

(eDISH) Evaluation of drug-induced serious hepatotoxicity using SAS® Graph

Jaimin Patel, AstraZeneca

03 May 2022

PHUSE US Connect 2022



What is eDISH ?

eDISH = **e**valuation of **D**rug-**I**nduced **S**erious **H**epatotoxicity

- It is one of the analysis method to assess “Liver Safety Data” for any investigational product.
- eDISH is very useful approach that organizes liver laboratory data by graphically displaying peak serum ALT (Alanine transaminase) and TB (Total Bilirubin) levels for each subject and can also provide direct links to the relevant clinical and laboratory data for each subject.



Why eDISH ?

- Currently, many pharmaceutical products having serious known/un-known side effects to liver and its functions.
- **Hepatotoxicity** is one of the most frequent cause for acute liver failure in patient treated with certain medicines or pharmaceutical preparations.
- This might also result in post-commercialization adverse regulatory decisions.
- The diagnosis of hepatotoxicity remains a difficult task because of the lack of reliable markers for use in general clinical practice.



Which data included in eDISH ?

- The most specific indicator of a drug-induced liver injury in clinical trials believed to be the occurrence of subjects experiencing drug-associated elevations in both serum ALT/AST and serum Total Bilirubin (TB) without a significant elevation in serum alkaline phosphatase (ALP).
- eDISH (evaluation of Drug-Induced Serious Hepatotoxicity) is a well described method/tool that visually represent liver laboratory data of **ALT/AST** and **Total Bilirubin** in form of **graph** by displaying peak levels for each subject. This is often known as **eDISH plots**.



How to generate eDISH Plots

Extraction

- Subject-wise ALT/AST and Total Bilirubin Data for Safety Laboratory Dataset (SDTM.LB/ADAM.ADLB)
- Relevant ULN (Upper Limit of Normal) value and treatment arm data.

Transformation

- Take the ratio of “Observed value - AVAL/ULN” for ALT/AST and Total Bilirubin data.
- Get the maximum ratio value for ALT/AST and Total Bilirubin per subject per treatment arm.

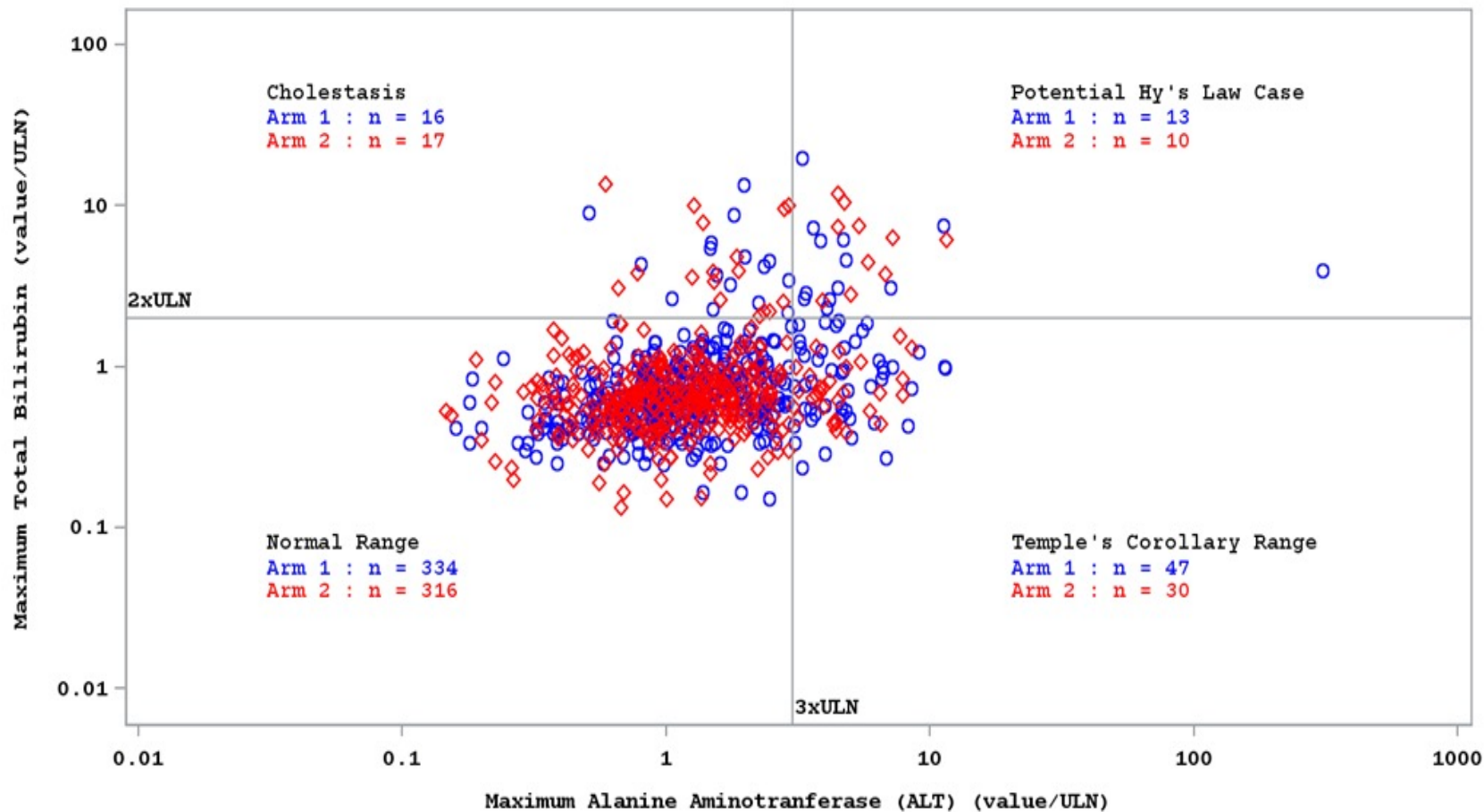
Loading

- Produce scatter plot to have
 - Y Axis => Total Bilirubin/ULN values
 - X Axis => ALT/ULN or AST/ULN
- Draw reference lines on this plot to divide data into 4 quadrants.
 - Y Axis => At Value 2
 - X Axis => At Value 3



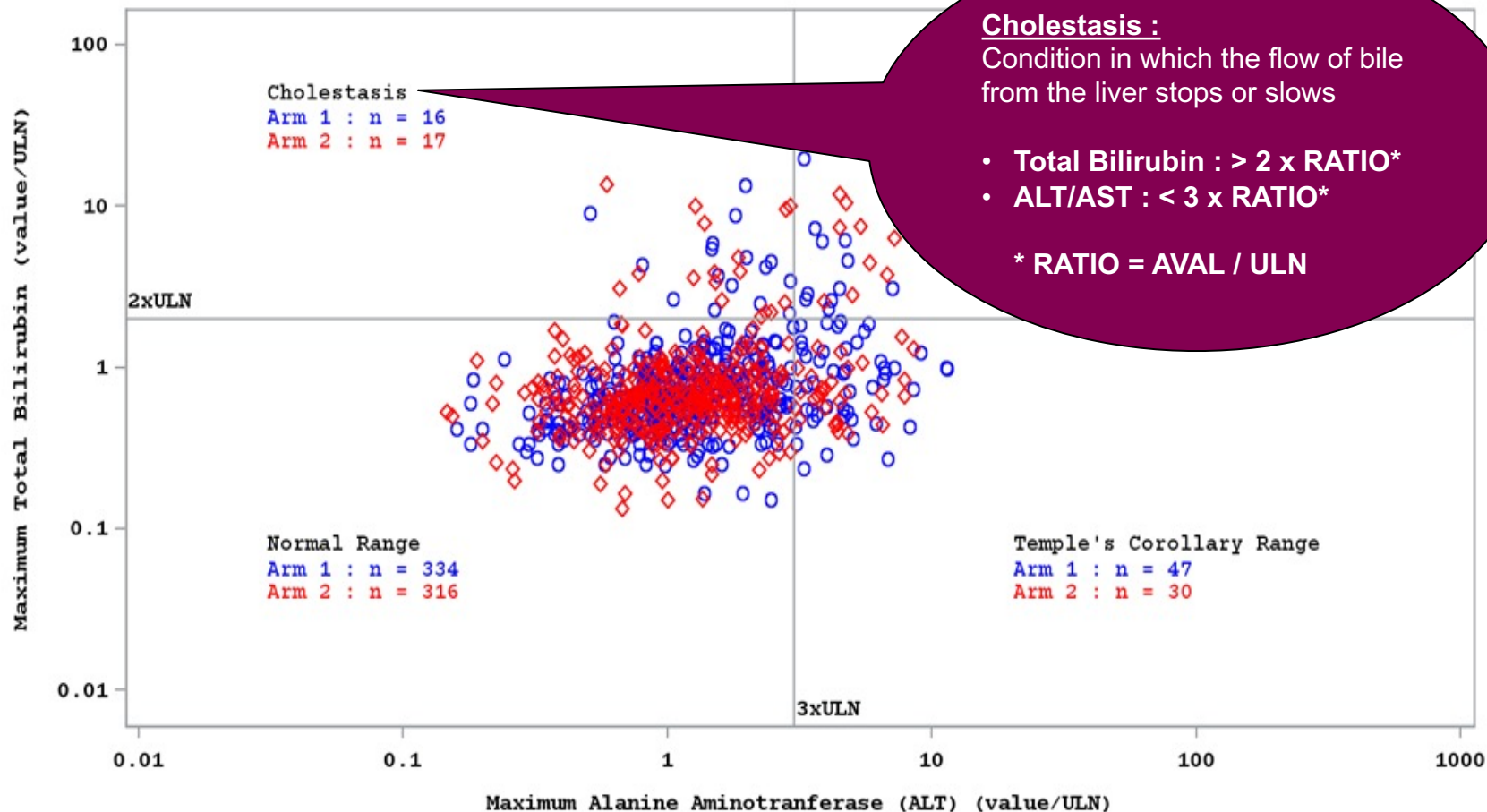
Sample eDISH plot Output using SAS® Graph

Figure 14.2.3.4.1 E-DISH Scatter Plot of Maximum Total Bilirubin vs Maximum ALT on Study
(Safety Analysis Set)



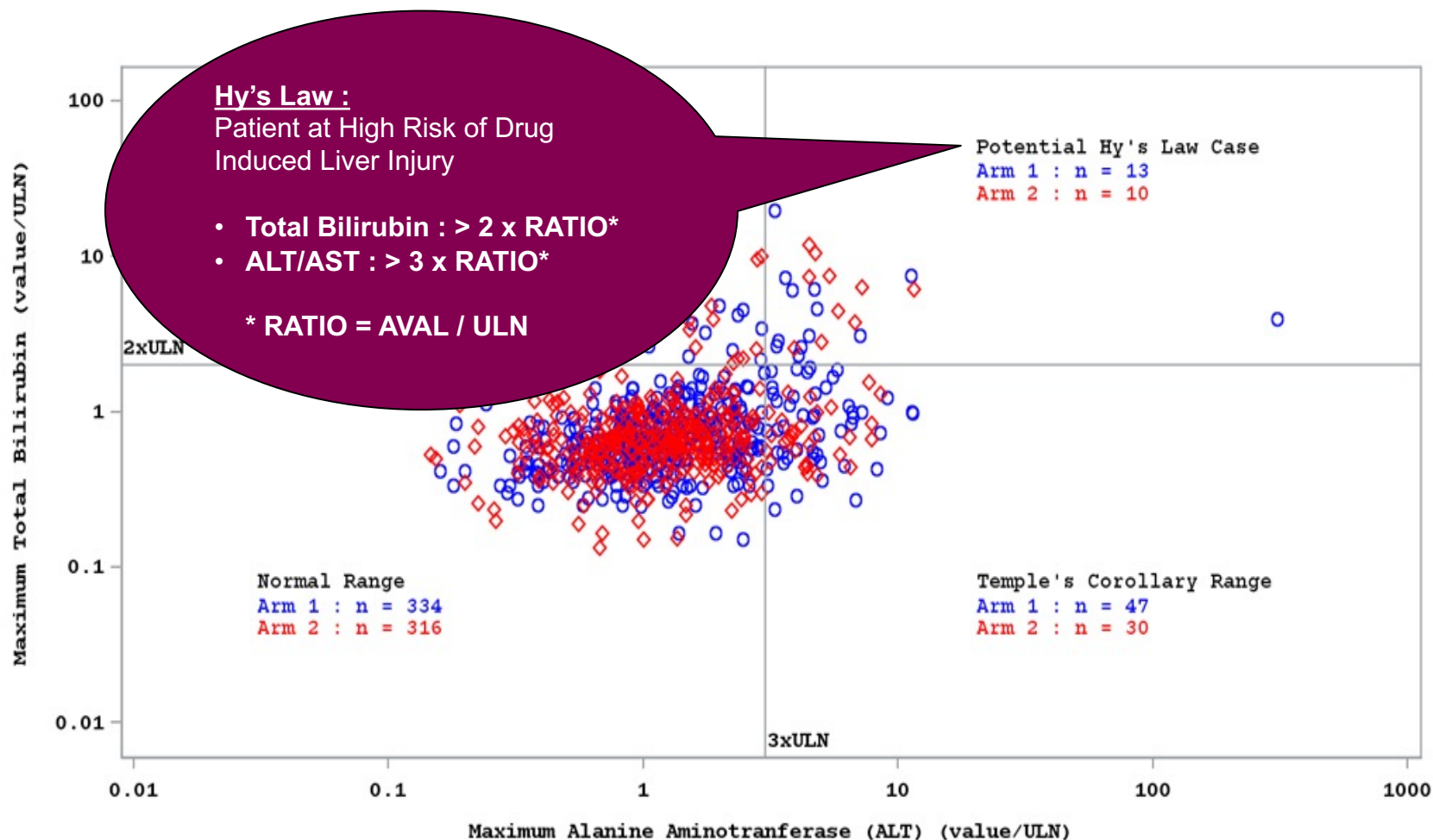
Interpretation of eDISH Plot : Upper Left Quadrant

Figure 14.2.3.4.1 E-DISH Scatter Plot of Maximum Total Bilirubin vs Maximum ALT on Study
(Safety Analysis Set)



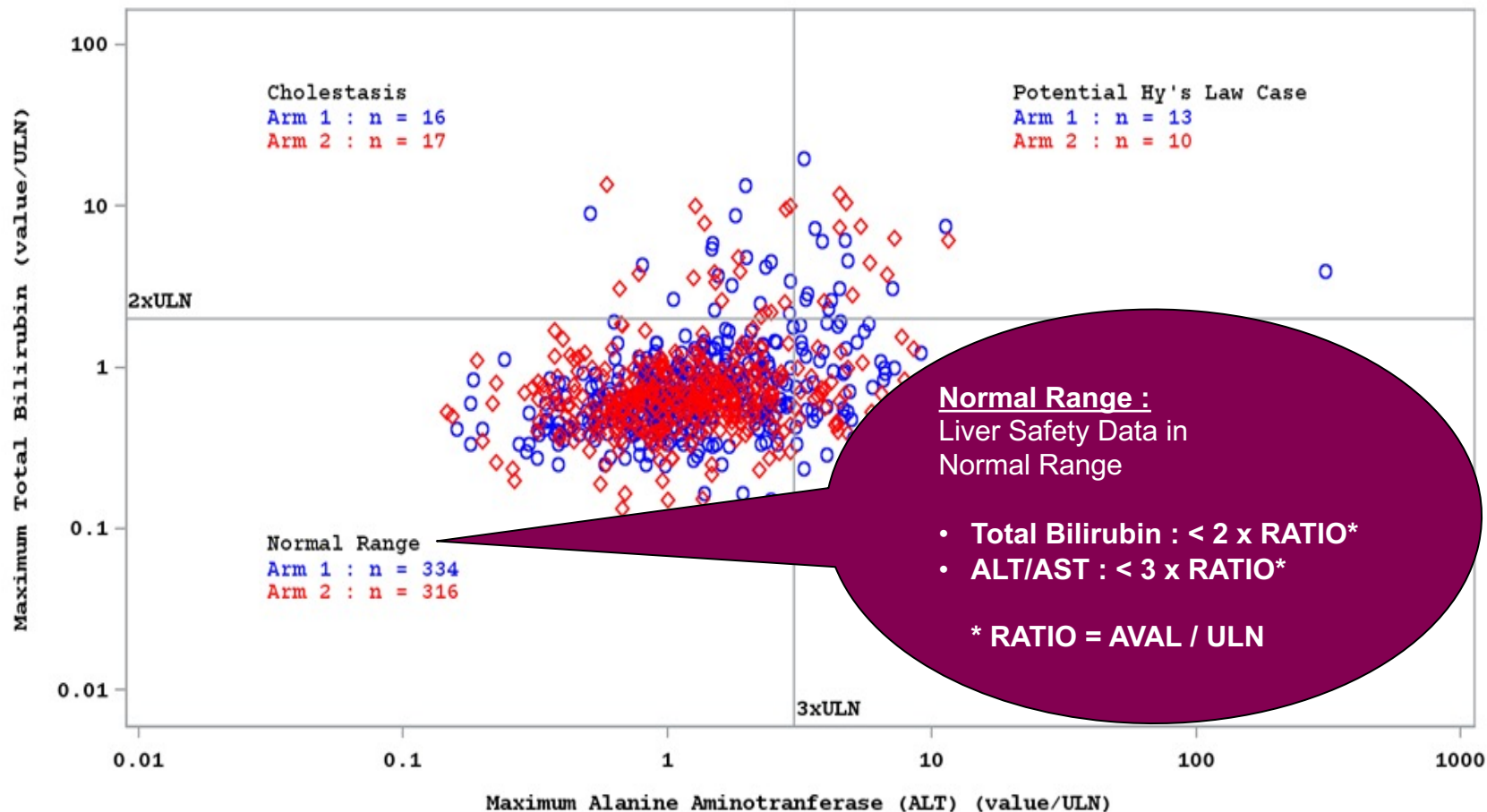
Interpretation of eDISH Plot : Upper Right Quadrant

Figure 14.2.3.4.1 E-DISH Scatter Plot of Maximum Total Bilirubin vs Maximum ALT on Study
(Safety Analysis Set)



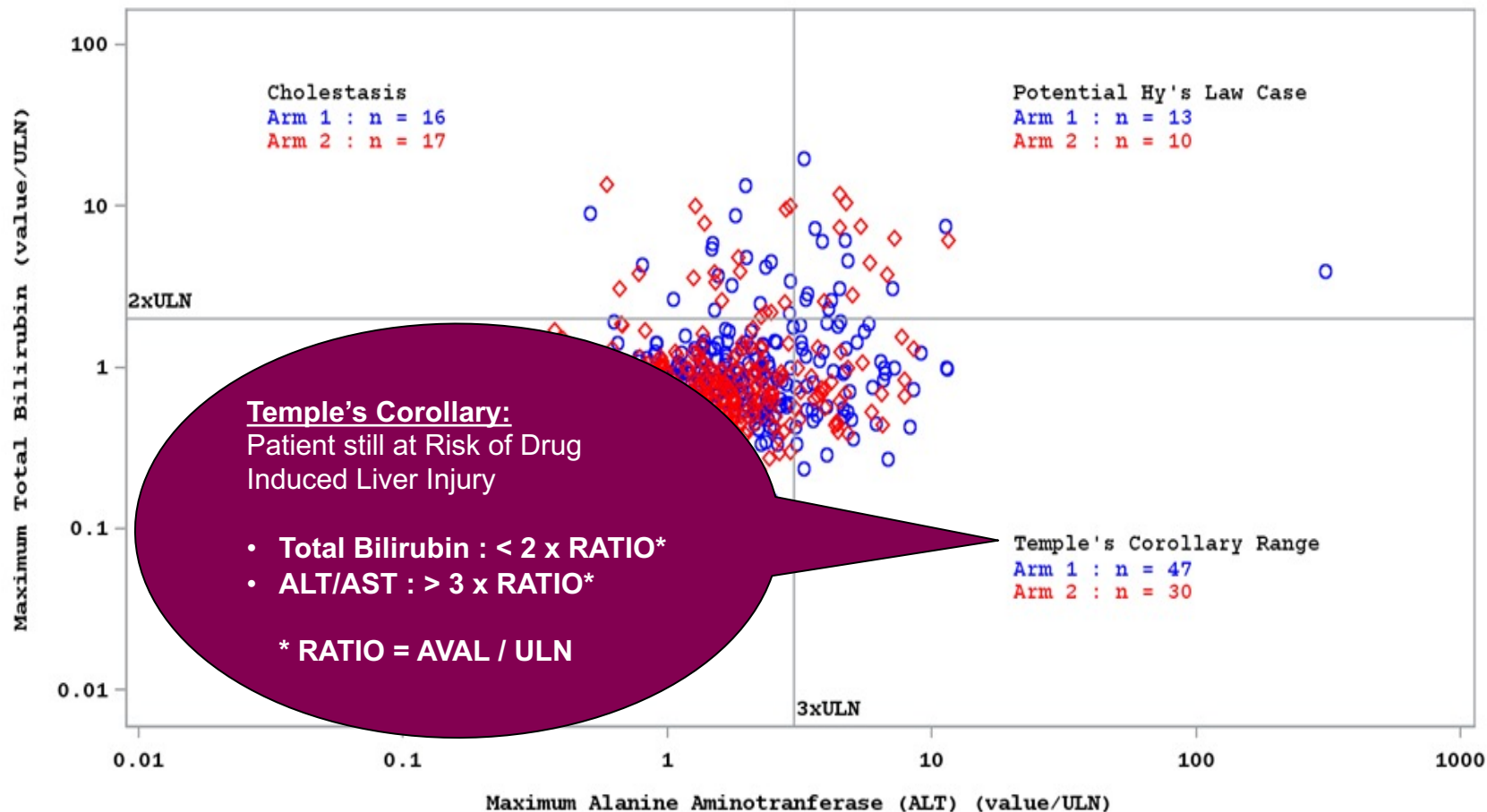
Interpretation of eDISH Plot : Lower Left Quadrant

Figure 14.2.3.4.1 E-DISH Scatter Plot of Maximum Total Bilirubin vs Maximum ALT on Study
(Safety Analysis Set)



Interpretation of eDISH Plot : Lower Right Quadrant

Figure 14.2.3.4.1 E-DISH Scatter Plot of Maximum Total Bilirubin vs Maximum ALT on Study
(Safety Analysis Set)



Conclusion :

- The **eDISH** approach is an **efficient and effective way to organize and examine large liver safety databases** for randomized controlled clinical trials.
- It **greatly facilitates a systematic and transparent examination of the relevant liver safety laboratory data.**
- This can be adopted as standard approach for assessing and studying liver safety issues in clinical trials.



Sample SAS Code :

- Appendix 1



Any Questions ??



Thank You.....

