

/*=====*

| Covance Study Number : COV- 106343 |

| Client Protocol ID : ZRHM-REXA-08-US |

| Program Name : t_anabioexp.sas |

| Purpose : Table Analysis of additional biomarkers Mixed model |

| Input Data : ADBX ADSL |

| Output Data : T_15_02_03_06 |

| |

| Macros Called : |

| |

| Originally Performed by : Seroan Zheng |

| Date/Time billed : 21May2015 |

| |

+=====+

| Modification History |

| |

| Programmer : Serona Zheng |

| Date : 01Jul2015 |

| Reason for Change : 1. Add 5 biomarkers for the primary: 'UMHBMCRE' 'U3HPMCRE' 'USPMACRE'
'UNNALCRE' 'CARBXHGB'|

| 2. Adjust column width for statistic |

| |

| Programmer : Serona Zheng |

| Date : 14Sep2015 |

| Reason for Change : Added base ne . and UCPDGR1 ne " condition to select analysis subjects based
on client comments|

+=====*/

options noquotelenmax;

***Create log file;

proc printto new

log="/cvn/projects/prj/development/000000106343/dev/tables/log/t_anabioexp_mix.log" ;

run;

%let status = Final;

proc format;

invalue paramid

'UMHBMCRE'=1

'U3HPMCRE'=2

'USPMACRE'=3

'CARBXHGB'=4

'UNNALCRE'=5

'CO'=6

'U1OHPCRE'=7

'UNNNCRE'=8

'U4ABPCRE'=9

'U1NACRE'=10

'U2NACRE'=11

'UOTOLCRE'=12

'UCEMACRE'=13

'UHEMACRE'=14

'UBAPCRE'=15

'UHMPMCRE'=16

'USBMACRE'=17

'UNEQCRE'=18

'UMHBM24U'=19

'U3HPM24U'=20

'USPMA24U'=21

'UNNAL24U'=22

'U1OHP24U'=23

'UNNN24U'=24

'U4ABP24U'=25

'U1NA24U'=26

'U2NA24U'=27

'UOTOL24U'=28

'UCEMA24U'=29

'UHEMA24U'=30

'UBAP24U'=31

'UHMPM24U'=32

'USBMA24U'=33

'UNEQ24U'=34

;

run;

%macro t_anabioexp_mix(t_name=,t_name_l=,t_pop1=,t_pop4=,t_title=,t_title_l=);

%let pgname=t_anabioexp_mix.sas;

%let table=&tflout.;

```

%let tflno=&t_name;

%let TFL_Part=%scan(&_SASPROGRAMFILE,-3,%str(/));

data _null_;

    tmp="&TFL_Part";

    if tmp not in ("dev" "qc") then call symput("TFL_Part", "prod");

    call symput('TFLpath', compress("&_SASPROGRAMFILE", ""));

run;

%put &tflpath;

***Get data from ADSL;

proc sort data=adam.adsl out=adsl; where pprot1fl = 'Y' or pprot4fl = 'Y';by usubjid;run;

***Get data from ADBX;

proc sort data=adam.adbx out=adbx1;

    where ((&t_pop1 = 'Y' and avisitn = 105) or (&t_pop4 = 'Y' and avisitn = 190)) and anl02fl = 'Y'
and anl01fl = 'Y' and dtype ne 'LOCF' and base ne . and UCPDGR1 ne " and

    paramcd in ('U1OHP24U' 'U1OHPCRE' 'UNNN24U' 'UNNNCRE' 'U4ABP24U' 'U4ABPCRE'
'U1NA24U' 'U1NACRE' 'UOTOL24U' 'UOTOLCRE' 'UCEMA24U' 'UCEMACRE'

'U2NA24U' 'U2NACRE' 'UHEMA24U' 'UHEMACRE'
'UBAP24U' 'UBAPCRE' 'UHMPMCRE' 'UHMPMCRE' 'USBMACRE' 'USBMA24U' 'UNEQ24U' 'UNEQCRE'

'UMHBM24U' 'UHMPM24U' 'USPMA24U' 'UNNAL24U'
'U3HPM24U' 'UMHBMCRE' 'U3HPMCRE' 'USPMACRE' 'UNNALCRE'); ***Add 5 biomarkers for the
primary;

    by usubjid paramn;

```

```
run;
```

```
proc sort data=adam.adbx out=adbx2;
```

```
    where ((&t_pop1 = 'Y' and avisitn = 105) or (&t_pop4 = 'Y' and avisitn = 190)) and anl02fl = 'Y'  
    and anl01fl = 'Y' and dtype ne 'LOCF' and base ne . and UCPDGR1 ne " and
```

```
        paramcd = 'CO' and (atptn = 6.45 or avisitn = 190);
```

```
    by usubjid paramn;
```

```
run;
```

```
proc sort data=adam.adbx out=adbx3;
```

```
    where ((&t_pop1 = 'Y' and avisitn = 105 and atptn = 6.45) or (&t_pop4 = 'Y' and avisitn = 190)) and  
    anl02fl = 'Y' and anl01fl = 'Y' and dtype ne 'LOCF' and base ne . and UCPDGR1 ne " and
```

```
        paramcd = 'CARBXHGB';
```

```
    by usubjid paramn;
```

```
run;
```

```
data adbx;
```

```
    set adbx1(in=a) adbx2(in=b) adbx3(in=c);
```

```
    if a or c then do;
```

```
        if aval not in (.,0) then do;
```

```
            logaval=log(aval);
```

```
                if base not in (.,0) then logbase=log(base);
```

```
            end;
```

```
        end;
```

```
    if b then avisit=strip(atpt);
```

```
run;
```

```
***Get decimal length;
```

```
data temp;
```

```
    set adbx;
```

```
    declen=lengthn(scan(strip(put(aval, best.)),2,"."));
```

```
run;
```

```
proc sql;
```

```
    create table dectemp
```

```
    as select distinct paramn, max(declen) as declen
```

```
    from temp
```

```
    group by paramn;
```

```
quit;
```

```
***Create param temp;
```

```
proc freq data=adbx;
```

```
table paramn*paramcd*param / list out=temp_p(drop=count percent);run;
```

```
***Calculate STAT;
```

```
%macro mix_nc(dsin_m,conf1=,var=,base=,dsout_m=,dsoutm_f=,logf=);
```

```
data anal;
```

```
    set &dsin_m;
```

```
    &conf1;
```

```
run;
```

```
proc sort data=anal;by paramn paramcd param avisitn avisit;run;
```

```
***Calculate STAT using MIXED model;
```

```
Proc mixed data=anal;
```

```
by paramn paramcd param avisitn avisit;
```

```
Class trtp sex UCPDGR1;
```

```
Model &var = &base sex UCPDGR1 trtp;
```

```
Lsmean trtp / pdiff =control('mCC') alpha=0.05 cl;
```

```
Lsmean trtp / pdiff =control('SA') alpha=0.05 cl;
```

```
ods output diffs = diffs;
```

```
ods output covparms = fit;
```

```
ods output lsmeans = lsmeans;
```

```
Run;
```

```
***prepare mean and ci for each group;
```

```
data lsmeans(where=(colord ne .));
```

```
length out stat $100;
```

```
merge lsmeans(in=a) dectemp;
```

```
by paramn;
```

```
if a;
```

```
***ordering columns of treatments*;
```

```
if trtp='THSm2.2' then colord=1;
```

```

else if trtp='mCC' then colord=2;

else if trtp='SA' then colord=3;


%if &var=logaval %then %do;

    if estimate ne . then estimatee=exp(estimate);

    if lower ne . then lowere=exp(lower);

    if upper ne . then uppere=exp(upper);

%end;

%else %do;

    estimatee=estimate;

    lowere=Lower;

    uppere=Upper;

%end;


    ***Gmean (CV%) row*;

ord=2;

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

    if estimatee ne . then out=compress(put(round(estimatee,0.01),12.2));

output;


ord=3;

stat='95% CI';

    if nmiss(lowere,uppere)=0 then out=compress(put(floor(100*lowere)/100,12.2))||',
'|compress(put(ceil(100*uppere)/100,12.2));

output;

run;

```



```
***prepare mean and ci for difference;
```

```
data diff;
```

```
merge diffs(in=a where=(trtp='THSm2.2')) fit(in=b rename=(estimate=rootmse));
```

```
by paramn paramcd param avisitn avisit;
```

```
if a;
```

```
run;
```

```
data diff;
```

```
length out stat $100;
```

```
merge diff(in=a) dectemp(in=c);
```

```
by paramn;
```

```
if a;
```

```
***ordering columns of treatments*;
```

```
if _trtp='mCC' then colord=4;
```

```
if _trtp='SA' then colord=5;
```

```
%if &var=logaval %then %do;
```

```
if estimate ne . then estimatee=exp(estimate);
```

```
if lower ne . then lowere=exp(lower);
```

```
if upper ne . then uppere=exp(upper);
```

```
/* MSE=(rootmse)**2;*/
```

```
MSE = rootmse;
```

```
CV_=100*sqrt(exp(MSE)-1);
```

```
cv = put(ceil(CV_*100)/100,12.2);
```

```

        ord=3;

stat='95% CI';

        out=compress(put(floor(100*lowere*100)/100,12.2))||',
'| |compress(put(ceil(100*uppere*100)/100,12.2));

        output;

ord=2;

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

        out=compress(put(round(100*estimatee,0.01),12.2))||'('||COMPRESS(cv)||')';

        output;

%end;

%else %do;

        estimatee=estimate;

        lowere=Lower;

        uppere=Upper;

ord=3;

stat='95% CI';

out=compress(put(floor(100*lowere)/100,12.2))||', '||compress(put(ceil(100*uppere)/100,12.2));

        output;


ord=2;

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

        out=compress(put(round(estimatee,0.01),12.2));

        output;

%end;

run;

```

```

***Calculate N;

proc univariate data=anal noprint;

  by paramn paramcd param avisitn avisit;

  class trtp;

  var &var;

  output out=num1 n=n1;

run;

```

```

data num1;

  length trtp $7;

  set num1(rename=(trtp=trtp1));

  trtp = trtp1;

  drop trtp1;

run;

```

```

data num1;

  merge num1(in=a) dectemp;

  by paramn;

  if a;

  ***ordering columns of treatments*;

  if trtp='THSm2.2' then colord=1;

  else if trtp='mCC' then colord=2;

  else if trtp='SA' then colord=3;

  ord=1;

  stat='n';

```

```

out=compress(put(n1,best.));

      if colord ne .;

run;

*p-value;

data pval1;

      length out stat $100;

      set diffs(keep=paramn paramcd param avisitn avisit trtp _trtp probt);

      by paramn avisitn avisit;

      where trtp="THSm2.2";

***ordering columns of treatments*;

      if first.avisitn then colord=4;

      if last.avisitn then colord=5;

      ord=4;

      stat='p-value (one-sided)';

      if probt = <.0001 then out="<0.001";

      else do;

          pval_=probt/2;

          if pval_ < 0.001 then out="<0.001";

          else if pval_ > 0.999 then out=">0.999";

          else if 0.001 < pval_ < 0.999 then out=put(pval_,5.3);

      end;

      if _trtp='SA' then call missing(out);

run;

```

```
***Get day 5 pvalue;
```

```
data p_d5;
```

```
    set pval1;
```

```
    if AVISITN = 105 and _trtp = 'mCC';
```

```
    rename probt = p_d5;
```

```
    keep paramn probt;
```

```
run;
```

```
data pval2;
```

```
    merge pval1(in=a) p_d5;
```

```
    by paramn;
```

```
    if a;
```

```
    if paramcd not in ('UNNN24U' 'UNNNCRE') and avisitn = 190 and (p_d5/2 > 0.025) then call  
missing(out);
```

```
run;
```

```
data tabout;
```

```
    set lsmeans diff num1 pval2;
```

```
    by paramn paramcd param avisitn avisit ;
```

```
run;
```

```
proc sort data=tabout nodupkey; by paramn paramcd param avisitn avisit ord stat out colord;run;
```

```
proc transpose data=tabout out=&dsout_m.(drop=_NAME_) prefix=col;
```

```
    by paramn paramcd param avisitn avisit ord stat;
```

```
    id colord;
```

```

var out;

run;

data &dsout_m;

    set &dsout_m;

    logf = &logf;

run;

%mend;

***Create model result to lst file;

ods rtf

file="/cvn/projects/prj/data/000000106343/TFL/dev/Tables/&t_name_1..rtf" ;

run;

title "&t_title_1";

%mix_nc(dsin_m=adbx,conf1=%str(if paramcd ne
'CO'),var=logaval,base=logbase,dsout_m=anl_f_nco,logf=1);

%mix_nc(dsin_m=adbx,conf1=%str(if paramcd eq 'CO'),var=aval,base=base,dsout_m=anl_f_co,logf=0);

ods rtf close;

data final1(drop=paramn);

    set anl_f_nco(in=a) anl_f_co(in=b);

    if paramcd = 'CO' then do;

```

```

        if stat = "Geometric LS Mean (CV%)" then stat = "LS Mean";

        else if stat = "" then stat = "";

        else stat = stat;

    end;

run;

data final1;

    set final1;

    paramn = input(paramcd,paramid.);

run;

proc sort data=final1;by paramn avisitn ord;run;

data final;

    set final1;

    by paramn avisitn ord;

    page = ceil(_n_/8);

    if avisitn = 105 then avisitn = 5;

    else if avisitn = 190 then avisitn = 90;

    if last.paramn then call symput('tpage',put(page,best.));

    if paramn = . then delete;

run;

data final;

    set final;

    if paramcd = 'CO' and avisit = 'DAY 5 - 20:00 - 21:30' then avisit = 'Day 5';

```

```
        if paramcd = 'CO' and avisit = 'DAY 90' then avisit = 'Day 90';  
run;
```

```
%put &tpage;  
%let tpage=&tpage;  
data tflds.&tflno.;  
        set final;  
run;
```

```
options number nodate orientation=landscape /* papersize=&p_pgsz */ missing=' '  
ods escapechar='$';  
%let linetop = \brdrt\brdrs\brdrw30; * needs to be 1.5pt so calculated in twips (1/20 pt) ;  
%let linebot = \brdrb\brdrs\brdrw30;  
%macro outrtf(blankn=, halfblnk=);  
  
%if &halfblnk=N %then %let halfblnk=;  
  
%else %if &halfblnk=Y %then %let halfblnk=\~;
```

```
ods path stdlib.t106343 (read) ;  
ods results off;  
  
ods rtf toc_data file="/cvn/projects/prj/data/000000106343/TFL/dev/Tables/&tflno..rtf" style=t106343  
startpage=yes headery=1440 footery=1440 ;  
  
ods noproctitle;
```



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

```
title ;
```

```
footnote;
```

```
%let wd=0;
```

```
ods proclabel=' ';
```

```
data comp;
```

```
    set final end=eof;
```

```
        where page=&i;
```

```
    call symput('param',param);
```

```
        call symput('paramcd',paramcd);
```

```
/* Amend title as needed */
```

```
    _firtitl="&t_title";
```

```
    _upcas=(length("Path: &TFLpath.")-  
length(compress("Path:&TFLpath.",'ABCDEFGHIJKLMNOPQRSTUVWXYZ')))/2;
```

```
    len=&blankn.-length("(page &i of &tpage)");
```

```
    if eof then do;
```

```
        call symput('_FSRTITL', trim(left(_firtitl)));
```

```
        call symput('_blankn', compress(put(len,best.)));
```

```
    end;
```

```
    drop _firtitl _upcas len;
```

```
run;
```

ods listing close;

* most set up in template others below;

* title arial 12pt bold with 12pt paragraph space below;

* all headers to be arial 11pt bold;

* data arial 10pt;

* headers to be central, text values left aligned and numeric centered around decimal point;

```
proc report data = comp missing headline headskip missing nowd split = '$' %if &i=1 %then %do;  
contents=' ' %end; %else %do; contents="" %end;; ;
```

```
column page paramn avisitn avisit ord stat col1 col2 col3 col4 col5;
```

```
define page      / order order=internal noprint;
```

```
define paramn    / order order = internal noprint;
```

```
define avisitn   / order order = internal noprint;
```

```
define ord       / order order=internal noprint;
```

```
define avisit    / order style={just=left cellwidth=2cm} style(header)={just=left} "Variable" id;
```

```
define stat      / display style={just=left cellwidth=3cm} style(header)={just=left} "Statistic";
```

```
define col1      / display style={just=c cellwidth=2cm} style(header)={just=center} "THSm2.2";
```

```
define col2      / display style={just=c cellwidth=2cm} style(header)={just=center} "mCC";
```

```
define col3      / display style={just=c cellwidth=2cm} style(header)={just=center} "SA";
```

```
%if &paramcd = CO %then %do;
```

```
define col4 / display style={just=c cellwidth=2cm} style(header)={just=center} "THSm2.2 -  
mCC Difference";
```

```
define col5 / display style={just=c cellwidth=2cm} style(header)={just=center} "THSm2.2 - SA  
Difference";
```

```
%end;
```

```
%else %do;
```

```
define col4 / display style={just=c cellwidth=2cm} style(header)={just=center} "THSm2.2 : mCC  
$Ratio (%)";
```

```
define col5 / display style={just=c cellwidth=2cm} style(header)={just=center} "THSm2.2 : SA  
$Ratio (%)";
```

```
%end;
```

```
break after page / page;
```

```
compute after avisitn;
```

```
line " ";
```

```
endcomp;
```

```
compute before page / style={just=left protectspecialchars=off fontsize=10pt};
```

```
line "&linetop";
```

```
line "&param";
```

```
endcomp;
```

```
compute before _page_ / style={just=left protectspecialchars=off};
```

```
line "\b\fs24\sa24&_FSRTITL." ; * \b = bold, \fs24 is font size 12pt, \sa24 is space after 12pt;
```

```
line "&linebot";
```

```
endcomp;
```

```

%if &paramcd = CO %then %do;

  compute after _page_/ style={just=left protectspecialchars=off pretext="&linetop."};

    line 'Note: Adjusted least squares (LS) means and confidence intervals (CIs) from an
Mixed model conducted with baseline value, study arm, sex and mCC consumption reported at
screening as fixed effect factors.';

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

    line '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 ' ';

    line 'Appendix 15.3.3.1';

    line "Study ID: ZRHM-REXA-08-US" " " "Program: &pgname" " " "Status: &status"
" " "&sysdate" " " "(Page &i of &tpage)";

  endcomp;

%end;

%else %do;

  compute after _page_/ style={just=left protectspecialchars=off pretext="&linetop."};

    line 'Note: Adjusted geometric least squares (LS) means and confidence intervals (CIs)
from an Mixed model conducted on log-transformed values with log-transformed baseline value, study
arm, sex and mCC consumption reported at screening as fixed effect factors. Geometrical CV% of the
ratio is estimated from the residual mean squares.';

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

    line '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 ' ';

    line 'Appendix 15.3.3.1';

```

```

line "Study ID: ZRHM-REXA-08-US" " " "Program: &pgname" " " "Status: &status"
" "&sysdate" " "(Page &i of &tpage)";

endcomp;

%end;

run;

%end;

ods rtf close;

ods results on;

ods path sashelp.tmplmst (read);

%mend ;

%outrtf(blankn=70, halfblnk=N);

***Deletes all SAS files in the WORK library that are available for processing;

proc datasets library=work kill;

run;

%mend;

***For table 15.2.3.6;

%t_anabioexp_mix(

t_name=T_15_02_03_06,

t_name_l=L_15_04_03_06,

t_pop1=pprot1fl,t_pop4=pprot4fl,

```

t_title=%str(Table 15.2.3.6 Sensitivity Analysis of Additional Biomarkers
of Exposure versus mCC and SA using Mixed Model on Day 5/90 Visit - PP Set),

t_title_l=%str(Listing 15.4.3.6 Sensitivity Analysis of Additional
Biomarkers of Exposure versus mCC and SA using Mixed Model on Day 5/90 Visit - PP Set)

);

options quotelenmax;

ods path WORK.TEMPLAT(UPDATE)

SASUSER.TEMPLAT(READ)

SASHELP.TMPLMST(READ) ;

ods listing;

proc printto ;

run;

***check the log, if there is any findings, please make sure to resolve;

%m_chklog(TFL_part=dev,pgm_type=tables,pgm_name=t_anabioexp_mix,serv=dev,covstudyid=000000
106343);