

```

%_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   : ZRHR-PK-02-JP;
%put NOTE: Program Name        : t_anlpk42.sas;
%put NOTE: Purpose              : table and figure of PK data Group 2;
%put NOTE: ;
%put NOTE: Input Data           : ADAM.ADPP;
%put NOTE: Output               : L_15_04_04_02(PK) T_15_2_4_2(PK) ;
%put NOTE: Macros Called        : _MPRINTTO;
%put NOTE: ;
%put NOTE: Programmed by        : cvn_ahall;
%put NOTE: Creation Date        : 2014-04-06;
%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         4) Conservative rounding of cv sd and
95% CI;
%put NOTE: 24Jun2014  AMH         5) Small n in statistics row;
%put NOTE: 24Jun2014  AMH         6) correct gmean statistic to read:
Geometric LS Mean (CV%);
%put NOTE: 24Jun2014  AMH         7) Ammend footnotes;
%put NOTE: 24Jun2014  AMH         8) Ammend statistic labels;
%put NOTE: 24Jun2014  AMH         9) Correct ratio column header;
%put NOTE: 24Jun2014  AMH        10) Add PK listing to reference list;
%put NOTE: 24Jun2014  AMH        11) Remove footnote reference for tmax;
%put NOTE: 24Jun2014  AMH        12) Add where clause used on dataset to
listing;
%put NOTE: 24Jun2014  AMH        13) Amend NNS footnote;
%put NOTE: 24Jun2014  AMH        14) TMAX on a seperate page and
different header;
%put NOTE: 07Aug2014  AMH        15) Combine footnotes [2] and [3];

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%put NOTE: 07Aug2014    AMH          16) correct footnotes [1] to 1 and [1]
to Note: 1: in footnote;
%put NOTE: 07Aug2014    AMH          17) Change where clause statement
depending on variable;
%put NOTE: 07Aug2014    AMH          18) add proc freq to output;
%put NOTE: 07Aug2014    AMH          19) Center output;
%put NOTE: 12Aug2014    AMH          20) ammend typo in listing title ;
%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                                     ;
*=====;

/* Calculate totals for products */
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 analgr1 colord subjid;
run;

proc freq data=adsl1(where=(not missing(colord))) noprint;
    table analgrln*analgr1*colord/ out =totals2(drop=percent
rename=(count=total));

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run;

data _null_;
    set totals2;
    call
    symput('tot' || strip(put(colord,best.)) || strip(put(analgrln,best.)), strip(
    put(total,best.)));
run;
*****;
* read in data ;
*****;
proc sort data=adam.adpp(where=(analgrln=2
and paramcd in ('AUCIFO','AUCINT','LAMZHL','TMAX','CMAX','AUCLST')
and not missing(aval) and crit3fl ne 'Y' and anl01fl='Y' AND
PPROTFL='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; /* 17) AMH 07Aug2014 */
ATTRIB PARAM1 LENGTH=$100; /* 18) AMH 07Aug2014 */
    set adpp1;
    IF PARAMCD IN ('AUCIFO','LAMZHL') THEN BYCLAUSE="crit3fl ne 'Y'";
ELSE BYCLAUSE="anl01fl='Y'"; /* 17) AMH 07Aug2014 */
    if paramcd='AUCIFO' then param1=tranwrd(param,'(0-inf)','`{sub(0-
inf)}');
    else if paramcd='AUCINT' then param1=tranwrd(param,"(0-
t')","`{sub(0-t')}");
    else if paramcd='TMAX' then
param1=tranwrd(strip(tranwrd(param,'max','`{sub max}'))/'*||'
[1]'/','T','t'); /* 11) AMH 24Jun2014 */
    else if paramcd='LAMZHL' then param1=tranwrd(param,'1/2','`{sub
1/2}');
    else if paramcd='CMAX' then param1=tranwrd(param,'max','`{sub max}');
    else if paramcd='AUCLST' then param1=tranwrd(param,'(0-
last)','`{sub(0-last)}'); /* 18) AMH 07Aug2014 */
    if trtcount>1 and aval not in (.,0) then do;
        logaval=log(aval);
        output adpp2;
    end;
    else output noanal;
run;

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/*treatment and parameter formats to display text rather than numbers for
listing*/
%fmt(datain=adpp2, start=paramn, label=param1, name=param); /* 18) AMH
07Aug2014 */

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

```

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

```

```

title1 j=1 "PAGESPLIT"; /*do not change*/
/*title2 j=1 'Parameter: #byval1'; */
/*title3 j=1 'Proc GLM Procedure';*/
/*TITLE2 J=L 'Proc Freq Procedure';*/
/*TITLE4 J=L "The where clause used on the dataset adam.adpp: crit3fl ne
'Y' and pprotfl='Y' and anl01fl='Y'";*/ /* 12) AMH 24Jun2014 */
/*TITLE3 J=L "The where clause used on the dataset adam.adpp:
pprotfl='Y'"; */ /* 12) AMH 24Jun2014 */

```

```

%let tflno=L_15_04_04_02(PK);

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

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ods trace on;
/**/
/*PROC FREQ DATA=ADPPMOD(WHERE=(PARAMCD IN ('CMAX','AUCLST'))); */
/*  TABLE PARAM*TREAT / CROSSLIST;*/
/*RUN;*/

```

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TITLE2 J=L 'Parameter: #byval1'; /* 18) AMH 07Aug2014 */
TITLE3 J=L 'Proc GLM Procedure';
TITLE4 J=L "The where clause used on the dataset adam.adpp: pprotfl='Y'
and #byval2";

```

```

proc glm data=adppmod(where=(paramcd ne 'TMAX')) order=internal;
by paramn BYCLAUSE; /* 17) AMH 07Aug2014 */
class subjid trtsega treat aperiodc;
model logaval= trtsega subjid(trtsega) aperiodc treat ;
lsmeans treat / pdiff=control('NRT gum') alpha=0.05 cl;
output out=pred p=pred r=resid;
ods output lsmeancl=lsmeans;
ods output lsmeandiffcl=diffs;
ods output FitStatistics=mse;
run;

```

```

proc glm data=adppmod(where=(paramcd ne 'TMAX')) order=internal;

```

```

by paramn BYCLAUSE; /* 17) AMH 07Aug2014 */
class subjid trtsega treat aperiodc;
model logaval= trtsega subjid(trtsega) aperiodc treat ;
lsmeans treat / pdiff=controlu('NRT gum') alpha=0.025 cl;
ods output lsmeans=pval;
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; /* 17) AMH 07Aug2014 */
plot resid*pred / vref=0;
plot resid*nscore;
run;
quit;

%mixout2(blankn=70, halfblnk=Y,title=Listing 15.4.4.2 Analysis of
Pharmacokinetic Parameters of Nicotine - Group-2 PK Population); /* 20)
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 diffs1;
merge diffs mse pval(keep=paramn probtdiff
where=(missing(probtdiff)=0));
by paramn;
if missing(probtdiff) then delete;
run;

/*Manipulate datasets for output all relevent stats on each row*/
/*_____*/
data tabout;
length out $100 stat $100;
set lsmeans(in=a) diffs1(in=b) num1(in=c) ;
analgr1n=2;
/*ordering columns of treatmnents*/
if b then colord=3;
else if treat='THS 2.2 Menthol' then colord=1;
else if treat='NRT gum' then colord=2;

```

```

/* N row*/
if c then do;
    ord=1;
    stat=/'N'/'n'; /* 4) AMH 24Jun2014 */
    out=compress(put(n1,best.));
    output;
end;

if a or b then do;
/*Back transformation*/
if a then estimatee=exp(lsmear);
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}'; /* 4)
AMH 24Jun2014 */ /* 6) AMH 24Jun2014 */ /* 16) 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))||')'; /*
3) 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));
/* 3) 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)); /* 3)
AMH 24Jun2014 */
        output;
    end;
/*P-value*/
if b then do;
    ord=4;
    stat='P-value (one-sided)';
    if probtdiff<0.001 then out='<0.001';
    else out=compress(put(probtdiff,8.3));
        if paramn=8 then delete;
        output;
    end;
run;

/*transpose for output*/
proc sort data=tabout;

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```

    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=7,
          label=THS 2.2 Menthol - NRT gum, ci=95);

data tabout1;
length col1 $100 col2 $100 col3 $100 stat $100;
set tmaxout ;
TMAX=1; /* 14) AMH 24Jun2014 */
analgrln=2;
/*ordering columns of treatments*/
/* N row*/
    ord=1;
    stat=/'N'/'n'; /* 4) 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]}'*/; /* 6) AMH
24Jun2014 */ /* 7) AMH 24Jun2014 */ /* 15) 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`{SUPER 2}'; /* 6) AMH 24Jun2014 */ /* 16) 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)); /* 3) AMH
24Jun2014 */
    output;
/*P-value*/
    ord=4;

```

```

        stat='P-value (one-sided)';
        col1='';
        col2='';
        if probt<0.002 then col3='<0.001';
        else col3=compress(put(probt/2,8.3));
        output;

run;

data allout;
set ttabout tabout1;
run;

proc sort data=allout; by analgr1n TMAX paramn ord; run;

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

/* treatment column headers and footnotes */
/*group 2*/
%let col12=THS 2.2 Menthol#(N=&tot12);
%let col22=NRT gum#(N=&tot22);
%let col32=THS 2.2 Menthol#:NRT gum Ratio (%);
%let foot2=%str(NRT gum = Nicotine Replacement Therapy gum);/* 13) AMH
22JUN2014 */

%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_02(PK);

options replace;
data table.T_15_02_04_2;
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 TMAX paramn; /* 14) AMH 24Jun2014 */
  retain page /*1 */count; /* 14) AMH 24Jun2014 */
  if first.paramn then count + 1;
  if count>3 OR FIRST.TMAX then do; page+1; /* 14) AMH 24Jun2014 */
  count=1;
  end;
  if last.analgrln then call symput("tpage",compress(put(page,best.)));
run;

```

```

/* Standard - leave this */
options number nodate orientation=landscape papersize=&p_pgsz missing='
' NOQUOTELNMAX/*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;
  IF TMAX=1 AND ANALGR1N=2 THEN call symput('COL32', 'THS 2.2
Menthol -#NRT gum (min)'); /* 14) AMH 24Jun2014 */
  flag=1;
  call symput('grp',compress(put(analgrln,best.)));
  /* Amend title as needed */
  _firtitl="Table 15.2.4.2 Analysis of Pharmacokinetic
Parameters of Nicotine - Group-2 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)));

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

    define flag / order noprint;
        define page / order order = internal noprint;
        define paramn / group order=internal style={just=left
cellwidth=2.5cm} "Variable";
        define ord / order order=internal noprint;
        define stat / display style={just=left cellwidth=3cm}
"Statistic";
        define coll / display style={just=c/*d*/ cellwidth=3cm}
style(header)={just=center} "&coll&grp";
        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"; /* 19) AMH 07Aug2014 */

    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;

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```

        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 CC is
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'; /* 16) AMH 07Aug2014 */
        LINE "Note: 2: 95% CI are estimated only for the median difference
based on the Hodges-Lehmann estimate."; /* 16) AMH 02Jul2014 */
/*          LINE "[2] Median Difference presented for THS 2.2 - NRT Gum.";
*/
/*          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=15.4.4.2 and 15.3.3.1); /* 9) AMH
24Jun2014 */

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

```