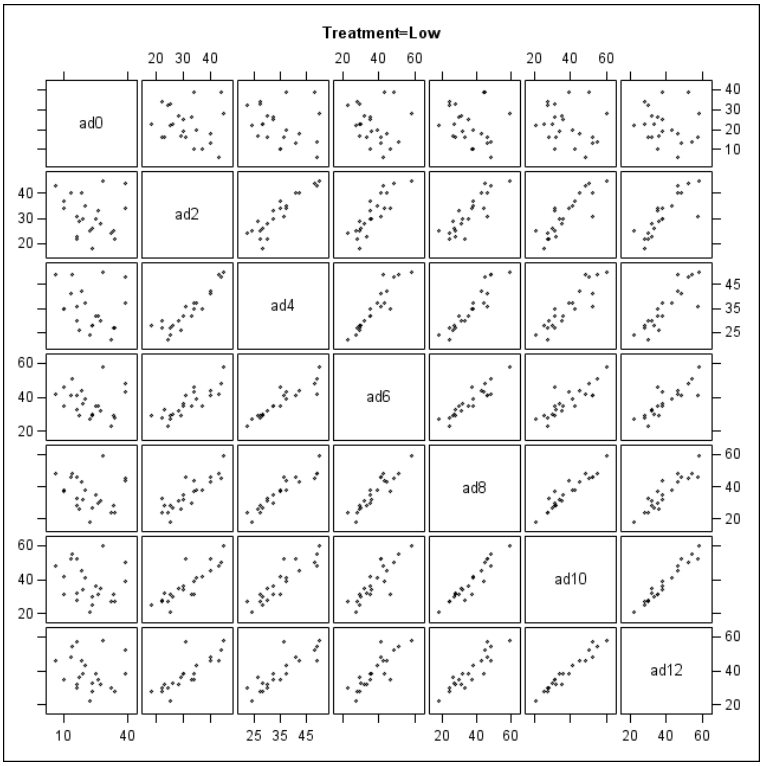

Figure A.3.4: Covariance Matrix Low Dose

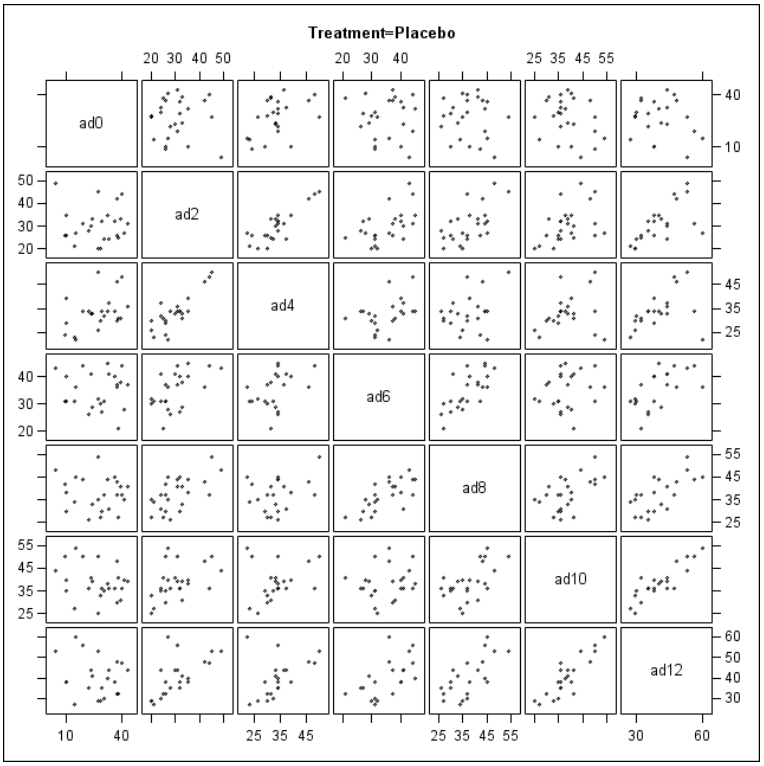

Figure A.3.5: Covariance Matrix Placebo

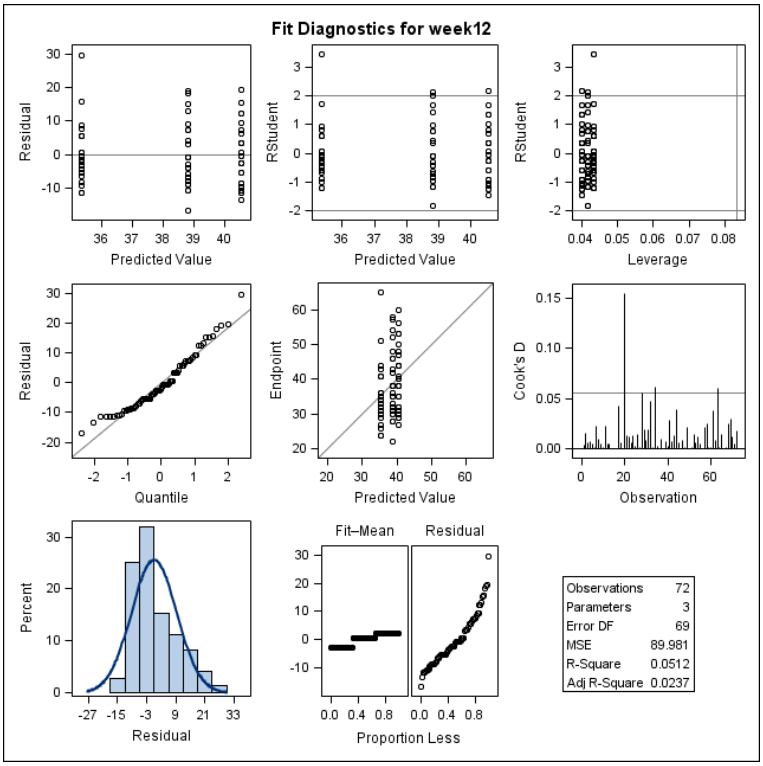

Figure A.3.6: ANOVA Diagnostic Plot (LOCF)

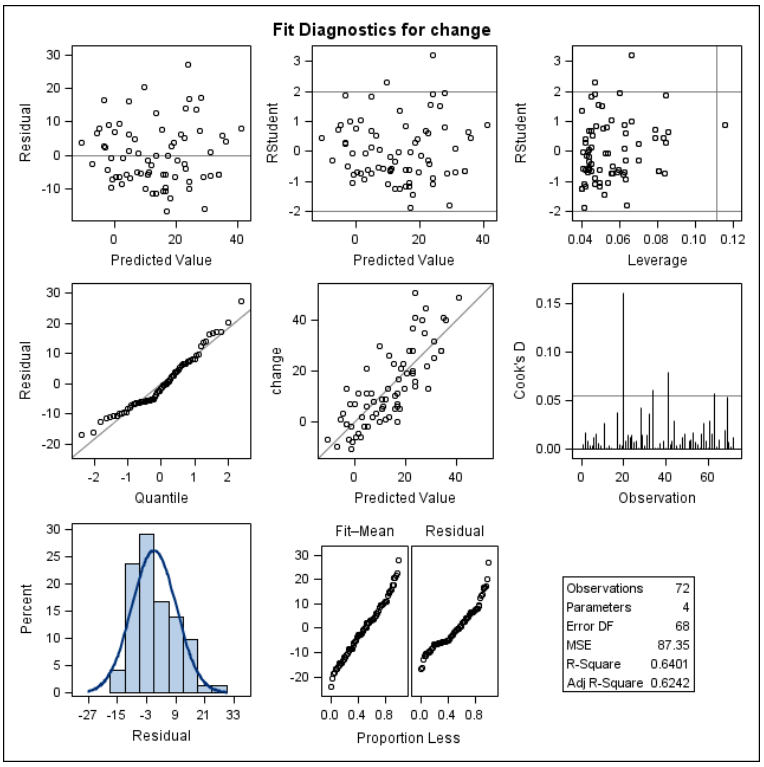

Figure A.3.7: ANCOVA Diagnostic Plot (LOCF)

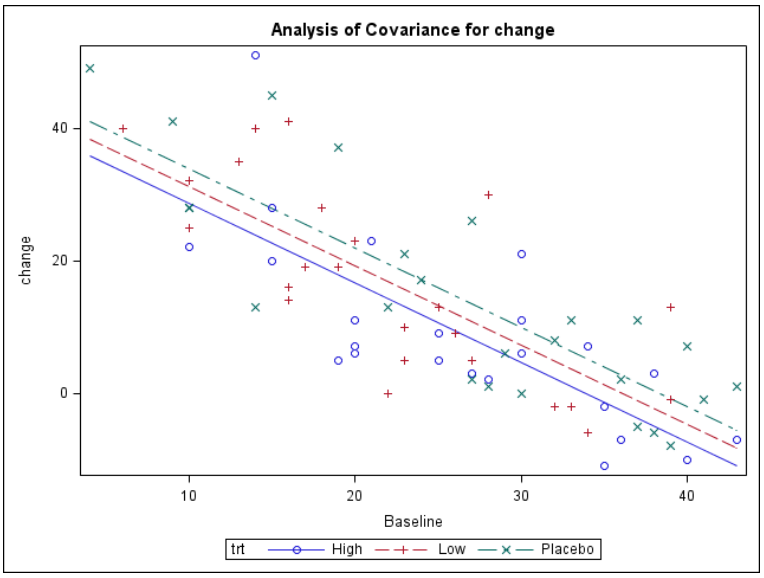

Figure A.3.8: ANCOVA Plot (LOCF)

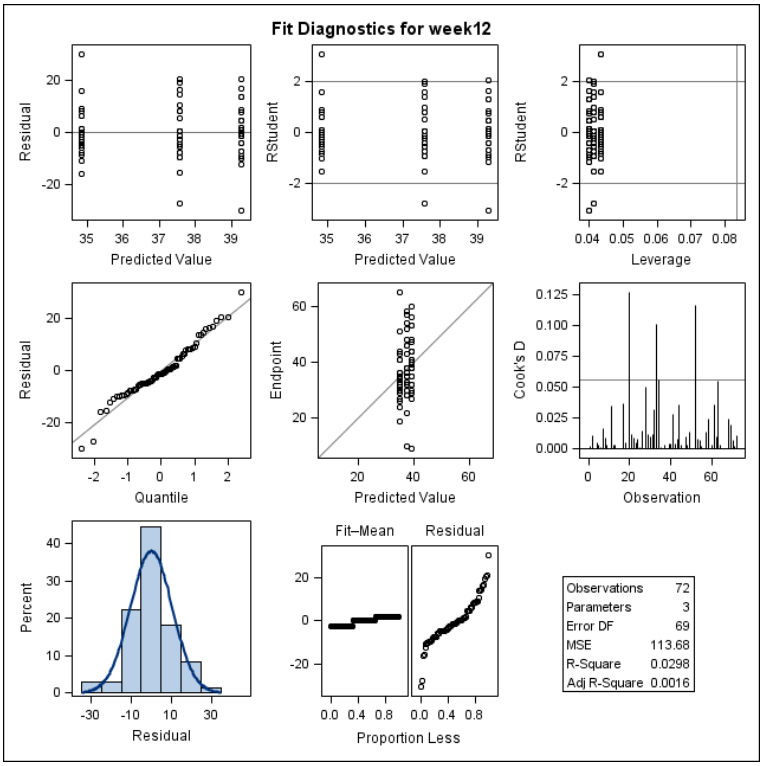

Figure A.3.9: ANOVA Diagnostic Plot (BOCF)

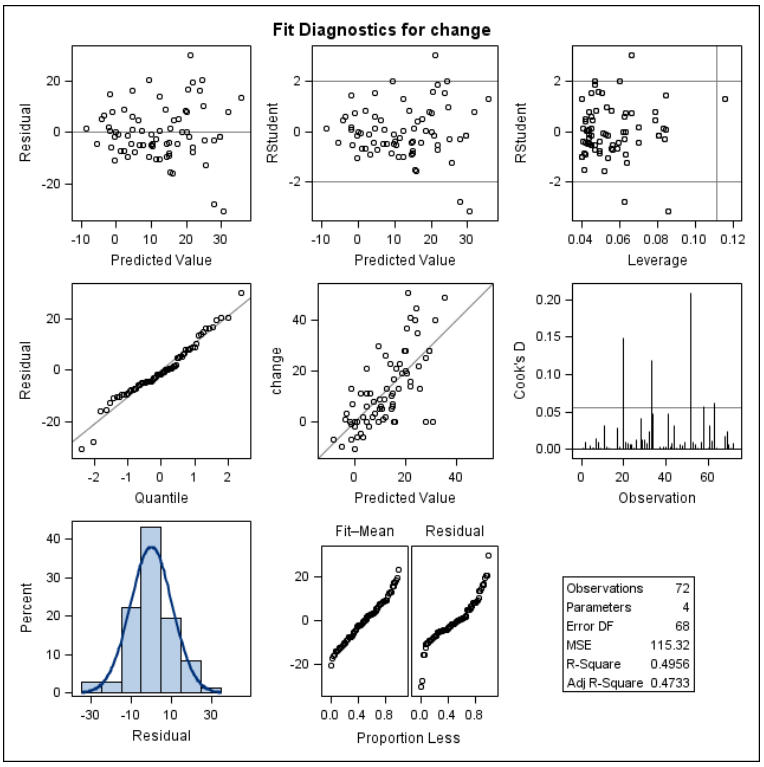

Figure A.3.10: ANCOVA Diagnostic Plot (BOCF)

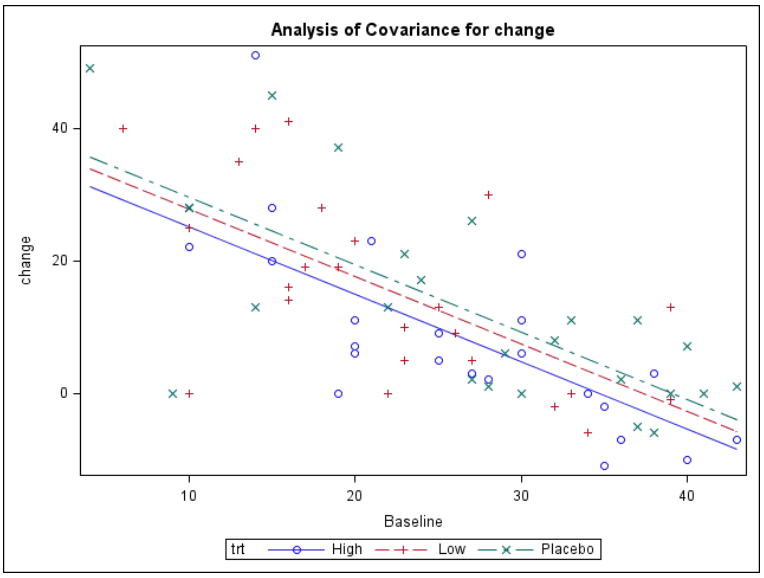

Figure A.3.11: ANCOVA Plot (BOCF)

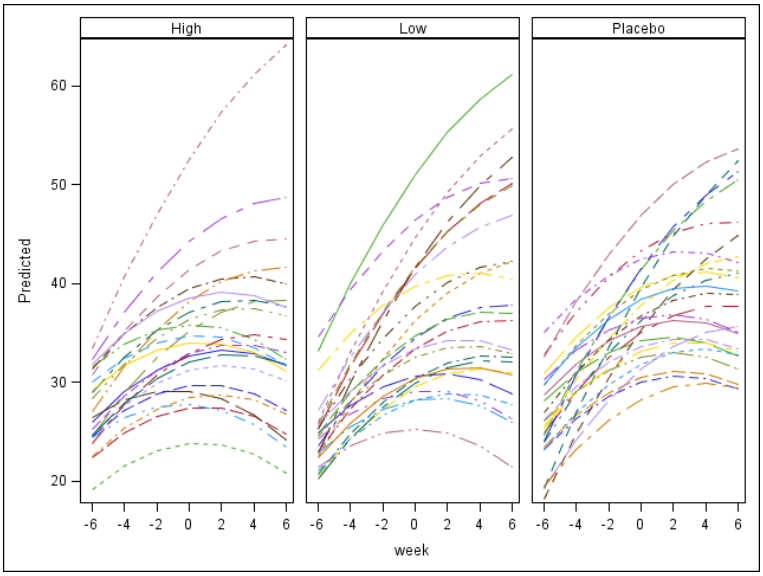

Figure A.3.12: Mix Model Predicted Values

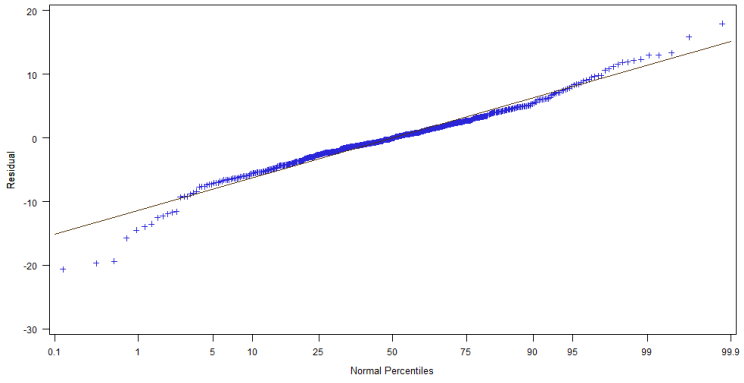

Figure A.3.13: Mix Model Residuals Normal Quantile Plot

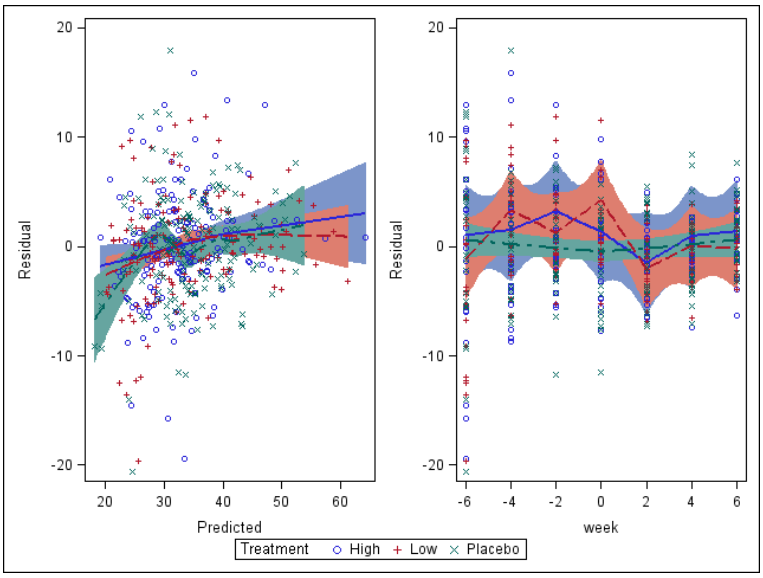

Figure A.3.14: Mix Model Residuals vs. Predicted Values

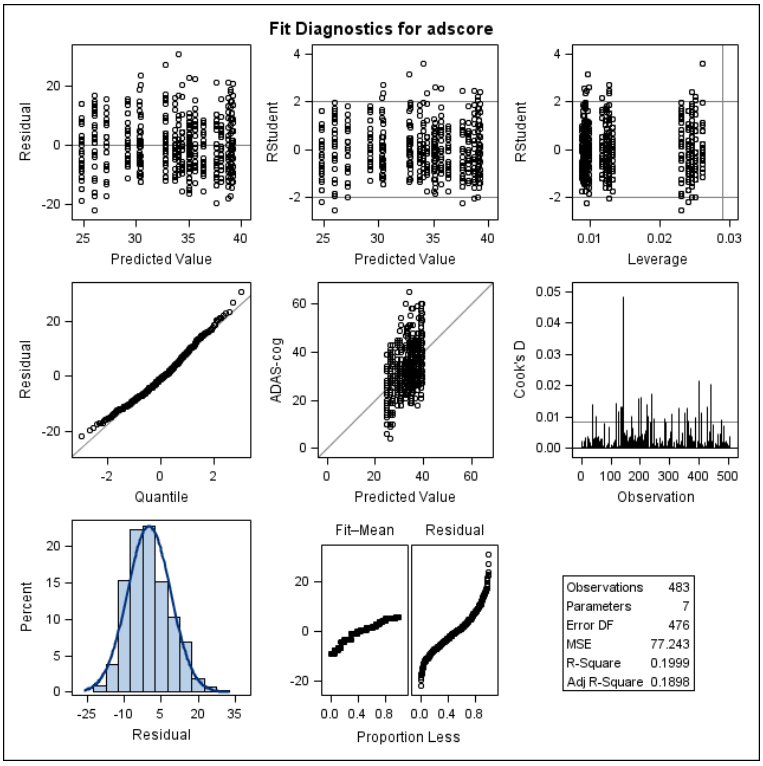

Figure A.3.15: ANCOVA Diagnostic Plot Independence Model

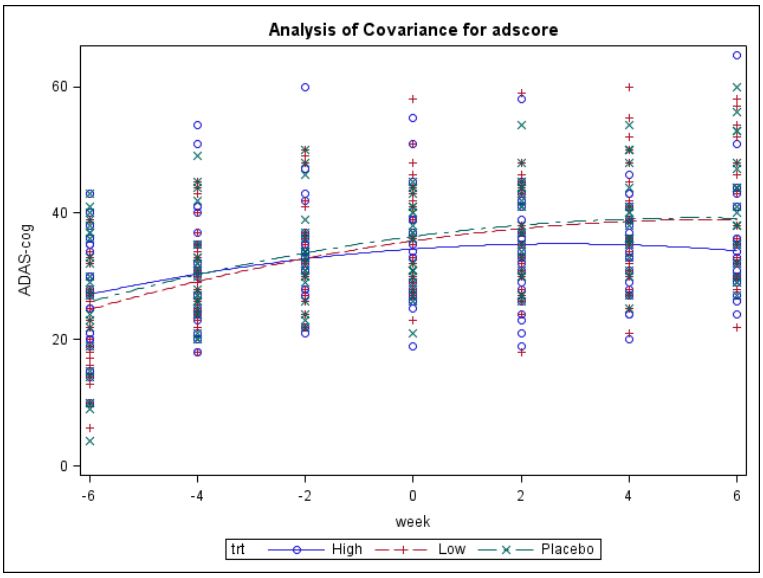

Figure A.3.16: ANCOVA Plot Independence Model

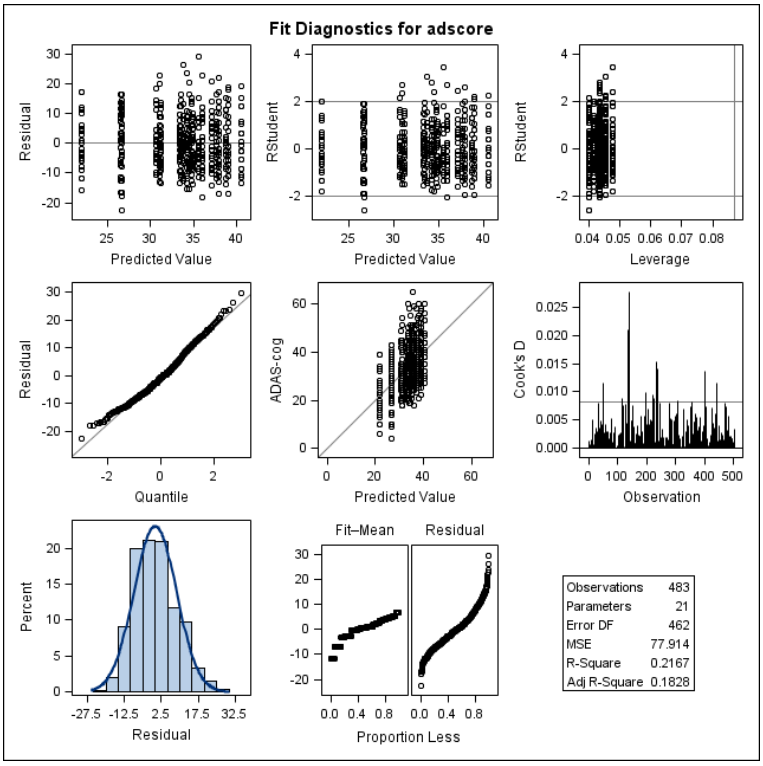

Figure A.3.17: Two-way ANOVA Diagnostic Plot

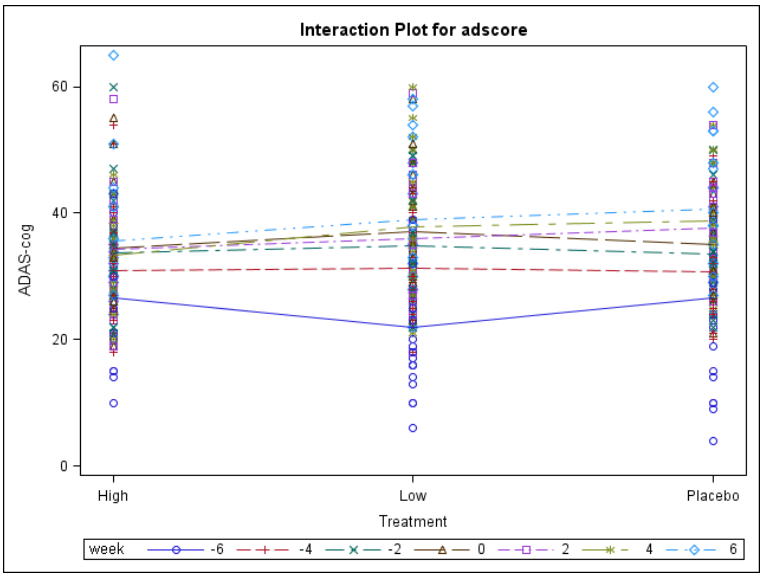

Figure A.3.18: Two-way ANOVA Interaction Plot