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ADaM and TFL for Drug-induced Liver Injury (DILI) Analysis

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ABSTRACT

In August 2022, the FDA CDER released guidance for standard safety tables. Drug-induced liver injury (DILI) is part of the analysis supporting new drug application. Sponsors often use Hy's Law criteria to create table and figures for this analysis.

The paper will explain Hy's Law criteria and present how to set up ADaM data from SDTM.LB. The maximum value of the post-baseline result should not only create Ratio to Analysis Range Upper Limit flag for subjects with the baseline results in normal ranges, but also Ratio to Baseline Value flag for subjects with baseline above the normal range. Sponsor may use the first ratio to do the analysis or use both when there are subjects enrolled study with abnormal results in ALT/AST and total bilirubin. ADaM data specification with blind dummy data illustration will be presented to show the Hy's Law can identify potential DILI cases.

To identify potential Hy's Law case, any post-baseline total bilirubin ≥ 2 x UNL on or within 30 days after post-baseline peak value ALT or AST ≥ 3 x UNL while ALP is < 2 x ULN. The figures show different combinations between ALT/AST and ALP vs total bilirubin, so that it would be clear to see if there are truly potential cases. If yes, what the AE or symptoms were like before or after 30 days of the lab toxicity occurred.

Lab results help identify potential DILI but stopping the trial needs safety team to assess.

INTRODUCTION

Dr. Hyman (Hy) Zimmerman in his classic landmark book[1] and publication brought insights in 1978 that drug-induced hepatic reactions cause hepatocellular injury and jaundice. He observed the severe hepatotoxicity could potentially lead to 10-15 percent mortality from acute liver failure (ALF). Dr. Robert Temple, CDER of the FDA, extended Zimmerman's observation in the 1980's from jaundice to elevated bilirubin and coined these terms as Hy's Law. This landmark law remains a cornerstone of hepatic safety assessment which became the FDA guidance on monitoring and assessment of hepatotoxicity in clinical trials.

The ratio of laboratory results in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (BILI) and alkaline phosphatase (ALP) to the upper limit of normal (ULN) indicates abnormal liver functions when it is greater than one. The Common Terminology Criteria for Adverse Events (CTCAE) v5.0[2] applies this ratio to determine the toxicity grade for hepatic adverse events. In 2022, FDA released Standard Safety Table and Figures[3]. It included Hy's Law analysis as shown in Table 26, Figure 12, 13, Table 29 and 30. This paper aims to demonstrate ADaM implementation and TFL production for the first two outputs.

REGULATORY GUIDANCE ON HY'S LAW

Based on the 2009 FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation[4], Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.

2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP).

3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

The guidance stated, discontinuation of treatment should be considered if:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

The guidance is critical to determine the risk of acute liver failure (ALF) in drug safety and to identify potential DILI cases in clinical trials and research. Health Canada[5] has similar guidance as well. To identify potential DILI cases, we first define the onset of the post-baseline ALT or AST > 3 x UNL, then check within 30 days of the onset date if the total bilirubin BILI > 2 x ULN while ALP < 2 x UNL. If the total bilirubin does not satisfy this condition, check the next visit where ALT/AST > 3 x ULN and check again if total bilirubin is > 2 x ULN while ALP < 2 x UNL within 30 days of the onset date.

ADAM DATA AND SPECIFICATIONS

The analysis data ADDILI (Data for Drug-induced Liver Injury) is Basic Data Structure (BDS). The input data can be SDTM.LB for safety monitoring or ADaM ADLB for CSR report. The potential DILI cases are under PARAMCD DILIxFL which is one subject per PARAMCD. The relevant specifications based on ADLB for TFL production are below:

ADDILI DERIVATIONS:

Column	Label	Type/ Length	Algorithm
USUBJID	Unique Subject Identifier	C 40	DM.USUBJID or ADLB.USUBJID
PARAMCD	Parameter Code	C 8	"ALT" = "Alanine Aminotransferase (U/L)" "AST "= "Aspartate Aminotransferase (U/L)" "ALP" = "Alkaline Phosphatase (U/L)" "BILI" = "Bilirubin (umol/L)" "DILI1FL"="ALT or AST >3xULN and Total Bilirubin >3xULN" "DILI2FL" = "ALT or AST >3xULN and Total Bilirubin >3xULN While Alkaline Phosphatase (ALP) >=2" "***DILI3FL" = "ALT or AST >3xULN and Total Bilirubin >3xULN While Alkaline Phosphatase (ALP) <2***"
PARAM	Parameter	C 100	Decoded value of PARAMCD based on code list
AVAL	Analysis Value	N	See Parameter Value Level Metadata
AVALC	Analysis Value (C)	C 40	See Parameter Value Level Metadata
ABLFL	Baseline Record Flag	C 1	Last non-missing values on or before the first treatment
BASE	Baseline Value	N	AVAL from the record for this USUBJID/PARAMCD where ABLFL = "Y"
R2BASE	Ratio to Baseline Value	N	Ratio to the baseline value. Set to AVAL/BASE for post baseline records.
R2ANRHI	Ratio to Analysis Normal Range Upper Limit	N	Ratio to the Analysis Normal Range Upper Limit. Set to AVAL/ANRHI for post baseline records
ATOXGR	Analysis Toxicity Grade	C 10	ADLB.ATOXGR where ADLB.PARAMCD in ("ALT", "AST", "BILI", "ALP"), or derive from SDTM.LB based on protocol specified criteria such as CTCAE v.5
ANL01FL	Analysis Flag 01	C 1	Set to 'Y' for the maximum post baseline value of R2ANRHI when PARAMCD in ("ALT", "AST").
ANL02FL	Analysis Flag 02	C 1	Set to 'Y' for the maximum post baseline value of R2ANRHI for BILI within 30 days of the onset of maximum R2ANRHI in ("ALT", "AST").

Column	Label	Type/ Length	Algorithm
MCRIT1	Analysis Multi-Response Criterion 1	C 40	Set to 'ALT Classification'
MCRIT1FL	Multi-Response Criterion 1 Evaluation	C 40	For ALT: set to "Normal" when ANRLO<=AVAL<=ANRHI; else set to "1 x ULN<ALT<=3 x ULN" when 1<R2ANRHI<=3; else set to "3 x ULN<ALT<=5 x ULN" when 3<R2ANRHI<=5; else set to "5 x ULN<ALT<=8 x ULN" when 5<R2ANRHI<=8; else set to "8 x ULN<ALT<=10 x ULN" when 8<R2ANRHI<=10; else set to "10 x ULN<ALT<=20 x ULN" when 10<R2ANRHI<=20; else set to "ALT>20 x ULN" when R2ANRHI>20; When base is > ANRHI, use REBASE to do the above assessment per study SAP
MCRIT2	Analysis Multi-Response Criterion 2	C 40	Set to 'AST Classification'
MCRIT2FL	Multi-Response Criterion 2 Evaluation	C 40	For AST: set to "Normal" when ANRLO<=AVAL<=ANRHI; else set to "1 x ULN<AST<=3 x ULN" when 1<R2ANRHI<=3;else set to "3 x ULN<AST<=5 x ULN" when 3<R2ANRHI<=5; else set to "5 x ULN<AST<=8 x ULN" when 5<R2ANRHI<=8; else set to "8 x ULN<AST<=10 x ULN" when 8<R2ANRHI<=10; else set to "10 x ULN<AST<=20 x ULN" when 10<R2ANRHI<=20; else set to "AST>20 x ULN" when R2ANRHI>20; When base is > ANRHI, use REBASE to do the above assessment per study SAP
MCRIT3	Analysis Multi-Response Criterion 3	C 40	Set to 'Total Bilirubin Classification'
MCRIT3FL	Multi-Response Criterion 3 Evaluation	C 40	For BILI: Set to 'Normal' when ANRLO<=AVAL<=ANRHI else set to "1 x ULN < BILI <= 1.5 x ULN" when 1<R2ANRHI<=1.5; else set to "1.5 x ULN < BILI <=2.0 x ULN" when 1.5<R2ANRHI<=2; else set to " 2.0 x ULN < BILI <=3.0*ULN" when 2<R2ANRHI<=3;else set to "BILI > 3 x ULN" when R2ANRHI >3; When base is > ANRHI, use REBASE to do the above assessment per study SAP.
MCRIT4	Analysis Multi-Response Criterion 4	C 40	Set to 'ALP Classification'
MCRIT4ML	Multi-Response Criterion 4 Evaluation	C 40	Set to 'ALP < 2.0 x ULN' when. < A2ANRHI<2; else set to 'ALP >= 2.0 x ULN' when R2ANRH>=2;

Note: the specification excluded standard BDS variable ADT, ADTM, ADY, ANRIND, ABRLO and ANRHI

Sponsor may use PARAM/PARAMCD rather than MCRITy/MCRITyML to represent the ratios separately.

The specification for potential DILI cases is below: it is one subject per param with ADT as the first onset date of the event. Sponsor may decide the interval, if not 30 days from the onset of ALT/AST > 3 x ULN in the protocol or SAP.

PARAMCD	Algorithm for AVALC	Comments
D1LI1FL	Set to 'Y' if R2ANRHI for BILI > 2 within 30 days of the onset when R2ANRHI for ALT or AST > 3.	Hy's law event first condition
D1LI2FL	Set to 'Y' if R2ANRHI for BILI > 2 and R2ANRHI for ALP >= 2 within 30 days of the onset when R2ANRHI for ALT or AST > 3; else set to 'N'.	Missing ALP is considered as ALP < 2 x ULN
D1LI3FL	Set to 'Y' if R2ANRHI for BILI > 2 and R2ANRHI for ALP < 2 within 30 days of the onset when R2ANRHI for ALT or AST > 3; else set to 'N'.	Missing ALP is considered as ALP < 2xULN. This is the potential Hy's Law event.

ADDILI SAMPLE DATA

Here is hypothetical ADDILI data following the above derivation rules:

- Though the first post-baseline ALT/AST value > 3 x ULN at Visit 7 but the total bilirubin within 30 days (same visit in this case) was 1.8 x ULN.
- Continue checking the next ALT/AST value > 3 x ULN at Visit 9, onset date 2023-03-20, the total bilirubin within 30 days (same visit in this case) was 2.17 x ULN and ALP was < 2 x ULN, this was potential Hy's Law event.
- ANL01FL and ANL02FL were set 'Y' for maximum ALT/AST ratio and BILI ratio for plot and further derive DILIxFL.

USUBJID	TR01SDT	PARAMCD	AVAL	AVALC	ADT	AVISIT	ADY	BASE	ANRHI	R2ANRHI	ANL01FL	ANL02FL
100-100-001	2022-08-09	ALT	60		2022-08-09	DAY 1	1	60	48	1.25		
100-100-001	2022-08-09	AST	86		2022-08-09	DAY 1	1	86	40	2.15		
100-100-001	2022-08-09	ALP	195		2022-08-09	DAY 1	1	195	129	1.51		
100-100-001	2022-08-09	BILI	13.68		2022-08-09	DAY 1	1	13.68	20.52	0.67		
100-100-001	2022-08-09	AST	121		2023-01-26	Visit 7	171	86	40	3.03		
100-100-001	2022-08-09	ALT	81		2023-01-26	Visit 7	171	60	48	1.69		
100-100-001	2022-08-09	ALP	206		2023-01-26	Visit 7	171	195	129	1.60		
100-100-001	2022-08-09	BILI	37.62		2023-01-26	Visit 7	171	13.68	20.52	1.83		
100-100-001	2022-08-09	AST	399		2023-03-20	Visit 9	224	86	40	9.98	Y	
100-100-001	2022-08-09	ALT	135		2023-03-20	Visit 9	224	60	48	2.81		
100-100-001	2022-08-09	ALP	230		2023-03-20	Visit 9	224	195	129	1.78		
100-100-001	2022-08-09	BILI	44.46		2023-03-20	Visit 9	224	13.68	20.52	2.17		Y
100-100-001	2022-08-09	DILI1FL		Y	2023-03-20		224					
100-100-001	2022-08-09	DILI3FL		Y	2023-03-20		224					
100-100-001	2022-08-09	DILI2FL		N	2023-03-20		224					

HOW ADDILI SUPPORTS HY'S LAW ANALYSIS

1. Create variable R2ANRHI/R2BASE as the ratio between post-baseline results to the Analysis Normal Range Upper Limit/Baseline value. This drives the rest of the derivations.
2. Use ANL01FL and ANL02FL to select the maximum (worst) result of ALT/AST and total bilirubin (BILI) for each subject within 30 days of post-baseline ALT/AST > 3.0 x ULN. FDA developed a graphic tool named eDISH[6] (Evaluation of Drug-Induced Serious Hepatotoxicity) plot to detect potential DILI cases. These two flags subset R2ANRHI for peak values of ALT/AST and bilirubin as the input data for eDISH plot and Figure 12 in the FDA 2022 safety TFL guidance. Please see Figure 1 below.
3. Create MCRIT*y* and MCRIT*y*FL due to various levels of R2ANRHI/R2BASE within each parameter. Be mindful with table production, when the ratio 8<R2ANRHI<=10 for ALT/AST, then it is true for all the levels with the ratio ≤ 10 as shown below:

Level 1 (>3.0 x ULN)	True
Level 2 (>5.0 x ULN)	True
Level 3 (>8.0 x ULN)	True

4. ATOXGR can be used for narratives or other standard analysis. Sponsor may derive the toxicity grade based on a version of CTCAE as defined in the protocol, the R2BASE would help to derive it when baseline result is abnormal.

TABLE AND FIGURE FOR DILI ANALYSIS

We integrated Table 26 into the FDA Standard Safety Tables and Figures: Integrated guide, August 2022 by adding additional highlighted levels for ALT/AST ratio > 8.0 and 20.0 > ULN per FDA 2009 guidance for trial stopping rule. This helps safety and study team to detect severe DILI cases.

MODIFIED DILI ANALYSIS TABLE

Summary of Drug Induced Liver Injuries

Safety Analysis Set

Laboratory Parameter	IMP 100 mg (N=11)	Placebo (N=5)
Alkaline Phosphatase (U/L)		
Level 1 (>1.5 x ULN)	3 (27.3)	0
Level 2 (>2.0 x ULN)	2 (18.2)	0
Level 3 (>3.0 x ULN)	0	0
Alanine Aminotransferase Chemistry (U/L)		
Level 1 (>3.0 x ULN)	0	0
Level 2 (>5.0 x ULN)	0	0
Level 3 (>8.0 x ULN)	0	0
Level 4 (>10.0 x ULN)	0	0
Level 5 (>20.0 x ULN)	0	0
Aspartate Aminotransferase Chemistry (U/L)		
Level 1 (>3.0 x ULN)	1 (9.1)	0
Level 2 (>5.0 x ULN)	0	0
Level 3 (>8.0 x ULN)	1 (9.1)	0
Level 4 (>10.0 x ULN)	0	0
Level 5 (>20.0 x ULN)	0	0
Bilirubin Chemistry (umol/L)		
Level 1 (>1.5 x ULN)	2 (18.2)	1 (20.0)
Level 2 (>2.0 x ULN)	1 (9.1)	0
Level 3 (>3.0 x ULN)	1 (9.1)	0
ALT or AST >3x ULN (U/L)[1]	1 (100.0)	0
Total Bilirubin (BILI) > 2.0 x ULN *	1 (100.0)	0
ALT or AST >3xULN and Total Bilirubin >2xULN *	1 (100.0)	0
With ALP < 2.0 x ULN *	1 (100.0)	0
With ALP >= 2.0 x ULN *	0	0

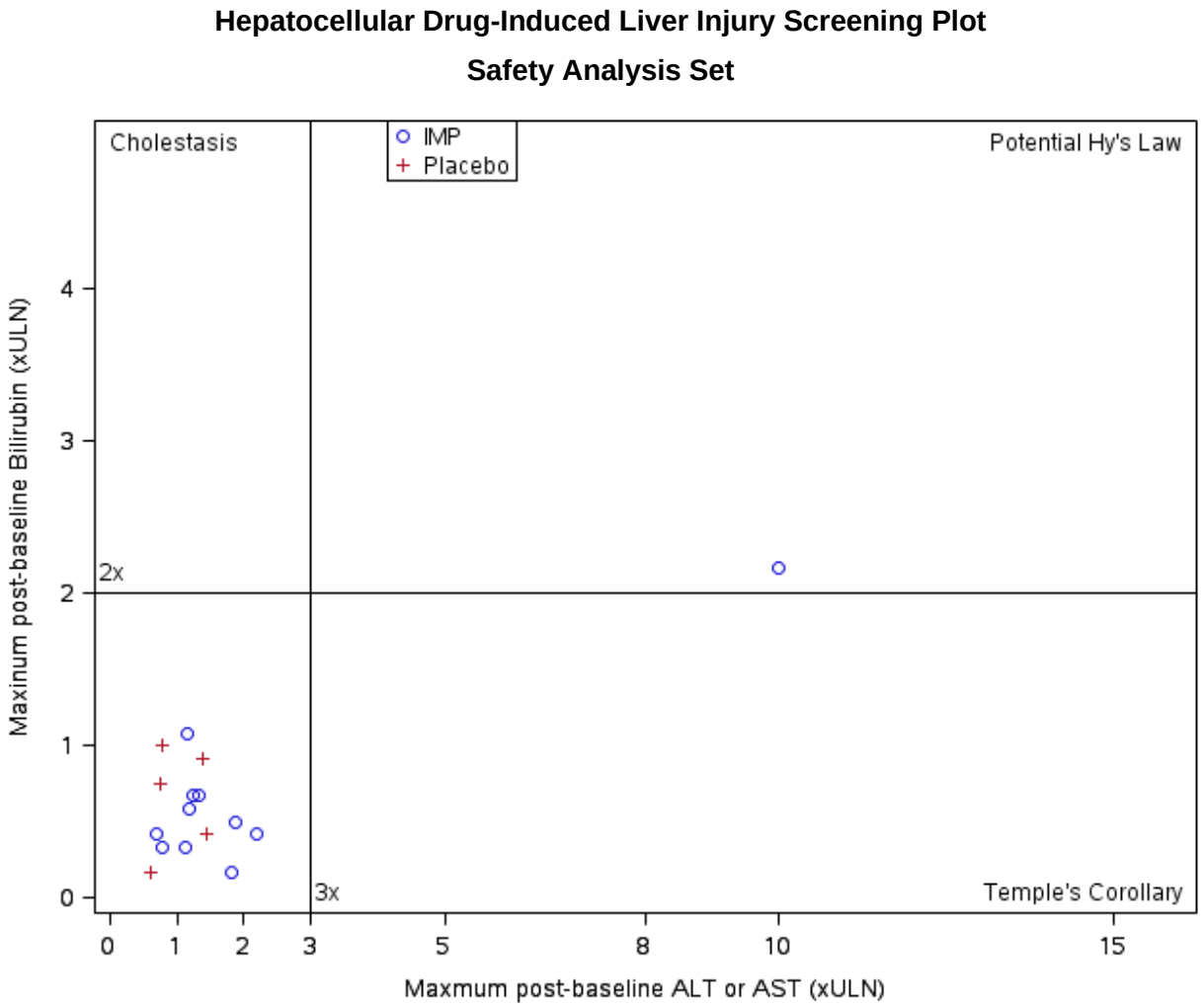
Data Source: ADDILI 26MAR2025:18:01:57 tsumdili.txt
Percentage was based on N for individual lab results. The analysis is on treatment approach as defined in SAP.
1. Hy's Law analysis considers the following conditions within 30 days from the onset of post-baseline ALT or AST > 3 x ULN.
*Percentage was based on the number of participants with ALT or AST > 3.0 x ULN.

Table interpretation

The table indicates although 2 subjects had ALP > 2 x ULN, but they are not the Hy's Law cases. There was only one subject with AST > 3 x ULN. The potential Hy's Law case is on the last highlighted row, where ALT/AST and total bilirubin all satisfied the conditions within the 30-day interval, and the ALP result is < 2 x ULN. The safety team needs to monitor adverse event before or after the Hy's law event to further assess if the subject should discontinue treatment due to DILI.

FIGURE 1 EDISH PLOT

The figure displayed consistent information as the table indicated. One subject had near 10 x ULN ALT/AST and a bilirubin result over 2 x ULN. It falls into the Hy's Law quadrant while the rest of the subjects had their results outside of Temple's Corollary[7]. The



CONCLUSION

It is essential to have straightforward and informative ADDILI analysis data to efficiently perform Hy's Law analysis. The DILIxFL and ANLxFL can quickly identify data for Hy's Law table and eDISH plot to detect potential DILI cases. This data can easily set up either from SDTM.LB or ADLB, effective for both routine safety monitoring and CSR appendix. Retaining the original four lab parameters in the data helps create

safety narratives with traceability. The potential DILI case identified through lab results need further assessment on corresponding AE by drug safety to decide the treatment discontinuation for the subject or the trial.

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