SAS APPLICATION FOR PHARMACOKINETIC EVALUATION AND ANALYSIS OF THE EFFECT OF TREATMENT WITH A NEW ANTIDEPRESSANT DRUG IN A POPULATION WITH MAJOR DEPRESSION

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Introduction

This paper describes an example of SAS® application for pharmacokinetic evaluation and analyzes the effect of treatment with a new pentapeptide antidepressant drug (INN 00835) developed by Innapharma, Inc. for the treatment of major depression [1, 2].

Study Design and Methods

A phase 2, double-blind, outpatient, randomized, fixed dose, placebo-controlled, parallel design study was conducted in 1998 at the Charter Hospital, Feighner Research Institute in San Diego, CA. Drug was administered subcutaneously once/day in two 5-day treatment cycles (from Monday to Friday) separated by two non-treatment days (Saturday and Sunday). Subjects meeting the entry criteria for major depression were randomly assigned to three treatment groups to receive either two cycles of drug, or one cycle of drug followed by the second cycle with placebo, or both cycles with placebo. The objective of the study was to evaluate tolerability, the safety profile and the effect of a second cycle of treatment versus placebo and versus the first cycle of treatment. Pharmacokinetic analysis, based on concentrations of drug in plasma, was used to evaluate the results. Requirements for enrollment included the following values for the psychometric tests at screening: 21-items Hamilton Depression Rating Scale (HAMD) ≥20, Carroll Self-Rating Depression Scale (CSRS) ≥18, and Global Impression Scale (Severity of Illness) ≥4. In addition Montgomery-Asberg Depression Rating Scale (MADR) and Visual Analog Scale (VAS) for mood, anxiety and mental clarity were used for efficacy evaluation. After two cycles of treatment, subjects had a 4-week follow-up period with one visit per week for clinical observation. Response to treatment was defined as 50% change (decrease) in HAMD from baseline. Plasma concentrations of INN 00835 were measured at 15 min., 30 min., and 1 hour after dosing. The highest observed Cmax from each subject treated with drug was selected to calculate a Minimum Projected Therapeutic Concentration (MPTC) as a mean of Cmax over population. The most relevant timepoints for the statistical analysis were Day 6 or Day 8 after enrollment - effect of the first cycle of treatment, Day 13 - effect of two cycles, and Day 19 (a week after the end of the treatment), when the peak effect was predicted. All statistical hypothesis assumed a significance level of 0.05 using two-tailed tests.

Population

Of the 55 subjects enrolled in the study, 22 were dosed with 2 cycles of drug, 11 with 1 cycle of drug and one of placebo, and 22 with placebo only. Fifty-one subjects completed the treatment and were included in the evaluable population. Twenty-four subjects (47.1%) were male and 27 (52.9%) were female. The average age was 43.25 years (45.8 for males and 41.0 for females).
The average weight was 183.0 pounds (193.4 for males and 173.8 for females). Mean values for medical history were: duration of illness - 9.4 years, number of depression episodes - 2.7, duration of episodes - 16.8 months, and duration of previous treatments - 12.3 months. There were no statistically significant differences between treatment groups in demographic characteristics, medical history and baseline efficacy parameters.

**SAS Application for Pharmacokinetic Analysis**

The SAS program for pharmacokinetic analysis included:

a. Calculation of Cmax and Area under the Curve (AUC) overall timepoints for each individual subject treated with drug.

b. Calculation of the descriptive statistics (mean, standard error) over population treated with drug, define the MPTC as a mean of distribution for Cmax.

c. Separation of entire population treated with drug into subgroups: within MPTC and below MPTC.

The main part of the SAS program for Pharmacokinetic Analysis is presented in Appendix 1.

**SAS Application for Efficacy Analysis**

The SAS program for efficacy analysis included:

a. Calculation of Change and Percent Change from Baseline for each of efficacy variables (HAMD, MADR, CSRS, CGI, VAS) by day for each individual subject.

b. Definition of Response as 50% Change (decrease) for HAMD by day for each individual subject.

c. Calculation of last observation carried forward (LOCF) for missing visits.

d. Merging of efficacy SAS data set with pharmacokinetic data set by subject number.

e. Separation of the placebo group and then of the drug treated groups by plasma concentration (within MPTC or below MPTC).

f. Calculation of descriptive statistics and corresponding P-value of difference between treatment groups.

g. Create output table for statistical report.

The main part of the SAS program for Efficacy Analysis is presented in Appendix 2 and Appendix 3.

**Results and Discussion**

All clinical data were recorded using BBN/Clintrial™ software. After double entry and control of validation all data were converted to SAS for analysis. INN 00835 was very well tolerated by all subjects and there was no evidence of any serious adverse event. Pharmacokinetic analysis included all evaluable subjects from the drug treated groups who had plasma concentration data at any timepoint. A strong pharmacodynamic correlation was observed between plasma concentration (Cmax and AUC) and response to treatment. The calculation of the MPTC for 29 subjects according to the SAS program for pharmacokinetics resulted in a value of 45.7 ng/mL. This value was used for the separation of all evaluable subjects, treated with drug, to the group of subjects with plasma concentration <MPTC (Plevel = “low,” n=16) and the group of subjects with plasma concentration ≥MPTC (Plevel =
The majority of subjects had the highest plasma concentration of drug at 15 min. after dosing. Table 1 presents the results for pharmacokinetic analysis.

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Effect of treatment was evaluated by comparison of the three treatment groups: placebo, drug group with plasma concentration \( \geq \text{MPTC} \) and drug group with plasma concentration \( <\text{MPTC} \). For the timepoints before Day 8 and for Day 8 the subjects with one cycle of treatment were combined with subjects who received two cycles of treatment. For the timepoints after Day 8, only subjects with two cycles of treatment were evaluated for comparison. Figure 1 shows the percent change from
baseline by timepoints for HAMD, MADR and CSRS. All results were obtained from Macros 1 and 2. As seen in the Figure 1, the effect of treatment with INN 00835 in subjects with plasma concentration ≥MPTC was significantly higher versus placebo group and the subjects with plasma concentration <MPTC. Significant response to treatment was observed within the first treatment cycle, the effect increased during the second treatment cycle (for subjects with plasma concentration ≥MPTC this increase was statistically significant for Day 13 versus Day 6) and peaked at one week after the treatment. Eighty-nine percent of subjects with plasma concentration ≥MPTC responded to treatment at the peak effect. The cluster analysis method to identify the subtypes within a study population using FASTCLUS procedure was presented previously in NESUG ‘99 [3].

Conclusions

SAS® is a powerful and flexible tool to analyze clinical data in the area of Clinical Psychiatry. This SAS Application for pharmacokinetic analysis and effect of treatment with the antidepressant drug INN 00835 played an important role in the interpretation of the results and in determining the range of doses for upcoming clinical trials.

References


Trademarks

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Figure 1. Reduction in Mean Percent Change for HAMD, MADR, CSRS for INN 00835 (Within and Below MPTC) and Placebo

- **INN 00835, Within MPTC (>= 45.7 ng/mL)**
- **INN 00835, Below MPTC (< 45.7 ng/mL)**
- **Placebo**

Key:
- * - P<=0.05
- # - P<=0.10

(Within vs Below MPTC)
(Within MPTC vs Placebo)
Appendix 1. The Program for Pharmacokinetic Analysis

data plasma_1;
  set plasma; /* SAS data set with plasma */
  if treat='Placebo' then delete;
  if treat='05 Days' then do;
  t_15=mean(of t1_15, t5_15, t12_15); /* Mean plasma for 15 min. over days */
  t_30=mean(of t1_30, t5_30, t12_30); /* Mean Plasma for 30 min. over days */
  t_60=mean(of t1_60, t5_60, t12_60); /* Mean Plasma for 60 min. over days */
  auc_1 =((t1_15 + t1_30 ) /2)*15 + (((t1_30  + t1_60 )/2)*30); /* AUC */
  auc_5  =((t5_15 + t5_30 ) /2)*15 + (((t5_30  + t5_60 )/2)*30);
  auc_12=((t12_15+t12_30)/2)*15 + (((t12_30+t12_60)/2)*30);
  c_max=max(of t1_15, t1_30, t1_60, t5_15, t5_30, t5_60, t12_15, t12_30, t12_60);
  end;
  else do;
  t_15=mean(of t1_15, t5_15);
  t_30=mean(of t1_30, t5_30);
  t_60=mean(of t1_60, t5_60);
  auc_1 =((t1_15 + t1_30 ) /2)*15 + (((t1_30  + t1_60 )/2)*30);
  auc_5  =((t5_15 + t5_30 ) /2)*15 + (((t5_30  + t5_60 )/2)*30);
  auc_12=((t12_15+t12_30)/2)*15 + (((t12_30+t12_60)/2)*30);
  c_max=max(of t1_15, t1_30, t1_60, t5_15, t5_30, t5_60, t12_15, t12_30, t12_60);
  end;
run;
/** MPTC - the Minimum Projected Therapeutic Concentration **/
proc means data=plasma_1 n nmiss std stderr min max range noprint;
  var c_max;
  output out=kinetic mean=mptc;
run;
data plasma_2;
  if _n_=1 then kinetic (keep=mptc);
  set plasma_1;
  if c_max=. then plevel='miss';
  else if c_max>=mptc then plevel='high';
  else plevel='low';
run;
proc sort data=plasma_2;
  by subjid;
proc print data=plasma_2;
  var subjid treat t1_15 t1_30 t1_60 t5_15 t5_30 t5_60 t12_15 t12_30 t12_60
c_max plevel;
run;

Appendix 2. MACRO 1 for Efficacy Analysis

%macro effic_1 (fl, name);
data psych;
  set &fl; /* SAS data set with Psychometric Score */
  by subjid;
  array hscore(*) hamd1 - hamd13;
  retain hamd1 - hamd13;
  if first.subjid then do i=1 to 13;
    hscore(i) = .;
  end;
  hscore(visit)=test_scr;
  if last.subjid then output;
  test =&name;
  keep test subjid subjinit hamd1 - hamd13 treat;
run;
data psych(rename=hamd1=d0 hamd2=d hamd3=d3 hamd4 = d5 hamd5=d6 hamd6=d8 hamd7=d10 hamd8=d12
  hamd9=d13 hamd10=d19 hamd11=d26 hamd12=d33 hamd13=d40));
set psych;
run;
/** Last Observation carried forward **/
data locf;
  set psych;
if \( d3 = . \) then \( d3 = d1 \);  if \( d5 = . \) then \( d5 = d3 \);  if \( d6 = . \) then \( d6 = d5 \);
if \( d8 = . \) then \( d8 = d6 \);  if \( d10= d8 \);  if \( d12= d10 \);
if \( d13= d12 \);  if \( d19= d13 \);  if \( d26= d19 \);
if \( d33= d26 \);  if \( d40= d33 \);
run;

data eff;
  set locf ;
  dd3 =d3-d1 ;  pd3=dd3/d1*100 ;  if pd3 <-50  then rd3='R' ;  else rd3='N' ;
  dd5 =d5-d1 ;  pd5=dd5/d1*100 ;  if pd5 <-50 then rd5='R' ;  else rd5='N' ;
  dd6 =d6-d1 ;  pd6=dd6/d1*100 ;  if pd6 <-50 then rd6='R' ;  else rd6='N' ;
  dd8 =d8-d1 ;  pd8=dd8/d1*100 ;  if pd8 <-50 then rd8='R' ;  else rd8='N' ;
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  dd26=d26-d1 ;  pd26=dd26/d1*100 ;  if pd26 <-50 then rd26='R' ;  else rd26='N' ;
  dd33=d33-d1 ;  pd33=dd33/d1*100 ;  if pd33 <-50 then rd33='R' ;  else rd33='N' ;
  dd40=d40-d1 ;  pd40=dd40/d1*100 ;  if pd40 <-50 then rd40='R' ;  else rd40='N' ;
run;
proc sort data=eff ;
  by subjid ;
/*  Merge Efficacy Data set and Pharmacokinetic Data set */
data eff_1 ;
  merge eff plasma_2 (keep=subjid plevel) ;
  by subjid ;
  if treat='Placebo' then plevel='plac' ;
  if plevel='miss' then delete ;
run ;
%mend effic_1  ;

Appendix 3. MACRO 2 for Efficacy Analysis

%macro effic_2 (fl, name, v, tpoint)  ;
data &fl&v  ;
  set eff_1 ;
  score=&tpoint ;
  if (treat='05 Days' and &v>=10) or plevel='miss' then delete  ;
run ;
proc sort data=&fl&v ;
  by plevel subjid ;
/* Descriptive statistics by group */
proc means data=&fl&v noprint ;
class plevel ;
var score ;
output out=m&fl&v n=n min=min max=max mean=mean stderr=stderr ;
run ;
data mk&fl&v ;
  set mk&fl&v ;
  trt=1 ;
  if plevel='plac' then tr=1 ;
  if plevel='high' then tr=2 ;
  if plevel='low ' then tr=3 ;
  if plevel='miss' then tr=4 ;
run ;
proc sort data=mk&fl&v ;
  by tr tr ;
data m&fl&v ;
  set m&fl&v ;
  by tr ;
array num(*) n1-n4 ;
array mi(*) mi1-mi4 ;
array ma(*) ma1-ma4 ;
array mn(*) mn1-mn4 ;
array se(*) se1-se4 ;
retain n1-n4 mi1-mi4 ma1-ma4 mn1-mn4 se1-se4 ;
if first.tr then do i=1 to 4 ;
```plaintext
num(i) = . ; mi(i) = . ; ma(i) = . ;

mn(i) = . ; se(i) = . ;

num(tr) = n ; mi(tr) = min ; ma(tr) = max ;

ma(tr) = round(mean, 0.01) ;

se(tr) = round(stderr, 0.01) ;

if last.trt then output ;

keep n1-n4 mi1-mi4 ma1-ma4 mn1-mn4 se1-se4 ;
run ;

data m&fl&v (rename=(n1=tot_n mi1=tot_mi ma1=tot_max mn1=tot_mean se1=tot_se n1=pla_n mi1=pla_mi ma1=pla_max

mn1=pla_mean se1=pla_se n1=high_n mi1=high_mi ma1=high_max

mn1=high_mean se1=high_se n1=low_n mi1=low_mi ma1=low_max

mn1=low_mean se1=low_se )) ;

set m&fl&v ;

test=&name ; visit=&v ;
run ;

/** Calculation P-values of the difference between groups **/

proc glm data= m&fl&v outstat=p1&fl&v noprint ;

class plevel ;

where plevel='high' or plevel='plac' ;

model score=plevel ;
run ;

data p1&fl&v (rename=(prob=hi_plac)) ;

set p1&fl&v ;

keep prob ; where _type_='SS3' ;
run ;

proc glm data= m&fl&v outstat=p2&fl&v noprint ;

class plevel ;

where plevel='high' or plevel='low' ;

model score=plevel ;
run ;

data p2&fl&v (rename=(prob=hi_low)) ;

set p2&fl&v ;

keep prob ; where _type_='SS3' ;
run ;

/* Merge Descriptive statistics with P-values */

data c&fl&v ;

merge m&fl&v p1&fl&v p2&fl&v ;
run ;
%mend effic_2 ;
```