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* Project : ZRHM-REXA-07-JP

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* Program name : t15020305_ZRHM-REXA-07_V1.sas

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* Author : M. SUN

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* Date created : 05/27/2015

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* Purpose : Table 15.2.3.5 Analysis of Additional Biomarkers of Exposure versus mCC and SA on Day 5/90 Visit ◆ FAS

* Revision History :

*

* Date Author Ref Revision (Date in YYYYMMDD format)

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*****,

```
%let prgname=T15020305_ZRHM_REXA_07_JP_V1;
```

```
options mprint;
```

```
ods escapechar='^';
```

```
options sasautos=("W:\pmp07\macros" sasautos) notes;
```

```
%init(delivery=9);
```

```
%titlecsv(prgname=&prgname.,version=3);
```

```
options missing="";
```

```
data adbx1;
```

```
set adam.adbx;
```

```
where anl02fl='Y';
```

```
if PARAMCD in ("CO", "CARBXHGB") and ATPT="DAY 5 - 20:00 - 21:30" and FASFL="Y" then output;
```

```
else if PARAMCD in ("UMHBMCRE", "U3HPMCRE", "USPMACRE", "UNNALCRE") and upcase(AVISIT) eq  
"DAY 5" and FASFL="Y" then output;
```

```
else if PARAMCD in ("CO", "CARBXHGB", "UMHBMCRE", "U3HPMCRE", "USPMACRE", "UNNALCRE") and  
upcase(AVISIT) eq "DAY 90" and FASFL="Y" then output;
```

```
else if (upcase(AVISIT) ="DAY 5" and FASFL="Y") or (upcase(AVISIT)="DAY 90" and FASFL="Y") then do;
```

```
if paramcd in (
```

```
"U1OHPCRE", "UNNNCRE", "U4ABPCRE", "U1NACRE", "U2NACRE", "UOTOLCRE", "UCEMACRE",  
"UHEMACRE", "UBAPCRE", "UHMPMCRE", "USBMACRE", "UNEQCRE",
```

```
"U3HPM24U", "UMHBM24U", "USPMA24U", "UNNAL24U", "U1OHP24U", "UNNN24U", "U4ABP24U",  
"U1NA24U", "U2NA24U", "UOTOL24U", "UCEMA24U", "UHEMA24U", "UBAP24U", "UHMPM24U",  
"USBMA24U", "UNEQ24U") then output;
```

```
end;
```

```
run;
```

```
/*
```

```
carbon monoxide
```

```
total 1-hydroxypyrene (total 1-OHP) pyrene Urine
```

```
total N-nitrosornicotine (NNN) N-nitrosornicotine Urine
```

```
4-aminobiphenyl (4-ABP) 4-aminobiphenyl Urine
```

```
1-aminonaphthalene (1-NA) 1-aminonaphthalene Urine
```

2-aminonaphthalene (2-NA) 2-aminonaphthalene Urine

o-toluidine (o-tol) o-toluidine Urine

2-cyanoethylmercapturic acid (CEMA) acrylonitrile Urine

2-hydroxyethylmercapturic acid (HEMA) ethylene oxide Urine

3-hydroxybenzo(a)pyrene benzo(a)pyrene Urine

3-hydroxy-1-methylpropyl-mercapturic acid

(HMPMA)

crotonaldehyde Urine

S-benzylmercapturic acid (S-BMA)

nicotine equivalents (NEQ)

*/

data adbx1;

set adbx1;

if paramcd='UMHBMCRE' then ord=1;

else if paramcd='U3HPMCRE' then ord=2;

else if paramcd='USPMACRE' then ord=3;

else if paramcd='CARBXHGB' then ord=4;

else if paramcd='UNNALCRE' then ord=5;

else if paramcd='CO' then ord=6;

else if paramcd='U1OHPCRE' then ord=7;

else if paramcd='UNNNCRE' then ord=8;

else if paramcd='U4ABPCRE' then ord=9;

else if paramcd='U1NACRE' then ord=10;

else if paramcd='U2NACRE' then ord=11;
else if paramcd='UOTOLCRE' then ord=12;
else if paramcd='UCEMACRE' then ord=13;
else if paramcd='UHEMACRE' then ord=14;
else if paramcd='UBAPCRE' then ord=15;
else if paramcd='UHMPMCRE' then ord=16;
else if paramcd='USBMACRE' then ord=17;
else if paramcd='UNEQCRE' then ord=18;

else if paramcd='UMHBM24U' then ord=19;
else if paramcd='U3HPM24U' then ord=20;
else if paramcd='USPMA24U' then ord=21;
else if paramcd='UNNAL24U' then ord=22;

else if paramcd='U1OHP24U' then ord=23;
else if paramcd='UNNN24U' then ord=24;
else if paramcd='U4ABP24U' then ord=25;
else if paramcd='U1NA24U' then ord=26;
else if paramcd='U2NA24U' then ord=27;
else if paramcd='UOTOL24U' then ord=28;
else if paramcd='UCEMA24U' then ord=29;
else if paramcd='UHEMA24U' then ord=30;
else if paramcd='UBAP24U' then ord=31;
else if paramcd='UHMPM24U' then ord=32;

```
else if paramcd='USBMA24U' then ord=33;
```

```
else if paramcd='UNEQ24U' then ord=34;
```

```
if ord>0;
```

```
run;
```

```
data adbx2;
```

```
set adbx1;
```

```
if paramcd ne 'CO' then do;
```

```
logaval=log(AVAL);
```

```
logbase=log(BASE);
```

```
end;
```

```
if upcase(AVISIT) eq "DAY 5" then dord=1;
```

```
if upcase(AVISIT) eq "DAY 90" then dord=2;
```

```
if paramcd='CO' then cotest=1; else cotest=2;
```

```
run;
```

```
proc sort data=adbx2;
```

```
by ord paramcd;
```

```
run;
```

```
data adbx2;
```

```
set adbx2 end=eof;
```

```
by ord paramcd;
```

```
if eof then call symputx('tottest',ord);
```

```
run;
```

```
%macro doit;
```

```
%trtrtfg(pgmname=&loutname., pgmid=1, new=0, style=, bookmark=%lowercase(&outname.));
```

```
%do i=1 %to &tottest;
```

```
%let getp&i=0;
```

```
%do j=1 %to 2;
```

```
proc sort data=adbx2 out=adbx2&i&j nodupkey;
```

```
by ord dord;
```

```
where ord=&i and dord=&j;
```

```
run;
```

```
data adbx2&i&j;
```

```
set adbx2&i&j;
```

```
call symputx("param&i",param);
```

```
call symputx("day&i",avisit);
```

```
keep paramcd param avisit ord dord;
```

```
run;
```

title1 bold j=l "<title1 &title2";

title2 "The where clause used on the dataset adam.adbx: fasfl='Y' and anl02fl='Y'";

title3 "param: &¶m&i, avisit: &&day&i" ;

proc glm data=adbx2;

where ord=&i and dord=&j;

class trtp sex UCPDGR1;

%if &i=6 %then %do;

model aval = base sex UCPDGR1 trtp;

%end;

%else %do;

model logaval = logbase sex UCPDGR1 trtp;

%end;

lsmeans trtp / pdiff =control('mCC') alpha=0.05 cl adjust=t;

lsmeans trtp / pdiff =control('SA') alpha=0.05 cl adjust=t;

ods output LSMeans=pval&i&j (keep=ProbtDiff trtp where=(TRTP="THSm2.2")); *p-value;

ods output LSMeanCL=LSMeanCL&i&j (keep=trtp lowercl uppercl lsmean); *lsmean, C.I. for each arm;

ods output LSMeanDiffCL=LSMeanDiffCL&i&j (keep=trtp _trtp lowercl uppercl difference
where=(TRTP="THSm2.2")); *lsmean and C.I. for ratios;

ods output FitStatistics=ROOTMSE&i&j (keep=rootmse); *RootMSE;

run;quit;

proc freq data=adbx2 noprint;

where ord=&i and dord=&j;

tables trtp/out=countn&i&j;

run;

```
data countn&i&j.1(keep=ord dord row col1) countn&i&j.2(keep=ord dord row col2)
countn&i&j.3(keep=ord dord row col3);
```

```
set countn&i&j;
```

```
length col1 col2 col3 $20; ord=&i; dord=&j;
```

```
if trtp='THSm2.2' then do;
```

```
row=2; col1=put(count,3.); output countn&i&j.1;
```

```
end;
```

```
if trtp='mCC' then do;
```

```
row=2; col2=put(count,3.); output countn&i&j.2;
```

```
end;
```

```
if trtp='SA' then do;
```

```
row=2; col3=put(count,3.); output countn&i&j.3;
```

```
end;
```

```
run;
```

```
data LSMeanCL&i&j.1(keep=ord dord row col1) LSMeanCL&i&j.2(keep=ord dord row col2)
LSMeanCL&i&j.3(keep=ord dord row col3);
```

```
set LSMeanCL&i&j(obs=3);
```

```
%if &i=6 %then %do;
```

```
%end;
```

```
%else %do;
```

```
lsmean = exp(lsmean); /* Ratio of geometric mean */
```

```
LowerCL = exp(LowerCL); /* 95% CI lower bound */
```



```

UpperCL = exp(UpperCL); /* 95% CI upper bound */

%end;

length col1 col2 col3 $20; ord=&i; dord=&j;

if trtp='THSm2.2' then do;

    row=3; col1=put(round(lsmear,0.01),7.2); output LSMeanCL&i&j.1;

    row=4; col1=put(round(floor(lowercl*100)/100,0.01),7.2)||',
'| |strip(put(round(ceil(uppercl*100)/100,0.01),7.2)); output LSMeanCL&i&j.1;

end;

else if trtp='mCC' then do;

    row=3; col2=put(round(lsmear,0.01),7.2); output LSMeanCL&i&j.2;

    row=4; col2=put(round(floor(lowercl*100)/100,0.01),7.2)||',
'| |strip(put(round(ceil(uppercl*100)/100,0.01),7.2)); output LSMeanCL&i&j.2;

end;

else if trtp='SA' then do;

    row=3; col3=put(round(lsmear,0.01),7.2); output LSMeanCL&i&j.3;

    row=4; col3=put(round(floor(lowercl*100)/100,0.01),7.2)||',
'| |strip(put(round(ceil(uppercl*100)/100,0.01),7.2)); output LSMeanCL&i&j.3;

end;

run;

data LSMeanDiffCL&i&j.1(keep=ord dord row col4 difference) LSMeanDiffCL&i&j.2(keep=ord dord row
col5);

set LSMeanDiffCL&i&j;

%if &i=6 %then %do;

    difference = difference; /* Ratio of geometric mean */

    LowerCL = LowerCL; /* 95% CI lower bound */

```

```

UpperCL = UpperCL; /* 95% CI upper bound */

%end;

%else %do;

difference = 100*exp(difference); /* Ratio of geometric mean */

LowerCL = 100*exp(LowerCL); /* 95% CI lower bound */

UpperCL = 100*exp(UpperCL); /* 95% CI upper bound */

%end;

length col4 col5 $20; ord=&i; dord=&j;

if _trtp='mCC' then do;

row=3; col4=put(round(difference,0.01),7.2); output LSMeanDiffCL&i&j.1;

row=4; col4=put(round(floor(lowercl*100)/100,0.01),7.2)||',
'| | strip(put(round(ceil(uppercl*100)/100,0.01),7.2)); output LSMeanDiffCL&i&j.1;

end;

if _trtp='SA' then do;

row=3; col5=put(round(difference,0.01),7.2); output LSMeanDiffCL&i&j.2;

row=4; col5=put(round(floor(lowercl*100)/100,0.01),7.2)||',
'| | strip(put(round(ceil(uppercl*100)/100,0.01),7.2)); output LSMeanDiffCL&i&j.2;

end;

run;

data ROOTMSE&i&j;

set ROOTMSE&i&j;

length col4cv $7; ord=&i; dord=&j;

CVperc=100*sqrt(exp(RootMSE**2)-1);

row=3; col4cv=put(round(ceil(CVperc*100)/100,0.01),7.2);

```

```

keep ord dord row col4cv;

run;

data pval&i&j;

set pval&i&j(obs=1);

set LSMeanDiffCL&i&j.1(where=(row=3) keep=row difference);

length col4 $20; ord=&i; dord=&j;

row=5;

%if &i=6 %then %do;

if (difference < 0) then Probt1=ProbtDiff/2;

else Probt1=1-ProbtDiff/2;

%end;

%else %do;

if (difference < 100) then Probt1=ProbtDiff/2;

else Probt1=1-ProbtDiff/2;

%end;

col4=put(Probt1,pvalue6.3);

%if &j=1 %then %do; call symputx("getp&i",Probt1); %end;

%else %do; if &&getp&i>0.05 then col4=""; %end;;

keep ord dord row col4;

run;

data struct&i&j;

```

```

set adbx2&i&j;

length hd $80 stat $40;

row=1; hd=param; output;

row=2; hd=propcase(avisit); stat='n'; output;

row=3; hd='';

%if &i=6 %then %do;

    stat='LS Mean';

%end;

%else %do;

    stat='Geometric LS Mean (CV%)';

%end;

```

```

output;

row=4; hd=''; stat='95% CI';output;

row=5; hd=''; stat='p-value (one-sided)';output;

keep ord dord row hd stat;

run;

```

```

data res&i&j;

    merge struct&i&j countn&i&j.1 countn&i&j.2 countn&i&j.3 LSMeanCL&i&j.1 LSMeanCL&i&j.2
    LSMeanCL&i&j.3 LSMeanDiffCL&i&j.1 LSMeanDiffCL&i&j.2 ROOTMSE&i&j pval&i&j;

    by ord dord row;

run;

```

```

data res&i&j;

```

```
set res&i&j;  
  
%if &i=6 %then %do;  
  
%end;  
  
%else %do;  
  
if row=3 then col4=trim(col4)||'('||strip(col4cv)||')';  
  
if row=3 then col5=trim(col5)||'('||strip(col4cv)||')';  
  
%end;  
  
run;
```

```
%end;  
%end;
```

```
ods rtf close;
```

```
data final;  
  
set %do i=1 %to &totttest; res&i.1 res&i.2 %end;;;;  
  
by ord dord;  
  
run;
```

```
data final;  
  
set final;  
  
by ord;  
  
if first.ord then pagen+1;  
  
drop difference;  
  
run;
```

```
data final;

set final;

by ord dord;

if first.dord and dord=2 then delete;

if stat='p-value' and col4="" then delete;

run;
```

```
data final;

set final end=eof;

by pagen;

if eof then call symputx("totalpage",pagen);

run;
```

```
data odata.&prgname.;

set final;

run;
```

```
%trtrtf(pgmname=&outname., pgmid=1, new=0, style=, bookmark=%lowercase(&outname.));

%do i=1 %to &totalpage;
```

```
title; footnote;
```

```
/*
```

```
title1 bold j=l "&title1 &title2";
```

title2 " ";

footnote1 bold h=12pt

"

_____";

footnote2 j=l h=9pt 'Note: Adjusted geometric least squares (LS) means and confidence intervals (CIs) from an ANCOVA model conducted with baseline value, '

'study arm, sex and mCC consumption reported at screening as fixed effect factors.';

footnote3 j=l h=9pt "Note: mCC = Menthol conventional cigarettes; THSm2.2 = Tobacco Heating System 2.2 Menthol.";

footnote4 j=l h=9pt "Note: p-value for one-sided test for comparison between THSm2.2 and mCC.";

footnote5 j=l h=9pt " ";

footnote6 h=9pt j=l "&APPENDIX.";

footnote7 h=9pt j=l "Study ID:ZRHM-REXA-07-JP Program: &prgname..sas Status:
&repversion./&fdate. Page: &i. of &totalpage";

*/

proc report data=final headskip headline nowd split='~' style=[outputwidth=100%] style(header
column)=[protectspecialchars=off];

where pagen=&i;

column pagen ord dord hd stat col1 col2 col3 col4 col5;

define pagen /order order=internal noprint;

define ord /order order=internal noprint;

define dord /order order=internal noprint;

define hd /display "Variable" style(column)=[cellwidth=12% just=l] style(header)=[just=l];

define stat /display "Statistic" style(column)=[cellwidth=15% just=l] style(header)=[just=l];

define col1 /display "THSm2.2" style(column)=[cellwidth=9% just=c];

define col2 /display "mCC" style(column)=[cellwidth=9% just=c];

```

define col3 /display "SA" style(column)=[cellwidth=9% just=c];

%if &i=6 %then %do;

define col4 /display "THSm2.2 - mCC~Difference" style(column)=[cellwidth=10% just=c];

define col5 /display "THSm2.2 - SA~Difference" style(column)=[cellwidth=10% just=c];

%end;

%else %do;

define col4 /display "THSm2.2 : mCC~Ratio (%)" style(column)=[cellwidth=10% just=c];

define col5 /display "THSm2.2 : SA~Ratio (%)" style(column)=[cellwidth=10% just=c];

%end;

```

COMPUTE before pagen;

LINE @1 " ";

ENDCOMP;

COMPUTE after dord;

LINE @1 "";

ENDCOMP;

compute before _page_ /style=[fontweight=bold fontsize=3.75];

line @1 "&title1 &title2";

line @1 "^R/RTF'\brdrb\brdrs\brdrw30\brsp20\b ' ";

endcomp;

compute after _page_ /style=[fontsize=1.75];

line @1 'Note: Adjusted geometric least squares (LS) means and confidence intervals (CIs) from an ANCOVA model conducted with baseline value, '

'study arm, sex and mCC consumption reported at screening as fixed effect factors.');

line @1 "Note: mCC = Conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.";

line @1 "Note: p-value is for the one-sided test for comparison between THSm2.2 and mCC. P-value at Day 90 is evaluated only if P-value at Day 5 "

"is significant, in all biomarkers except for Total NNAL.";

line @1 " ";

line @1 "&APPENDIX.";

line @1 "Study ID:ZRHM-REXA-07-JP Program: &fprgname..sas Status: &repversion./&fdate.
Page: &i. of &totalpage";

endcomp;

run;

%end;

ods listing;

ods rtf close;

%mend;

%doit;