How a SAS/IntrNet tool was created at the FDA for the detection of potential drug-induced liver injury using data with CDISC standard

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ABSTRACT

The assessment of potential drug-induced liver injury (DILI) has emerged as an ever-challenging task for the drug regulatory agency because of the low incidence of the finding and the burdensome work of searching through data on hundreds or thousands of subjects. A software tool is much needed to assist reviewers of clinical trial data to accomplish the task of finding sometimes rare but serious cases of special interest among the great majority that are not. Once found, the cases need to be evaluated as to the likelihood that the cause was the drug in question, and not one of many possible disease causes. In this paper, the author describes the creation of a visualization tool with drill-down capabilities for detailed study of the rare cases of special interest to implement an innovative method that is well recognized in the medical community for DILI assessment. This tool, named eDISH (Evaluation of Drug Induced Serious Hepatotoxicity) now is used by FDA scientists for their regulatory reviews of new drug applications (NDA). The eDISH tool was created using SAS/IntrNet and Application Dispatcher's Application Broker. The author reveals some important technical details of eDISH. In addition, he provides examples of how CDISC terms help FDA reviewers use eDISH.

INTRODUCTION

At FDA, medical and statistical reviewers need to assess potential of drug-induced liver injury (DILI) from experimental drugs as part of the regulatory evaluation. Following development of rapid spectrophotometric assays of aminotransferase activity in serum in the mid-1950's as a more sensitive indicator of liver cell injury than older methods, many people had believed that the problem should be handled by tracking changes of some serum enzyme activities, such as alanine aminotransferase (ALT), over a period of time. Raised serum ALT is a quite sensitive marker of hepatocellular injury, but it is not specific enough for use in detecting rare events. Such a method is still being used within the scientific community. In 1968, the late Dr. Hyman J. Zimmerman delivered in the George Kober Lecture a speech titled "The Spectrum of Hepatotoxicity." His speech ushered in fresh thinking, and pointed out that when enough liver cells are injured enough to cause jaundice, the situation may be very serious, with possible mortality if further injury occurs. A flaw of the old method is that elevated serum enzyme activities indicate liver injury to some extent, but do not measure liver function. However, bilirubin clearance does measure one of the liver's functions and is very highly specific. A new concept is to observe the combination of ALT and serum concentration of total bilirubin (TBL) so that subjects of concern may be detected. This idea of Dr. Zimmerman was applied by Dr. John R. Senior to the regulatory setting. He proposed that, based on the observation of ALT-TBL pair, a subject (patient) with potentially serious DILI may be found. Furthermore, by subsequently tracing back to these subjects' entire medical profiles over the whole course of observation in the study, the case of DILI may be confirmed and the likelihood that it was indeed drug-induced can be adjudicated. If we can do all those things, then we may answer the ultimate question: does the experimental drug can cause liver injury? This job needs to be done and must be done effectively and easily. This article details how eDISH was created and how it works in evaluation of DILI.

PROBLEM

To use this approach in a regulatory setting, we are faced with a number of challenges:

First, relevant data are not always prepared and provided by the drug sponsor's staff in a coherent fashion (i.e., following a uniform standard). According to the FDA reviewers' experience, liver-test data are provided with other laboratory information organized in formats varying from drug sponsor to drug sponsor. The FDA reviewers devote a great deal of time and energy in data exploration, reorganization, and formatting.

Secondly, the traditional data tabulation and visual inspection methods in the evaluation of DILI, which are still commonly employed, does not effectively do the job, even if the data are in place for analysis. DILI typically may occur beyond a short-term drug use. The cases of DILI are relatively few among those exposed to the drug. An ideal analysis data file is very large in size, representing a study of long duration. For such a large data file, a new analytical method has to be developed. We want to "see" all subjects at a glance, and the cases of interest should "stand out" to be noticed.

Finally, conventional statistical practice is to begin with a large number of individual data points for a single variable, summarize them in a statistical process, and finally reach statistical conclusions by way of p-values and confidence intervals. This typically is the case for Phase-3 premarketing efficacy trials. However, in the safety arena, it requires

the statistician to reverse the process: begin with a case of interest, drill-down to a particular individual, and investigate the profile of that individual, using many variables that change over a period of time. To assist FDA medical reviewers in the DILI assessment, a new computation method needs to be developed in order to summarize the subjects' data in some fashion, inspect the summarized data, identify the cases of interest, and then quickly drill-down to find the individuals' entire records over the period of observation.

Clearly we need a review tool that works best to implement the analytical method. The tool should work with data in CDISC terms. In addition, the tool should be user-friendly.

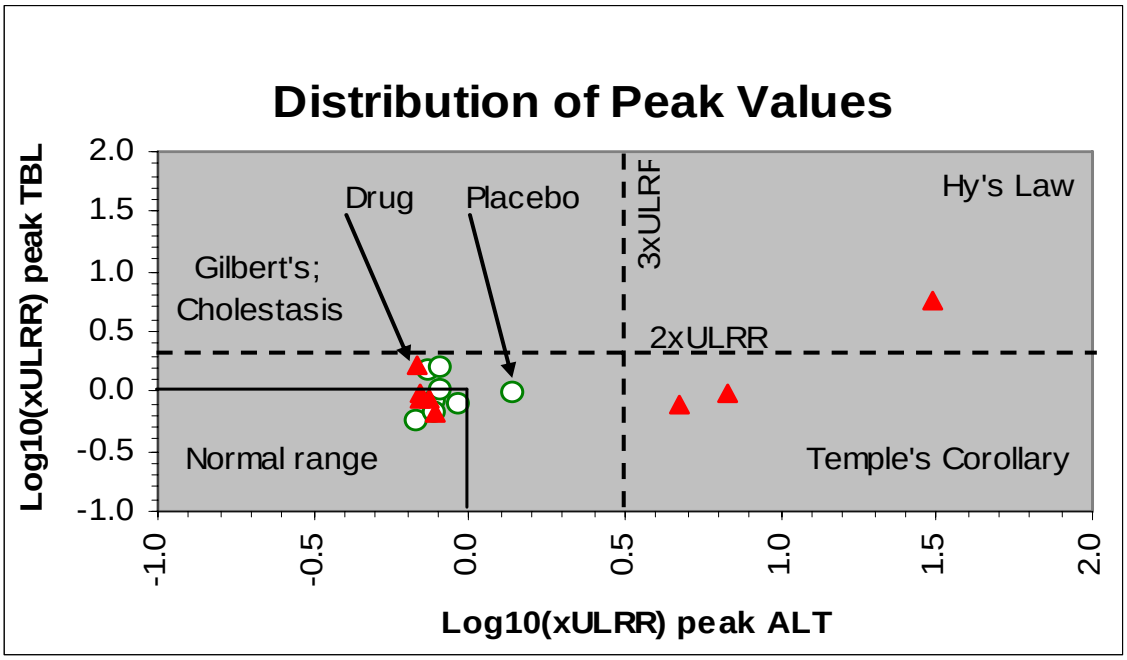
METHOD

The development of eDISH has gone through roughly three phases: (1) the concept development, (2) the data structure planning, and (3) the creation of eDISH including tests using real-life data in the regulatory setting. The eDISH development is a team project: Dr. John R. Senior provides constant leadership and direction for the project. Dr. Kate Gelperin contributes knowledge and insight of the regulatory experience in the evaluation of the clinical studies on which the tool development is based. We developed a practical solution by creating a review tool for the DILI evaluation using SAS/IntrNet.

-1- The Development of the eDISH Concept

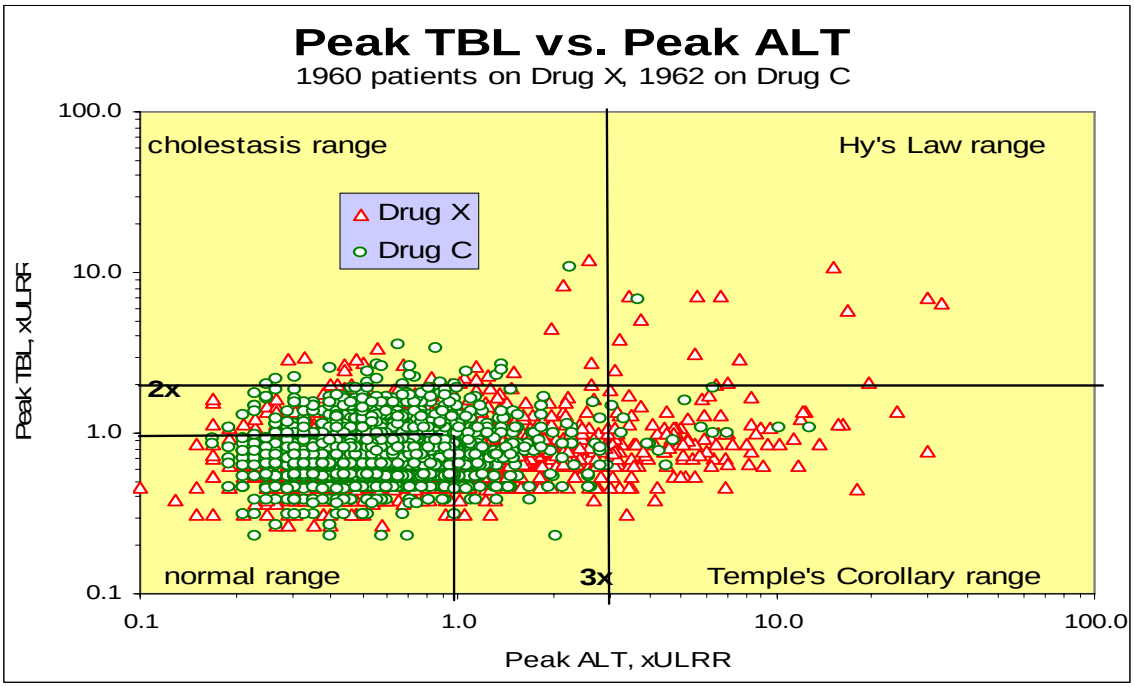
Figure 1 was created by Dr. John Senior using Excel to illustrate the concept of the eDISH method. Each dot on the plane represents one subject in the clinical study. In the graph, for each subject, the peak TBL (total bilirubin) times the upper limit of the reference range (ULRR) is plotted against the peak ALT times the upper limit of the reference range (ULRR), on a log10 scale. It should be understood that the peak TBL and peak ALT may or may not (most likely not) happen on the same day of liver testing. This graph illustrates the approach proposed by late Dr. Hyman J. Zimmerman to use both the indicator of hepatocellular injury (ALT and the measure of impaired liver function (TBL) together. The two reference lines, 2xULRR for TBLxULRR and 3xULRR for ALTxULRR, are drawn to divide the plane into four quadrants. Normal cases are in the lower left quadrant. It is important to note that the upper right quadrant is referred as Hy's Law quadrant, including potentially DILI cases. Any subject that falls in the Hy's Law quadrant is subject to further special investigation to adjudicate the case.

Figure 1 eDISH concept



Taking the eDISH concept to the next level, Figure 2 shows the eDISH method used for a real-life clinical study. This study included more than 3900 subjects randomized to either the experimental drug "X" in red triangles or the control drug "C" as a comparator in green circle. The experimental drug was not recommended for approval for the use in the U.S. by the advisory panel and was subsequently withdrawn from the foreign market. Note that the Hy's Law range included subjects almost exclusively from the "X" group (14X vs. 1C).

Figure 2 eDISH plot using real-life clinical study data



We considered this study suitable for the tool development. Here are the reasons:

1. The data included multiple "Hy's Law" cases including numerous cases of possible liver injury, some but not all of which were drug induced.
2. The study had a long duration of three years.
3. The study data include complete serial ALT, TBL, AST, and ALP measurements which were crucial for the determination of DILI.
4. The study included clinical narratives for many subjects that may hold a key to the final adjudication of DILI causality.

Using the data of this study, a battery of calculations and derivations were made to create some most important variables. Graphs such as shown in Figure 2, above, were created in Excel. This initial work produced results that were used as benchmarks to verify and confirm the correctness of the eDISH tool.

-2- The Development of Data Structure

After ~~a~~ careful planning for the data structure and requirements for eDISH, we decided the variables required to be included for the DILI evaluation. The FDA medical reviewers played a key role in this phase of work. Our principle was to select a small number of the outcome variables representing their original measurements. We decided to derive other variables using SAS programs so that we had full confidence of the derivation algorithms. We limited the number of required variables to the minimum and did not repeat the same variable in different data sets. There were essentially two types of variables: Those with liver test results that could change over a period of time (e.g., ALT, TBL, etc.) and those unlikely to change during the course of clinical study (height, gender, etc.). For the former, each subject had multiple records over the course of study; while for the latter, each subject had only one record. Besides, there was a need to have an additional data set to hold text strings describing and explaining the chemistry findings. Note that the information in this data set is crucial, because it may hold a key to explain the chemistry data shown by the visualization leading to the adjudication of DILI. With this data set, the questions of whether the experimental drug might cause a liver injury may have a satisfactory answer.

CDISC initiatives on the data standardization are an important development for clinical trial data coming to the FDA for regulatory decisions. The Analysis Dataset Model (ADaM) Group subgroup is helpful in a unique way in setting data standards for statistical data submissions. However, the data sets prepared by the drug sponsor today may not be directly plugged into eDISH. On one hand, the data submitted from drug sponsors may be very diverse in format and quality. On the other hand, the demand for the use of eDISH appears to be increasing over time, and eDISH is

currently being used in ongoing NDA reviews. Having taken that reality into consideration, we concluded that it is necessary to spell out the data requirements for eDISH. The data requirements need to be carefully defined and simple to follow. The data requirements have to be an integrated part of eDISH. Table 1, below, explains the data requirements for the liver data file in CDISC terms.

Table 1 Requirements for the liver data

Requirement	Standard variable	The variable means...	Variable-type
1. Required	STUDYID	Unique identifier for a study within the submission	Char
2. Required	USUBJID	Unique subject identifier within the submission	Char
3. Required	TRTCD	Treatment Code	Num
4. Required	TRTGRP	Treatment Group	Char
5. Required	EXSTDT	Start Date of Dose	Char (ISO 8601 YYYY-MM-DD)
6. Required	EXDT	Date of Exam	Char (ISO 8601 YYYY-MM-DD)
7. Required	EXENDT	End Date of Dose	Char (ISO 8601 YYYY-MM-DD)
8. Required	ALT	Serum alanine aminotransferase activity (U/L)	Num
9. Required	ALT_REF_HIGH	ALT High Normal Range (U/L)	Num
10. Required	BILI	Total serum bilirubin concentration (mg/dL)	Num
11. Required	BILI_REF_HIGH	BILI High Normal Range (mg/dL)	Num
12. Required	AST	Serum aspartate aminotransferase (U/L)	Num
13. Required	AST_REF_HIGH	AST High Normal Range (U/L)	Num
14. Required	ALP	Alkaline phosphatase (U/L)	Num
15. Required	ALP_REF_HIGH	ALP High Normal Range (U/L)	Num
16. Optional	ONPROTOC	Subject on Protocol at the Time of exam (Y/N)	Num
17. Optional	GGT	Gamma glutamyl transferase (U/L)	Num

Table 2, below, also as an integrated part of eDISH, explains the data requirements for the demographic data file in CDISC terms.

Table 2 Requirements for the demographic data

Requirement	Standard variable	The variable means...	Variable-type
1. Required	STUDYID	Unique identifier for a study within submission	Char
2. Required	USUBJID	Unique subject identifier within submission	Char
3. Required	INVID	Investigator Identifier	Char
4. Optional	INVNAM	Investigator Name	Char
5. Optional	INVDESC	Investigator Description	Char
6. Required	BIRTHDT	Date of birth	Char (ISO 8601 YYYY-MM-DD)
7. Required	SEX	Sex (M/F)	Char
8. Optional	RACE	Race (WHITE, BLACK, OTHER)	Char
9. Optional	COUNTRY	Country	Char
10. Required	HEIGHT	Height in cm	Num
11. Required	WEIGHT	Weight in kg	Num
12. Required	COMPLETE	Subject completing the study (Y/N)	Char
13. Required	DROPDT	Date subject discontinued the study (Y/N)	Char (ISO 8601 YYYY-MM-DD)
14. Required	DROPREAS	Reason for discontinuation	Char
15. Required	NARRATE	Availability of Patient Narratives (Y/N)	Char

Table 3, below, explains the data requirements for the clinical narrative data file. Note that only STUDYID and USUBJID are of CDISC terms. The variable NARRATIVE is a character variable which can hold about 4,000 characters in a long text string.

Table 1 Requirements for the clinical narrative data

Requirement	Standard variable	The variable means...	Variable-type
1. Required	STUDYID	Unique identifier for a study within the submission	Char
2. Required	USUBJID	Unique subject identifier within the submission	Char
3. Required	NARRATIVE	Clinical Narrative*	Char

* Requirements for Variable NARRATIVE - To the medical writer:

It is not necessary to include all subjects in this patient narrative data set. However, make sure to include narratives

Requirement	Standard variable	The variable means...	Variable-type

for subjects with either ALT >3xULN or TBL > 2xULN.

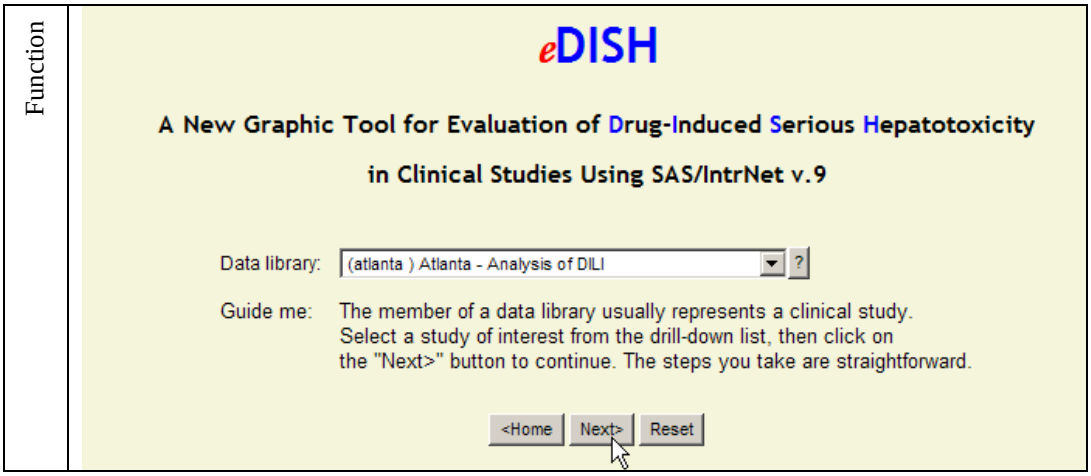
The narratives should include information described in the following points:
1. Indication
2. Subject's medical history and concomitant medications
3. Dates and laboratory values of diagnostic tests done to evaluate liver disease including X-ray, ultrasound, or liver biopsy
4. Time course of any signs or symptoms of liver disease, including jaundice
5. Differential diagnosis and final diagnosis of liver disease
6. The study site investigator and the sponsor's assessment of relationship of study drug to abnormal hepatobiliary lab results or adverse events
7. Clinical course of liver-related adverse events including treatment and outcome
8. Complete information about the resolution, or progression, of increased ALT or total bilirubin in each of these study subjects, including time to complete resolution of all hepatobiliary lab results, or most current available patient status for any cases in which the events had not resolved at the time of report preparation.
9. It is also helpful to include in the narrative:
- Dose and duration of study therapy in weeks
- Laboratory values for ALT, AST, ALP, TBL and corresponding dates of measurements

This data requirement reflects regulatory experience. The 9-point instruction was based on internal discussions that lead to an information request letter to the drug sponsor. The instruction spells out what's needed for the evaluation.

-3- eDISH in Action

To demonstrate how eDISH is used in action; we begin with the portal of eDISH shown in a screen shot shown in Figure 3, below. The subsequent figures consist of screen shots and accompanying explanations. These figures show you the several steps of eDISH in action. Some parts of the SAS programs are demonstrated to explain the behind-the-scene actions that produce those dynamic web pages. For the consideration of readability, some portions of those programs have been simplified by cutting out portions only affecting the style of the web page.

Figure 3 Portal of eDISH



Explanation

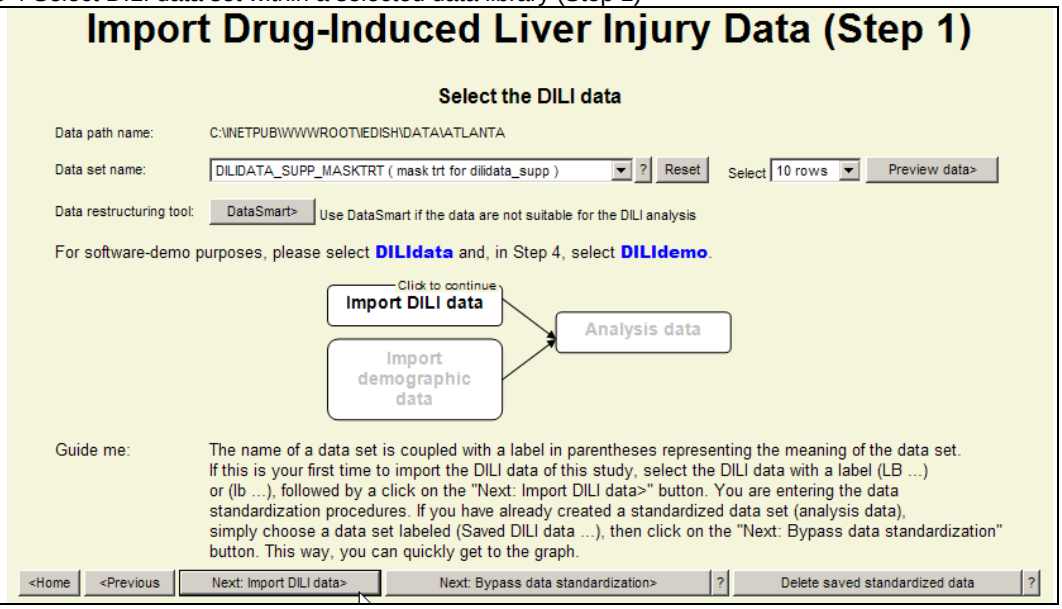
```
   …
data _null_;
  file _webout;
  set datalist end=end; /* datalist: a list of LIBNAMEs */
if _N_=1 then do;
   …
  put '<form method=”POST” action="' "%superq(_url)" '">';
  put '<input type=hidden name="_service"
      value="' "%superq(_service)" '">';
  put '<input type=hidden name="_program"
      value="' "%superq(_pgmlib)" '.input1.sas">';
  put '<table>';
  put '<tr><td>Data library: </td>'
      '<td><select name="libref" size="1">';
  put '<option value=" " selected>
      --Selected data library--';
end;
  put '<option value="' libname '">' '(' libname ') - '
      libdesc;
if end then do;
  put '</select>'
   …
Note: In this example, the data library guides the user to a specific data
library (LIBNAME), where the DILI evaluation will be performed. Each data
library represents a clinical study.
```

Having selected a data library, the user is able to select and import data sets into the eDISH system. The eDISH system is designed in the following way for the data import: For the first-time use of a study's data, the user must go though a 7-step procedure to put the incoming data sets in place. As a result, a final analysis data set is created and permanently saved as in the system with a name defined by the user. The same study will be analyzed many times during the course of the regulatory review, probably by several reviewers over an extended period of time. For the repeat use of the analysis data, the user can simply bypass the 7-step data import procedure and go directly to the previously saved data set. The initial 7-step procedure is necessary because users of eDISH will be faced with variations of incoming data files submitted by different drug sponsors each of which has it own standard. It remains to be seen when the CDISC/ADaM standard is fully implemented several years from now, whether eDISH can be modified to "plug in" the incoming data files. Currently the data-importing procedures must be applied.

Figure 4 demonstrates the step to import the DILI data set. The user is given an instruction under "Guide me" for where to go for the next step. A click on the question mark near the command button explains the function of the button. A diagram on the screen indicates that the user is at the first phase of importing data files.

Figure 4 Select DILI data set within a selected data library (Step 1)

Function

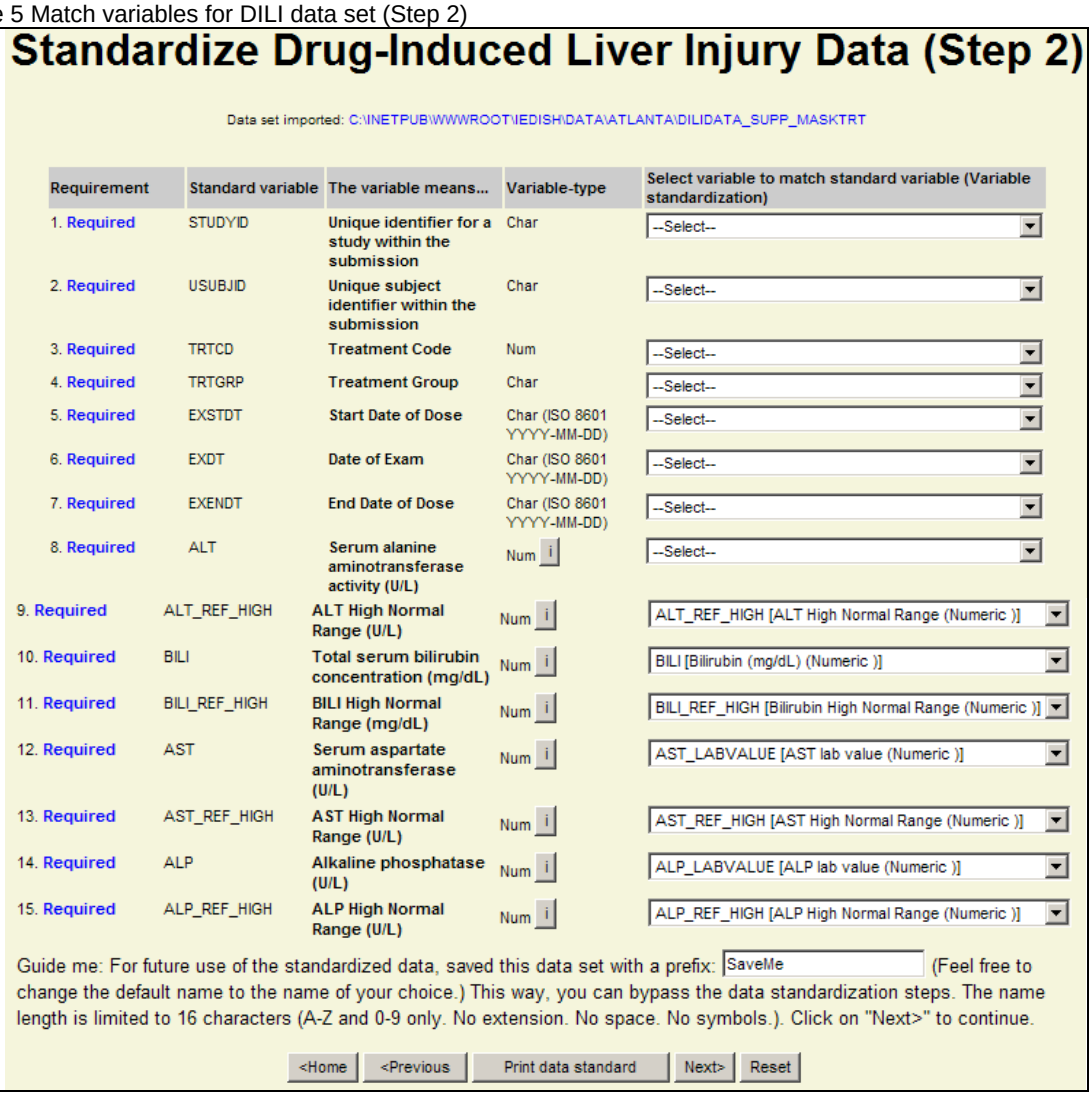


Explanation	
	Note: In this example, the user is in a data library named ATLANTA, where the DILI evaluation will be performed. Next step: Click on “Next: Import DILI data” to continue.

Figure 5 demonstrates that eDISH is flexible to the extent that the variable names in the incoming data set do not need to be exactly the same as those required by the eDISH standard. This is a practical consideration: On one hand, the drug sponsor may not follow the data requirements exactly. On the other hand, it may not be reasonable to reject the data from the drug sponsor simply for minor deviations from eDISH requirement or the CDISC/ADaM standard. Step 2 helps get the incoming data into the eDISH system.

Figure 5 Match variables for DILI data set (Step 2)

Function



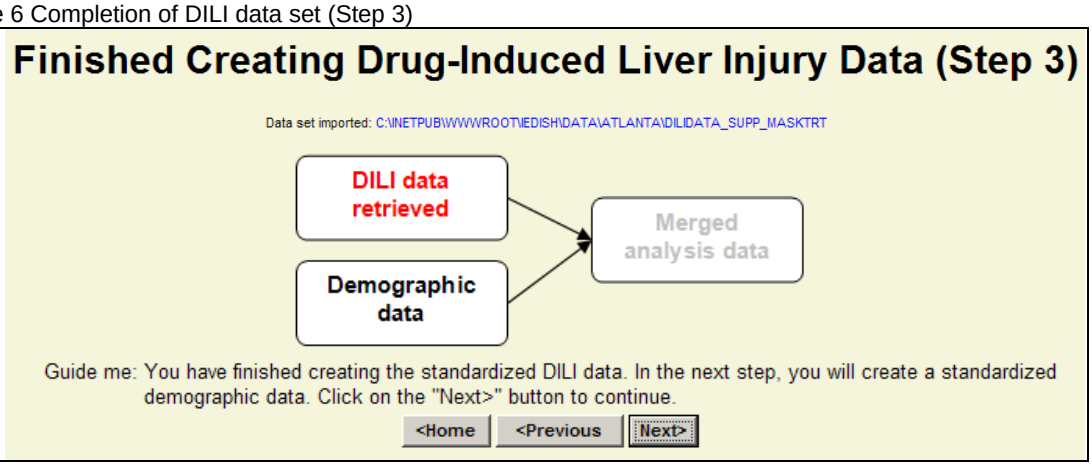
Explanation

```
 …
*** STUDYID ***;
%let num=%eval(&num+1);
%let id=%eval(&id+1);
data _null_;
  file _webout;
  set dsview end=no_more;
  /*Dsview includes a list of the variables*/
  if _n_=1 then do;
    put '<tr>';
    put '<td valign=top>' "&num"
    '. <font color=blue><b>Required</b></font></td>';
    put '<td valign=top>';
    put 'STUDYID';
    put '</td>';
    put '<td valign=top><b>'
    'Unique identifier for a study within the
     submission</b></td>'
    '<td valign=top>Char</td>';
    put '<td valign=top>';
    put '<select name="STUDYID" size="1" tabindex="'
        "&id" '">';
    put '<option value=" " selected>--Select--';
  end;
  put '<option value="' varname '">' varname
    ' [' varlabel ' (' vartype ')' ']';
  if no_more then do;
  put '</select>';
  put '</td>';
  put '</tr>';
  end;
run;
…
Note:  This is one part of the SAS program that makes the closest matches
of the variables from the incoming data set.

Next step: The user specifies the name of the final analysis data set for
repeat uses. Click on “Next” to continue.
```

Figure 6 indicates the completion of the DILI data import. The user is ready to import the demographic data set.

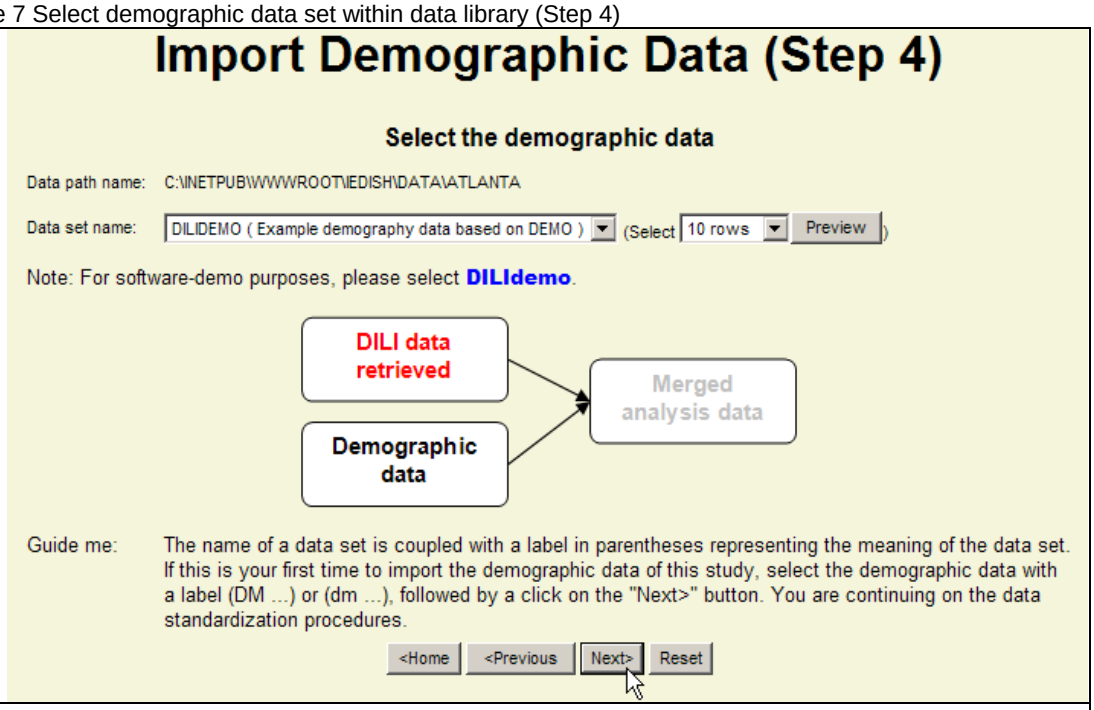
Figure 6 Completion of DILI data set (Step 3)

Function



Explanation	… Proc SQL noprint; Create table DILIINDIV_1 as select STUDY as STUDYID label="Unique identifier for a study within the submission ", PATIENT as USUBJID label="Unique subject identifier within the submission", TREATMENT as TRTCD label="Treatment Code", TRTGRP as TRTGRP label="Treatment Name", DATEVISIT as EXDT label="Date of Exam", DATEFIRSTDOSE as EXSTDT label="Start Date of Dose", DATELASTDOSE as EXENDT label="End Date of Dose", ALT as ALT label="Serum alanine aminotransferase activity", BILI as BILI label="Total serum BILIrubin concentration ", AST_LABVALUE as AST label="AST", ALP_LABVALUE as ALP label="ALP", ALT_REF_HIGH as ALT_REF_HIGH label="ALT High Normal Range", BILI_REF_HIGH as BILI_REF_HIGH label="BILI High Normal Range", AST_REF_HIGH as AST_REF_HIGH label="ALT High Normal Range", ALP_REF_HIGH as ALP_REF_HIGH label="ALT High Normal Range" from atlanta.DILIDATA_SUPP_MASKTRT; … Note: The program portion, above, was created by the SAS program. In this selected part of the SAS program, a SQL procedure renames the incoming variables. For example, the incoming variable, PATIENT, is renamed to USUBJID. Next step: Click on “Next” to continue.

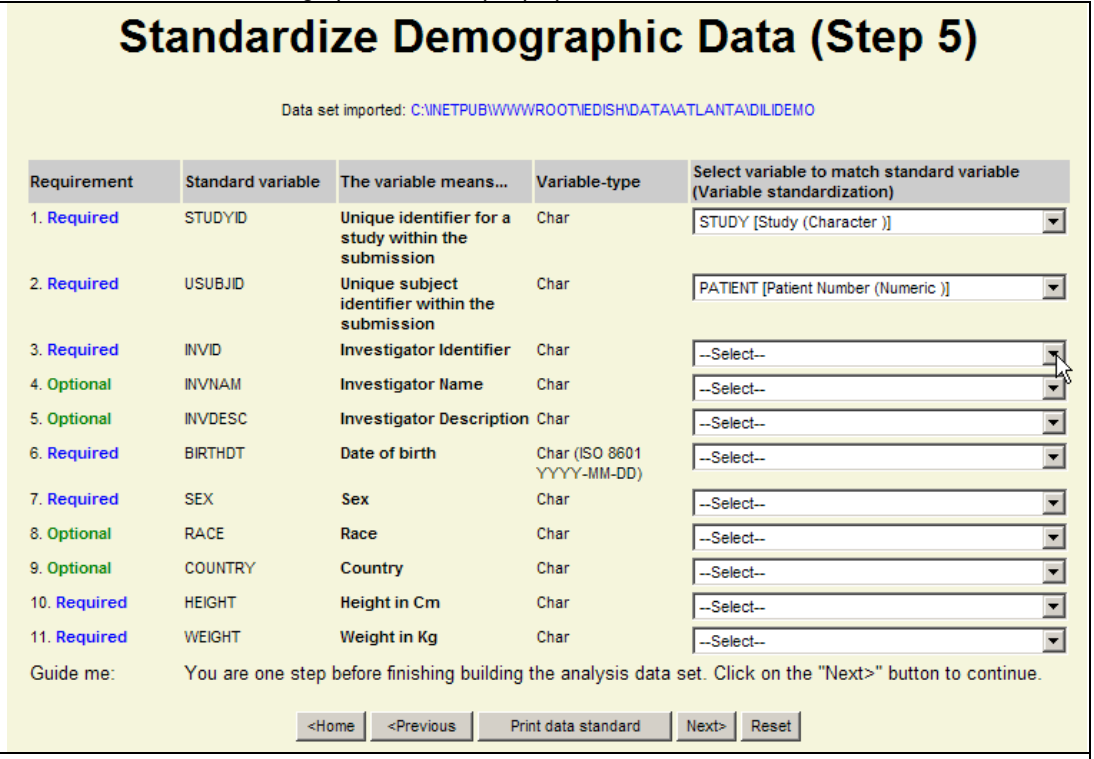
Figure 7 Select demographic data set within data library (Step 4)

Function	
Explanation	Note: In this example, the user will select the demographic data set in the same data library. The completion of this step enables eDISH to merge the demographic data with the DILI data set to produce an analysis data set permanently saved for repeat use. Next step: Click on “Next” to continue.

The function of Step 5 is similar to that of Step 2 (for the DILI data). The program matches variables from the incoming demographic data set to those used by eDISH.

Figure 8 Match variables for demographic data set (Step 5)

Function



Explanation

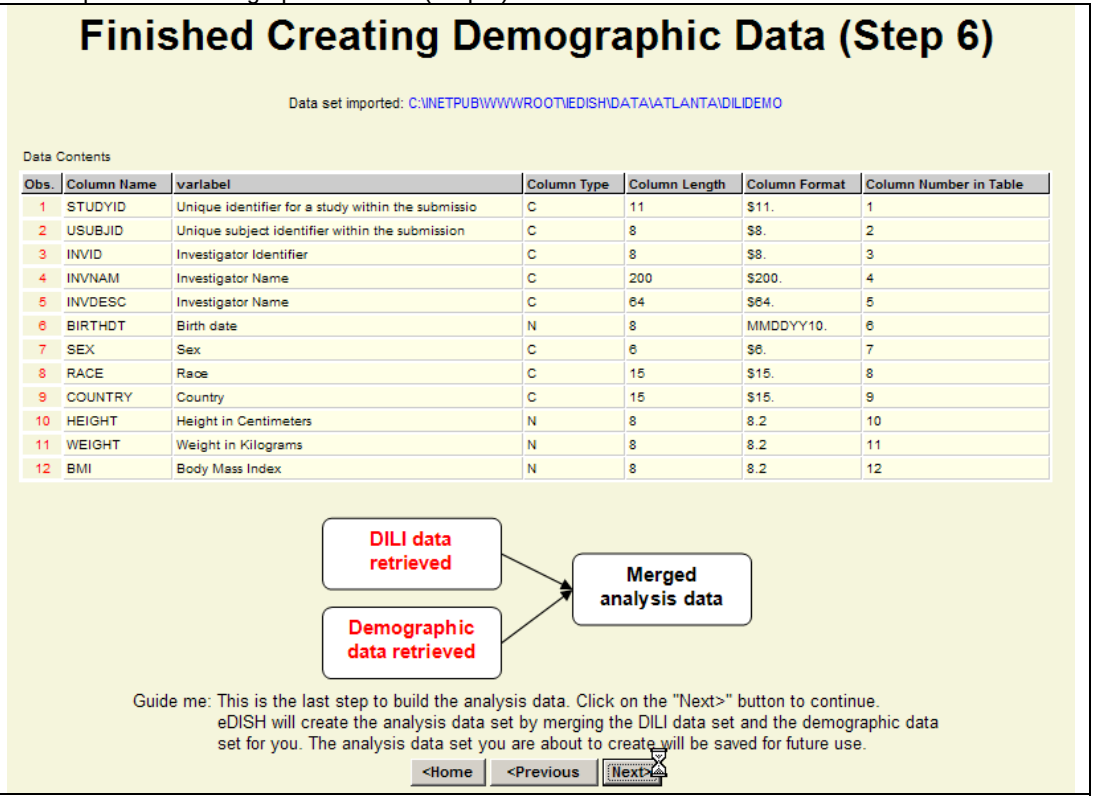
Note: The program matches variables from the incoming demographic data set to those used by eDISH.

Next step: Click on “Next” to continue.

Figure 9 finishes the import of the demographic data set. eDISH is ready to merge the two to create a single analysis data set.

Figure 9 Completion of demographic data set (Step 6)

Function



Obs.	Column Name	varlabel	Column Type	Column Length	Column Format	Column Number in Table
1	STUDYID	Unique identifier for a study within the submissio	C	11	$11.	1
2	USUBJID	Unique subject identifier within the submission	C	8	$8.	2
3	INVID	Investigator Identifier	C	8	$8.	3
4	INVNAM	Investigator Name	C	200	$200.	4
5	INVDESC	Investigator Name	C	64	$64.	5
6	BIRTHDT	Birth date	N	8	MMDDYY10.	6
7	SEX	Sex	C	6	$6.	7
8	RACE	Race	C	15	$15.	8
9	COUNTRY	Country	C	15	$15.	9
10	HEIGHT	Height in Centimeters	N	8	8.2	10
11	WEIGHT	Weight in Kilograms	N	8	8.2	11
12	BMI	Body Mass Index	N	8	8.2	12

Explanation

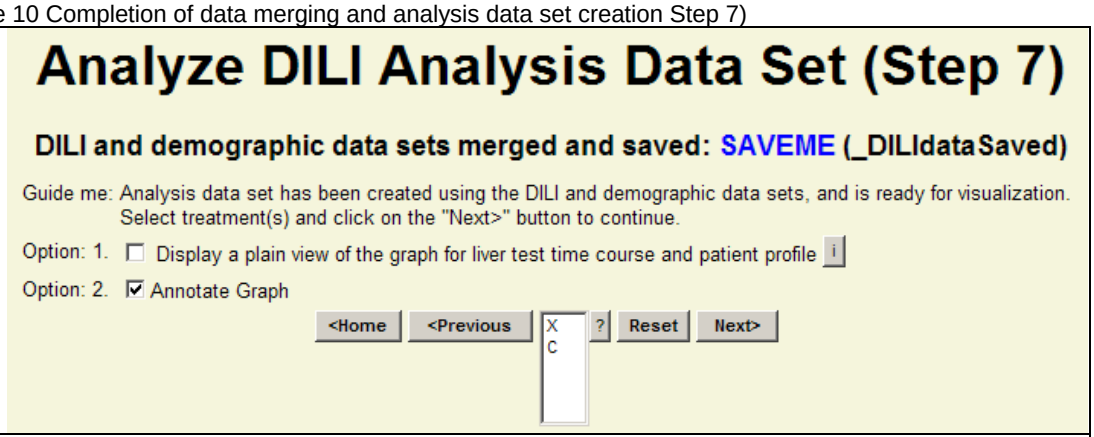
Note: Just like Step 3, a variable-renaming process was performed. As the result of this step, two data sets have been created.

Next step: Click on “Next” to continue. In the next step, the DILI and demographic data sets are merged.

For the analysis, the data procedures, described as Steps 1-7, need to be performed only once. Figure 10 shows that the final analysis data set, named SAVEME_DILIdataSaved defined by the user, was created and saved for repeat analyses. The same data set usually is analyzed multiple times likely by different reviewers during the course of NDA review, for the analysis of patients of interest cannot be completed in short order.

Figure 10 Completion of data merging and analysis data set creation Step 7)

Function



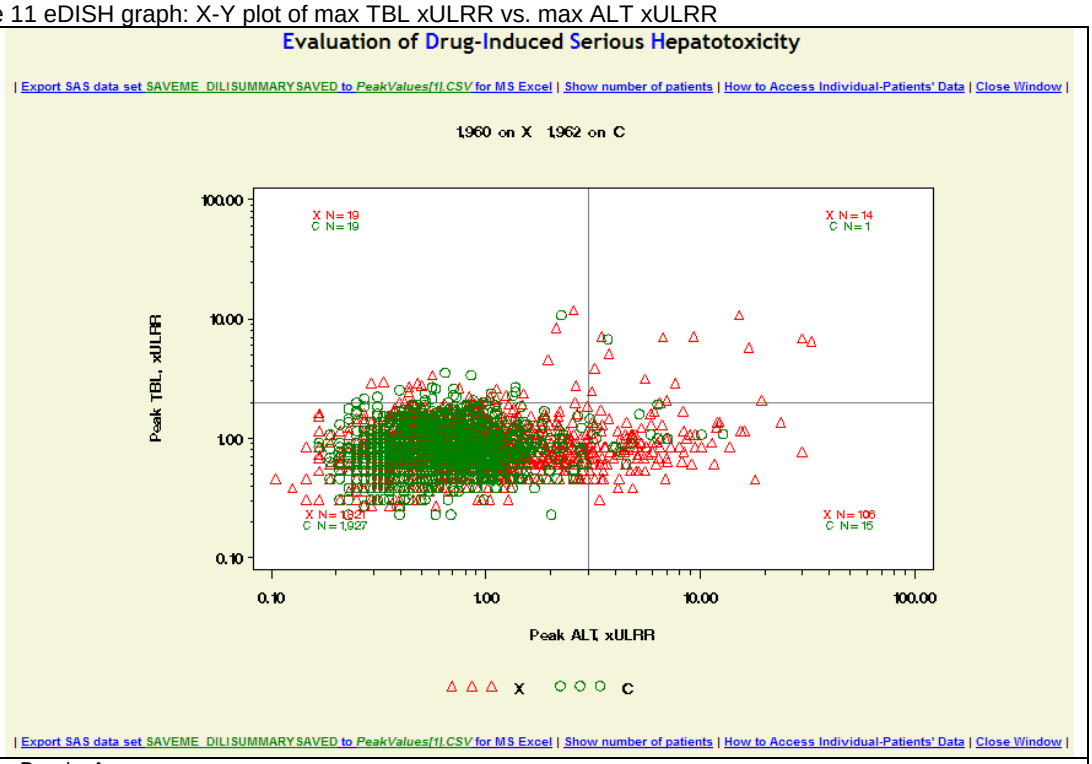
Explanation

```
…
data &libref..&savedname._DILIdataSaved
     (label="Saved DILI data with demo info-for rerun");
  merge save.DILIindiv(in=a) save.TEMPDEMO(in=b);
  by STUDYID USUBJID;
  if a and b;
…
Note: The DILI and demographic data sets are merged. This step completes
the data reconstruction for the time use of this study data. For
subsequent analysis of eDISH, these steps can be bypassed.

The eDISH visualization can begin with the following options:

Option 1: With the box checked, the user can view the eDISH graph and also
direct the analytical result of a selected subject to a pdf file for
printing. This option is useful when the user wish to obtain a complete
analysis of a subject on a single sheet. Leaving the box unchecked, the
user can only view the analytical result on the web browser.

Option 2: With the box checked, the user xxx

Next step: Choose at least one treatment, and then click on “Next” to
continue. On the next screen, all individuals will be displayed.
```

The eDISH visualization is demonstrated on Figure 11. eDISH takes advantage of the drill-down capability of the SAS graph and implemented for this graph. The user moves the mouse over a subject, the coordinates will appear. The subject’s unique ID (USUBJID) will appear. The subjects are clickable so that when the user clicks on the subject, he will drill-down to the subject’s time-course data to be shown on Figure 12.

Figure 11 eDISH graph: X-Y plot of max TBL xULRR vs. max ALT xULRR

Function



Explanation

```
…Part A…
data DrilldownData;
 set _LAST_;
 PointDrill='href="'||trim(symget('_thissession'))||
   '&_program='||"%superq(_pgmlib)"||
 %if %superq(outputRTFfile)=N %then %do;
   '.ExantaIndiv.sas'
 %end;
 %else %do;
   '.ExantaIndivPrint.sas'
 %end;
 ||'&savedname='||"&savedname"||'&patsel='|| trim(left(usubjid))||
 '&libref='||"&libref"||'&libreforig='||"&libreforig"||
 '&memname1='||"&memname1"||'&yval='||trim(log10maxbilixuln)||
 '&xval='||trim(log10maxaltxuln)||'&trtval='||trim(TRTCD)||
 '&noscale=Y'||'&bypass='||"&bypass"||'&showds='||"N"||
 '&_debug='||"&debug"||'" alt="Patient: '||trim(left(usubjid))||
 ', Max ALT='||trim(left(put(maxaltxuln,8.2)))||
 ', Max TBL='||trim(left(put(maxbilixuln,8.2)))||
 '" target="_blank" onMouseOut="javascript: window.status='||
 "'Patient: "||trim(left(usubjid))||", Max ALT="||
 trim(left(put(maxaltxuln,8.2)))||', Max TBL='||
 trim(left(put(maxbilixuln,8.2)))||"'"||'; return+true;" ';
 PointDrill=compress(PointDrill);
run;

…Part B…
proc gplot data=DrilldownData;
plot maxbilixuln*maxaltxuln=TRTCD/html=PointDrill frame
haxis=axis1 vaxis=axis2 vref=(2) href=(3) legend=legend1&showanno;
run;
(Both Parts A and B are part of a SAS program.)
```

Note: In the graph shown in Figure 11, for each subject in the clinical study, the peak TBL (total bilirubin) times the upper limit of the reference range (ULRR) is plotted against the peak ALT times the upper limit of the reference range (ULRR), on a log10 scale. This study includes 3,922 subjects randomized to either the experimental drug in red

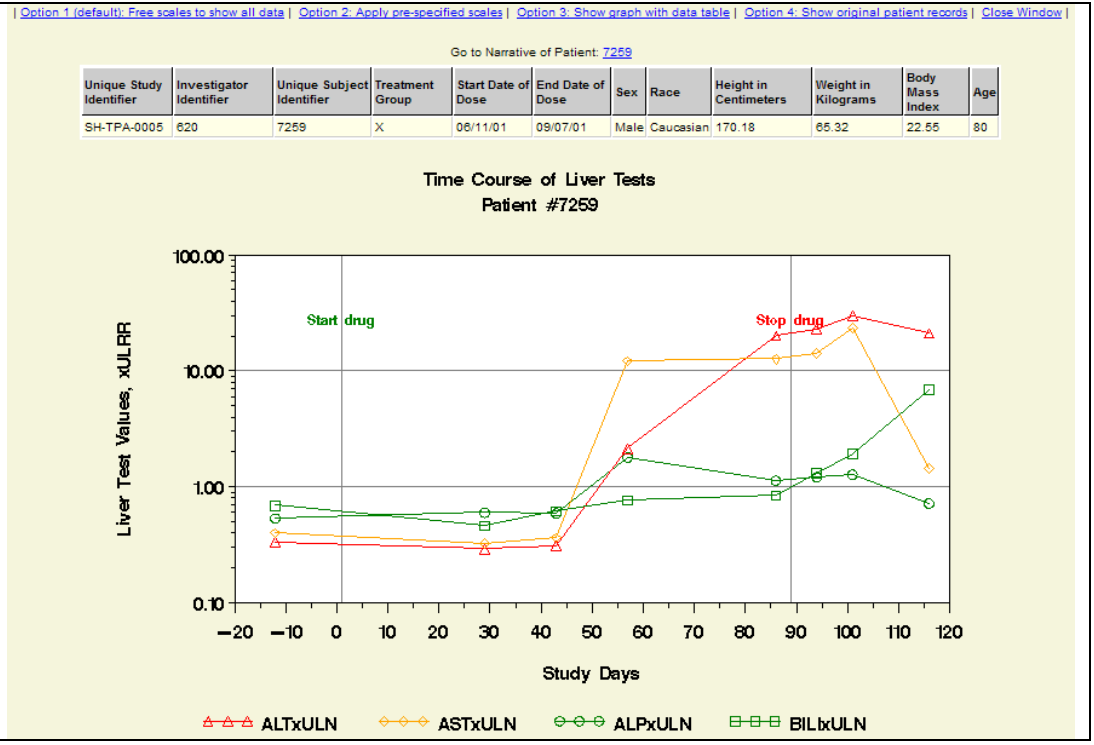
triangles or the existing drug as a comparator in green circle. Two reference lines, 2xULRR for TBLxULRR and 3xULRR for ALTxULRR, are drawn to divide the plane into four quadrants. It is important to note that the upper right quadrant is referred as Hy's Law quadrant. Each symbol on the plane represents a subject. A subject falls in the Hy's Law quadrant is subject to further investigation to decide whether it is the case of DILI. The ratio of the number of subjects treated with drug X and that with C is 14:1, representing the great difference in potentially Hy's Law cases between the two treatments. To adjudicate the cases in the Hy's Lay quadrant, we must investigate each subject in the quadrant by displaying his/her liver tests over time, as well as the clinical narrative for the subject.

Explanation for the selected SAS program segments, Parts A and B: To accomplish this task described, above, we created a data set named DrilldownData for which we added a character variable, PointDrill, a hyperlink triggering the next SAS program graphing liver-test-value changes over time for the selected subject. As part of the hyperlink, the macro variable, &pastel, carries the subject's ID to the next SAS program: '&patsel='|| trim(left(usubjid)). In the GPLOT procedure, the option, html=PointDrill, is used to enable the drill-down functionality so that each point on the X-Y graph becomes clickable.

Figure 12 shows the time-source liver data for selected subject No.7259 who was treated with drug X. Note that the ALT and AST values start to rise almost 6 weeks before the TBL values, which rise even after stopping the study drug administration.

Figure 12 Drill-down to time-source liver data

Function



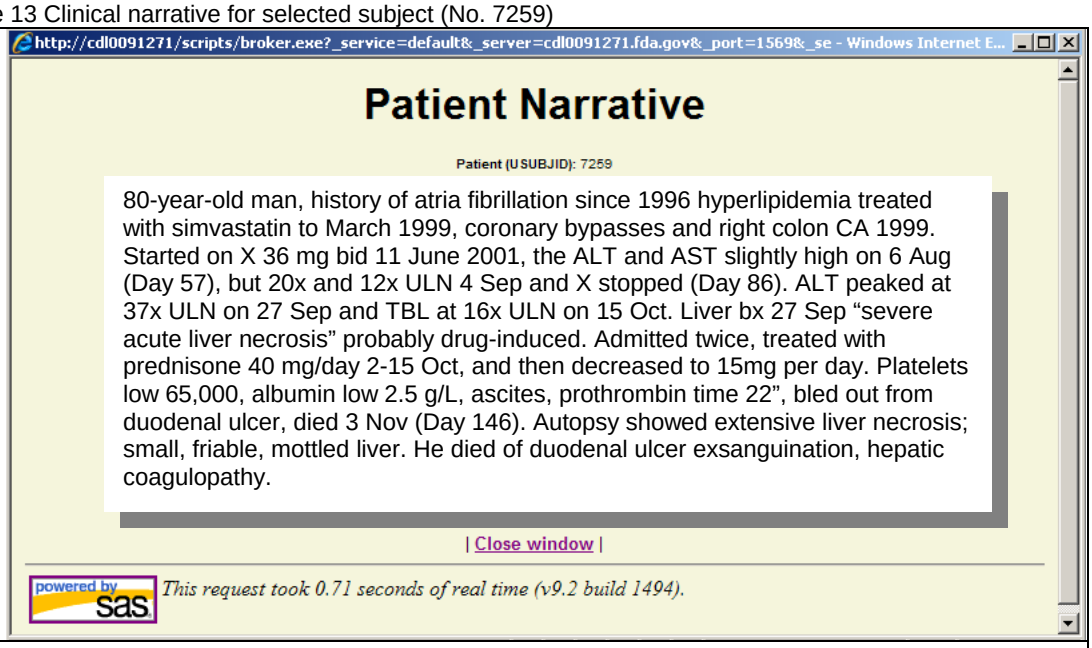
Explanation

```
…
%*** create time-course liver test data ***;
%global patsel SubjectOnGraph …;
%let SubjectOnGraph=&patsel;

proc sql noprint;
  create table timecoursedata
  as select USUBJID, studydays,
     altxuln, bilixuln, astxuln, alpxuln,
     EXSTDT, EXDT, EXENDT
  from &libref..&memname1
  where USUBJID ="&SubjectOnGraph"
  order by studydays;
quit;
…
Note: When the preceding SAS program triggers this program, the patient's
ID via macro variable, &patsel, is passed to this program. This program
helps the creation of the time-course liver test data set used to produce
the graph. This graph along with the clinical narrative helps adjudicate
the case of DILI.

Next step: Click on the hyper linked subject's ID, the clinical narrative
for the patient, if available, will appear.
```

The time-course liver test data provide an important aspect of the patient's liver function. The visualization of the data helps identify the subjects of concern quickly. However, the data, based on chemistry, may not answer the ultimate questions: Does the experimental drug cause liver injury. Causality can be better explained by evaluating the serum chemistry data and the clinical narratives together. An ideal clinical narrative should be prepared by a medical writer using information from case report form and physician's diagnosis and treatment. Figure 13, as an example for this paper, is the clinical narrative for subject No. 7259.

Figure 13 Clinical narrative for selected subject (No. 7259)

Function



Explanation

```
Note: The content of the narrative is slightly enlarged for better visual
effect. The clinical interpretation based on this narrative and the time-
source liver test data suggest that this is a Hy's Law case, i.e., it is
concluded that the serious liver injury was caused by Drug X the patient
received.
```

Ideally, the narratives should be stored in a data set. In the submission of this NDA the narratives came as PDF files. So, the narrative data set was created by us by hand. Fortunately, there are only a small number of subjects in the Hy's Law range that need clinical narratives for the DILI evaluation in most clinical trials.

As a brief technical note, eDISH consists of one portal page html file, a little fewer than 50 SAS programs working as integral parts of the tool, along with other PowerPoint files for informational purposes. Except for the eDISH portal page, all the other web pages are produced dynamically during the eDISH run by SAS programs. The debug mode revealing the SAS log files is not available for the production web side. The method, POST, is used as much as it can be to prevent unwanted intervention. The server runs SAS 9.1.3 on Windows XP. It is used for SAS/IntrNet applications alone.

The characteristics of eDISH are summarized in the following points:

- eDISH suites analyses of liver data including large numbers of subjects with long study durations.
- eDISH facilitates an at-a-glance summary view on one screen of clinical lab results for all subjects in the clinical study.
- eDISH has a drill-down capability from the summary views of all subjects to a time-course view of individual subject, which opens the subject's demographic characteristics, liver-testing results over time, and clinical narrative. It is a tool to adjudicate DILI cases. It is available to all the FDA reviewers.
- eDISH requires a high data standard. Incoming data in conformity with the CDISC standard terms help run eDISH smoothly.

CONCLUSION

The eDISH tool runs SAS/IntrNet Application Dispatcher. It helps FDA medical reviewers evaluate and determine whether the experimental drug was the cause of liver injury. eDISH is particularly useful in analyzing large numbers of subjects (in thousands) followed for an extended period of time, and display all cases of interest at-a-glance. The drill-down capability enables the reviewer to evaluate further based on individual time-course liver test data one subject at a time. The on-screen "Guide Me" instructs the user to fulfill programming requirements so the preset goal can be reached successfully. Easy access of eDISH is available for the FDA reviewer from the web locally and remotely with VPN access.

The eDISH tool currently is used in ongoing drug evaluation and research as demand increases. It is a review tool as well as a working progress. We are improving eDISH based on input from review decisions. We are also creating a number of auxiliary programs. One of them is a tool to help prepare clinical narratives as a SAS data set. It is a SAS/IntrNet application by itself.

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