

Dataset Integrity Check for Safety,  
Tolerability, and Pharmacokinetics of L-  
Ornithine Phenylacetate in Patients with  
Acute Liver Injury/Failure and  
Hyperammonemia

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## 1 Standard Disclaimer

The intent of this DSIC is to provide confidence that the data distributed by the NIDDK repository is a true copy of the study data. Our intent is not to assess the integrity of the statistical analyses reported by study investigators. As with all statistical analyses of complex datasets, complete replication of a set of statistical results should not be expected in secondary analysis. This occurs for a number of reasons including differences in the handling of missing data, restrictions on cases included in samples for a particular analysis, software coding used to define complex variables, etc. Experience suggests that most discrepancies can ordinarily be resolved by consultation with the study data coordinating center (DCC), however this process is labor-intensive for both DCC and Repository staff. It is thus not our policy to resolve every discrepancy that is observed in an integrity check. Specifically, we do not attempt to resolve minor or inconsequential discrepancies with published results or discrepancies that involve complex analyses, unless NIDDK Repository staff suspect that the observed discrepancy suggests that the dataset may have been corrupted in storage, transmission, or processing by repository staff. We do, however, document in footnotes to the integrity check those instances in which our secondary analyses produced results that were not fully consistent with those reported in the target publication.

## 2 Study Background

## 3 Archived Datasets

All the SAS data files, as provided by the Data Coordinating Center (DCC), are located in the STOP\_ALF/Data folder in the data package. For this replication, variables were taken from the “form00.sas7bdat”, “registrydata.sas7bdat”, “form10.sas7bdat”, “form14c1.sas7bdat”, “form01.sas7bdat”, “form03.sas7bdat”, and “form04.sas7bdat” datasets.

## 4 Statistical Methods

Analyses were performed to duplicate results for the data published by Stravitz et al [1] in the journal Hepatology in 2017. To verify the integrity of the dataset, descriptive statistics were computed.

## 5 Results

For Table 1 in the publication [1], [Baseline Clinical Characteristics of the Entire Study Population According to Renal Function Cohort](#), Table A lists the variables that were used in the replication and Table B compares the results calculated from the archived data files to the results published in Table 1.

## 6 Conclusions

The NIDDK repository is confident that the STOP-ALF data files to be distributed are a true copy of the study data.

## 7 References

[1] R. Todd Stravitz, Michelle Gottfried, Valerie Durkalski, Robert J. Fontana, A. James Hanje, David Koch, Bilal Hameed, Daniel Ganger, Ram M. Subramanian, Stan Bukofzer, William R. Ravis, Kristen Clasen, Averell Sherker, Lanna Little, and William M. Lee; for the Acute Liver Failure Study Group. "Safety, Tolerability, and Pharmacokinetics of L-Ornithine Phenylacetate in Patients with Acute Liver Injury/Failure and Hyperammonemia". *Hepatology* (2017).

**Table A:** Variables used to replicate Table 1: Baseline Clinical Characteristics of the Entire Study Population According to Renal Function Cohort

<b>Table Variable</b>	<b>dataset.variable</b>
Renal Function	form00.f00q01 form00.f00q20
ALI	registrydata.f00ali
HE grade	form10.f10q05
OPA $\geq$ 72 hours	form14c1.f14c1qb form14c1.f14c1qc form14c1.f14c1qd form14c1.f14c1qe
Age, years	form00.age
Female sex	form01.f01q01
Acetaminophen	registrydata.f16q87
Alanine aminotransferase, IU/L	form03.alt
International normalized ratio	form03.f03q14
Bilirubin, mg/dL	form03.bilirubin
Ammonia, $\mu$ M	form04.f04cqe
Creatinine, mg/dL	form03.creat
CRRT	

**Table B:** Comparison of values computed in integrity check to reference article Table 1 values

Renal Function	Characteristic at Start of OPA Infusion	Manuscript (n=47)	DSIC (n=47)	Diff. (n=0)
Normal	ALI, %	46.7	46.7	0.0
	HE grade, % - 0/1	56.6	43.3	13.3
	HE grade, % - 2/3	26.7	26.7	0.0
	HE grade, % - 4	16.7	16.7	0.0
	OPA ≥72 hours, %	76.7	76.7	0.0
	Age, years, median (range)	35.0 (28.0-47.0)	35.0 (28.0-47.0)	0.0 (0.0-0.0)
	Female sex, %	80.0	80.0	0.0
	Acetaminophen, %	83.3	83.3	0.0
	Alanine aminotransferase, IU/L, median (range)	4305 (1562-7190)		
	International normalized ratio, median (range)	3.1 (2.5-3.3)	3.1 (2.5-3.2)	0.0 (0.0-0.1)
	Bilirubin, mg/dL, median (range)	4.0 (2.8-8.0)		
	Ammonia, μM, median (range)	89.0 (70.0-125.0)		
	Creatinine, mg/dL, median (range)	0.7 (0.5-0.9)	0.7 (0.5-0.9)	0.0 (0.0-0.0)
	CRRT, %	3.3		
Impaired	ALI, %	35.3	35.3	0.0
	HE grade, % - 0/1	41.2	41.2	0.0
	HE grade, % - 2/3	23.5	23.5	0.0
	HE grade, % - 4	35.3	35.3	0.0
	OPA ≥72 hours, %	76.4	76.5	0.1
	Age, years, median (range)	38.0 (30.0-53.0)	38.0 (30.0-53.0)	0.0 (0.0-0.0)
	Female sex, %	41.2	41.2	0.0
	Acetaminophen, %	41.2	41.2	0.0
	Alanine aminotransferase, IU/L, median (range)	3695 (892-6025)		

Renal Function	Characteristic at Start of OPA Infusion	Manuscript (n=47)	DSIC (n=47)	Diff. (n=0)
	International normalized ratio, median (range)	3.3 (2.2-3.7)	3.0 (2.1-3.7)	0.3 (0.1-0.0)
	Bilirubin, mg/dL, median (range)	7.5 (3.4-17.6)		
	Ammonia, $\mu$ M, median (range)	103.0 (73.0-137.0)		
	Creatinine, mg/dL, median (range)	2.5 (2.0-3.8)	2.5 (2.0-3.8)	0.0 (0.0-0.0)
	CRRT, %	58.8		

## Attachment A: SAS Code

```

/*****
STOP-ALF
Saved As: /prj/niddk/ims_analysis/STOP_ALF/prog_initial_analysis/check.table1.sas
Programmer: Anne Taylor
Date Written: 01Apr2019
Purpose: To check Table 1 of Safety, Tolerability, and Pharmacokinetics of L-Ornithine
         Phenylacetate in Patients with Acute Liver Injury/Failure and Hyperammonemia.
*****/

options validvarname=upcase mprint;

title 'STOP-ALF';
title2 "Program Saved As: %sysfunc(getoption(sysin))";

libname puds '/prj/niddk/ims_analysis/STOP_ALF/private_orig_data/PUDS/PUDS';

proc format;
  value renalfx
    1='Normal'
    2='Impaired'
  ;
  value yesno
    0='No'
    1='Yes'
  ;
  value hegrade
    .='Missing'
    1-2='0/1'
    3-4='2/3'
    5='4'
  ;
  value sex
    1='Male'
    2='Female'
  ;
  value etiology
    1='Acetaminophen'
    2-15='Other'
  ;

proc sort data=puds.form00 out=form00;
  by subject_id;

proc sort data=puds.registrydata out=registrydata;
```

```

    by subject_id;

***select baseline record from hepatic encephalopathy form***;
data form10bl;
    set puds.form10;
    if zvisitnm='Baseline';

proc sort data=form10bl;
    by subject_id;

proc sort data=puds.form14c1 out=form14c1;
    by subject_id f14c1qb;

***flag subjects with OPA infusion >=72 hours***;
data infusion;
    set form14c1;
    by subject_id;
    retain start;
    if first.subject_id then start=dhms(f14c1qb,input(substr(f14c1qc,1,2),2.),0,0);
    if last.subject_id then do;
        infusion_dur=(dhms(f14c1qd,input(substr(f14c1qe,1,2),2.),0,0)-start)/3600;
        if 1<=infusion_dur<72 then opa72hr=0;
        else opa72hr=1;
        output;
        end;
    keep subject_id opa72hr;
    label opa72hr='OPA >=72 hours';

proc sort data=puds.form01 out=form01;
    by subject_id;

***select baseline record from labs form***;
data form03bl;
    set puds.form03;
    if zvisitnm='Baseline';
    keep subject_id alt f03q14 bilirubin creat;

proc sort data=form03bl;
    by subject_id;

***select screening/enrollment record from ammonia form***;
data form04scr;
    set puds.form04;
    if f04cqa=2;
    keep subject_id f04cqe;

proc sort data=form04scr;
    by subject_id;

***merge files***;
data table1;

```

```

merge form00 (in=in_form00 keep=subject_id f00q01 f00q20 age f00q28)
registrydata (in=in_regdata keep=subject_id f00ali f16q87)
form10bl (in=in_form10 keep=subject_id f10q05)
infusion (in=in_form14c1)
form01 (in=in_form01 keep=subject_id f01q01)
form03bl (in=in_form03)
form04scr (in=in_form04)
;
by subject_id;
if not first.subject_id then abort;
if not (in_form00 and in_regdata and in_form14c1 and in_form01 and in_form03) then abort;

***flag normal vs. impaired renal function***;
if f00q01=1 or f00q20=1 then renalfx=1;
else if f00q20=2 then renalfx=2;
else abort;

label renalfx='Renal Function'
f00ali='ALI'
f10q05='HE grade'
f01q01='Sex'
f16q87='Primary Etiology'
alt='Alanine aminotransferase'
f03q14='International normalized ratio'
f04cqe='Ammonia'
;

%macro pct(character);
proc tabulate data=table1 missing;
class &character renalfx;
table &character,renalfx*(colpctn=' '*f=12.1);
format f00ali opa72hr yesno.
f10q05 hegrade.
f01q01 sex.
f16q87 etiology.
renalfx renalfx.
;
title4 'Table 1 - Baseline Clinical Characteristics of the Entire Study Population According to Renal Function Cohort';
run;
%mend pct;

%macro medrng(character);
proc tabulate data=table1 missing;
class renalfx;
var &character;
table &character,renalfx*(median q1 q3)*f=12.1;
format renalfx renalfx.;
run;
%mend medrng;

%pct(f00ali);

```

```
%pct (f10q05);  
%pct (opa72hr);  
  
%medrng (age);  
  
%pct (f01q01);  
%pct (f16q87);  
  
%medrng (alt);  
%medrng (f03q14);  
%medrng (bilirubin);  
%medrng (f04cqe);  
%medrng (creat);
```