

FDA

**U.S. FOOD & DRUG
ADMINISTRATION**

OFFICE OF COMPUTATIONAL SCIENCE

Safety Review: Approach & Tools

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Disclaimer

The views and opinions presented here represent those of the speakers and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.



01 | Safety Review Approach



02 | Review Tools





SAFETY REVIEW APPROACH

Former Primary Reviewer's View

Example: NDA Review of Updating Proposed Prescribing Information (PI)

Sponsor's Proposed PI:

Warnings & Precautions:

- Suicidality (class labeling)
- Dizziness/Somnolence
- Withdrawal of AEDs
(anti-epileptic drug)

Safety Issues Identified from IND Stage

Chemical or Biological Epitopes of Concern

Product Class Issues



Review Tools

Final PI:

Boxed Warning:

- Serious Psychiatric and Behavioral Reactions

Warnings & Precautions:

- Suicidality (class labeling)
- Dizziness/Somnolence
- Falls
- Withdrawal of AEDs

NDA/BLA Multi-disciplinary Review and Evaluation

Section 8.2: Review of Safety

- 8.2.1 Safety Review Approach
- 8.2.2 Review of the Safety Database
- 8.2.3 Adequacy of Applicant's Clinical Safety Assessments
- 8.2.4 **Safety Results**
- 8.2.5 Analysis of Submission-Specific Safety Issues
- 8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability
- 8.2.7 Safety Analyses by Demographic Subgroups
- 8.2.8 Specific Safety Studies/Clinical Trials
- 8.2.9 Additional Safety Explorations
- 8.2.10 Safety in the Postmarket Setting
- 8.2.11 Integrated Assessment of Safety





Assess the adequacy of overall exposure and submission-specific aspects of the safety database

- Is safety population sufficiently diverse to represent the expected target population?



Assess whether pooled analyses facilitate the detection of drug-related adverse events



Assess the breadth of the safety data

- Does it facilitate the generalizability of safety findings?

Were applicant's safety evaluations during a product's development program adequate?

- Were all reasonably applicable clinical safety evaluations conducted?
- Were these evaluations performed at the appropriate time(s) during the trial(s)?





Assess consistency of the data provided comparing information from a variety of sources:

- case report forms (CRFs), case report tabulations and narrative summaries
- submitted datasets



Did certain sites, countries, or regions report minimal or zero adverse events?



Are the adverse events reported similarly across all sites, countries, or regions?



Are the adverse events common at certain sites, countries, or regions?

Is applicant's approach to safety reasonable and appropriate?

- Is process for recording, coding, and categorizing adverse events (AEs) acceptable?
- Has applicant provided accurate definitions of AEs and serious adverse events (SAEs) in the protocol(s)?
- Has the applicant defined "treatment emergent" adverse events (TEAEs) and is the definition appropriate?
- Is the methodology and frequency of routine clinical testing adequate?



1

To evaluate the adequacy of the data available to support the safety analysis and to identify the limitations of those data

- Assessments of whether the extent of exposure at relevant doses is adequate

2

To identify and closely examine serious adverse events that could signal important problems with a drug

- Assess whether adverse reactions are severe enough to prevent its use altogether, to limit its use, or require special risk management efforts?

3

To identify and estimate the frequency of the common (usually nonserious) adverse events

- Directly related or possibly causally related to the use of the drug

4

To identify unresolved safety concerns, such as the absence of data from high-risk populations or potential interactions that will need attention

- Before approval, or should it be assessed in the post marketing period

Additional Safety Review Tasks

Identify factors that predict the occurrence of adverse reactions, including subject-related and drug-related factors



Identify, where possible, ways to avoid adverse reactions (e.g., dosing, monitoring) and ways to manage them when they occur



For a drug that is to be approved, provide a comprehensive evaluation of risk information adequate to support a factual and sufficient summary in labeling



REVIEW TOOLS

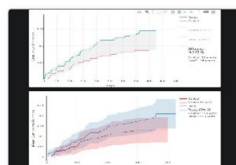
8.24 Safety Results

- Deaths
- Serious Adverse Events
- Dropouts and/or Discontinuations due to Adverse Events
- Significant Adverse Events
- Treatment Emergent Adverse Events and Adverse Reactions
- Laboratory Findings
- Vital Signs
- Electrocardiograms (ECGs)
- QT



Tools NDA/BLA Safety Review

- MAED (MedDRA-based Adverse Events Diagnostics)
- Commercially available tools that facilitate dataset analyses
- Other review tools:
 - SAS and R
 - R Shiny Tools:
 - AE Temporal, Demographic, Hepatotoxicity, and Napoleon's March
 - CDER Clinical Investigator Site Selection Tool (CISST)
 - FDALabel

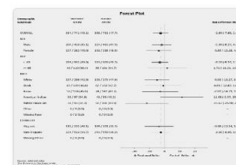


AE Temporal Tool

Longitudinal analysis of adverse events through Kaplan-Meier and Mean Cumulative Function

[User Guide](#)

[Start Setup](#)



Demographic Tool

Performs demographic subgroup analysis through a web app

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Hepatotoxicity Tool

Examine drug-induced liver injury through composite visualization

[User Guide](#)

[Start Setup](#)



Napoleon's March

Longitudinal visualization of disposition categories

[User Guide](#)

[Start Setup](#)

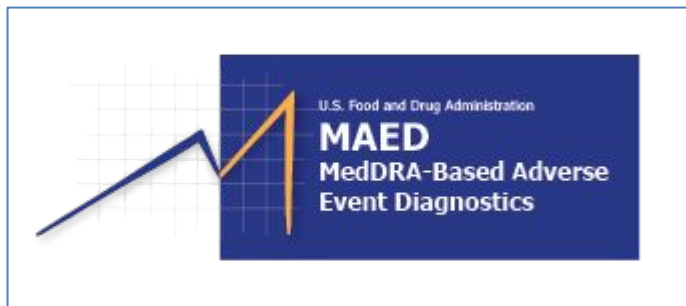
- **Perform exploratory adverse event analyses**



- Incidence tables of AEs in MedDRA hierarchy (MAED or commercially available tools)
- Forest Plots (commercially available tools)
- Structured MedDRA Query (SMQ) analyses (MAED or commercially available tools)
- Custom MedDRA Query (CMQ) analyses (MAED)
- Laboratory and Vitals Analyses (commercially available tools)
- Hy's Law Analyses (commercially available tools)

- **Review individual patients**

- Graphical Patient Profiles (commercially available tools)
- Narratives
- Case Report Forms (CRFs)



- **MAED Functions:**
 - Runs all levels of the MedDRA hierarchy
 - Runs all SMQs
 - Performs custom queries (add PTs from excel file)
 - Matches the AE terms to MedDRA terms

- **MAED Outputs:**
 - Excel file for all requested analyses
 - 2 Augmented datasets (sas7bdat, xpt) with new variables added to the original AE dataset
 - MAED AE Dataset with new MedDRA hierarchy variables
 - MAED SMQ Dataset with new SMQ variables



MAED SMQ Analyses

A1 f _x WARNING: THIS IS ONLY AN EXPLORATORY ANALYSIS!										
A B C D E F G H I J K										
WARNING: THIS IS ONLY AN EXPLORATORY ANALYSIS!										
* after SMQ name indicates SMQ with narrow terms only. Broad search will yield the same results.										
Number in parenthesis before SMQ name represents SMQ level.										
P-values should be used for ranking purposes only, not for determining statistical significance.										
	200 mg (N = 410)			200 mg (N = 415)			400 mg (N = 196)			
SMQ (Narrow Search)	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	Events
(2) Gastrointestinal nonspecific symptoms and	184	101	24.63	136	87	20.96	51	34	17.35	88
(1) Gastrointestinal nonspecific inflammation and	195	103	25.12	149	92	22.17	52	35	17.86	97
(1) Hearing and vestibular disorders	43	31	7.56	20	12	2.89	6	6	3.06	4
(2) Vestibular disorders	39	27	6.59	19	11	2.65	6	6	3.06	2
(1) Hyponatraemia/SIADH	16	15	3.66	9	9	2.17	3	3	1.53	1
(1) Depression and suicide/self-injury	22	17	4.15	15	10	2.41	9	8	4.08	15
(2) Depression (excl suicide and self injury)	22	17	4.15	9	8	1.93	9	8	4.08	14
(2) Leukopenia	10	8	1.95	8	6	1.45	3	3	1.53	4
(1) Ocular motility disorders	8	8	1.95	8	4	0.96	3	3	1.53	3
(1) Dyslipidaemia *	13	11	2.68	21	12	2.89	8	4	2.04	9
(1) Haematopoietic cytopenias	12	9	2.2	10	7	1.69	5	5	2.55	6
(1) Extrapyrimal syndrome	6	5	1.22	2	1	0.24	0	0	0	3
(1) Thyroid dysfunction	5	5	1.22	7	7	1.69	2	2	1.02	3
(2) Hypothyroidism	5	5	1.22	4	4	0.96	1	1	0.51	3
(2) Hearing impairment	4	4	0.98	1	1	0.24	0	0	0	2
(1) Hepatic disorders	7	3	0.73	8	4	0.96	3	3	1.53	2
(2) Drug related hepatic disorders -	7	3	0.73	7	3	0.72	3	3	1.53	2
(3) Liver related investigations, signs and	7	3	0.73	7	3	0.72	2	2	1.02	2
(1) Lack of efficacy/effect *	3	3	0.73	1	1	0.24	2	2	1.02	1
(4) Disorders of sinus node function *	2	2	0.49	4	4	0.96	0	0	0	0
(1) Ocular infections	2	2	0.49	1	1	0.24	0	0	0	0
(1) Hypertension *	16	12	2.93	13	11	2.65	9	6	3.06	13
(2) Gastrointestinal nonspecific inflammation	3	3	0.73	7	7	1.69	0	0	0	2
(2) Thrombocytopenia	2	2	0.49	1	1	0.24	1	1	0.51	1
(1) Asthma/bronchospasm	1	1	0.24	0	0	0	1	1	0.51	0
(1) Dementia	1	1	0.24	0	0	0	0	0	0	0
(2) Dystonia	1	1	0.24	2	1	0.24	0	0	0	0
(2) Parkinson-like events	1	1	0.24	0	0	0	0	0	0	0
(1) Gastrointestinal perforation, ulceration,	3	2	0.48	3	2	0.48	0	0	0	0
(2) Gastrointestinal haemorrhage *	2	1	0.24	2	1	0.24	0	0	0	0
(2) Oropharyngeal allergic conditions *	0	0	0	0	0	0	0	0	0	0
(2) Gingival disorders *	2	2	0.48	2	2	0.48	1	1	0.51	0

Algorithmic SMQ

Broad SMQ

Narrow SMQ

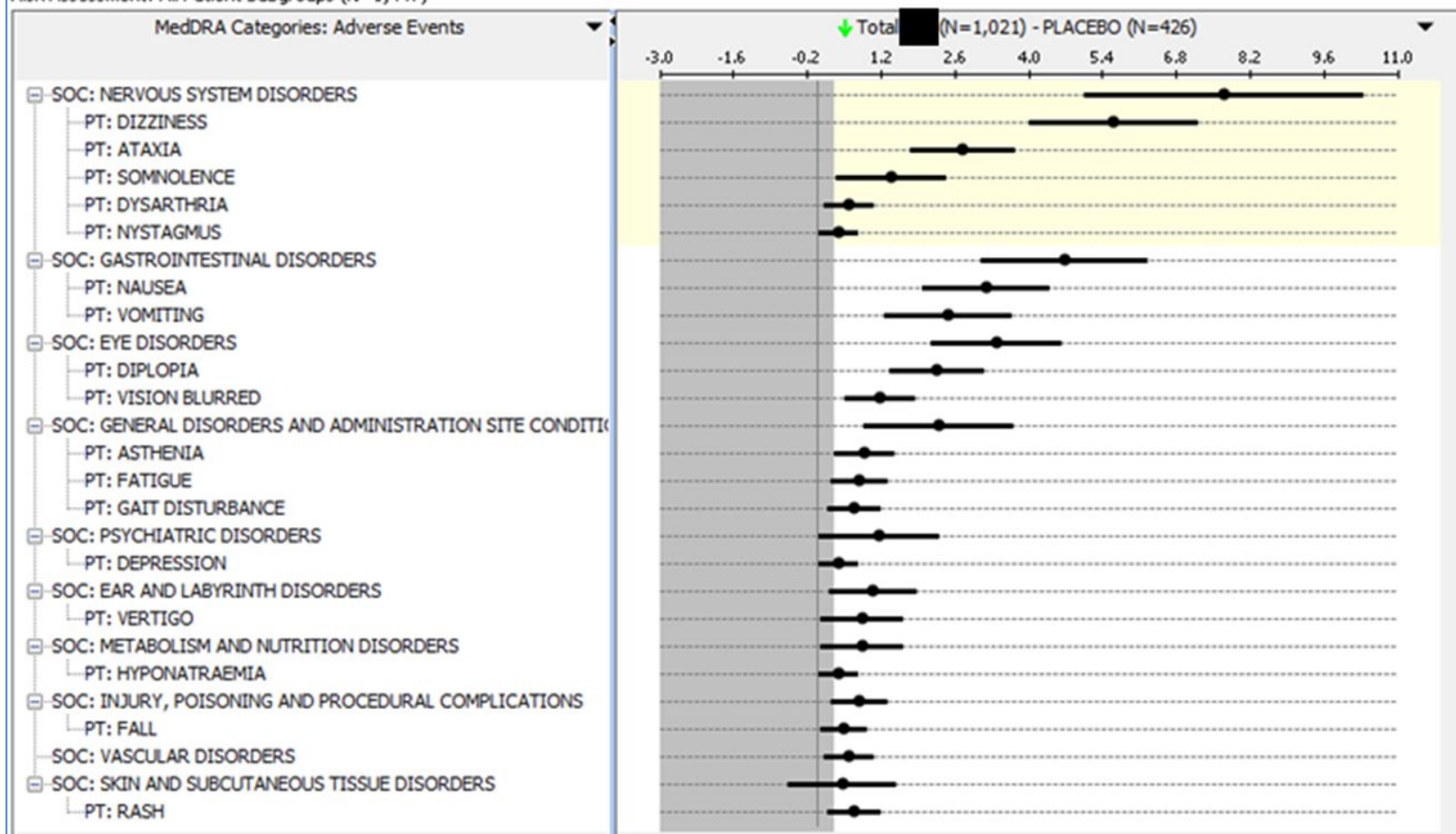
Introduction SOC HLG HLT PT Broad Algorithmic Narrow

Incidence Table by SOC

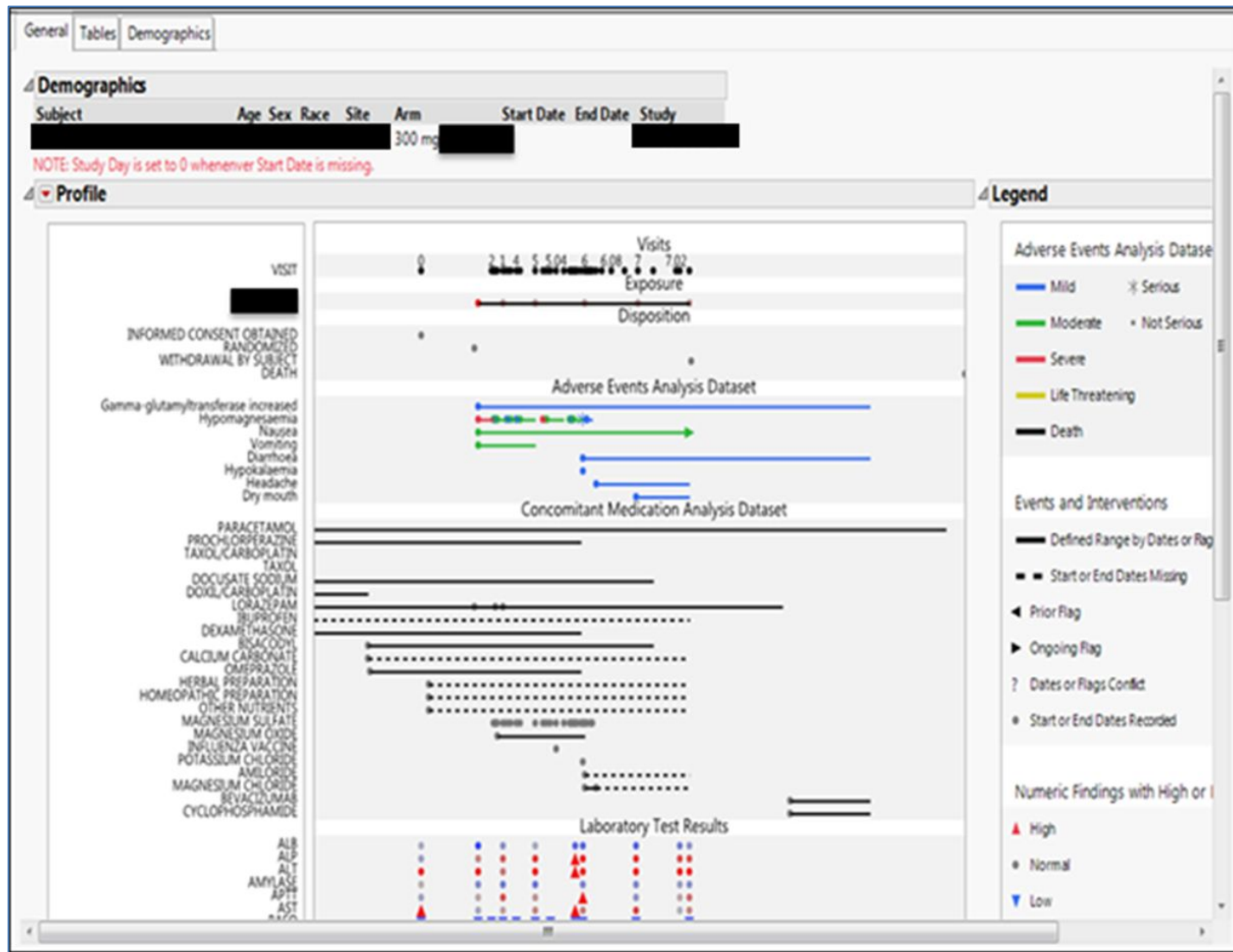
Body System or Organ Class	Placebo	2 mg	4 mg	8 mg	12 mg
Blood And Lymphatic System Disorders	5 (1.25%)	6 (3.90%)	3 (1.97%)	15 (3.78%)	2 (0.83%)
Cardiac Disorders	10 (2.50%)	4 (2.60%)	1 (0.66%)	9 (2.27%)	4 (1.65%)
Ear And Labyrinth Disorders	8 (2.00%)	6 (3.90%)	8 (5.26%)	26 (6.55%)	15 (6.20%)
Endocrine Disorders	1 (0.25%)	2 (1.30%)	1 (0.66%)	0 (0.00%)	2 (0.83%)
Eye Disorders	16 (4.00%)	3 (1.95%)	8 (5.26%)	31 (7.81%)	22 (9.09%)
Gastrointestinal Disorders	82 (20.50%)	23 (14.94%)	16 (10.53%)	84 (21.16%)	56 (23.14%)
General Disorders And Administration Site Conditions	52 (13.00%)	25 (16.23%)	26 (17.11%)	104 (26.20%)	81 (33.47%)
Hepatobiliary Disorders	0 (0.00%)	0 (0.00%)	2 (1.32%)	1 (0.25%)	1 (0.41%)
Immune System Disorders	6 (1.50%)	0 (0.00%)	1 (0.66%)	1 (0.25%)	3 (1.24%)
Infections And Infestations	94 (23.50%)	35 (22.73%)	29 (19.08%)	96 (24.18%)	52 (21.49%)
Injury, Poisoning And Procedural Complications	51 (12.75%)	15 (9.74%)	11 (7.24%)	61 (15.37%)	60 (24.79%)
Investigations	32 (8.00%)	11 (7.14%)	14 (9.21%)	44 (11.08%)	34 (14.05%)
Metabolism And Nutrition Disorders	15 (3.75%)	7 (4.55%)	2 (1.32%)	24 (6.05%)	28 (11.57%)
Musculoskeletal And Connective Tissue Disorders	45 (11.25%)	13 (8.44%)	14 (9.21%)	53 (13.35%)	41 (16.94%)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	2 (0.50%)	0 (0.00%)	0 (0.00%)	2 (0.50%)	0 (0.00%)
Nervous System Disorders	137 (34.25%)	53 (34.42%)	55 (36.18%)	244 (61.46%)	176 (72.73%)
Pregnancy, Puerperium And Perinatal Conditions	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.25%)	0 (0.00%)
Psychiatric Disorders	55 (13.75%)	17 (11.04%)	11 (7.24%)	74 (18.64%)	57 (23.55%)
Renal And Urinary Disorders	5 (1.25%)	5 (3.25%)	1 (0.66%)	6 (1.51%)	7 (2.89%)
Reproductive System And Breast Disorders	6 (1.50%)	6 (3.90%)	4 (2.63%)	6 (1.51%)	6 (2.48%)
Respiratory, Thoracic And Mediastinal Disorders	39 (9.75%)	3 (1.95%)	10 (6.58%)	32 (8.06%)	23 (9.50%)
Skin And Subcutaneous Tissue Disorders	33 (8.25%)	7 (4.55%)	14 (9.21%)	43 (10.83%)	20 (8.26%)
Social Circumstances	1 (0.25%)	0 (0.00%)	1 (0.66%)	0 (0.00%)	1 (0.41%)
Surgical And Medical Procedures	1 (0.25%)	0 (0.00%)	0 (0.00%)	1 (0.25%)	0 (0.00%)
Vascular Disorders	10 (2.50%)	0 (0.00%)	0 (0.00%)	10 (2.52%)	4 (1.65%)
Subjects(filtered)	294 (73.50%)	111 (72.08%)	111 (73.03%)	350 (88.16%)	227 (93.80%)
1stCollItemSubjects	400 (100.00%)	154 (100.00%)	152 (100.00%)	397 (100.00%)	242 (100.00%)

Figure 1. TEAEs leading to discontinuation with $\geq 0.4\%$ Risk Difference (Total Drug-Placebo), Phase 3 Epilepsy Controlled Pool

Risk Assessment: All Patient Subgroups (N=1,447)

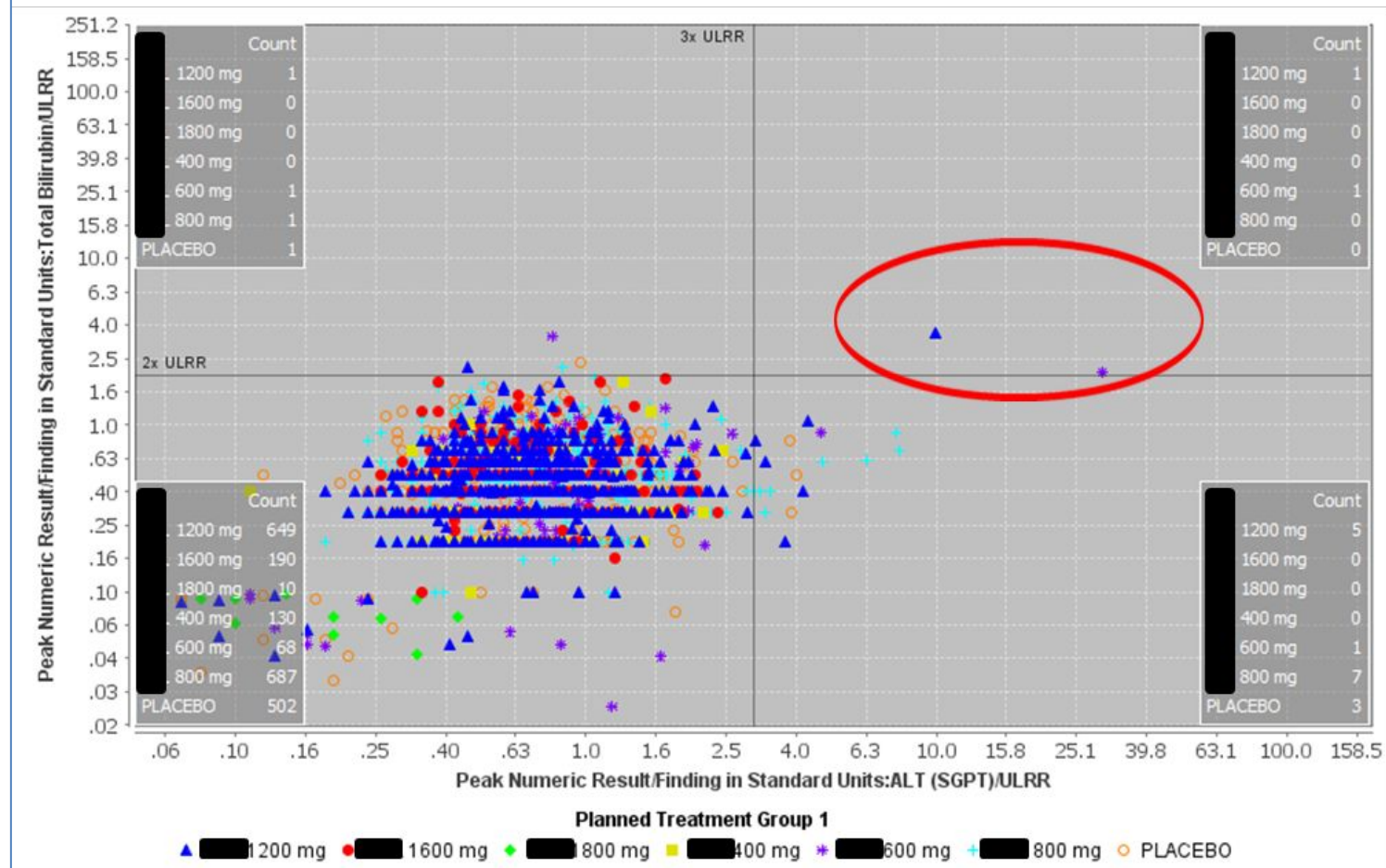


Graphical Patient Profile

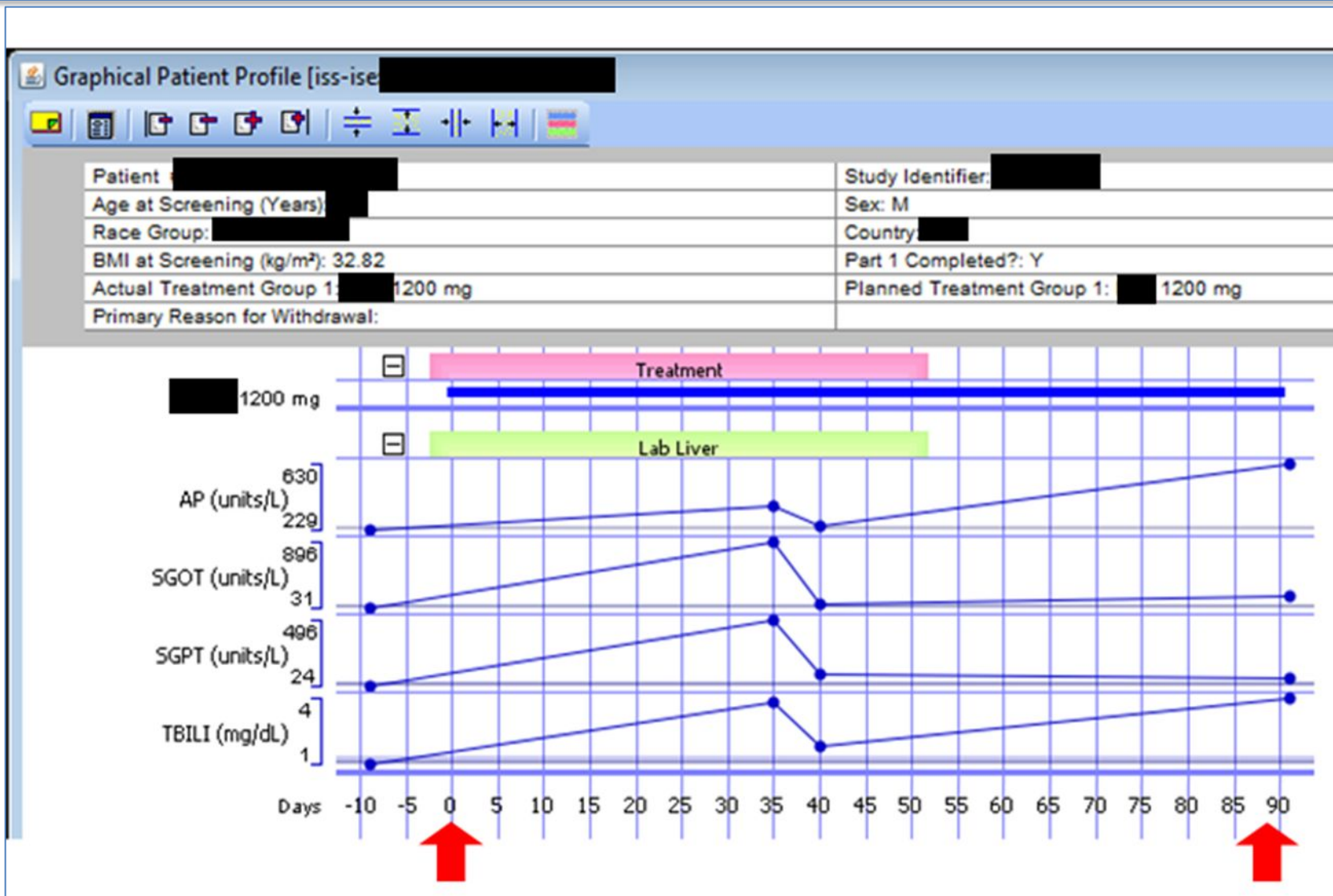


Plots to Identify Potential Hy's Law Cases

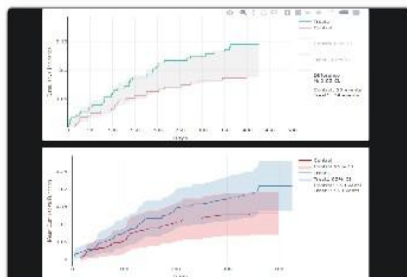
Figure 1. Hy's Law Plot: ALT>3xULN vs TBili>2xULN with ALP <2xULN, Nonepilepsy Double-blind Pool (includes Study 206)



Graphical Patient Profile



Analysis Toolbox – R Shiny Tools

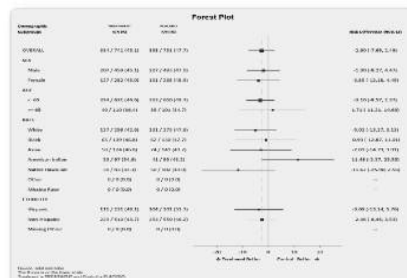


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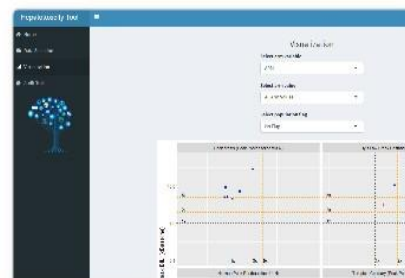


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