

```
/*=====
=====*
```

```
| Covance Study Number   : 000000106343          |
| Program Name           : t_senanl_boexp.sas      |
| Purpose                : Sensitivity Analysis of COHB, MHBMA, 3-HPMA, S-PMA, and total NNAL  |
|                        :                          |
|                        : on Day 5/90 - primary obj - pp
|                        :                          |
| Input Data             : ADAM.ADBX              |
| Output Data            : T_15_02_03_01_02        |
| Macros Called          : m_printto, m_logchk     |
| Originally Performed by : kpothuri              |
| Date                   : 23Apr2015              |
|                        :                          |
|                        :                          |
```

```
|=====
=====|
```

```
| Modification History          |
|-----|
| Modified by                   :                    |
| Modification Date             :                    |
| Modification Description      :                    |
```

```
+=====
=====*/
```

```
options notes source source2 nofullstimer validvarname=upcase missing=' ' NOQUOTELNMAX;
```

```
ods _all_ close;
```

```
ods listing;
```

```
%m_printto(route=YES);
```

```
*=====;
```

```
* START OF PROGRAM CODE ;
```

```
*=====;
```

```
proc datasets lib=work nolist memtype=data kill; quit;
```

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

```
/* Standard - leave this */
```

```
data _null_;
```

```
    tmp("&TFL_Part");
```

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

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

```
        call symput('TFLprg',reverse(scan(strip(reverse(compress("&_SASPROGRAMFILE", ""))),1,"/")));
```

```
run;
```

```
proc sort data=adam.adbx out=bx_units (keep=paramcd param paramn avalu) nodupkey; by paramcd;
```

```
where paramcd in ("CARBXHGB", "UMHBMCRE", "U3HPMCRE", "USPMACRE", "UNNALCRE"); run;
```

```
data _null_;
```

```
    set bx_units;
```

```
    call symput ("u_" || compress(paramcd), strip(param));
```

```
    call symput ("n_" || compress(paramcd), strip(put(paramn,best.)));
```

```
run;
```

```
%put &u_CARBXHGB &u_UMHBMCRE &u_U3HPMCRE &u_USPMACRE &u_UNNALCRE;
```

```
%put &n_CARBXHGB &n_UMHBMCRE &n_U3HPMCRE &n_USPMACRE &n_UNNALCRE;
```

```
%macro p (tabn=, day=, where=, seq=, dset=);
```

```
*Counts;
```

```
proc sort data=adam.adbx(where=(DTYPE ne "LOCF" and anl02fl= 'Y' and anl01fl= 'Y' and &where))
```

```
    out=adbxin1;
```

```
    by SUBJID;
```

```
run;
```

```
proc freq data=adbxin1 (where=(BASE ne .)) noprint;
```

```
    table trtp/out=f_param (drop=percent);
```

```
run;
```

```
data f_param;
```

```
length count_ $27;
```

```
    set f_param;
```

```
    if trtp="THSm2.2" then trtp="THS";
```

```
    count_=put(count,best.);
```

```
run;
```

```
proc transpose data=f_param out=t_count;
```

```
    id trtp;
```

```
    var count_;
```

```
run;
```

```
data adbx1 missing;
```

```
    set adbxin1;
```

```

if aval not in (.,0) and base not in (.,0) then do; *need to add BASE for missing value calculation;

    logaval=log(aval);

        logbase=log(base);

    output adbx1;

end;

else output missing;

run;

proc mixed data=adbx1;

    Class trtp sex UCPDGR1;

    Model logaval = logbase sex UCPDGR1 trtp / outp=pred;

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

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

    ods output lsmeans=lsmeans (keep=trtp lower upper estimate); *each arm;

    ods output diffs=diffs (keep=trtp lower upper probt estimate); *ratios;

    ods output covparms=estimate(rename=(estimate=mse)); *MSE;

run;

*RootMSE;

data mse;

    set estimate;

    format mse;

run;

data _null_;

    set mse;

```

```

        call symput ("e_" || compress(covparm), strip(put(mse,best.)));

run;

%put &e_residual;

*lsmean and C.I. for ratios;

data diffs1;

    set diffs;

    format lower upper estimate Probt;

    where trtp="THSm2.2";

    if _n_=1 then labnum="MCC";

    if _n_=2 then labnum="SA";

run;

data LSM_CL;

    set diffs1;

    diff_=exp(estimate);

    L_CI_=exp(lower);

    U_CI_=exp(upper);

    Cl=compress(put(floor(100*L_CI_*100)/100,12.2))||',
' || compress(put(ceil(100*U_CI_*100)/100,12.2));

    MSE=&e_residual;

    CV_=10000*sqrt(exp(MSE)-1);

    CV=put((ceil(CV_)/10000)*100,12.2);

```

```

lsmean_=compress(put(round(100*diff_,0.01),12.2))||'('||compress(CV)||')';

run;

proc transpose data=LSM_CL out=t_LSM_CL (rename=(SA=ths_sa_ratio mcc=ths_mcc_ratio));

    id labnum;

    var lsmean_ CI;

run;

*p-value;

data stat_pval;

    set diffs1;

    if not missing(Probt) then pval_=Probt/2;

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

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

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

run;

proc transpose data=stat_pval out=t_stat_pval (rename=(SA=ths_sa_ratio mcc=ths_mcc_ratio));

    id labnum;

    var pval;

run;

*lsmean, C.I.;

proc sort data=lsmeans out=lsmeans1 nodupkey; by trtp estimate lower upper; run;

data lsmeans1;

    set lsmeans1;

```

```

        format estimate lower upper;

run;

data stat;

    set lsmeans1;

    lsmean_ = put(exp(estimate),8.2);

    LowerCL_ = exp(Lower);

    UpperCL_ = exp(Upper);

    Cl = compress(put(floor(100*LowerCL_)/100,8.2)) || ',
'| | compress(put(ceil(100*UpperCL_)/100,8.2));

    if trtp="THSm2.2" then trtp="THS";

run;

proc transpose data=stat out=t_stat;

    id trtp;

    var lsmean_ Cl;

run;

*set of stats for one day;

proc sort data=t_count; by _name_; run;

proc sort data=T_STAT; by _name_; run;

data set5;

    merge t_count T_STAT;

    by _name_ SA THS MCC;

run;

```

```

proc sort data=set5; by _name_; run;

proc sort data=t_lsm_cl; by _name_; run;

data set5_a;

    merge set5 t_lsm_cl;

    by _name_;

run;

data &dset (drop=THS_SA_RATIO THS_MCC_RATIO THS SA MCC);

length _name_ $30 visit $20;

    set set5_a t_stat_pval;

    seq=&seq; *depends on what day;

    tabn=&tabn; *parameter;


    if _name_="COUNT_" then do;

        _name_="n";

        visit="&day";

        num=1;

    end;

    else if _name_="LSMEAN_" then do;

        _name_="Geometric LS Mean (CV%)";

        num=2;

    end;

    else if _name_="CI" then do;

        _name_="95% CI";

        num=3;

    end;

```



```

else if _name_="PVAL" then do;
    _name_="p-value (one-sided)";
    num=4;
end;

SA_=strip(SA);
THS_=strip(THS);
MCC_=strip(MCC);
THS_MCC_RATIO_=strip(THS_MCC_RATIO);
THS_SA_RATIO_=strip(THS_SA_RATIO);

run;

proc sort data=&dset; by num; run;

%mend p;

*Sensitivity analysis - primary obj - pp set;

%p(tabn=1, day=Day 5,
where=%str(pprot1fl="Y" and paramcd="CARBXHGB" and avisitn=105 and atpt="DAY 5 - 20:00 - 21:30"),
seq=1, dset=cohb_5);

%p(tabn=1, day=Day 90,
where=%str(pprot4fl="Y" and paramcd="CARBXHGB" and avisitn=190),
seq=2, dset=cohb_90);

%p(tabn=2, day=Day 5,
where=%str(pprot1fl="Y" and paramcd="UMHBMCRE" and avisitn=105), seq=1, dset=mhbma_5);

%p(tabn=2, day=Day 90,

```

```
where=%str(pprot4fl="Y" and paramcd="UMHBMCRE" and avisitn=190), seq=2, dset=mhbma_90);
```

```
%p(tabn=3, day=Day 5,
```

```
where=%str(pprot1fl="Y" and paramcd="U3HPMCRE" and avisitn=105), seq=1, dset=HPMA_5);
```

```
%p(tabn=3, day=Day 90,
```

```
where=%str(pprot4fl="Y" and paramcd="U3HPMCRE" and avisitn=190), seq=2, dset=HPMA_90);
```

```
%p(tabn=4, day=Day 5,
```

```
where=%str(pprot1fl="Y" and paramcd="USPMACRE" and avisitn=105), seq=1, dset=PMA_5);
```

```
%p(tabn=4, day=Day 90,
```

```
where=%str(pprot4fl="Y" and paramcd="USPMACRE" and avisitn=190), seq=2, dset=PMA_90);
```

```
%p(tabn=5, day=Day 5,
```

```
where=%str(pprot1fl="Y" and paramcd="UNNALCRE" and avisitn=105), seq=1, dset=NNAL_5);
```

```
%p(tabn=5, day=Day 90,
```

```
where=%str(pprot4fl="Y" and paramcd="UNNALCRE" and avisitn=190), seq=2, dset=NNAL_90);
```

```
%let l_name = %str(L_15_04_03_01_02);
```

```
%let t_title_l = %nrquote(Listing 15.4.3.1.2 Sensitivity Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and  
Total NNAL on Day 5/90 Visit for THS 2.2 Menthol versus mCC for the Primary Objective using Mixed  
Model- PP Set);
```

```
ods rtf
```

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

```
title "&t_title_l";
```

options orientation=landscape;

%p(tabn=1, day=Day 5,

where=%str(pprot1fl="Y" and paramcd="CARBXHGB" and avisitn=105 and atpt="DAY 5 - 20:00 - 21:30"),

seq=1, dset=cohb_5);

%p(tabn=1, day=Day 90,

where=%str(pprot4fl="Y" and paramcd="CARBXHGB" and avisitn=190),

seq=2, dset=cohb_90);

%p(tabn=2, day=Day 5,

where=%str(pprot1fl="Y" and paramcd="UMHBMCRE" and avisitn=105), seq=1, dset=mhbma_5);

%p(tabn=2, day=Day 90,

where=%str(pprot4fl="Y" and paramcd="UMHBMCRE" and avisitn=190), seq=2, dset=mhbma_90);

%p(tabn=3, day=Day 5,

where=%str(pprot1fl="Y" and paramcd="U3HPMCRE" and avisitn=105), seq=1, dset=HPMA_5);

%p(tabn=3, day=Day 90,

where=%str(pprot4fl="Y" and paramcd="U3HPMCRE" and avisitn=190), seq=2, dset=HPMA_90);

%p(tabn=4, day=Day 5,

where=%str(pprot1fl="Y" and paramcd="USPMACRE" and avisitn=105), seq=1, dset=PMA_5);

%p(tabn=4, day=Day 90,

where=%str(pprot4fl="Y" and paramcd="USPMACRE" and avisitn=190), seq=2, dset=PMA_90);

%p(tabn=5, day=Day 5,

```
where=%str(pprot1fl ="Y" and paramcd="UNNALCRE" and avisitn=105), seq=1, dset=NNAL_5);
```

```
%p(tabn=5, day=Day 90,
```

```
where=%str(pprot4fl ="Y" and paramcd="UNNALCRE" and avisitn=190), seq=2, dset=NNAL_90);
```

```
ods rtf close;
```

```
*assemble for one parameter;
```

```
%macro param_set (param_5=, param_90=, dset_1=, page=, parm=);
```

```
data all;
```

```
    set &param_5 &param_90;
```

```
run;
```

```
data dum;
```

```
length visit $200;
```

```
    seq=1;
```

```
    num=0;
```

```
    visit="&parm";
```

```
    output;
```

```
    seq=1;
```

```
    num=5;
```

```
    visit="";
```

```

        output;

run;

data &dset_1;

    merge dum all;

    by seq num visit;

    pageord=&page;

run;

%mend param_set;


%param_set (param_5=cohb_5, param_90=cohb_90, dset_1=cohb, page=4, parm=&u_CARBXHGB);

%param_set (param_5=mhbma_5, param_90=mhbma_90, dset_1=mhbma, page=1,
parm=&u_UMHBMCRE);

%param_set (param_5=HPMA_5, param_90=HPMA_90, dset_1=HPMA, page=2, parm=&u_U3HPMCRE);

%param_set (param_5=PMA_5, param_90=PMA_90, dset_1=PMA, page=3, parm=&u_USPMACRE);

%param_set (param_5=NNAL_5, param_90=NNAL_90, dset_1=NNAL, page=5, parm=&u_UNNALCRE);


data comb (drop=THS_SA_RATIO_SA_);

    set cohb mhbma HPMA PMA NNAL;

    by pageord;

run;


%macro anlout (din=, tfl=, tabname=);

```

```
%let tflno=&tfl.;
```

```
data tflds.&tflno;
```

```
    set &din;
```

```
run;
```

```
data tflds.&tflno;
```

```
    set tflds.&tflno end=last;
```

```
    by pageord;
```

```
    if last then call symputx("page", pageord);
```

```
run;
```

```
%put &page;
```

```
/* Standard - leave this */
```

```
options number nodate orientation=landscape 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;
```

```
/* Standard - macro for paging */
```

```
%macro outrtf(blankn=130, halfblnk=N);
```

```
%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/&TFL_Part./Tables/&tflno..rtf"
style=t106343 startpage=yes headery=1440 footery=1440 ;

ods noproctitle;

%do i=1 %to &page;

title ;

footnote;

%let wd=0;

ods proclabel = ' ';

data comp;

    set tflds.&tflno end=eof;

        where pageord=&i;

        /* Amend title as needed */

            _firtitl="&tabname";

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

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

            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;

/* Update with your variables as needed */

```

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

```

```

column pageord visit _name_ ths_ mcc_ THS_MCC_RATIO_;

define pageord / order order = internal noprint;

define visit /"Variable" display style={just=left cellwidth=2.0cm}
style(header)={just=left} "";

define _name_ /"Statistic" display style={just=left cellwidth=2.0cm} style(header)={just=left} "";

define ths_ /"THSm2.2" display style={just=c cellwidth=1.2cm}
style(header)={just=center} ;

define mcc_ /"mCC" display style={just=c cellwidth=1.2cm}
style(header)={just=center};

```



```
define THS_MCC_RATIO_ /"THSm2.2 : mCC$ Ratio (%)" display style={just=c  
cellwidth=1.4cm} style(header)={just=center};
```

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

```
compute after pageord;
```

```
line " ";
```

```
endcomp;
```

```
compute before pageord / style={protectspecialchars=off};;
```

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

```
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;
```

```
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; THSm2.2 = Tobacco Heating System  
2.2 Menthol.';
```

```
line 'Note: p-value for 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 'Note: For the primary analysis, Total NNAL is evaluated at Day 90 while the  
other biomarkers are evaluated at Day 5. For the secondary analysis, Total NNAL is evaluated at Day 5  
while the other biomarkers are evaluated at Day 90.';
```

```
line ";
```

```
line 'Appendix 15.3.3.1 and 15.3.3.2';
```

```
line "Study ID: ZRHM-REXA-08-US Program: &TFLprg Status: &status"  
&_blankn.*"\~\~" "&sysdate" &_blankn.*"\~\~" "(Page &i of &page)";
```

```
endcomp;
```

```
run;
```

```
%end;
```

```
ods rtf close;
```

```
ods results on;
```

```
ods path sashelp.tmplmst (read);
```

```
%mend ;
```

```
%outrtf(blankn=36, halfblnk=N);
```

```
ods listing;
```

```
%mend anlout;
```

```
%anlout (din=comb, tfl=%str(T_15_02_03_01_02), tabname=%str(Table 15.2.3.1.2 Sensitivity  
Analysis of COHb, MHBMA, 3-HPMA, S-PMA, and Total NNAL on Day 5/90 Visit for THS 2.2 Menthol  
versus mCC for the Primary Objective using Mixed Model - PP Set));
```

```
*=====;
```

* END OF PROGRAM CODE ;

*=====;

%m_logchk;