

PP20

PhUSE CSS White Paper on Analyses
Associated With Hepatotoxicity

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WG5 Project 08: Introduction

Project Purpose:

- Create 6 white papers outlining recommended analyses for common Tables, Figures, and Listings (TFLs) for clinical trial study reports and integrated summary documents,
- Develop code created in the PhUSE wiki for the recommended TFLs.

WG5 Project 08: 6 White Paper Topics

1. Analyses and Displays Associated with Measures of Central Tendency – With a Focus on Vitals, ECGs, and Labs in Phase 2-4 Clinical Trials and Integrated Submission Documents
2. Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal – With a Focus on Vitals, ECGs, and Labs in Phase 2-4 Clinical Trials and Integrated Submission Documents
3. Analyses and Displays Associated with Adverse Events and Deaths – With a Focus on Phase 2-4 Clinical Trials and Integrated Submission Documents
4. Analyses and Displays Associated with Demographics, Medications, and Disposition – With a Focus on Phase 2-4 Clinical Trials and Integrated Submission Documents
- 5. Analyses and Displays Associated with Hepatotoxicity – With a Focus on Phase 2-4 Clinical Trials and Integrated Submission Documents**
6. Analyses and Displays Associated to Pharmacokinetics – with a focus on clinical trials

PhUSE CSS Working Group

WG 1: Data Validation and Quality Assessment

WG 2: Standardizing data within the Inspection Site Selection Process

WG 3: Challenges of Integrating and Converting Data across Studies

WG 4: Standards Implementation Issues with the CDISC Data Models

WG 5: Development of Standard Scripts for Analysis and Programming

WG 6: Non-Clinical Roadmap and Impacts on Implementation

PO1: Look for existing scripts and store them in the repository

PO2: Define validation steps for scripts in the repository

PO3: Establish platform (repository) for sharing scripts

PO4: Legal ownership and issues in open source repository

PO5: Create templates for documenting scripts

PO6: Process for creating and editing scripts in Google Code

PO7: Develop communication plan for standard scripts

PO8: Create white papers providing recommended display and analysis including Table, List and Figure shells

1. Analysis and Displays Associated with Measures of Central Tendency – With a Focus on Vitals, ECGs, and Labs in Phase 2-4 Clinical Trials and Integrated Submission Documents

2. Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal – With a Focus on Vitals, ECGs, and Labs in Phase 2-4 Clinical Trials and Integrated Submission Documents

3. Analysis and Displays Associated with Adverse Events – With a Focus on Phase 2-4 Clinical Trials and Integrated Submission Documents

4. Analysis and Displays Associated with Demographics, Medications, and Disposition – With a Focus on Phase 2-4 Clinical Trials and Integrated Submission Documents

5. Analysis and Displays Associated with Hepatotoxicity – With a Focus on Phase 2-4 Clinical Trials and Integrated Submission Documents

6. Analysis and Displays Associated to Non-Compartmental Pharmacokinetics – with a focus on clinical trials

White Paper Status: Preliminary Draft

|Analyses and Displays Associated with Hepatotoxicity – With a Focus on Phase 2-4 Clinical Trials and Integrated Submission Documents

Version 1.0
Created xx XXXX 201x

A White Paper by the PhUSE Computational Science Symposium Development of Standard Scripts for Analysis and Programming Working Group

This white paper does not necessarily reflect the opinion of the institutions of those who have contributed.

Overview of FDA Guidance: July 2009

- “Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation”
- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>
- Addresses how laboratory measurements that signal the potential for such drug-induced liver injury (DILI) can be obtained and evaluated during drug development
- Severe DILI is **RARE**: often <1 in 10,000

Laboratory Tests of Interest

- ALT
- AST
- Total Bilirubin (TBL)
- Alkaline Phosphatase (ALP)

Hyman (Hy) Zimmerman, M.D. (1914-1999), a major scholar of DILI

Hy's Law: Observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury.

Hy's Law: 3 Components

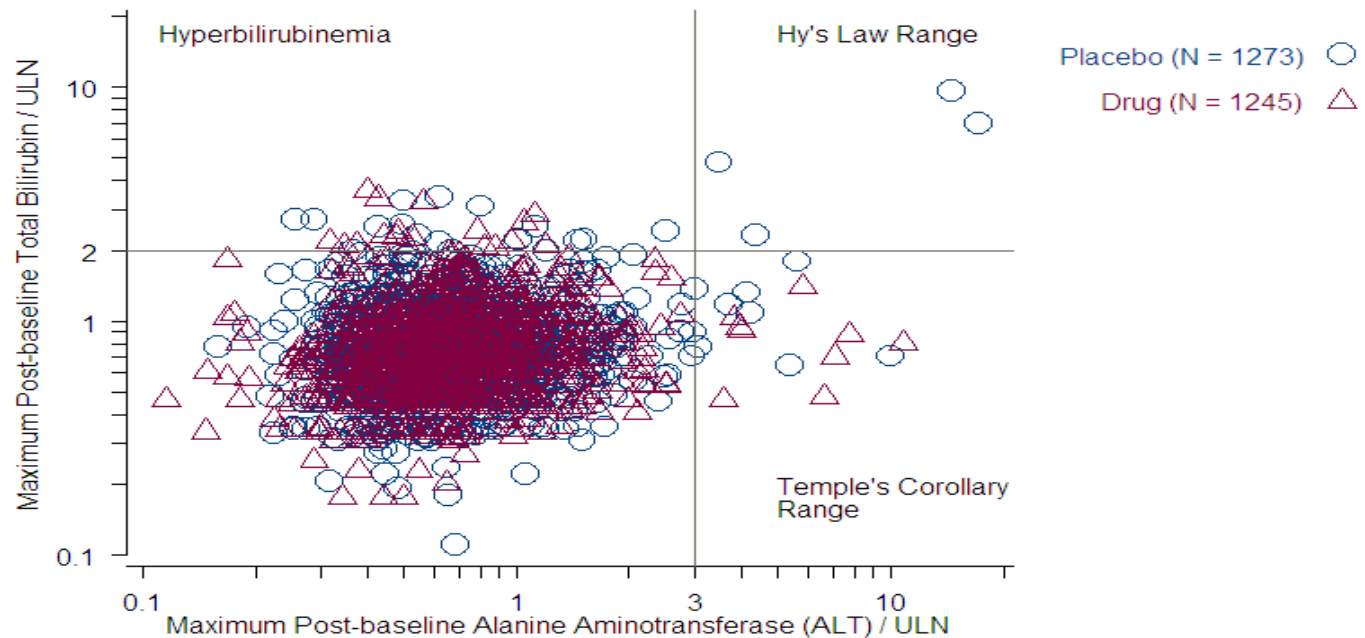
1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show 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



Hy's Law

- Proposed Figure for evaluation: Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH)

Maximum Total Bilirubin vs. Maximum Alanine Aminotransferase



ULN = upper limit of normal of the reference range
Points do not necessarily represent values from the same blood draw.

Laboratory Elevations of Interest

Proposed tabular summaries, including graphs:

- 3x-, 5x-, 10x-, and 20xULN elevations of AST, ALT, and either ALT or AST (AT)
- Any elevations of TBL to $>2\times\text{ULN}$
- Any elevations of ALP $>1.5\times\text{ULN}$
- Elevation of AT ($>3\times\text{ULN}$) accompanied by elevated bilirubin ($>1.5\times\text{ULN}$, $>2\times\text{ULN}$)

General Considerations:

- How to incorporate baseline value
- Whether to report P-values and Confidence Intervals

Adverse Events Analysis

Analysis of the following Standardized MedDRA Queries (SMQs) can be used to assess liver injury and function, and summarized by both broad and narrow terms. The MedDRA preferred terms should be nested within the SMQ.

- *Broad and narrow terms in the liver related investigations, signs and symptoms SMQ (20000008)*
- *Broad and narrow terms in the cholestasis and jaundice of hepatic origin SMQ (20000009)*
- *Broad and narrow terms in the hepatitis non-infections SMQ (20000010)*
- *Broad and narrow terms in the hepatic failure, fibrosis and cirrhosis and other liver damage SMQ (20000013)*
- *Narrow terms in the liver-related coagulation and bleeding disturbances SMQ (20000015)*

Adverse Events Analysis

Possible Table Layout, details to be determined.

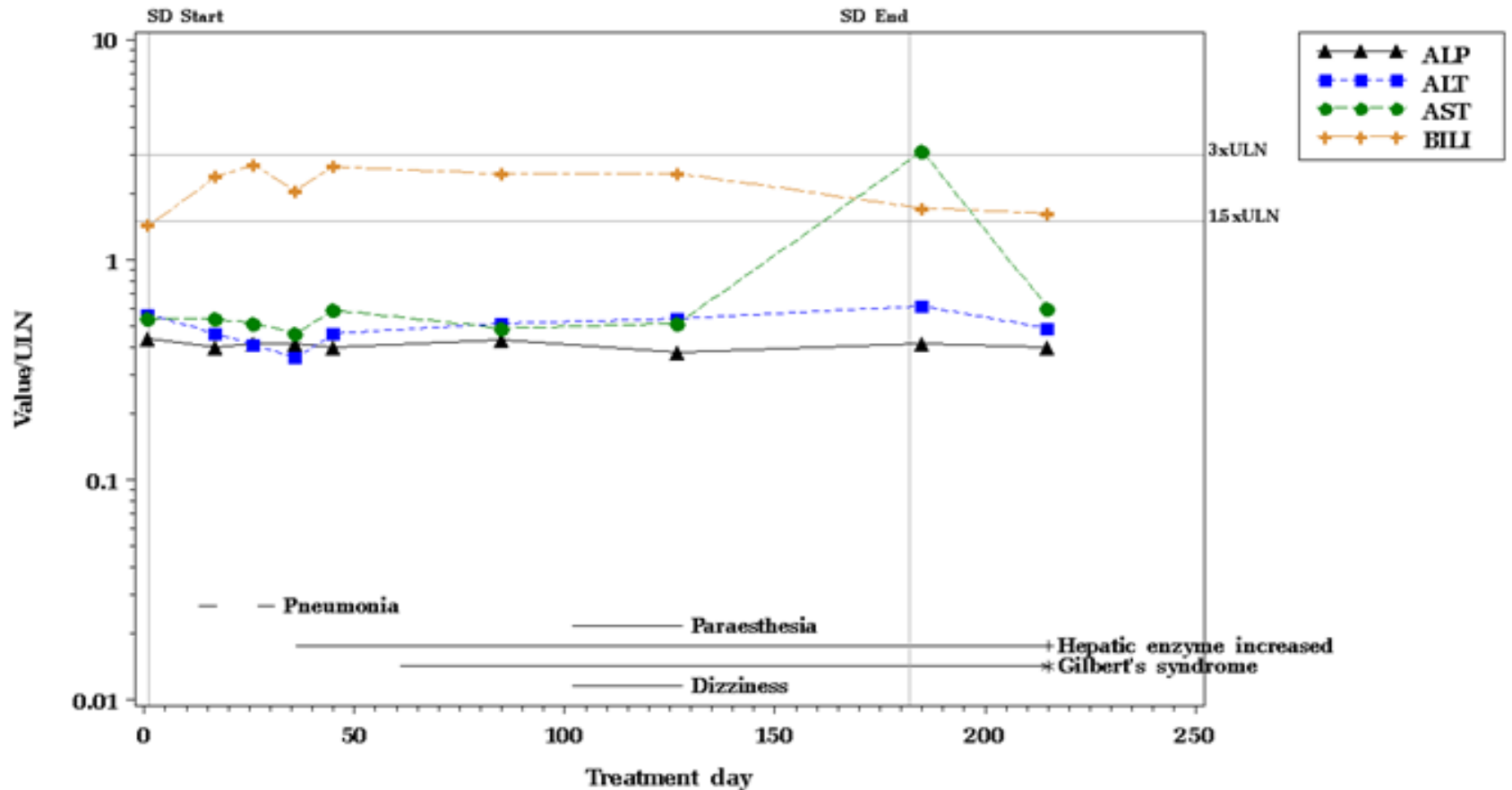
Broad Definition	Treatment A		Treatment B	
Narrow definition	(N=xxx)		(N=xxx)	
Preferred Term	n	(%)	n	(%)
Number of subjects reporting treatment emergent adverse events	xx	(xx.x)	xx	(xx.x)
Liver related investigations, signs and symptoms SMQ (20000008)	xx	(xx.x)	xx	(xx.x)
Preferred Term 1	xx	(xx.x)	xx	(xx.x)
Preferred Term 2	xx	(xx.x)	xx	(xx.x)
Preferred Term 3	xx	(xx.x)	xx	(xx.x)
Preferred Term n	xx	(xx.x)	xx	(xx.x)
Cholestasis and jaundice of hepatic origin SMQ (20000009)	xx	(xx.x)	xx	(xx.x)
Preferred Term n+1	xx	(xx.x)	xx	(xx.x)
Preferred Term n+2	...	...	...	...
Preferred Term n+3	xx	(xx.x)	xx	(xx.x)
... and so on ...				

Individual Display

- Patients for further interest summarized graphically, including:
 - Laboratory results vs ULN
 - Dosing start/stop day
 - Relevant Adverse event start/stop day
 - Dates of other important events (important medication start/stop days, transplantation date, etc.)

Individual Display

Possible Figure Layout, details to be determined.



Conclusions

- Draft 1 of the white paper is currently in preliminary draft form
- Next Steps include:
 - Collect feedback
 - Other displays for consideration
 - Maintain consistency with displays in other white papers
- This white paper provides guidance and foundation for the work in the Script-athon, for **e-DISH plot**.
- For further information, www.phusewiki.org
- Please contact Terry.Walsh@astellas.com