

```

%_mprintto;
options notes nosource;
proc datasets lib=work nolist memtype=data kill; quit;
/* Standard - leave this */
%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",""));
run;
%put NOTE:
=====;
%put NOTE: Covance Study Number : 000000106326;
%put NOTE: Client Protocol ID   : ZRHM-PK-05-JP;
%put NOTE: Program Name        : t_anlpk41.sas;
%put NOTE: Purpose              : table and figure of secondary PK data;
%put NOTE: ;
%put NOTE: Input Data           : ADAM.ADPP;
%put NOTE: Output               : L_15_04_04_01(PK) T_15_2_4_01(PK) ;
%put NOTE: Macros Called        : _MPRINTTO;
%put NOTE: ;
%put NOTE: Programmed by        : cvn_ahall;
%put NOTE: Creation Date        : 2014-30-04;
%put NOTE: SAS Version          : 9.3;
%put NOTE: ;
%put NOTE: == Latest Run
=====;
%put NOTE: Run by                : &sysuserid;
%put NOTE: Date/Time             :
%sysfunc(putn(%sysfunc(date()),e8601da.))T%sysfunc(putn(%sysfunc(time()),
e86011z.));
%put NOTE: ;
%put NOTE: == Modification History
=====;
%put NOTE: Date      Initials    No. Reason;
%put NOTE: 24Jun2014  AMH         2) Conservative rounding for the CV, SD
and 95% CI;
%put NOTE: 24Jun2014  AMH         3) Small n in statistics row ;
%put NOTE: 24Jun2014  AMH         4) correct gmean statistic to read:
Geometric LS Mean (CV%);
%put NOTE: 24Jun2014  AMH         5) Ammend footnotes;
%put NOTE: 24Jun2014  AMH         6) Ammend statistic labels;
%put NOTE: 24Jun2014  AMH         7) Add PK listing to reference list;
%put NOTE: 24Jun2014  AMH         8) Remove footnote reference tmax;
%put NOTE: 24Jun2014  AMH         9) Add where clause used on dataset to
listing;
%put NOTE: 24Jun2014  AMH         10) Amend Menthol to menthol;
%put NOTE: 24Jun2014  AMH         11) TMAX on seperate page with seperate
headers;
%put NOTE: 07Aug2014  AMH         12) Center output;
%put NOTE: 07Aug2014  AMH         13) Combine footnotes [1] and [2];

```

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%put NOTE: 07Aug2014    AMH          14) correct footnotes [1] to 1 and [1]
to Note: 1: in footnote;
%put NOTE: 07Aug2014    AMH          15) Add paramter totals to listing;
%put NOTE: 07Aug2014    AMH          16) Change where clause depending on
variable;
%put NOTE: 12Aug2014    AMH          17) Ammend listing typo;
%put NOTE: ;
%put NOTE:
=====;
options notes source source2 nofullstimer validvarname=upcase missing=' '
NOQUOTELNMAX/*turn off warnings about quoted strings to long*/;;
ods _all_ close;
ods listing;

/*formats macro and appendix output macros*/
%include
"/cvn/projects/prj/development/000000106326/dev/adhoc/TMPLTMIX.sas";
/*Wilcoxon Signed Rank Macro*/
%include
"/cvn/projects/prj/development/000000106326/dev/adhoc/WSIGRANK.sas";

*=====;
* START OF PROGRAM CODE                                     ;
data adsl;
    set adam.adsl(where=(pprotfl='Y'));
    if analgrln=1 then do;
        if index(trt01a,'THS 2.2') or index(trt02a,'THS 2.2') then
colord=1;
        output;
        if index(trt01a,'CC') or index(trt02a,'CC') then colord=2;
        output;
    end;
    else if analgrln=2 then do;
        if index(trt01a,'THS 2.2') or index(trt02a,'THS 2.2') then
colord=1;
        output;
        if index(trt01a,'NRT') or index(trt02a,'NRT') then colord=2;
        output;
    end;
    else if missing(analgrln) then delete;
run;

proc sort data=adsl nodupkey out=adsl1;
    by analgrln analgrl colord subjid;
run;

proc freq data=adsl1(where=(not missing(colord))) noprint;
    table analgrln*analgrl*colord/ out =totals2(drop=percent
rename=(count=total));
run;

data _null_;

```

```

        set totals2;
        call
symput('tot' || strip(put(colord,best.)) || strip(put(analgrln,best.)), strip(
put(total,best.)));
run;
/*ALL subject exclusions*/ /* 15) AMH 06Aug2014 start of new code*/
data listlab;
set adam.adpp;
run;
%fmt(datain=listlab, start=paramcd, label=param, name=parama);

```

```

data pk;
set adam.adpp(where=(paramcd in ('AUCIFO' 'LAMZHL') and pprotfl='Y'));
if Crit3fl='Y' then crit3n=1;
if crit5fl='Y' then crit5n=1;
run;

```

```

proc sql;
create table excl as
select *, sum(crit3n) as crit3ns, sum(crit5n) as crit5ns
from pk
group by usubjid, paramcd;
quit;

```

```

data pk01;
set excl;
where crit3ns>0 or crit5ns>0;
drop crit3n crit5n crit3ns crit5ns;
run;

```

```

/*exclude subjects with <2 periods*/
data pkper;
set adam.adpp(where=(paramcd in ('CMAX' 'AUCLST' 'AUCIFO' 'AUCINT'
'LAMZHL' 'TMAX') and PPROTFL='Y'));
missn=missing(aval);
run;

```

```

proc sql;
create table exc2 as
select *, sum(missn) as missns, count(distinct aperiod) as percount
from pkper
group by usubjid, paramcd;
quit;

```

```

data pk02;
set exc2;
where missns>0 or percount<2;
drop missn missns percount;
run;

```

```

data pk03;
set pk02 pk01;

```

```

run;

proc sql;
create table pk04 as
select distinct  analgrln, usubjid, paramcd
from pk03
order by analgrln, paramcd, usubjid;
run;

DATA subs;
attrib paramcd length=$8;
      SET ADAM.ADSL(WHERE=(PPROTFL='Y'));
      IF MISSING(ANALGR1N) THEN DELETE;
      do paramcd='CMAX','AUCLST','AUCIFO','AUCINT','LAMZHL' ,'TMAX';
      output;
      end;
      keep analgrln usubjid paramcd;
RUN;

proc sort data=subs; by analgrln paramcd usubjid; run;

data totals;
merge subs pk04(in=a);
by analgrln paramcd usubjid;
if a then exclusion='Yes';
else exclusion='No';
format paramcd parama. ;
run;
/* 15) AMH 06Aug2014 end of new code */

*****;
* read in data ;
*****;
proc sort data=adam.adpp(where=(analgrln=1
and paramcd in ('AUCIFO','AUCINT','LAMZHL','TMAX')
and not missing(aval) and crit3fl ne 'Y' and anl01fl='Y'))
      out=adpp;
      by subjid paramcd;
run;

/*Count number of datapoints for each subject and parameter*/
proc sql;
create table adpp1 as
select *, count(distinct trtan) as trtcount
from adpp
group by paramcd, subjid;
quit;

/* take logs and exclude subjects with <2 timepoints*/
data adpp2 noanal;
      ATTRIB BYCLAUSE LENGTH=$100; /* 16) AMH 07Aug2014 */
set adpp1;

```

```

IF PARAMCD IN ('AUCIFO','LAMZHL') THEN BYCLAUSE="crit3fl ne 'Y'";
ELSE BYCLAUSE="anl01fl='Y'";

    IF paramcd='AUCIFO' then param=tranwrd(param,'(0-inf)','`{sub(0-
inf)})');
    else if paramcd='AUCINT' then param=tranwrd(param,"(0-t)","`{sub(0-
t)})");
    else if paramcd='TMAX' then
param=tranwrd(strip(tranwrd(param,'max','`{sub max}'))/'*||'
[1]*/,'T','t');
    else if paramcd='LAMZHL' then param=tranwrd(param,'1/2','`{sub
1/2}');
        if trtcount>1 and aval not in (.,0) then do;
            logaval=log(aval);
            output adpp2;
        end;
    else output noanal;
run;

/*treatment and parameter formats to display text rather than numbers for
listing*/
%fmt(datain=adpp2, start=paramn, label=param, name=param);

data adppmod;
    attrib treat length=$15;
    set adpp2;
    format paramn param. ;
    treat=trta;
run;

proc sort data=adppmod; by paramn subjid; run;

title1 j=1 "PAGESPLIT"; /*do not change*/

%let tflno=L_15_04_04_01(PK);

%mixout1(fileout=/cvn/projects/prj/data/000000106326/TFL/&TFL_Part./&tfln
o);
options ps=28;

    /* 15) AMH 07Aug2014 */
/*title2 j=1 'Number of subjects included and excluded for each PK
parameter - Group #byval1 PK Population'; */
/*proc freq data=totals; */
/*    by analgrln;*/
/*    table paramcd*exclusion/ crosslist;*/
/*run;*/

title2 j=1 'Parameter: #byval1';
title3 j=1 'Proc GLM Procedure';
TITLE4 J=L "The where clause used on the dataset adam.adpp: pprotfl='Y'
and #byval2"; /* 16) AMH 07Aug2014 */

```

```
/*TITLE4 J=L "The where clause used on the dataset adam.adpp: crit3fl ne
'Y' and pprotfl='Y' and anl01fl='Y'";*/ /* 7) AMH 24Jun2014 */
```

```
proc glm data=adppmod(where=(paramcd ne 'TMAX')) order=internal;
by paramn BYCLAUSE; /* 16) AMH 07Aug2014 */
class subjid trtsega treat aperiodc;
model logaval= trtsega subjid(trtsega) aperiodc treat ;
lsmeans treat / pdiff=control('mCC') alpha=0.05 cl;
output out=pred p=pred r=resid;
ods output lsmeancl=lsmeans;
ods output lsmeandiffcl=diffs;
ods output FitStatistics=mse;
run;
```

```
/*Residual Plots*/
title3 j=1 'Residual Plots';
options ps=27; /*change this for proc plot*/
```

```
proc rank data=pred out=resid normal=vw ;
by paramn;
ranks nscore;
var resid;
run;
```

```
proc plot data=resid hpercent=50;
by paramn BYCLAUSE; /* 16) AMH 07Aug2014 */
plot resid*pred / vref=0;
plot resid*nscore;
run;
quit;
```

```
%mixout2(blankn=70, halfblnk=Y,title=Listing 15.4.4.1 Analysis of
Secondary Pharmacokinetic Parameters of Nicotine - Group-1 PK
Population); /* 17) AMH 12Aug2014 */
```

```
/*data counts*/
proc univariate data=adppmod(where=(paramcd ne 'TMAX')) noprint;
by paramn;
class treat;
var logaval;
output out=num1 n=n1;
run;
```

```
data diffsl;
merge diffs mse;
by paramn;
run;
```

```
/*Manipulate datasets for output all relevent stats on each row*/
/*_____*/
data tabout;
length out $100 stat $100;
```

```

set lsmeans(in=a) diffls1(in=b) num1(in=c) ;
analgrln=1;
/*ordering columns of treatments*/
if b then colord=3;
else if treat='THS 2.2 Menthol' then colord=1;
else if treat='mCC' then colord=2;

/* N row*/
if c then do;
    ord=1;
    stat=/'N'/'n'; /* 3) AMH 24Jun2014 */
    out=compress(put(n1,best.));
    output;
end;

if a or b then do;
/*Back transformation*/
if a then estimatee=exp(lsmean);
if b then estimatee=exp(difference);
lowere=exp(lowercl);
uppere=exp(uppercl);
geocv=100*sqrt(exp(rootmse**2)-1);
/*Gmean (CV%) row*/
    ord=2;
    stat=/'GMean (CV%)'/'Geometric LS Mean (CV%)`{SUPER 1}'; /*
3) AMH 24Jun2014 */ /* 5) AMH 24Jun2014 */ /* 14) AMH 07Aug2014 */
    if colord=3 then
out=compress(put(round(100*estimatee,0.01),8.2))||'
('||compress(put(/round(geocv,0.01)*CEIL(GEOCV*100)/100,8.2))||')'; /*
2) AMH 24Jun2014 */
    else out=compress(put(round(estimatee,0.01),8.2));
    output;
/*95% CI row*/
    ord=3;
    stat='95% CI';
    if colord=3 then
out=compress(put(/round(100*lowere,0.01)*FLOOR(100*100*LOWERE)/100,8.2)
)||',
'||compress(put(/round(100*uppere,0.01)*CEIL(100*100*UPPERE)/100,8.2));
/* 2) AMH 24Jun2014 */
    else
out=compress(put(/round(lowere,0.01)*FLOOR(100*LOWERE)/100,8.2))||',
'||compress(put(/round(uppere,0.01)*CEIL(100*UPPERE)/100,8.2)); /* 2)
AMH 24Jun2014 */
    output;
end;
run;

/*transpose for output*/
proc sort data=tabout;
    by analgrln paramn ord colord;
run;

proc transpose data=tabout out=ttabout(drop=_NAME_) prefix=col;

```

```

    by analgrln paramn ord stat;
    id colord;
    var out;
run;

/*Tmax analysis*/

data tmax;
set adppmod(where=(paramcd='TMAX'));
vol=subjidn;
run;

%wsigrank(dset=tmax, out=tmaxout, by=paramn, var=aval, from=trtan,
test=4, refs=5,
          label=THS 2.2 Menthol - mCC, ci=95);

data tabout1;
length col1 $100 col2 $100 col3 $100 stat $100;
set tmaxout ;
TMAX=1; /* 11) AMH 24Jun2014 */
analgrln=1;
/*ordering columns of treatments*/
/* N row*/
ord=1;
stat=/'N'/'n'; /* 3) AMH 24Jun2014 */
col1=compress(put(n,best.));
col2=compress(put(n,best.));
col3='';
output;
/*Gmean (CV%) row*/
ord=2;
stat=/'GMean (CV%)'/'Median'/'`{SUPER [2]}'*/; /* 5) AMH
24Jun2014 */ /* 6) AMH 24Jun2014 */ /* 13) AMH 07Aug2014 */
col1=compress(put(round(medtest,0.01),8.2));
col2=compress(put(round(medref,0.01),8.2));
col3=compress(put(round(estimate,0.01),8.2));
output;
/*95% CI row*/
ord=3;
stat='95% CI`{SUPER2}'; /* 5) AMH 24Jun2014 */ /* 13) AMH
07Aug2014 */ /* 14) AMH 07Aug2014 */
col1='';
col2='';

col3=compress(put(/'round(lower,0.01)'/FLOOR(100*LOWER)/100,8.2))||',
'||compress(put(/'round(upper,0.01)'/CEIL(100*UPPER)/100,8.2)); /* 2) AMH
24Jun2014 */
output;

run;

data allout;
set ttabout tabout1;
run;

```



```

proc sort data=allout; by analgrln TMAX paramn ord; run; /* 11) AMH
24Jun2014 */

/* Standard - macro for paging */
%macro outrtf(blankn=68, halfblnk=N, ref=);

/* treatment column headers and footnotes */
/*group 1*/
%let col11=THS 2.2 Menthol# (N=&tot11);
%let col21=mCC# (N=&tot21);
%let col31=THS 2.2 Menthol:mCC#Ratio (%);
%let foot1=%str(mCC = menthol conventional cigarettes); /* 10) AMH
24Jun2014 */

%if &halfblnk=N %then %let halfblnk=;
%else %if &halfblnk=Y %then %let halfblnk=\~;

/* Standard - just change the number to match the listing you're working
on. Also change the letters in the*/
/* bracket, eg ccb = current cigarette brands. Make sure to do this at
the top of the code too. */

    %let tflno=T_15_02_04_01(PK);

    options replace;
    data table.T_15_02_04_1;
    set allout;
    run;
    options noreplace;

/* Standard - leave this */
%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",""));
run;

/*page numbers*/
data paging;
    set allout;
    by analgrln;
    IF TMAX=1 THEN PAGE=2;
    ELSE page=1;
    if last.analgrln then call symput("tpage",compress(page,best.));
run;

/* Standard - leave this */

```

```

options number nodate orientation=landscape papersize=&p_pgsz missing='
' NOQUOTELENMAX/*turn off warnings about quoted strings too long*/;
ods escapechar='`';
%let linetop = \brdrt\brdrs\brdrw30; * needs to be 1.5pt so calculated
in twips (1/20 pt) ;
%let linebot = \brdrb\brdrs\brdrw30;
%let linebot2 = \brdrb\brdrs\brdrw15;

```

```

ods path stdlib.tl06326 (read) ;
ods results off;
ods rtf toc_data/* contents*/
file="/cvn/projects/prj/data/000000106326/TFL/&TFL_Part./&tflno..rtf"
style=tl06326 startpage=yes headery=1440 footery=1440 ;
ods noproctitle;

```

```

%do i=1 %to &tpage;

```

```

ODS PROCLABEL = ' ';
title ;
footnote;
%let wd=0;

```

```

data comp;
    set paging end=eof;
    by paramn ord;
    where page=&i;
    flag=1;
        IF TMAX=1 AND ANALGR1N=1 THEN call symput('COL31', 'THS
2.2 Menthol -#mCC (min)'); /* 11) AMH 24Jun2014 */
        IF TMAX=1 AND ANALGR1N=2 THEN call symput('COL32', 'THS 2.2 Menthol
-#NNS (min)'); /* 11) AMH 24Jun2014 */
        call symput('grp',compress(put(analgr1n,best.)));
        /* Amend title as needed */
        _firtitl="Table 15.2.4.1 Analysis of Secondary
Pharmacokinetic Parameters of Nicotine - Group-1 PK Population";
        _upcas=(length(_firtitl)-
length(compress(_firtitl,'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;

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* 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 missing nowd spanrows split =
'#'
%IF &I=1 %THEN %DO; CONTENTS=' ' %END; %ELSE %DO; CONTENTS='' %END;;
    column flag page paramn ord stat col1 col2 col3;

    define flag / order noprint;
        define page / order order = internal noprint;
        define paramn / group style={just=left cellwidth=2.5cm}
"Variable";
        define ord / order order=internal noprint;
        define stat / display style={just=left cellwidth=3cm}
"Statistic";
        define col1 / display style={just=c/*d*/ cellwidth=3cm}
style(header)={just=center} "&&col1&grp"; /* 12) AMH 07Aug2014 */
        define col2 / display style={just=c/*d*/ cellwidth=3cm}
style(header)={just=center} "&&col2&grp";
        define col3 / display style={just=c/*d*/ cellwidth=3cm}
style(header)={just=center} "&&col3&grp";

    break after page / page;

    break before flag / page %IF &I=1 %THEN %DO;
        CONTENTS="&_FSRTITL" %END; %ELSE %DO; CONTENTS='' %END;;

    compute before page / 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 paramn;
        line " ";
    endcomp;

/* 5) AMH 24Jun2014 */
    compute after _page_ / style={just=left protectspecialchars=off
pretext="&linetop."};
/*      line 'Note: GMean and 95%CI are the adjusted geometric least
squares means and confidence intervals from an ANOVA model conducted on
log-transformed data with sequence, subject within sequence, period and
product exposure as fixed effect factors. Geometrical CV% of the ratio is
estimated from the residual mean square error.';*/
        line "Note: &&foot&grp; THS = Tobacco Heating System.";
/*      line "[1] For t`{SUB max} the medians for each product and the
median difference and 95% confidence interval between THS 2.2 and mCC is

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reported. The 95% CI is based on the Hodges-Lehmann estimate.";/*/ /* 2)
AMH 27May2014 */
LINE 'Note: 1: Geometric LS Mean and 95% CI are the adjusted geometric
least squares means based on an ANOVA model. Geometrical CV% of the ratio
is estimated only for the ratio'; /* 14) AMH 02Jul2014 */
LINE "Note: 2: 95% CI are estimated only for the median difference based
on the Hodges-Lehmann estimate."; /* 13) AMH 07Aug2014 */
/*LINE "[2] Median Difference presented for THS 2.2 - CC."; /* 14) AMH
07Aug2014 */
/*LINE "[3] The 95% CI is based on the Hodges-Lehmann estimate. ";/*/

line "";
    line "Appendix &ref.";
        line "Path: &TFLpath." &_blankn.*"\~\~" "(Page &i of
&tpage)";
            line "Program Run: &sysdate   &sysuserid   Program Status:
&status";
        endcomp;

run;
%end;
ods rtf close;
ods results on;
ods path reset;

%mend ;

%outrtf(blankn=70, halfblnk=Y, ref=15.4.4.1 and 15.3.3.1); /* 7) AMH
24Jun2014 */

proc printto ; run;
*=====;
* END OF PROGRAM CODE ;
*=====;

```