THE META-ANALYSIS (PROC MIXED) OF TWO PILOT CLINICAL STUDIES WITH A NOVEL ANTIDEPRESSANT

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INTRODUCTION

The paper explores the use of a meta-analysis (SAS/STAT®, PROC MIXED) of the first two pilot clinical studies with the new antidepressant. Meta-analysis is based on primary efficacy variable such as a Hamilton Depression Rating Scale (HAMD) score for all evaluated time points including treatment and follow-up periods.

METHOD

A. Studies Design

The combined data was obtained from two pilot, phase 2, parallel design, single-center clinical studies in which a novel antidepressant was used to treat a population with major depression. Inpatients (N=52) were enrolled in the first study [1] and outpatient (N=55) – in the second study [2]. Both studies investigated the efficacy and safety of the new drug for one or two 5-day treatment cycles. The study design is presented in Figure 1 and some parameters for both studies are summarized in Table 1.

A pharmacokinetic analysis of the studies permitted the definition of the Minimum Projected Therapeutic Concentration (MPTC) and allowed for the subsequent division of the study population into three treatment subgroups: placebo subgroup (all subjects from placebo group), drug-treated subgroup 1 with concentration of drug in plasma (CDP) above MPTC, and drug-treated subgroup 2 with CDP below MPTC.

B. Outcome Measures

The primary outcome measure was HAMD-21 (% change from baseline). Response to treatment was defined for each subject as >50% change in HAMD-21 from baseline. Primary outcome measure was calculated for each subject and then by treatment group. Some additional psychometric scores were analyzed as a secondary outcome measure.

C. Statistical Model for Meta-Analysis

There supposedly was no heterogeneity between two pilot clinical trials considered for meta-analysis. A fixed effects statistical model was used and this model included the following factors: two studies, three treatment groups, interaction between studies and treatment groups, and covariance from baseline (Day 1, the first day of treatment). For fixed effects model two procedures from SAS/STAT® (PROC MIXED and PROC GLM) produce the same output. But only PROC MIXED is presented as an example for following SAS code because
we are planning to extend this model with a random effect for some factors in the incoming clinical trials.

**D. SAS CODE**

```sas
/* Combine Efficacy Data from two Clinical */
/* trials and rename the common variables */
data for_meta;
  set hamd_2a (rename=(d7=d13 dd7=dd13
      pd7=pd13 rd7=rd13))
     hamd_2b (rename=(d19=w1 d26=w2
      d33=w3 d40=w4
      dd19=dw1 dd26=dw2
dd33=dw3 dd40=dw4
      pd19=pw1 pd26=pw2
      pd33=pw3 pd40=pw4
      rd19=rw1 rd26=rw2
      rd33=rw3 rd40=rw4));
run;

proc sort data=for_meta;
  by group study treat subjid;
proc print data=for_meta;
  var study subjid treat group pd3 pd5
    pd6 pd8 pd10 pd12 pd13 pd19=pw1
    pd26=pw2 pd33=pw3 pd40=pw4;
  format group groupf. ;
title 'Combined Efficacy Data for Meta-Analysis';
run;

proc sort data=for_meta;
  by study group ;
/* Macro for Meta-Analysis */
/* by Time Point */
%macro meta (tp) ;
proc mixed data= for_meta ;
  class study group ;
  model &tp=study group study*group d1 ;
  lsmeans study group / pdiff ;
  format group groupf. ;
title 'Fixed effect model for two studies,';
  three treatment groups, interaction,';
  and covariance';
run ;
%mend ;

%macro meta (pw1) ;
/* Variables in PROC MIXED: */
/* study – Study ID (2A, 2B) ; */
/* group – Treatment groups (subgroup 1 – */
/* CDP above MPTC, subgroup 2 – */
/* CDP below MPTC, placebo) ; */
/* d1 – HAMD at baseline (Day 1) ; */
```

```
RESULTS

For combined data there was a relatively even distribution of demographic characteristics: age, sex, weight and medical history in the three treatment groups. The mean baseline HAMD-21 scores on Day 1 before dosing were close by treatment group. There were no significant differences between the three randomized treatment groups in the baseline values of any of the other psychometric tests, either. Figure 2 presents SAS meta-analysis output for one time point (Week 1 after the end of the treatment with peak effect of response among all time-points). Figure 3 shows effect of statistical separation between subjects with CDP \( \geq \)MPTC versus placebo and versus subjects with CDP <MPTC.

CONCLUSIONS

SAS/STAT® is a very power tool for meta-analysis in drug development with new antidepressants. While our findings summarize the results from pilot studies with a limited sample and take into consideration the pharmacokinetic evaluation, meta-analysis successfully created a very comprehensive picture of the separation of the drug-treated population with a plasma level above MPTC from placebo and from the population with a plasma level below MPTC. There was statistically significant independent effect of the treatment in the studies identified (F = 9.15, DF = 2, P = 0003), while there was no statistical effect across the studies (F = 2.36, DF = 1, P = 0.1283), the interaction between studies (F = 0.85, DF = 2, P = 0.4319) and treatment groups. For change and percent change for HAMD-21 from baseline, there was a statistically significant effect of baseline for all follow-up time points (F = 5.83, DF = 1, P = 0.0180). The information from meta-analysis prompted further clinical testing of nemifitide to investigate its effectiveness as an important novel antidepressant.

REFERENCE


TRADEMARK

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CONTACT INFORMATION

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Park Ridge, NJ 07656
E-mail: LSVERDLOV@AOL.COM
FIGURE 1. STUDY DESIGN

TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>2A STUDY</th>
<th>2B STUDY</th>
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<tr>
<td><strong>Type of Study</strong></td>
<td>Randomized, double-blind, placebo-controlled, INPATIENT, single center</td>
<td>Randomized, double-blind, placebo-controlled, OUTPATIENT, single center</td>
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<tr>
<td><strong>Number of Arms</strong></td>
<td>Two (N=52)</td>
<td>Three (N=55)</td>
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<tr>
<td></td>
<td>a. Drug, 5 doses (N=26)</td>
<td>a. Drug, 10 doses (N=22)</td>
</tr>
<tr>
<td></td>
<td>b. Placebo (N=26)</td>
<td>b. Drug, 5 doses (N=11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c. Placebo (N=22)</td>
</tr>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td>a. Unipolar Depressed Patients (DSM-IV)</td>
<td>a. Unipolar Depressed Patients (DSM-IV)</td>
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<td></td>
<td>b. HAMD &gt; 20</td>
<td>b. HAMD &gt; 20</td>
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<td><strong>Administration</strong></td>
<td>Subcutaneously, one cycle, once/day for 5 days</td>
<td>Subcutaneously, one or two cycles, once/day for 5 days</td>
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<td><strong>Follow-Up Period</strong></td>
<td>4 weeks</td>
<td>4 weeks</td>
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<td><strong>Pharmacokinetics</strong></td>
<td>Pre-dose, 1, 7, 24 hr after dosing</td>
<td>Pre-dose, 15 min, 30 min, 1 hr, 2 hr, 4 hr after dosing</td>
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<td><strong>Minimum Projected Therapeutic Concentration (MPTC) (ng/mL)</strong></td>
<td>5 ng/mL at 1 hr</td>
<td>45.7 ng/mL at 15 min</td>
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</table>
FIGURE 2. SAS OUTPUT

Model for drug-treated subgroup 1 (CDP above MPTC), subgroup 2 (CDP below MPTC) and Placebo,
Time point: Week 1, Covariance with Day 1

The Mixed Procedure
Model Information
Data Set WORK.FOR_META
Dependent Variable pw1
Covariance Structure Diagonal
Estimation Method REML
Residual Variance Method Profile
Fixed Effects SE Method Model-Based
Degrees of Freedom Method Residual

Class Level Information
Class Levels Values
study       2    Phase 2A Phase 2B
group       3    High Plasma Low Plasma Placebo

Dimensions
Covariance Parameters 1
Columns in X 13
Columns in Z 0
Subjects 1
Max Obs Per Subject 100
Observations Used 89
Observations Not Used 11
Total Observations 100

Covariance Parameter Estimates
Cov Parm        Estimate
Residual        827.78

Fit Statistics
Res Log Likelihood -403.2
Akaike’s Information Criterion -404.2
Schwarz’s Bayesian Criterion -405.4
-2 Res Log Likelihood 806.4

Type 3 Tests of Fixed Effects

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The Mixed Procedure
Least Squares Means

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Differences of Least Squares Means

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</table>
FIGURE 3. META-ANALYSIS: REDUCTION IN HAMD (PERCENT CHANGE FROM BASELINE)

% Change from baseline (HAM-D-21)

Evaluation Day

CDP - Concentration of Drug in Plasma
MPTC - Minimum Projected Therapeutic Concentration