STANDARD SAFETY TABLES AND FIGURES:

INTEGRATED GUIDE

Center for Drug Evaluation and Research (CDER)

Biomedical Informatics and Regulatory Review Science (BIRRS) Team

Please email ONDbiomedicalInformatics@fda.hhs.gov with any questions.

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Abbreviations and Acronyms

ADBMI	associate director of biomedical informatics
ADSL	subject-level analysis dataset
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIRRS	Biomedical Informatics and Regulatory Review Science
BILI	bilirubin
BLA	biologics license application
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDS	clinical data scientist
CI	confidence interval
CKD	chronic kidney disease
CPK	creatine phosphokinase
DB	direct bilirubin
DILI	drug-induced liver injury
DIMI	drug-induced muscle injury
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
OCMQ	OND custom medical query
FOG	follow-on guide
FPG	fasting plasma glucose
GLP	glucagon-like peptide
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
IG	integrated guide
IP	investigational product
ISS	integrated summary of safety
KM	Kaplan-Meier

LDL	low-density lipoprotein
MB	myocardial band
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NIH	National Institutes of Health
OSAE	on-study adverse event
OTAE	on-treatment adverse event
PT	preferred term
SAE	serious adverse event
SAFFL	safety population flag
SAP	statistical analysis plan
SDTM	study data tabulation model
SGLT	sodium-glucose cotransporter
SMQ	standardized MedDRA query
SOC	system organ class
ST&F	safety tables and figures
TB	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USUBJID	unique subject identifier
V	visit
WBC	white blood cell

1. Introduction

1.1. Background

Clinical reviewers use tables and figures to describe and interpret clinical trial safety data submitted in marketing applications. Use of consistent displays of tables and figures can result in more streamlined and efficient marketing application review. To foster consistency in safety review and display of clinical data during FDA review of marketing applications, the ST&F Working Group developed the ST&Fs (IG and TAGs) with the following goals: (1) establish a standard set of safety analytic tables and figures; and (2) create an integrated guide (IG) containing associated instructions to support clinical reviewers in their use of the ST&F outputs during safety data review.

1.2. Glossary

Adverse Event (AE)[1] refers to any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Adverse Event Severity[2] is used to describe (by the investigator) the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).

Adverse Event of Special Interest (AESI)[3] refers to an event (serious or non-serious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate.

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[1] See 21 CFR 312.32(a); see also the guidance for industry: *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012)
[2] See the guidance for industry: *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (March 1995)
[3] See the guidance for industry: *E2F Development Safety Update Report* (August 2011)

Adverse Reaction[1] is any adverse event caused by a drug.[4] Adverse reaction implies a greater degree of certainty about causality than suspected adverse reaction, which means any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Dosage[5] refers to a specific amount of drug administered at a specific frequency (and over a certain duration, if applicable).

Dose[5] refers to a specific amount of drug taken at one time.

Serious Adverse Events (SAEs)[1] refer to any adverse event that (at any dose) results in death, is life-threatening, results in hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect. Other important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, the subject is jeopardized and requires medical or surgical intervention to prevent one of the outcomes listed above.

Targeted Analysis Guides (TAGs) are additional analyses to further explore a potential safety signal in targeted area.

Treatment refers to the trial intervention received by the study participant (e.g., investigational product, control).

Treatment-Emergent Adverse Event (TEAE) refers to the occurrence of an AE or worsening of an existing AE during or after the first treatment.

Trial Arms refers to any therapeutic, prophylactic, or diagnostic agent including drug products, biological products (such as therapeutic protein products), and combination products (such as drug-device combination products). Trial arms include the agent being tested and any controls (for example, placebo or active comparator).

1.3. General Considerations

In general, safety analyses are descriptive in nature, and confidence intervals for the risk difference presented are not adjusted for multiplicity but provide information on the strength of the association. The standardized tables and figures included in the ST&F IG are primarily intended for making comparisons based on safety data generated from randomized, concurrent, controlled trials for the

[4] For purposes of prescription drug labeling, "an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event" (21 CFR 201.57(c)(7)).

[5] See the guidance for industry: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format* (March 2010)

purposes of signal detection[6]. ST&F may be generated for pooled analyses as well as for individual trials and when needed, customized based on the approach to analysis. In general, a separate package should be generated for registration trials, individual trials that differ substantially in important characteristics (e.g., lead-in period, enrichment, population, duration), and any other clinical trial(s) of interest to the review team. For trials with unique study designs (e.g., cross-over designs, designs with multiple stages of randomization), there should be a discussion about the specifics of the design and whether customized analyses or presentations may be warranted.

Before ST&F can be generated, it is important that the cross-disciplinary review team collaborate with the Associate Director of Bioinformatics (ADBMI) and Clinical Data Scientist (CDS) teams to align on the approach to the safety analysis to be presented in the ST&Fs. It should be noted that the approach to analysis adopted for the ST&Fs does not necessarily apply to all aspects of the safety assessment. In particular, the analysis of adverse events of special interest (AESI) may require a more extensive approach (e.g., with recurrent event analysis or time-to-event analysis). Additional targeted analyses (e.g., TAGs, custom targeted analysis) may also be required to further assess any potential safety signal(s) identified during safety review.

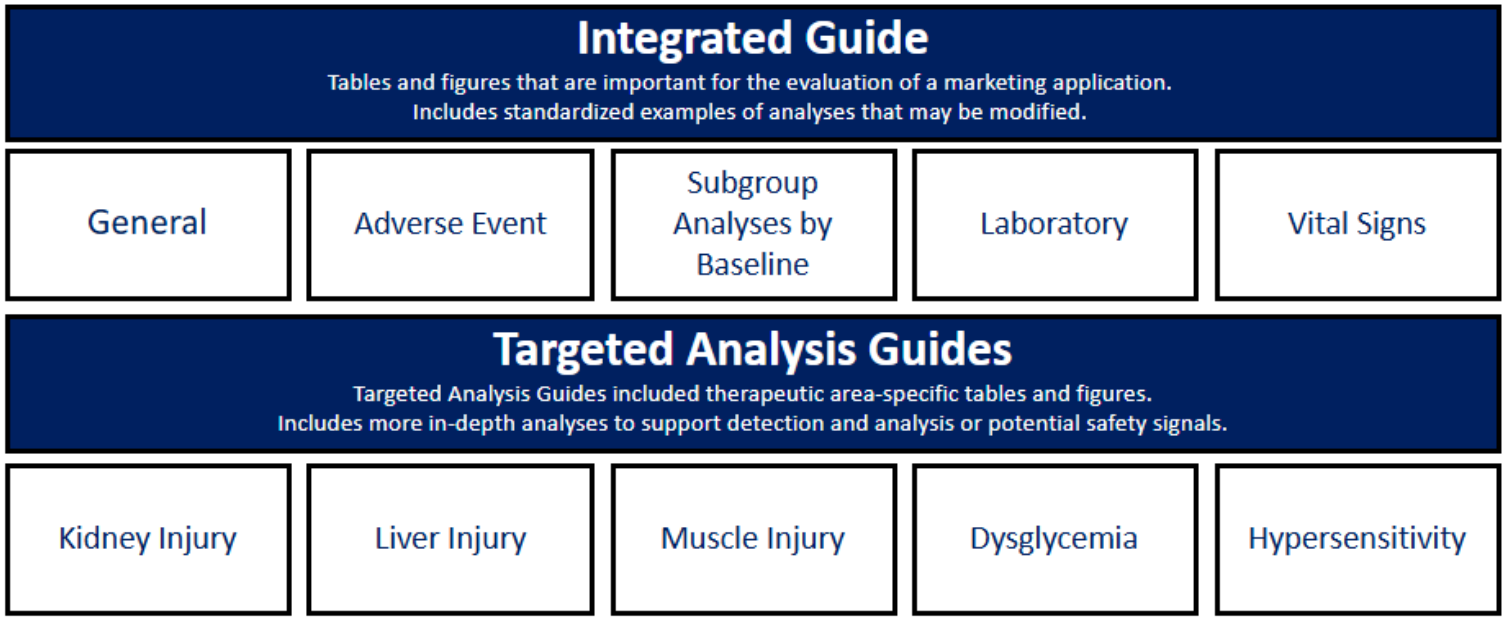
1.4. Organization

When examining the ST&F IG, it is important to note that the instructions for clinical reviewers to help interpret or modify the analyses precede the safety tables and figures (where applicable) and references (if any) to expanded tables and/or other displays of data are placed after a table and/or figure. Cross-referenced tables and figures are linked for convenience.

Organization of the safety tables and figures are presented in Diagram 1 below. Safety analyses are grouped into sections such as Adverse Event Analyses, Subgroup Analyses by Baseline Characteristics, Laboratory Analyses, etc. Additionally, clinical reviewers may request one of the ST&F Targeted Analysis Guides (TAG) to further explore a potential safety signal previously identified or identified upon review of the initial ST&F IG.

[6] Approaches to safety analyses of open-label extension studies are discussed in Section 2.6 Open-Label Extension

Diagram 1. Standard Safety Tables and Figures Organization



1.5. Default Output

Within each section, safety analyses are organized into the following grouped analyses:

1. **Core** (Section 2): This section contains routine analyses for safety review. Tables and figures found in the Core section are generated in every ST&F package. Clinical reviewers should evaluate all analyses contained in the Core sections of the IG.
2. **Expanded** (Section 3): This section contains more in-depth analyses of the tables and figures presented in the Core section to allow drill-down as needed. Tables and figures found in the Expanded section are also generated in every ST&F package.
3. **Optional** (Section 4): This section contains alternative displays of the table and figures found in the Core and Expanded sections as well as subject-level listings. Tables and figures found in the Optional section are not automatically provided but can be generated upon request.

1.6. Customization

As the clinical team progresses in their review, they may request additional custom tables, figures, and analyses to further explore potential safety concerns that arise during the review process. Clinical reviewers should refer to the "**Customization**" comments section for each table or figure (if applicable) for additional instructions on how to customize the referenced analysis.

2. Core Safety Tables and Figures

2.1. Summary of Trials Analyzed

This section contains safety tables and figures that present the following information: clinical trial(s) submitted, demographics, disposition, and duration of exposure.

2.1.1. Clinical Trials Submitted in Support of Efficacy and Safety Determinations

Background and Instructions

Table 1: Clinical Trials Submitted in Support of Efficacy and Safety includes all trials submitted in support of the marketing application. The table includes all important characteristics of interest, including elements of trial design (e.g., randomized, double-blind, parallel-group, multicenter, crossover, dose-response, randomized withdrawal, open-label, long-term extension); type of control (e.g., placebo concurrent, dose-comparison concurrent, no treatment concurrent, active treatment concurrent, historical); trial population; trial endpoints; and sample size. The primary interest is typically in the safety analysis population (i.e., all subjects exposed to at least one dose of randomized treatment).

Customization

Inclusion of additional trials of interest may be requested by the review team.

Example Table

Table 1. Clinical Trials Submitted in Support of Efficacy and Safety Determinations for [Drug]

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
Trial X NCT #	Subjects with moderate to severe disease as defined by XX baseline or clinical characteristics	Control type: Randomization: Randomization ratio: Blinding: Key design features:	Drug name dosage A (N=X), XX weeks Drug name dosage B (N=X), protocol-specified dose adjustment permitted; XX weeks. Control (N=X), XX weeks Route of administration: (oral tablet with drug X mg and IM injection for drug Y mg) Duration:	Primary: clinical response at week XX, as defined by XX Secondary: clinical response at week X, as defined by XX	Planned: YYY Actual: ZZZ	Centers: X Countries: Y
Trial Y NCT #	Subjects completing X weeks treatment or withdrawn due to treatment failure in Trial X; or nonresponders after completion in trials X and Y	Control type: Randomization: Randomization ratio: Blinding: Key design features:	**Part 1** Drug name dosage A (N=X) Drug name dosage B (N=X) Drug name dosage C (N=X) **Part 2** Drug name dosage D (N=X) Control (N=X) Route of administration: (all taken orally BID with drug name dosage D) Duration:	Long-term durability of efficacy and long-term safety	Planned: YYY Actual: ZZZ	Centers: X Countries: Y

Source: [include Applicant source, datasets and/or software tools used].
Note: Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
Abbreviations: BID, twice daily; IM, intramuscular; No., number; N, number of subjects in treatment arm; NCT, national clinical trial.

2.1.2. Demographics and Baseline Clinical Characteristics

Background and Instructions

For Table 2: Demographics and Baseline Clinical Characteristics , consider the key baseline characteristics and subpopulations with different disease characteristics that could influence the effectiveness or safety of the drug. The latter may include baseline entry criteria and other specific characteristics that were recorded but not considered as entry criteria, such as duration, stage, or severity of disease; a history of failure on particular treatments; comorbid conditions; use of relevant concomitant medications; risk factors; or baseline laboratory measurements not part of the entry criteria (e.g., LDL cholesterol, C-reactive protein levels, kidney function, or

hepatic function) that could affect safety. Depending on the geographic makeup of the trial, the region of participation rather than country may be included.

Table 2 is typically generated for each trial listed in Table 1: Clinical Trials Submitted in Support of Efficacy and Safety. When there is missing data in one of the demographic categories, a row labeled as "Missing" will be included in this table and explanatory footnotes added. The table currently displays placeholder values for the characteristics. These placeholder values will change to reflect the data from the respective clinical trial. Demographic characteristics in this table will reflect the Clinical Data Interchange Standards Consortium (CDISC) controlled terminology when submitted data conforms to CDISC data standards.

Customization

In addition to the standard groupings, the clinical reviewer may request custom age groups (e.g., <45, 45 to <65 years, etc.), additional baseline characteristics (e.g., anthropometric measurements such as body mass index [BMI], disease characteristics such as medical history of diabetes) to be displayed as needed. For trials that include older subjects (e.g., Alzheimer's disease trials), additional geriatric age subgroups may be included (e.g., 65 to 74 years of age, 75 to 84 years of age, and 85 years of age and older). Refer to the guidance for industry *E7 Studies in Support of Special Populations: Geriatrics, Questions and Answers* (March 2012).[7]

[7] See the FDA guidance for industry and Food and Drug Administration Staff *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/collection-race-and-ethnicity-data-clinical-trials

Example Table

Table 2. Demographics and Baseline Clinical Characteristics, Safety Population, Pooled Analysis (or Trial X)

Characteristic	Drug Name Dosage A N=XXX	Control N=XXX	Total Population N=XXX
Sex, n (%)			
Male	X (Y)	X (Y)	X (Y)
Female	X (Y)	X (Y)	X (Y)
Age, years			
Mean (SD)	X (Y.YY)	X (Y.YY)	X.X (Y.YY)
Median (min, max)	X (Y, Z)	X (Y, Z)	X (Y, Z)
Age groups (years), n (%)			
Group 1	X (Y)	X (Y)	X (Y)
Group 2	X (Y)	X (Y)	X (Y)
Race, n (%)			
American Indian or Alaska Native	X (Y)	X (Y)	X (Y)
Asian	X (Y)	X (Y)	X (Y)
Black or African American	X (Y)	X (Y)	X (Y)
Native Hawaiian or other Pacific Islander	X (Y)	X (Y)	X (Y)
White	X (Y)	X (Y)	X (Y)
Not reported	X (Y)	X (Y)	X (Y)
Other	X (Y)	X (Y)	X (Y)
Unknown	X (Y)	X (Y)	X (Y)
Ethnicity, n (%)			
Hispanic or Latino	X (Y)	X (Y)	X (Y)
Not Hispanic or Latino	X (Y)	X (Y)	X (Y)
Not reported	X (Y)	X (Y)	X (Y)
Unknown	X (Y)	X (Y)	X (Y)
Country of participation, n (%)			
Country A	X (Y)	X (Y)	X (Y)
Country B	X (Y)	X (Y)	X (Y)
Clinical baseline characteristics, n (%)			
Characteristic A	X (Y)	X (Y)	X (Y)
Characteristic B	X (Y)	X (Y)	X (Y)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: n, number of subjects with given characteristic; N, number of subjects in treatment arm; SD, standard deviation.

2.1.3. Subject Screening and Enrollment

Background and Instructions

The following enrollment populations are reflected in Table 3: Subject Screening and Enrollment below:

- **Screened population (subjects screened)**: All subjects screened for entry into the trial.
- **Screening failure population**: All subjects who failed to meet inclusion/exclusion criteria.
- **Enrolled population (subjects enrolled):** All subjects who signed a consent form for participation in the trial.
- **Randomized population (subjects randomized):** All subjects randomized to a trial arm. Often referred to as the intent-to-treat population.

Customization

The review team may request a list of reasons for screen failure, such as “subject noncompliance,” “consent withdrawn,” “inclusion/exclusion criteria not met,” “other,” and/or a breakdown of “inclusion/exclusion criteria not met” and “other.” Understanding reasons for screen failure can be informative to assess the generalizability of the trial.

Example Table

Table 3. Subject Screening and Enrollment, Screening Population, Trials A and B

Disposition	Trial A N=XXX n (%)	Trial B N=XXX n (%)
Subjects screened	X (Y)	X (Y)
Screening failures	X (Y)	X (Y)
Subjects enrolled	X (Y)	X (Y)
Subjects randomized	X (Y)	X (Y)

Source: [include Applicant source, datasets and/or software tools used].
Abbreviations: n, number of subjects in specified population or group; N, number of subjects in specific trial.

2.1.4. Subject Populations

Background and Instructions

The following trial populations are reflected in Table 4: Subject Populations below:

- **Intent-to-treat population (ITT):** Includes every subject who is randomized according to randomized trial arm assignment.
- **Modified intent-to-treat population (mITT):** Subset of the intent-to-treat population that excludes a predefined subject population.
- **Safety population:** All subjects considered in the safety analyses who received at least one dose of the study drug in the trials or studies submitted.
- **Per-protocol population:** Only those subjects who completed the treatment originally allocated and planned without specified protocol violations.

Customization

N/A

Example Table

Table 4. Subject Populations, Randomized Population, Pooled Analysis (or Trial X)

Population	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)
Subjects randomized	X (Y)	X (Y)
ITT population	X (Y)	X (Y)
mITT population	X (Y)	X (Y)
Safety population	X (Y)	X (Y)
Per-protocol population	X (Y)	X (Y)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat; n, number of subjects in specified subset of the treatment arm; N, number of subjects in treatment arm.

2.1.5. Discontinuation of Treatment or Trial Participation

Background and Instructions

Table 5: Discontinuation of Treatment or Trial Participation currently displays reason for discontinuation placeholder values, which may be important in understanding the risk and benefit profile of the intervention. These placeholders will be replaced with the values found in the clinical trial data, specifically the disposition dataset. Note that discontinuation reasons reported in the dataset may not accurately reflect all reasons for treatment or trial discontinuation, due to variations in collection approaches. Drill-down analyses (e.g., review individual narratives) may be needed to ensure that treatment or trial discontinuation was not due to a safety concern.

Customization

Clinical reviewer(s) may request more information (e.g., a listing of reported reasons) about the "other" causes as needed.

Example Table

Table 5. Discontinuation of Treatment or Trial Participation, Safety Population, Pooled Analysis (or Trial X)

Reasons for Discontinuation	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)
Discontinued treatment	X (Y)	X (Y)
Reason for discontinuation 1	X (Y)	X (Y)
Reason for discontinuation 2	X (Y)	X (Y)
Reason for discontinuation 3	X (Y)	X (Y)
Reason for discontinuation 4	X (Y)	X (Y)
Discontinued trial	X (Y)	X (Y)
Reason for discontinuation 1	X (Y)	X (Y)
Reason for discontinuation 2	X (Y)	X (Y)
Reason for discontinuation 3	X (Y)	X (Y)
Reason for discontinuation 4	X (Y)	X (Y)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: n, number of subjects in specified subset of the treatment arm; N, number of subjects in treatment arm.

2.1.6. Duration of Treatment Exposure

Background and Instructions

N/A

Customization

Discuss appropriate time points for duration of treatment with the CDS. Consider adding metrics such as dose intensity and relative dose intensity as appropriate (e.g., for oncology trials or studies):

- **Dose intensity** is the total amount of drug given in a fixed unit of time (usually 1 week), and thus is a function of dose and frequency of administration.
- **Relative dose intensity** is the ratio of “delivered” to the “planned” dose intensity and can be expressed as a percentage. A relative dose intensity of 100% indicates that the drug was administered at the dose planned per protocol, without delay, and without cancellations.

Example Table

Table 6. Duration of Treatment Exposure, Safety Population, Pooled Analysis (or Trial X)

Parameter	Drug Name Dosage A N=XXX	Control N=XXX
Duration of treatment, weeks (or months, or days, or cycles)		
Mean (SD)	X (Y)	X (Y)
Median (min, max)	X (Y, Z)	X (Y, Z)
Interquartile range	X – Y	X – Y
Total exposure (person-years)	X	X
Subjects treated, by duration, n (%)		
≥1 day	X (Y)	X (Y)
≥1 month	X (Y)	X (Y)
≥3 months	X (Y)	X (Y)
≥6 months	X (Y)	X (Y)
≥12 months	X (Y)	X (Y)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: n, number of subjects with given treatment duration; N, number of subjects in treatment arm; SD, standard deviation.

2.1.7. Time to Permanent Discontinuation of Treatment

Background and Instructions

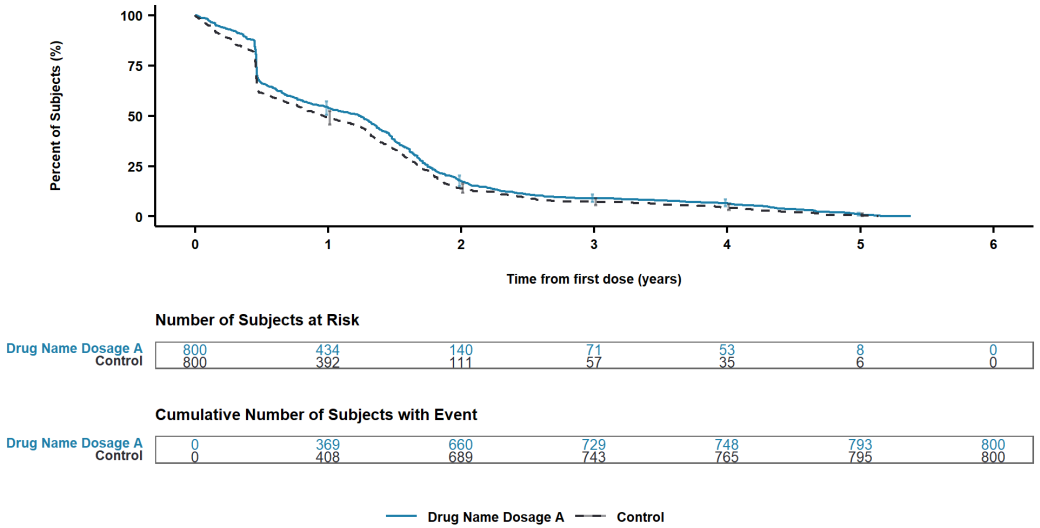
The period displayed in Figure 1: Kaplan-Meier Plot: Time to Permanent Discontinuation of Treatment is typically the treatment period as specified by the protocol and does not include the follow-up period, during which the subject is no longer on treatment.

Customization

A similar figure for time to subjects discontinuation from the trial may be requested.

Example Figure

Figure 1. Kaplan-Meier Plot: Time to Permanent Discontinuation of Treatment, Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Time to permanent discontinuation of treatment is defined as the duration of time from first dose to last dose of study agent for each subject, regardless of the reason for treatment discontinuation.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Note: This figure depicts Kaplan-Meier estimates (log-rank test) of the cumulative percentage of subjects that discontinued treatment by a given time point.
Note: The vertical bars shown on the plotted lines indicates the 95% confidence interval of probability of remaining on treatment at the corresponding time point at the corresponding time points.

2.2. Adverse Event Analyses

This section provides an analysis of AEs, including serious AEs (SAEs), AEs leading to discontinuation, and AESIs. Analyses are also presented by OND Custom Medical Queries (OCMQs), formerly known as FDA Medical Queries (FMQs), arranged by organ system. Adverse event tables can be produced for pooled analyses, individual pivotal/registration trials, and any other trials of interest to the clinical reviewer. TEAE is defined as the occurrence of an AE or worsening of an existing AE during or after the first treatment. In the analyses of TEAEs, it is important to consider whether to include AEs following treatment discontinuation (i.e., on-study versus on-treatment analyses).

OND Custom Medical Queries

OCMQs were developed based on the most frequently reported labeled adverse reactions and requests from review divisions. However, OCMQs do not encompass all potentially relevant groupings. Therefore, reviewers are advised to utilize additional grouping methods, such as Standardised MedDRA Queries (SMQs) or custom queries, as appropriate. These analyses may be generated by using available review tools or requested from CDS. This approach ensures comprehensive safety signal detection and evaluation.

Narrow terms indicate a high degree of certainty that the OCMQ concept occurred, while broad terms should be considered more exploratory or hypothesis generating. Broad OCMQ analysis incorporates narrow OCMQ PTs to maximize sensitivity. Preferred terms can appear within more than one OCMQ. For instance, the PT Cerebral hemorrhage occurs in the narrow category for both Hemorrhage and Stroke-TIA OCMQs. Therefore, to avoid double counting of AEs, the results of different OCMQs should not be combined. For tables that include OCMQs, all OCMQs are evaluated by default. In general, AE terms are ordered by decreasing risk difference. In displays of OCMQ data, tables are arranged by organ system; if there are multiple OCMQs within the organ system, OCMQs are ordered by decreasing risk difference. For further analyses, including those listed by AE term, refer to Section 3.2 Expanded Adverse Event Analyses.

Based on assessment of the OCMQ analyses, the clinical reviewer may choose to include only specific groupings or none, depending on which are deemed most informative for their review. If, after receiving the ST&F package, the clinical reviewer notes that one or more OCMQs or individual AE terms in the AE and SAE tables appear to have a meaningful increase in frequency in the investigational arm(s), they may request additional OCMQ tables (e.g., Table 41: Subjects With Select Narrow FDA Medical Queries and Table 42: Subjects With Select Broad FDA Medical Queries) from the Optional Adverse Event Analyses (Section 4.1) to explore the data for specific subjects.

Start Date Considerations

When AEs are reported on the start date of drug administration, clinical reviewers should determine how they are categorized (e.g., pre- or post-initiation of study drug, time of event versus time of start of study drug). Any AE that started prior to randomization and worsens in severity after administration of the IP should be included in the safety analysis. If the start date is missing (which may suggest poor data quality), then the more conservative approach is typically used by including the AE in the safety analysis.

2.2.1. Overview of Adverse Events

Background and Instructions

Table 7: Overview of Adverse Events summarizes AEs and includes incidence of SAEs based on individual components of the SAE criteria. The event values listed in this example table are placeholders that reflect CDISC controlled terminology. The values will be replaced by those found in the clinical trial data. When CDISC controlled terminology is used in the clinical trial data, the events shown in this table will reflect the controlled terminology.

Customization

Clinical reviewers may discuss with CDS if they would like to designate additional AEs as “Serious” and include them in the “Other” category in the table. These additional AEs may include important medical events that do not result in death, are not life-threatening, and do not require hospitalization but that jeopardize the subject and require medical or surgical intervention to prevent one of these outcomes.

Example Table

Table 7. Overview of Adverse Events, Safety Population, Pooled Analysis (or Trial X)

Adverse Event Category	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[1]
SAE[2]	X (Y)	X (Y)	X (Y, Z)
Death	X (Y)	X (Y)	X (Y, Z)
Life-threatening	X (Y)	X (Y)	X (Y, Z)
Initial or prolonged hospitalization	X (Y)	X (Y)	X (Y, Z)
Disability or permanent damage	X (Y)	X (Y)	X (Y, Z)
Congenital anomaly or birth defect	X (Y)	X (Y)	X (Y, Z)
Other	X (Y)	X (Y)	X (Y, Z)
AE leading to permanent discontinuation of treatment	X (Y)	X (Y)	X (Y, Z)
AE leading to action taken of treatment[3]	X (Y)	X (Y)	X (Y, Z)
Action 1	X (Y)	X (Y)	X (Y, Z)
Action 2	X (Y)	X (Y)	X (Y, Z)
Action 3	X (Y)	X (Y)	X (Y, Z)
Any AE[5]	X (Y)	X (Y)	X (Y, Z)
Severity 1	X (Y)	X (Y)	X (Y, Z)
Severity 2	X (Y)	X (Y)	X (Y, Z)
Severity 3	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[2] SAEs classified by Applicant as [insert Applicant's definition of SAE].
[3] Subjects may be counted more than once.
[4] Severity scale as defined by the protocol.
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with at least one event; N, number of subjects in treatment arm; SAE, serious adverse event.

2.2.2. Serious Adverse Events

2.2.2.1. Deaths

Background and Instructions

The clinical reviewer should be aware that sometimes not all deaths are captured in the submitted datasets. All deaths included in submitted datasets (e.g., death details and AE datasets) should be included in this table without regard to the investigator or applicant's judgment about causality. The clinical reviewer should ensure that all deaths that occurred during the trial, including those reported from other sources (e.g., case narratives) are discussed in the review. In general, deaths should be assessed using an on-study analysis as there is likely some latency to the observance of death after a serious AE.

Customization

After analyzing the initial presentation of Table 8: Deaths , consider requesting a KM plot for deaths (if numerous). Consider requesting a similar table that displays results by individual trials or studies of large size, for populations at high risk, or for trials or studies that include many deaths.

Example Table

Table 8. Deaths, Safety Population, Pooled Analysis (or Trial X)

Deaths	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[1]
Death details	X (Y)	X (Y)	X (Y, Z)
Cause of death 1	X (Y)	X (Y)	X (Y, Z)
Cause of death 2	X (Y)	X (Y)	X (Y, Z)
Adverse events[2] with an outcome of death	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[2] Treatment-emergent AE defined as [definition]. MedDRA version X.
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with adverse event; N, number of subjects in treatment arm; PT, preferred term.

2.2.2.2. All Individual Subject Deaths

Background and Instructions

Table 9: All Individual Subject Deaths provides a list of all subject deaths from the AE and disposition datasets. AEs with an outcome of death from AE datasets and subjects who died due to natural causes are only listed in the disposition datasets. The trial day of death below shows the date of death, not the date of onset of SAE leading to death.

Customization

After analyzing the initial presentation of Table 9, the clinical reviewer may discuss with the CDS whether an additional column for investigator's assessment of relatedness or clinical reviewer's assessment of relatedness is desired. The clinical reviewer may also request from the CDS a graphical subject profile for subjects who died.

Example Table

Table 9. All Individual Subject Deaths, Safety Population, Pooled Analysis (or Trial X)

Treatment Arm	Unique Subject ID	Age	Sex	Dosing Duration (Days)	Study Day of Death	MedDRA PT	Verbatim Term
Drug A	X	X	X	X	X	PT1	VT1
Control	X	X	X	X	X	PT2	VT2

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: ID, identification; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; VT, verbatim term.

2.2.2.3. Subjects With Serious Adverse Events by System Organ Class and Preferred Term

Background and Instructions

N/A

Customization

N/A

Example Table

Table 10. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Analysis (or Trial X)

System Organ Class Preferred Term	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[1]
Any SAE	X (Y)	X (Y)	X (Y, Z)
SOC1	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
PT3	X (Y)	X (Y)	X (Y, Z)
SOC2	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
PT3	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: SAEs classified by Applicant as [insert Applicant's definition of SAE].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: CI, confidence interval; n, number of subjects with adverse event; N, number of subjects in treatment arm; PT, preferred term; SAE, serious adverse event; SOC, system organ class.

2.2.2.4. Subjects With Serious Adverse Events by Organ System and OND Custom Medical Queries (Narrow)

Background and Instructions

Table 11: Subjects With Serious Adverse Events provides a list of SAEs by organ system and OCMQs (narrow). Refer to Table 29 to view the specific preferred terms under each OCMQ.

Customization

Clinical reviewer may request a similar table of SAEs by organ system and OCMQs (broad) from CDS. Based on the assessment of the OCMQ results, clinical reviewer may request Table 41: Subjects With Select Narrow FDA Medical Queries found in Section 4.1 Optional Adverse Event Analyses to explore data on specific subjects.

Example Table

Table 11. Subjects With Serious Adverse Events by Organ System and OCMQ (Narrow), Safety Population, Pooled Analysis (or Trial X)

Organ System[1] OCMQ (Narrow)	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[2]
Organ System 1			
OCMQ1	X (Y)	X (Y)	X (Y, Z)
OCMQ2	X (Y)	X (Y)	X (Y, Z)
Organ System 2			
OCMQ3	X (Y)	X (Y)	X (Y, Z)
OCMQ4	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: SAEs classified by Applicant as [insert Applicant's definition of SAE].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Each OCMQ is aligned to a single organ system based on clinical judgment. Please be aware that some OCMQs may contain PTs from more than one MedDRA SOC.
[2] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: CI, confidence interval; OCMQ, OND custom medical query; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with adverse event; N, number of subjects in treatment arm; PT, preferred term; SAE, serious adverse event; SOC, system organ class.

2.2.3. Adverse Events Leading to Treatment Discontinuation by Preferred Term

2.2.3.1. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term

Background and Instructions

N/A

Customization

N/A

Example Table

Table 12. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Pooled Analysis (or Trial X)

System Organ Class Preferred Term	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[1]
Subjects with at least one AE leading to treatment discontinuation	X (Y)	X (Y)	X (Y, Z)
SOC1	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
PT3	X (Y)	X (Y)	X (Y, Z)
SOC2	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
PT3	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with at least one event; N, number of subjects in treatment arm; PT, preferred term; SOC, system organ class.

2.2.3.2. Subjects With Adverse Events Leading to Treatment Discontinuation by Organ System and OND Custom Medical Queries (Narrow)

Background and Instructions

Refer to Table 30: Subjects With Adverse Events Leading to Discontinuation for AEs leading to treatment discontinuation by organ system, OCMQs (narrow), and the specific preferred terms for these OCMQs.

Customization

Clinical reviewers may request a similar table of OCMQs (broad) leading to treatment discontinuation. Clinical reviewers may also request tables from Section 4.1 Optional Adverse Event Analyses to explore the data on specific subjects.

Example Table

Table 13. Subjects With Adverse Events Leading to Treatment Discontinuation by Organ System and OCMQ (Narrow), Safety Population, Pooled Analysis (or Trial X)

Organ System[1] OCMQ (Narrow)	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[2]
Organ System 1			
OCMQ1	X (Y)	X (Y)	X (Y, Z)
OCMQ2	X (Y)	X (Y)	X (Y, Z)
Organ System 2			
OCMQ3	X (Y)	X (Y)	X (Y, Z)
OCMQ4	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Each OCMQ is aligned to a single organ system based on clinical judgment. Please be aware that some OCMQs may contain PTs from more than one MedDRA SOC.
[2] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with adverse event; N, number of subjects in treatment arm; PT, preferred term; SOC, system organ class.

2.2.4. General Adverse Events

2.2.4.1. Subjects With Adverse Events by System Organ Class

Background and Instructions

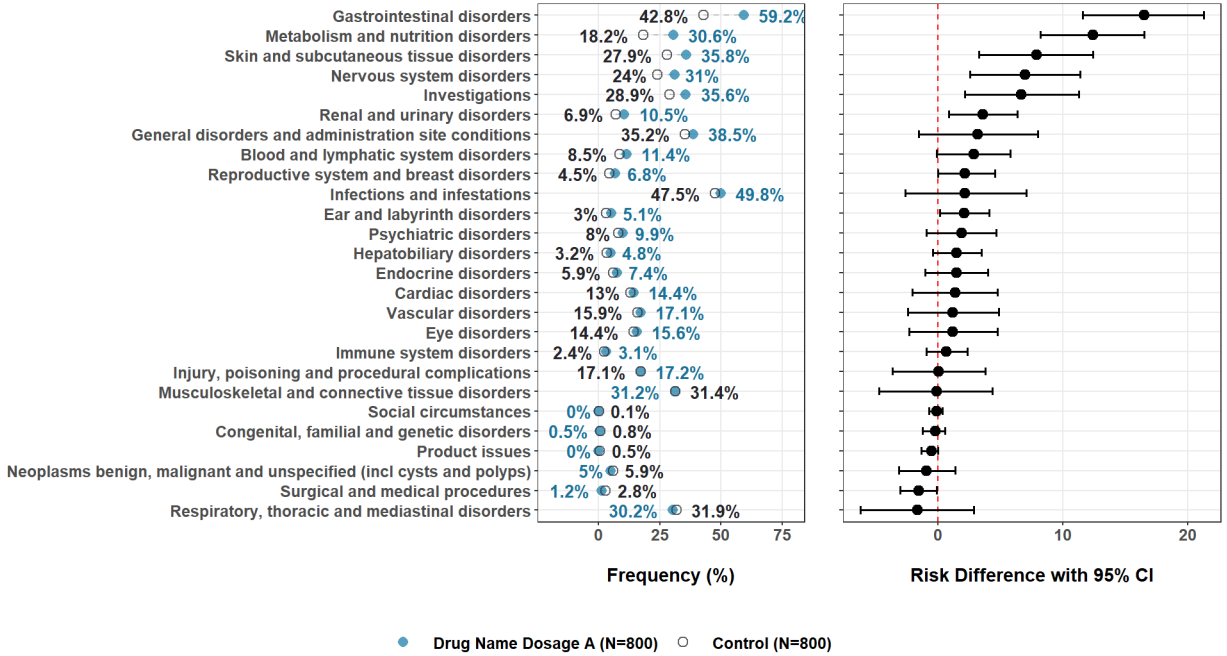
N/A

Customization

N/A

Example Figure

Figure 2. Subjects With Adverse Events by System Organ Class, Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: AE, adverse event; CI, confidence interval; incl, including; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm.

2.2.4.2. Subjects With Adverse Events by System Organ Class and Preferred Term

Background and Instructions

Table 14: Subjects With Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Analysis (or Trial X) presents the entire table of AEs by SOC, while Table 15: Subjects With Common Adverse Events shows common AEs by PT. Review of PTs by SOC can elucidate potential imbalances within the same body system that may not be as apparent when looking at individual AEs.

Customization

The full list of PTs to be included in this table may lead to a multi-page table and affect readability. In this case, the review team could consider displaying this table using a frequency cutoff for ease of review. The full table containing all data can be reviewed in the spreadsheet provided by CDS.

Example Table

Table 14. Subjects With Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Analysis (or Trial X)

System Organ Class Preferred Term	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[1,2]
SOC1	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
PT3	X (Y)	X (Y)	X (Y, Z)
SOC2	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
PT3	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[2] Table display is ordered by the risk difference.
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with at least one event; N, number of subjects in treatment arm; PT, preferred term; SOC, system organ class.

2.2.4.3. Subjects With Common Adverse Events Occurring at ≥X% Frequency by Preferred Term

Background and Instructions

For Table 15: Subjects With Common Adverse Events , it is important to review the entire table (or spreadsheet) produced by the CDS before deciding on the appropriate cutoff to be presented in the review. Depending on the data presented, a >5%, >2%, or >1% frequency or none may be an appropriate cutoff. After analyzing this table, clinical reviewer should refer to Table 14: Subjects With Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Analysis (or Trial X) to view the entire table of AEs and to support product labeling section 6.1 "Adverse Reactions – Clinical Studies Experience."

Customization

Discuss the percent frequency cutoff with the CDS.

If the review team wishes to summarize the within-arm summary of incidence using an incidence rate rather than cumulative incidence, then an example table such as Table 16: Incidence Rate Analysis would be created that depicts that incidence rate for each treatment arm, as well as the rate difference.

Example Tables

Table 15. Subjects With Common Adverse Events Occurring at ≥X% Frequency by Preferred Term, Safety Population, Pooled Analysis (or Trial X)

Preferred Term[1]	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[2,3]
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
PT3	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Coded as MedDRA preferred terms.
[2] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[3] Table display is ordered by the risk difference.
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with adverse event; N, number of subjects in treatment arm; PT, preferred term.

Table 16. Incidence Rate Analysis, Safety Population, Pooled Analysis (or Trial X)

Preferred Term	Drug Name Dosage A n (IR), per 100 PY[1]	Control n (IR), per 100 PY[1]	Incident Rate Difference % (95% CI)[2,3]
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
PT3	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] IR = incidence rate (expressed per 100 PY), where exposure is calculated [insert method of calculation].
[2] Rate difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control). Indicate the method used to calculate the rate difference confidence interval.
[3] Table display is ordered by the rate difference.
Abbreviations: AE, adverse event; CI, confidence interval; IR, incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with AE; N, number of subjects in treatment arm; PT, preferred term; PY, person-years.

2.2.4.4. Subjects With Adverse Events ≥X% in Any Treatment Arm by OCMQs (Narrow)

Background and Instructions

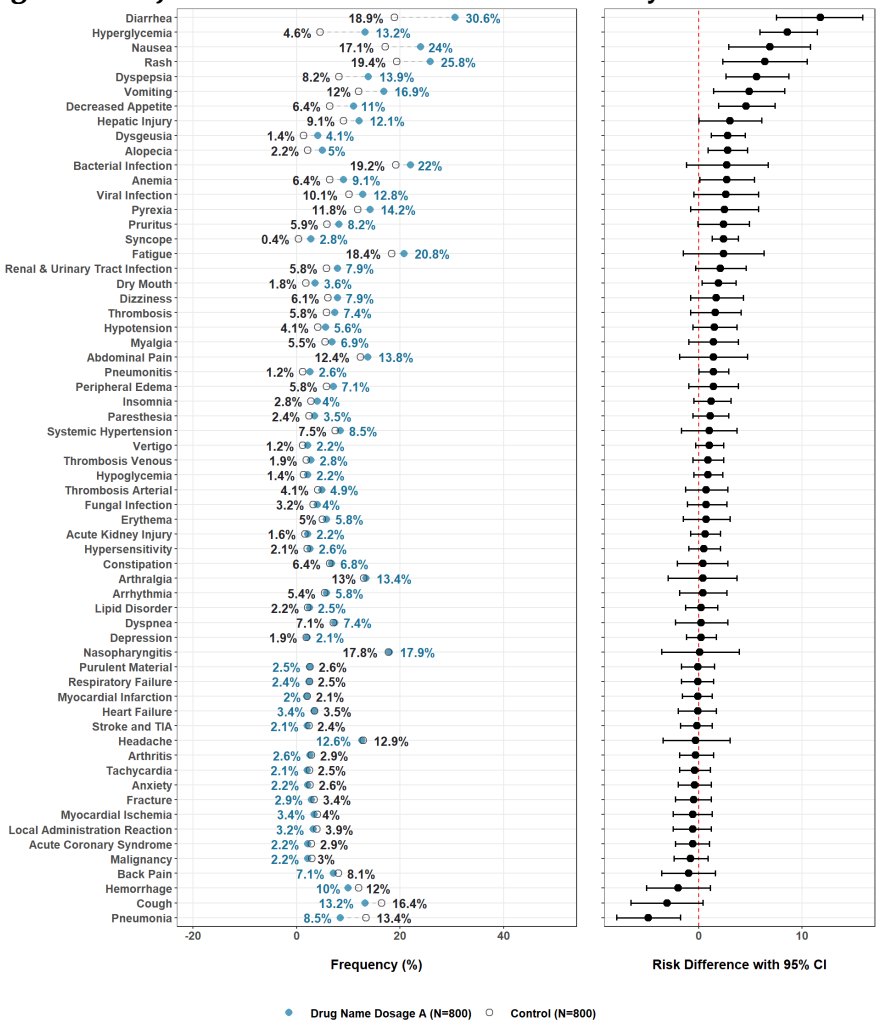
N/A

Customization

N/A

Example Figure

Figure 3. Subjects With Adverse Events ≥X% in Any Treatment Arm by OCMQ (Narrow), Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Note: Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).

Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; N, number of subjects in treatment arm; MedDRA, Medical Dictionary for Regulatory Activities; TIA, transient ischemic attack.

2.2.4.5. Subjects With Adverse Events by Organ System and OND Custom Medical Queries

Background and Instructions

For Table 17: Subjects With Adverse Events by Organ System , it is important to review the entire table (or spreadsheet) produced by the CDS before deciding on the appropriate cutoff to be presented in the review. Depending on the data presented, a >5%, >2%, or >1% frequency or none may be an appropriate cutoff. Refer to Table 31 Subjects With Adverse Events by Organ System, OCMQ (Narrow) and Preferred Term, Safety Population, Pooled Analysis (or Trial X) to view specific preferred terms under each narrow OCMQ by organ system.

Customization

After analyzing, clinical reviewers may request to view specific preferred terms under each broad OCMQ by organ system. Based on the assessment of the OCMQ results, clinical reviewers may request Table 41: Subjects With Select Narrow FDA Medical Queries and Table 42: Subjects With Select Broad FDA Medical Queries found in Section 4.1 Optional Adverse Event Analyses to explore the data on specific subjects.

Example Table

Table 17. Subjects With Adverse Events by Organ System and OCMQ, Safety Population, Pooled Analysis (or Trial X)

	Narrow OCMQs			Broad OCMQs[1]		
Organ System[2] OCMQ	**Drug Name Dosage A N=XXX n (%)**	**Control N=XXX n (%)**	**Risk Difference % (95% CI)[3]**	**Drug Name Dosage A N=XXX n (%)**	**Control N=XXX n (%)**	**Risk Difference**
Organ System 1						
OCMQ1	X (Y)	X (Y)	X (Y, Z)	X (Y)	X (Y)	X (Y, Z)
OCMQ2	X (Y)	X (Y)	X (Y, Z)	X (Y)	X (Y)	X (Y, Z)
OCMQ3	X (Y)	X (Y)	X (Y, Z)	X (Y)	X (Y)	X (Y, Z)
Organ System 2						
OCMQ4	X (Y)	X (Y)	X (Y, Z)	X (Y)	X (Y)	X (Y, Z)
OCMQ5	X (Y)	X (Y)	X (Y, Z)	X (Y)	X (Y)	X (Y, Z)
OCMQ6	X (Y)	X (Y)	X (Y, Z)	X (Y)	X (Y)	X (Y, Z)
Organ System 3						
OCMQ7	X (Y)	X (Y)	X (Y, Z)	X (Y)	X (Y)	X (Y, Z)
OCMQ8	X (Y)	X (Y)	X (Y, Z)	X (Y)	X (Y)	X (Y, Z)
OCMQ9	X (Y)	X (Y)	X (Y, Z)	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Broad OCMQ analysis incorporates narrow OCMQ preferred terms to maximize sensitivity.
[2] Each OCMQ is aligned to a single organ system based on clinical judgment. Please be aware that some OCMQs may contain PTs from more than one MedDRA SOC.
[3] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with at least one event; N, number of subjects in treatment arm. PT, preferred term; SOC, system organ class.

2.2.5. Adverse Events of Interest and Adverse Events of Special Interest

Clinical reviewers may request analyses in this section to further investigate any AEs identified during application review or prespecified Adverse Event of Special Interests (AESI) that warrant further analysis.

- Adverse Event of Interest – Any AEs that warrant further analysis.
- Adverse Event of Special Interest (AESI) - A subset of AE of Interest that are pre-specified in the protocol and should have been previously discussed with the review division.

For the assessment of the above, the review team should discuss the approach to analysis for each AE of Interest and whether the statistical methodologies should be more complex (e.g., accounting for recurrent events, time-to-event) than those used for the general assessment of safety. In some cases, AEs of Interest are not defined based solely on a single MedDRA preferred terms but on a group of PTs or adjudicated results (e.g., major adverse cardiovascular event).

2.2.5.1. Summary Assessment of [Insert AE of Interest]

Background and Instructions

Table 18: Summary Assessment of [Insert AE of Interest] is created for each AE of interest and may be created for any AEs identified during application review that may warrant further analysis. The table name should be updated to reflect the event being displayed. The approach to analysis and summary of safety data should be tailored to each AE.

Customization

Discuss with CDS specific AEs and other information (e.g., laboratory information) to be included in Table 18 to provide a complete picture of the AE of Interest. When information across different datasets is combined, carefully consider the number of subjects used as the denominator in analyses, as they may differ across datasets.

Example Table

Table 18. Summary Assessment of [Insert AE of Interest], Safety Population, Pooled Analysis (or Trial X)

AE of Interest Assessment	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[1]
[Insert AE of Interest][2]	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
Maximum severity[3]			
Severity 1	X (Y)	X (Y)	X (Y, Z)
Severity 2	X (Y)	X (Y)	X (Y, Z)
Severity 3	X (Y)	X (Y)	X (Y, Z)
SAE[4]	X (Y)	X (Y)	X (Y, Z)
Death	X (Y)	X (Y)	X (Y, Z)
Life-threatening	X (Y)	X (Y)	X (Y, Z)
Initial or prolonged hospitalization	X (Y)	X (Y)	X (Y, Z)
Disability or permanent damage	X (Y)	X (Y)	X (Y, Z)
Congenital anomaly or birth defect	X (Y)	X (Y)	X (Y, Z)
Other	X (Y)	X (Y)	X (Y, Z)
Resulting in treatment discontinuation	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[2] Use OCMQ grouping if appropriate.
[3] Severity scale as defined by the protocol.
[4] SAEs classified by Applicant as [insert Applicant's definition of SAE].
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; OCMQ, OND custom medical query; n, number of subjects with at least one event; N, number of subjects in treatment arm; PT, preferred term; SAE, serious adverse event.

2.2.5.2. Time to Onset of [Insert AE of Interest]

Background and Instructions

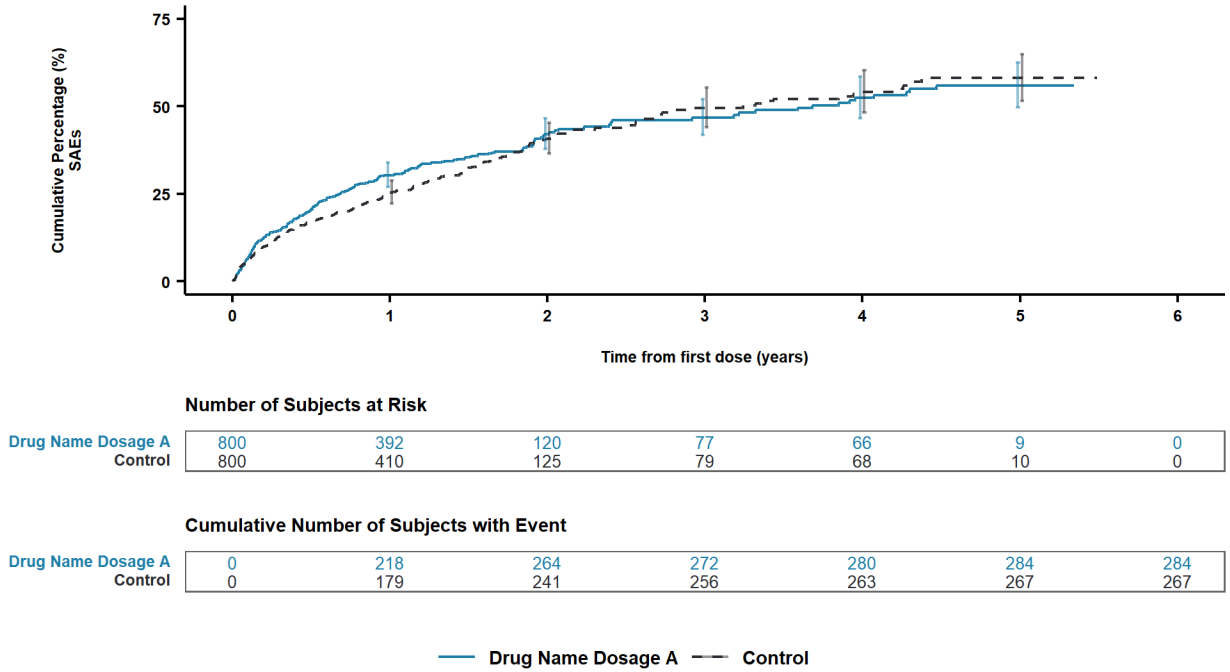
A KM plot considers remaining subjects in the trial and displays cumulative incidence over time. A KM plot or cumulative incidence plot for AE of interest can be helpful. Figure 4: Kaplan-Meier Plot: Time to Onset includes an example of time to onset for SAEs. This is an example figure that can be generated for any AE of interest. If the number of subjects is too small (if N in at least one group is <8), KM plots may not be informative.

Customization

Figure 4 can be created for each AE of interest. The figure name should be updated to reflect the event being displayed.

Example Figure

Figure 4. Kaplan-Meier Plot: Time to Onset of [Insert AE of Interest], Safety Population, Pooled Analyses (or Trial)



Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Note: This figure depicts Kaplan-Meier estimates of the cumulative percentage of subjects that experience an AE of interest by a given time point. If a subject experienced more than one AEs of special interest, the earliest AE start day was used as event time.
Note: The vertical bars shown on the plotted lines indicates the 95% confidence interval of probability of incidence at the corresponding time points.
Abbreviations: AE, adverse event; AESI, adverse event of special interest.

2.3. Subgroup Analyses by Baseline Characteristics

The benefit-risk profile of an investigational drug product may differ across subgroups of subjects who share certain baseline characteristics. “Subgroup analysis” refers to evaluation of treatment effects for a specific safety or efficacy endpoint within a population subset. Subgroup analyses during the safety review may be used to assess for potential differences in safety among different population subsets and to identify populations that may be more vulnerable to certain adverse drug effects (e.g., greater increase on drug vs. control in the rate of certain AEs in females compared to males).

Documenting who participated in the key clinical trials by demographic subgroups (sex, age, race, and ethnicity) and any subgroup-specific differences in safety and effectiveness, if available, is required under FDA Safety and Innovation Act Section 907. An example overview of AEs by demographic subgroup is shown in Table 51: Overview of Adverse Events by Demographic Subgroup, Safety Population, Pooled Analysis (or Trial X).

2.3.1. Subjects With [Insert OCMQ/AE of Interest] by Demographic Subgroups

Background and Instructions

The list of AEs or OCMQs for subgroup analysis should only include AEs or OCMQs that are of interest to the review team. Requesting subgroup analyses on a large number of AEs or OCMQs without a specific rationale for the inclusion is usually not appropriate. The clinical reviewer should work with the CDS to determine the AE terms for which subgroup incidences are provided in Table 19: Subjects With [Insert FMQ/PT of Interest]. This may be AESIs, OCMQs, or specific AE PTs that were found to be notably higher in the study drug arm. Subgroup analyses can be provided for imbalances in safety laboratory analyte measurements meeting level 2 increases or decreases (e.g., increase in ALT or decreases in eGFR). Table 19 is generated for each grouping or AE of interest. The table name should be updated to reflect the event being displayed.

Customization

Provide to the CDS any additional potentially relevant subgroups beyond the standard demographic subgroups that may shed light on which subjects are most susceptible to the safety event of interest (e.g., subgroups by baseline diseases [e.g., cardiovascular disease, diabetes, CKD stage], concomitant medication, or anthropometric characteristics [e.g., BMI]). The clinical reviewer should discuss appropriate age groups for the subgroup analysis with the CDS. An overview of subjects with SAEs (Table 50) and AEs (Table 51) can be requested by the review team.

Example Table

Table 19. Subjects With [Insert OCMQ/AE of Interest] by Demographic Subgroups, Safety Population, Pooled Analysis (or Trial X)

Characteristic	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)
Any [insert OCMQ/PT of interest]	X (Y)	X (Y)
Sex		
Male	X/Y (Z)	X/Y (Z)
Female	X/Y (Z)	X/Y (Z)
Age group, years		
Group 1	X/Y (Z)	X/Y (Z)
Group 2	X/Y (Z)	X/Y (Z)
Group 3	X/Y (Z)	X/Y (Z)
Group 4	X/Y (Z)	X/Y (Z)
Race		
American Indian or Alaska Native	X/Y (Z)	X/Y (Z)
Asian	X/Y (Z)	X/Y (Z)
Black or African American	X/Y (Z)	X/Y (Z)
Multiple	X/Y (Z)	X/Y (Z)
Native Hawaiian or other Pacific Islander	X/Y (Z)	X/Y (Z)
White	X/Y (Z)	X/Y (Z)
Not reported	X/Y (Z)	X/Y (Z)
Other	X/Y (Z)	X/Y (Z)
Unknown	X/Y (Z)	X/Y (Z)
Ethnicity		
Hispanic or Latino	X/Y (Z)	X/Y (Z)
Not Hispanic or Latino	X/Y (Z)	X/Y (Z)
Not reported	X/Y (Z)	X/Y (Z)
Unknown	X/Y (Z)	X/Y (Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: OCMQ, OND custom medical query; n, number of subjects with adverse event; N, number of subjects in treatment arm; N_s, total number of subjects for each specific subgroup; PT, preferred term.

2.4. Laboratory Analyses

The following standard ST&F are intended for routine safety analyses of laboratory parameters for NDAs and BLAs. This section provides an analysis of laboratory data, including measures of central tendency and outlier analyses. If analyses in this section pose a concern, further analyses, including alternate tabulations and visualizations of data, are provided in Section 3 Expanded Safety Tables and Figures for the clinical reviewer's initial review. Additional analyses may be required, such as shift plots, specific outlier criteria, and last value on-treatment analyses, all of which can be found in Section 4 Optional Safety Tables and Figures for clinical reviewers to request.

In general, laboratory data from all visits (i.e., unscheduled and scheduled visits; central and local laboratory) should be included in the safety review. Laboratory results obtained during unscheduled trial visits occurring outside of the protocol-specified visit window should be included in the data for the nearest protocol-specified visit or analyzed per the SAP. The specific approach used will need to be indicated in a footnote.

Results considered to be "extreme values" (as indicated in Table 58: Extreme Serum, Plasma, and Whole Blood Chemistry Laboratory Values Suggestive of Laboratory Error, Table 59: Extreme Serum, Plasma, and Whole Blood Hematology Laboratory Values Suggestive of Laboratory Error, and Table 60: Extreme Vital Sign Values Suggestive of Error) are removed from the mean change from baseline over time figures.

2.4.1. Missing and Existing Data Analysis

2.4.1.1. Proportion of Subjects Remaining in Trial at Each Visit by Availability of [Insert Lab Value] Result

Background and Instructions

Figure 5: Proportion of Subjects Remaining in Trial at Each Visit by Availability of [Insert Lab Value] Result, Safety Population, Pooled Analysis (or Trial X) is provided for ALT, AST, ALP, TB, serum creatinine, and eGFR by default when theses laboratory measures are available. This figure displays the percent of subjects remaining in trial with the laboratory test by visit (solid bar), the percent of subjects remaining in trial with missing laboratory test by visit (open bar), and the percent of subjects remaining in the trial (bar height). The x-axis displays trial visits as a discrete variable rather than a continuous variable.

During the planning meeting with the CDS, clinical reviewers should discuss the definition of "missing" data and reflect protocol-specified trial visits. This graph should evaluate the actual data obtained during the trial rather than the planned trial procedures as

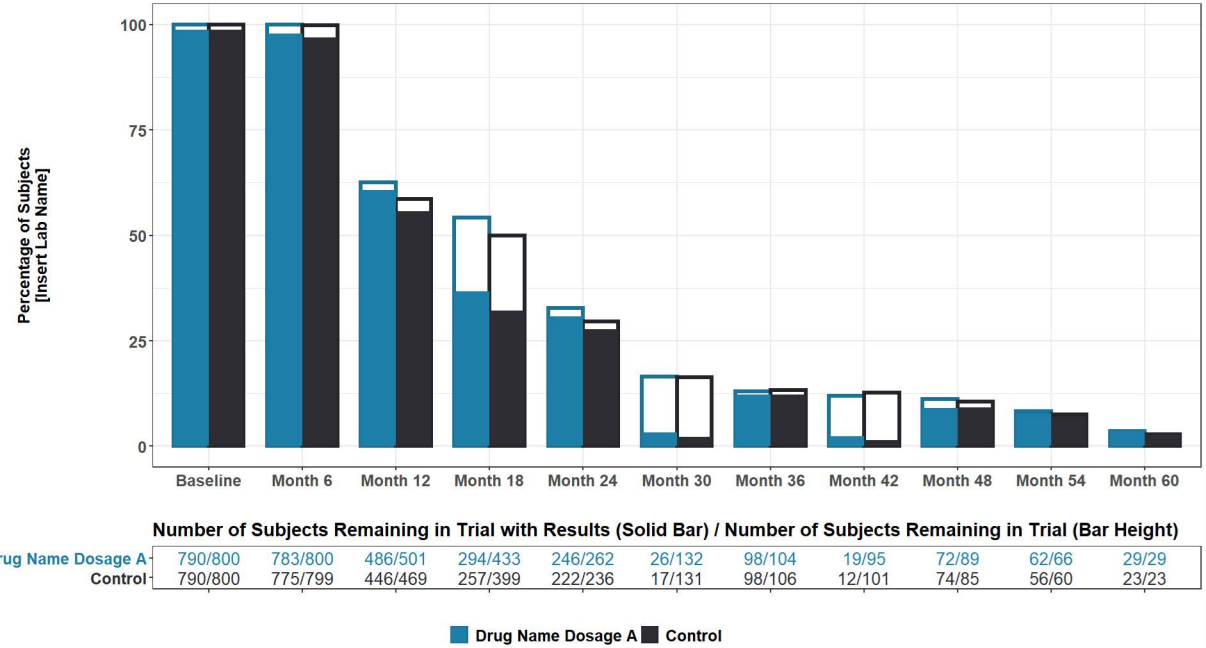
stated in the protocol. Alternatively, clinical reviewers may request more data from the applicant before proceeding. The figure name should be updated to reflect the laboratory parameter being displayed.

Customization

Clinical reviewers should review the protocol(s) and discuss with the CDS the duration (e.g., until the end of treatment, until sometime after the end of treatment, or until the end of the trial) and population (e.g., randomized or treated) to use. Similar figures can be requested for any analyte or vital signs of interest (e.g., blood pressure, gamma-glutamyl transferase, international normalized ratio, BMI) to the clinical reviewer.

Example Figure

Figure 5. Proportion of Subjects Remaining in Trial at Each Visit by Availability of [Insert Lab Value] Result, Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Note: The frequency of laboratory measurements presented here is based on actual data collected.
Note: The time frame (e.g., by day, week, month) that corresponds best with the prespecified visit # is used as the trial visit (± protocol-defined # days).

Note: The solid bar indicates the percent of subjects remaining in the trial with the laboratory result. The open bar indicates the percent of subjects remaining in the trial and are missing the laboratory result. The bar height indicates the percent of subjects remaining in the trial.
Abbreviations: ALT, alanine aminotransferase.

2.4.2. Laboratory Data Change Over Time From Baseline Analyses

Background and Instructions

The following figures are provided to display mean changes in laboratory values over time and are presented in clinically relevant groupings:

- Figure 6: Mean General Chemistry Data Change From Baseline Over Time by Treatment Arm, Safety Population, Pooled Analyses (or Trial X) will be generated with data for each of the following: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, glucose, calcium, magnesium, phosphate (mg/dL), protein (total), albumin, creatine phosphokinase, amylase, and lipase.
- The *Mean Kidney Function Data Change from Baseline Over Time* figure will be generated with data for each of the following: creatinine, eGFR, and creatinine clearance.
- The *Mean Liver Biochemistry Data Change from Baseline Over Time* figure will be generated with data for each of the following: ALT, AST, ALP, TB, DB, gamma-glutamyl transpeptidase, and international normalized ratio.
- The *Mean Lipids Data Change from Baseline Over Time* figure will be generated with data for each of the following: total cholesterol, HDL, LDL, and triglycerides.
- The *Mean Hematology Data Change from Baseline Over Time* figure will be generated with data for each of the following: WBC count, hemoglobin, platelets, lymphocytes, neutrophils, eosinophils, prothrombin time, and activated partial thromboplastin.

A pooled summary of changes over time is most applicable when the visit schedules are the same across trials or studies. Careful consideration should be used when providing a summary of changes over time from pooled trials in which some time points are from one trial, and other time points are from another trial.

Results considered to be “extreme values” (as indicated in Table 58: Extreme Serum, Plasma, and Whole Blood Chemistry Laboratory Values Suggestive of Laboratory Error and Table 59: Extreme Serum, Plasma, and Whole Blood Hematology Laboratory Values Suggestive of Laboratory Error in Section 5.2 Extreme Clinical Laboratory and Vital Sign Values) are removed from the mean change from baseline over time figures. Trial data that exceed these thresholds are likely to represent measurement or reporting errors, as such data are considered unlikely to occur in living humans. The purpose of these thresholds is to help identify potential quality issues with

the data. While some references were identified to inform these thresholds, many of them are simply based on clinical opinion. Some of the thresholds are based on the most extreme result that has been previously documented in humans. In those cases, the threshold was set at a moderately more extreme value than the previously documented result. This was done to minimize the chance that results reported in trials or studies would be inappropriately determined to be too extreme to be correct. For instance, the highest documented CPK value identified during a literature search was approximately 701,000 U/L. Based on that information, a threshold of 800,000 U/L was selected.

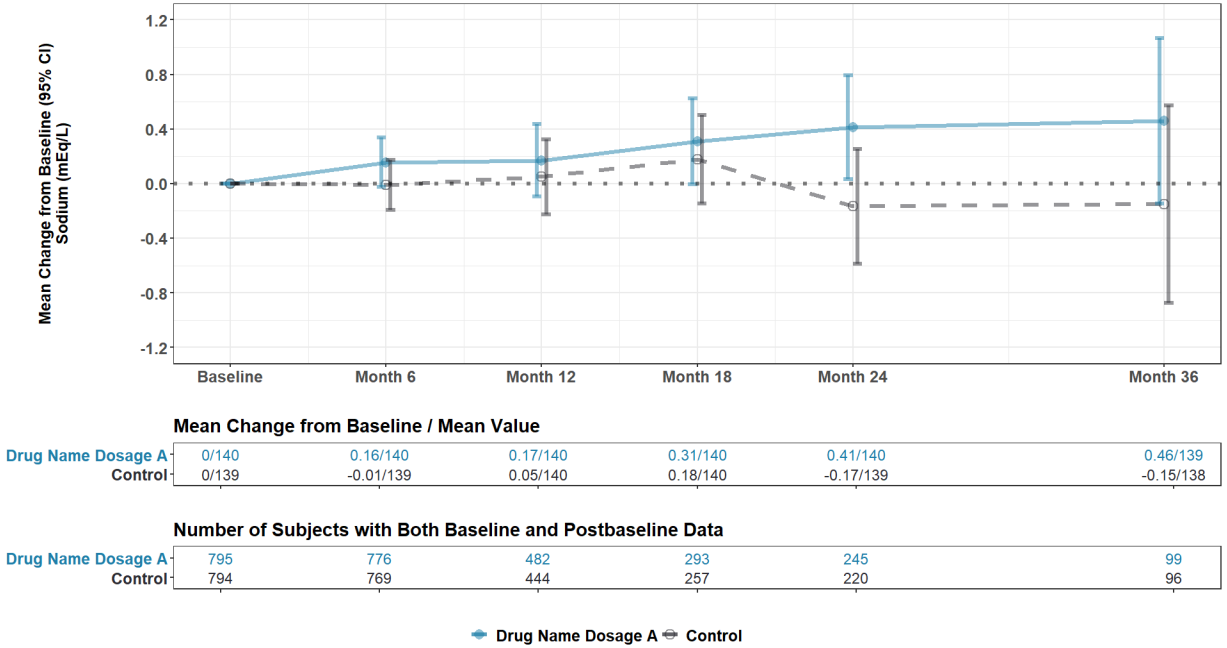
Customization

To avoid the inclusion of noise in figures, time points with data from fewer than 10% of subjects in all trial groups are excluded. Clinical reviewers can further discuss and refine this approach as needed with the CDS team.

If, after reviewing the initial presentation, the clinical reviewer is interested in a different presentation of the data, they may request CDS to generate additional displays such as the median, interquartile range, and/or outlier box plot graphs (refer to Section 4.3 Optional Laboratory Analyses) and the mean laboratory data change from baseline over time tables (refer to Section 3.3 Expanded Laboratory Analyses).

Example Figure

Figure 6. Mean General Chemistry Data Change From Baseline Over Time by Treatment Arm, Safety Population, Pooled Analyses (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Note: If a timepoint is reached where there are only a few subjects remaining in the trial (e.g., less than 5%), consideration should be made to truncate this graph as the results would not be considered a reliable indicator of the true mean.
Note: Subjects with both baseline and postbaseline data available are included in the mean change from baseline calculations at each visit. The number of subjects reflects only those included in the mean change from baseline calculations, rather than the total number of subjects.
Note: The vertical bars shown on the plotted lines indicate the 95% confidence interval of the mean change at the corresponding time points.
Note: Only central laboratory data were used for the plot.
Abbreviations: CI, confidence interval.

2.4.3. Outlier Analyses

Background and Instructions

The following tables are provided to display laboratory analyte values exceeding specified levels and can be used to assess the severity of abnormalities and identify important outliers. Subject counts are cumulative for each abnormality threshold.

- The *Subjects with General Chemistry Analyte Values with Values Exceeding Specified Levels* table will be generated with data for each of the following: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, glucose, calcium, magnesium, phosphate (mg/dL), protein (total), albumin, creatine phosphokinase, amylase, and lipase.
- Table 20: Subjects With Kidney Function Analyte Values Exceeding Specified Levels will be generated with data for each of the following: creatinine, eGFR, and creatinine clearance.
- The *Subjects with Liver Biochemistry Analyte Values Exceeding Specified Levels* table will be generated with data for each of the following: ALT, AST, ALP, TB, DB, gamma-glutamyl transpeptidase, and international normalized ratio.
- The S*ubjects with Lipids Analyte Values Exceeding Specified Levels* table will be generated with data for each of the following: total cholesterol, HDL, LDL, and triglycerides.
- The *Subjects with Hematology Analyte Values Exceeding Specified Levels* table will be generated with data for each of the following: WBC count, hemoglobin, platelets, lymphocytes, neutrophils, eosinophils, prothrombin time, and activated partial thromboplastin.

It is recommended to include the percentage of subjects with abnormality level criteria at any time during the trial and within a specific time frame. To determine this time frame, consider trial design, drug half-life, concomitant medications, or other factors that may be important for assessment.

In certain populations where an established grading system already exists, such as for subjects with HIV (e.g., “NIH [National Institutes of Health] Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events”) and malignancy (e.g., “Common Terminology Criteria for Adverse Events”), the established system may be used as appropriate. When not using pre-established laboratory grading systems, these tables are generated using the criteria listed in Table 56: Abnormality Level Criteria for Chemistry Laboratory Results and Table 57: Abnormality Level Criteria for Hematology Laboratory Results. These criteria were selected based on clinical opinion in order to detect outlier results. The individual thresholds do not correspond with specific safety outcomes.

If there are abnormalities or differences between arms, Table 52: Subjects With Last On Treatment Chemistry Value ≥ Level 2 and Table 53: Subjects With Last On Treatment Hematology Value ≥Level 2 will also be generated.

Customization

Discuss with the CDS and clearly note any prespecified cutoff criteria or time frame used in laboratory analysis.

Example Table

Table 20. Subjects With Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Pooled Analysis (or Trial X)

Parameter	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[1]
Creatinine, high (mg/dL)			
Level 1 (≥1.5x baseline)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 2 (≥2.0x baseline)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 3 (≥3.0x baseline)	X/Y (Z)	X/Y (Z)	X (Y, Z)
eGFR, low (mL/min/1.73 m^2)			
Level 1 (≥25% decrease)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 2 (≥50% decrease)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 3 (≥75% decrease)	X/Y (Z)	X/Y (Z)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Threshold Levels 1, 2, and 3 are defined by Table 56. Abnormality Level Criteria for Chemistry Laboratory Results.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Note: Subject counts are cumulative for each abnormality threshold.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; n, number of subjects meeting the specified laboratory criteria; N, number of subjects in treatment arm; N_s, total number of subjects with data available for the laboratory test of interest.

2.4.4. Liver Injury Screening Analyses

The liver injury screening analyses include the following four analyses: Missing and Existing Data Analysis, Hepatocellular DILI Screening Plots, Cholestatic DILI Screening Plot, and Comparison of Subjects with Maximal Treatment-Emergent Liver Test Abnormalities.

2.4.4.1. Missing and Existing Data Analysis

Refer to Section 2.4.1 Missing and Existing Data Analysis for missing data analysis for liver-related laboratory parameters.

2.4.4.2. Hepatocellular DILI Screening Plots

Background and Instructions

The main purpose of Figure 7: Hepatocellular Drug Induced Liver Injury Screening Plot is to identify subjects with potential hepatocellular DILI, that has led to sufficient liver damage (approaching 50% of the total liver volume) to result in decreased bilirubin excretion and cause jaundice. Such hepatocellular jaundice due to DILI is considered a “Hy’s Law” case, which can carry a 10% to 50% mortality from acute liver failure (in pretransplantation days). Hy’s Law cases may only constitute a small fraction of all subjects with hepatocellular DILI, so that the size of the study population needs to be sufficiently large to detect these cases. The presence of even one or two such cases may be sufficient to jeopardize drug approval or raise concerns for postmarketing safety.

In the default plot, each subject is plotted based on their maximum ***post-baseline*** TB (y-axis) and transaminase (ALT or AST, whichever is higher). Each value is expressed as multiples of ULN. Dashed lines in this plot represent TB and transaminase cutoffs of 2x ULN and 3x ULN (default), respectively and are based on Hy’s Law criteria.

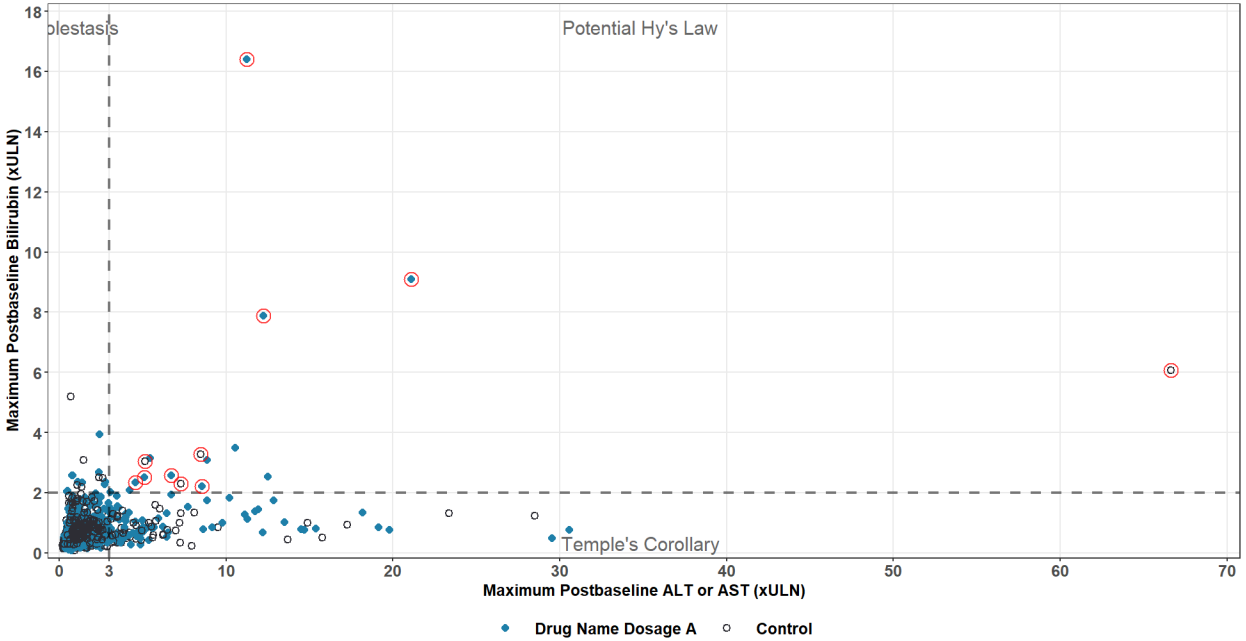
Customization

Note that because the reported ULNs may vary between laboratory sites, the default graph displays AST or ALT normalized to the reported ULNs. Clinical reviewers may request a similar graph displaying the measured values of liver biochemistry tests rather than normalized values but should note that a cutoff line depicting 3x ULN for transaminases will not be drawn due to the variations in reported normal ranges. Clinical Reviewers may also request this analysis to be performed using an alternative time frame (e.g., 15 days or 45 days) to assess for concurrent transaminase and TB elevation based on specific drug and/or subject characteristics.

In trials that enroll subjects with abnormal baseline liver biochemistry values (i.e., elevated baseline AST, ALT, ALP, etc.), an additional series of plots can be requested using other reference limits: 1) multiples of baseline values (e.g., ALT 3x baseline); and 2) absolute transaminase level increases above the baseline values (e.g., ALT >200 U/L above baseline levels) based on suspicion of significant liver injury risk as suggested by preclinical signal, mechanism of action, class effect etc. Note that in subjects with elevated baseline transaminase values, who show improvements in their transaminase levels and in essence, establish a new lower “baseline” during the trial, clinical reviewers may consider using the new lower transaminase values in subsequent assessment for potential DILI “baseline” (i.e., DILI assessment in subjects who normalize their transaminase levels after initiation of study drug should use normal range cutoffs rather than multiples of baseline in potential DILI assessment).

Example Figure

Figure 7. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case was defined as having any post-baseline total bilirubin equal to or exceeding 2x ULN after a postbaseline ALT or AST equal to or exceeding 3x ULN. Those subjects who meet total bilirubin equal to or exceeding 2x ULN criteria within 30 days of the ALT or AST equal to or exceeding 3x ULN criteria are circled in red. All subjects with at least one postbaseline ALT or AST and total bilirubin are plotted. Refer to Table 21. Subjects in Quadrant of Interest for Potential Hepatocellular DILI Screening Plot, Safety Population, Pooled Analysis (or Trial X) for subject counts for each quadrant.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

2.4.4.3. Cholestatic DILI Screening Plot

Background and Instructions

While ALP elevations can be attributed to other sources (e.g., bone), significant ALP elevation in the setting of hepatic dysfunction (e.g., jaundice) may suggest cholestatic DILI. The cholestatic screening plot (Figure 8) is analogous to the hepatocellular screening plot (Figure 7) and is intended to quickly identify cases of possible serious cholestatic DILI.

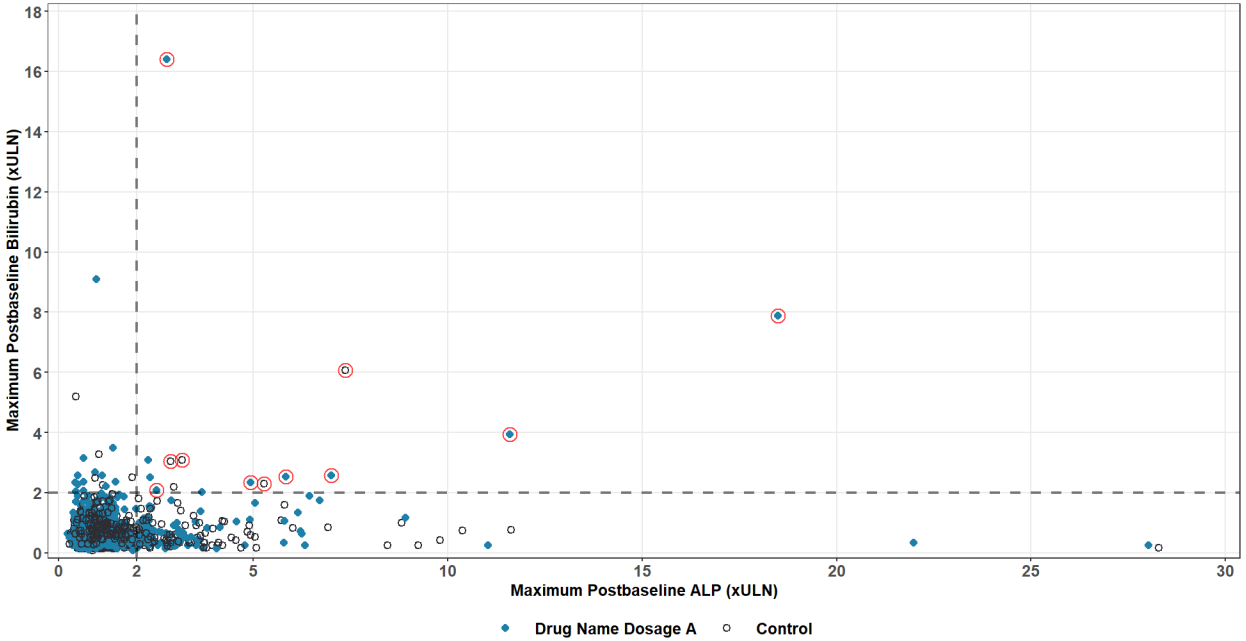
Maximum post-baseline TB is plotted against maximum post-baseline ALP rather than ALT or AST. The quadrants are similarly defined by TB >2x ULN, but the ALP cut-off is >2x ULN as the default. Red circled cases in the right upper quadrant indicates subjects who had their maximum bilirubin within 30 days (default) of ALP becoming >2x ULN. However, cases in the right upper quadrant are not considered Hy's Law cases nor are cases in the right lower quadrant considered Temple's Corollary cases. These labels do not apply to the cholestatic plot. Moreover, cholestatic DILI cases in the right upper quadrant do not carry the 10% to 50% mortality rate from acute liver failure (in pretransplantation days) of a Hy's Law case. Nevertheless, the combination of ALP >2x ULN and jaundice is concerning for cholestatic injury deserving exploration. Similar to the hepatocellular screening plot, the cholestatic screening plot provides a visual assessment of imbalances between arms and numbers of cases by quadrants.

Customization

Similar to the hepatocellular DILI screening plot, clinical reviewers may request this plot according to a customized time frame (e.g., 45 days or 60 days) and alternative cutoffs for TB and ALP levels.

Example Figure

Figure 8. Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Each data point represents a subject plotted by their maximum ALP versus their maximum total bilirubin values in the postbaseline period.
A potential cholestatic drug-induced liver injury case (red circled) was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after postbaseline ALP became equal to or exceeding 2X ULN. Refer to Table 22. Subjects in Quadrants of Interest for Potential Cholestatic DILI Screening Plot, Safety Population, Pooled Analysis (or Trial X) for subject counts for each quadrant.
Abbreviations: ALP, alkaline phosphatase; ULN, upper limit of normal.

2.4.4.4. Comparison of Subjects With Maximal Treatment-Emergent Liver Test Abnormalities

2.4.4.4.1. Subjects in Quadrant of Interest for Potential DILI Screening Plots

Background and Instructions

Table 21: Subjects in Quadrant of Interest for Potential Hepatocellular DILI Screening Plot and Table 22: Subjects in Quadrants of Interest for Potential Cholestatic DILI Screening Plot are intended to demonstrate potential imbalances in the subjects who are found in each quadrant of concern between trial arms using maximum treatment-emergent liver test abnormalities. These tables help to differentiate potential hepatocellular and cholestatic DILI cases between trial arm groups.

Customization

N/A

Example Tables

Table 21. Subjects in Quadrant of Interest for Potential Hepatocellular DILI Screening Plot, Safety Population, Pooled Analysis (or Trial X)

Quadrant	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)
Potential Hy's Law (right upper quadrant)	X/Y (Z)	X/Y (Z)
Cholestasis (left upper quadrant)	X/Y (Z)	X/Y (Z)
Temple's corollary (right lower quadrant)	X/Y (Z)	X/Y (Z)
Total	**X/Y (Z)**	**X/Y (Z)**

Source: [include Applicant source, datasets and/or software tools used]
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: DILI, drug-induced liver injury; n, number of subjects meeting the specified laboratory criteria; N, number of subjects in treatment arm; N_s, total number of subjects with laboratory data available.

Table 22. Subjects in Quadrants of Interest for Potential Cholestatic DILI Screening Plot, Safety Population, Pooled Analysis (or Trial X)

Quadrant	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)
BILI ≥2x ULN and ALP ≥2x ULN (right upper quadrant)	X/Y (Z)	X/Y (Z)
BILI ≥2x ULN and ALP <2x ULN (left upper quadrant)	X/Y (Z)	X/Y (Z)
BILI <2x ULN and ALP ≥2x ULN (right lower quadrant)	X/Y (Z)	X/Y (Z)
Total	**X/Y (Z)**	**X/Y (Z)**

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; n, number of subjects meeting the specified laboratory criteria; N, number of subjects in treatment arm; N_s, total number of subjects with laboratory data available; ULN, upper limit of normal.

2.5. Vital Signs

The following standard figures are intended for routine safety analyses of vital signs for NDAs and BLAs that do not present special concerns. If analyses in this section pose a concern, further analyses, including alternate tabulations and visualizations of data and specific outlier criteria, are provided in Section 3.4 Expanded Vital Sign Analyses. If the study drug is believed to significantly alter vital signs, additional analyses may be required, such as an assessment of the subjects with changes in blood pressure medication or shift tables. Note that the reference ranges used to generate the displays in this section reflect the adult population only; a customized approach will be necessary for trials that enroll pediatric populations.

Similar to laboratory analyses, vital signs data from both unscheduled and scheduled visits should be included in all vital signs analyses. Vital signs results obtained during unscheduled trial visits that occurred outside of a protocol-specified visit window should be included in the data for the nearest protocol-specified visit or analyzed per the SAP. The specific approach will be indicated in the footnote. Consider requesting 2.4.1 Missing and Existing Data Analysis for any vital sign(s) of interest.

2.5.1. Vital Signs Data Change Over Time From Baseline Analyses

A pooled summary of changes over time is most applicable when the visit schedules are identical across trials or studies. Careful consideration should be used when providing a summary of changes over time from pooled trials or studies in which some time points are from one trial and other time points are from another trial.

Background and Instructions

Figure 9: Mean Vital Sign Data Change from Baseline Over Time is generated from data for each of the following: systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature.

To avoid the presentation of noise, Figure 9 does not include time points with data from fewer than 10% of subjects in all treatment arm groups. The clinical reviewer can further discuss and refine this approach as needed with the CDS team.

Results considered to be “extreme values” as indicated in Table 60: Extreme Vital Sign Values Suggestive of Error in Section 5.2 Extreme Clinical Laboratory and Vital Sign Values are removed from the mean change from baseline over time figures. Trial data that exceed these thresholds are likely to represent measurement or reporting errors, as such data are considered unlikely to occur in living humans. The purpose of these thresholds is to help identify potential quality issues with the data. While some references were identified to inform these thresholds, many of the thresholds were simply based on clinical opinion. Some of the thresholds were based on the most extreme result that had been previously documented in humans. In those cases, a threshold that was moderately more extreme

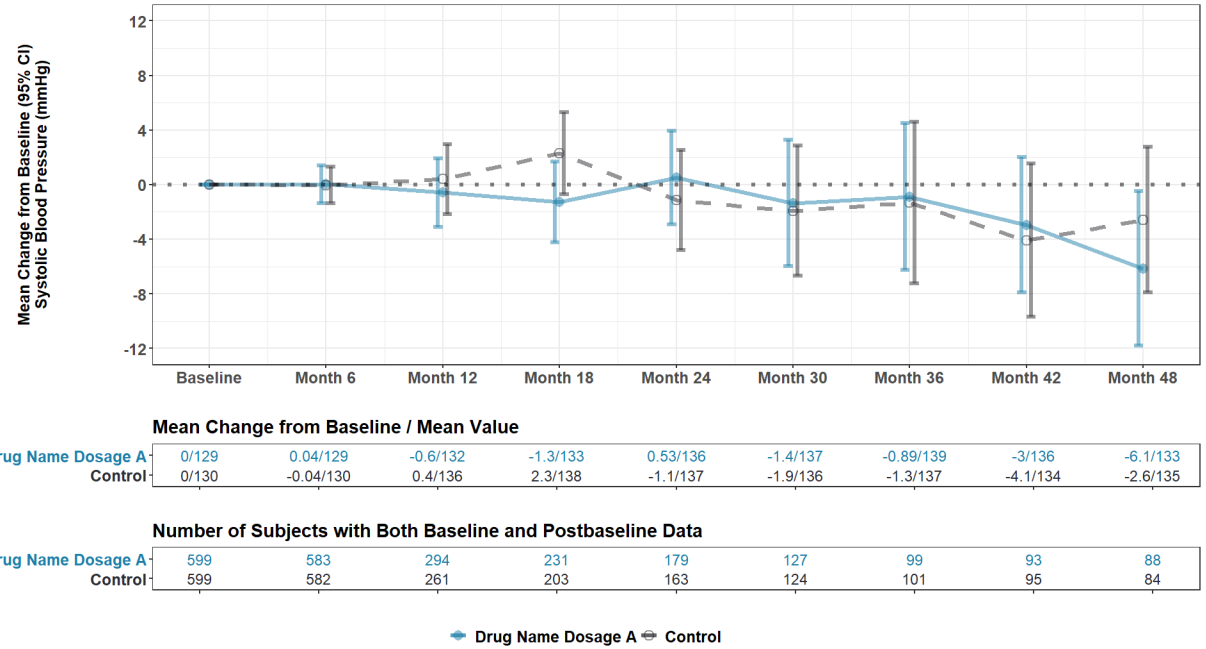
than the previously documented result was selected. This was done to minimize the chance that results reported in trials or studies would be inappropriately determined to be too extreme to be correct. For instance, the highest documented human body temperature identified by literature search is approximately 115º F. Based on that information, a threshold of 120º F was selected.

Customization

N/A

Example Figure

Figure 9. Mean Vital Sign Data Change From Baseline Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Note: If a timepoint is reached where there are only a few subjects remaining in the trial (e.g., less than 5%), consideration should be made to truncate this graph as the results would not be considered a reliable indicator of the true mean.
Note: Vital sign results obtained during unscheduled trial visits that occur outside of a protocol-specified visit window are in the data for the nearest protocol-specified visit.
Note: Subjects with both baseline and postbaseline data available are included in the mean change from baseline calculations at each visit. The number of subjects reflects only those included in the mean change from baseline calculations, rather than the total number of subjects.

Note: The vertical bars shown on the plotted lines indicates the 95% confidence interval of probability of incidence at the corresponding time points.
Abbreviations: CI, confidence interval.

2.5.2. Outlier Analyses

2.5.2.1. Median and Interquartile Range of Vital Sign Data Over Time by Treatment Arm

Background and Instructions

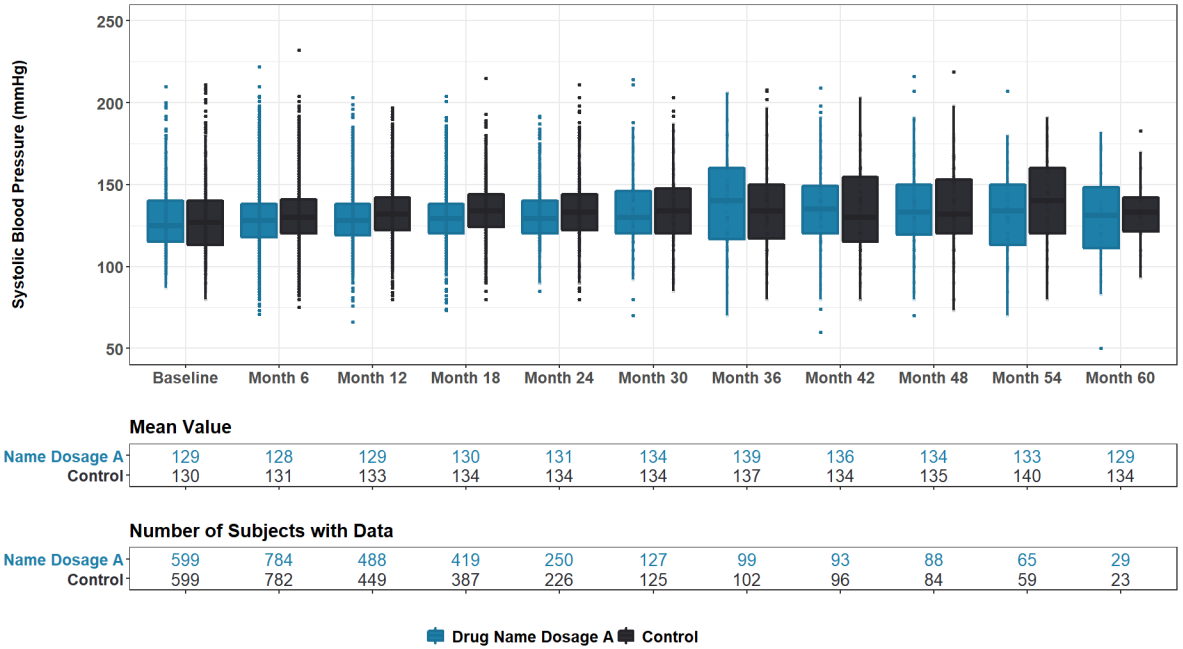
Figure 10: Median and Interquartile Range of Vital Sign Data Over Time will be generated from data for each of the following: systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature.

Customization

N/A

Example Figure

Figure 10. Box Plot: Median and Interquartile Range of Vital Sign Data Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers =1.5X the interquartile range; individual outliers are those beyond this range.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].

2.6. Open-Label Extension

Open-label extension (OLE) data may be used to identify rare AEs that require large amounts of exposure to identify a single incidence or only become apparent with a longer exposure duration (e.g., malignancies). Relative to safety data generated from adequate and well-controlled trials, interpretation of safety from OLE periods (refer to definition in Section 2.6.1 Definition of Open-Label Extension) may be limited by the lack of blinding, the lack of a randomized, concurrent control group, differences in information ascertainment (e.g., frequency of visits), and participant dropout. Examples shell tables and figures focus on AE data, but similar approaches and considerations can be applied to other dataset domains (e.g., laboratory data, vital sign data).

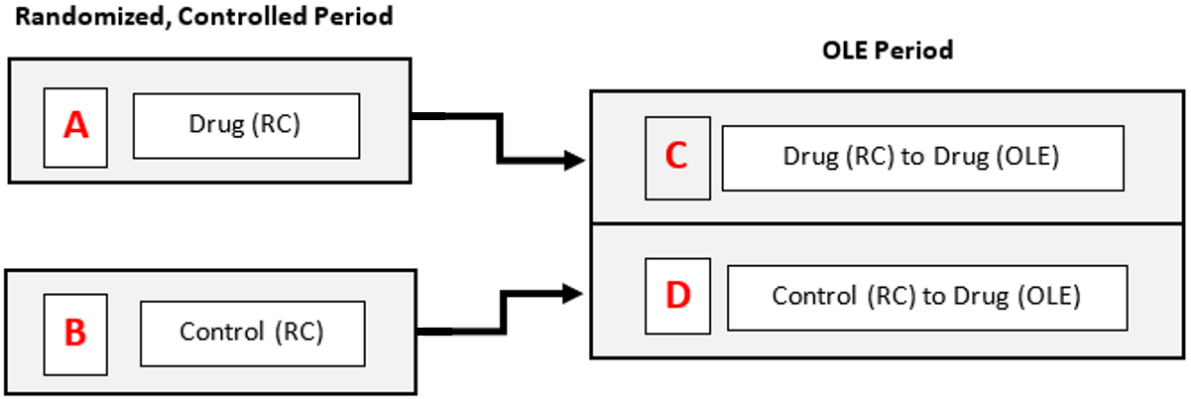
2.6.1. Definition of Open-Label Extension

For purposes of this guide, the OLE period is considered to occur after an RC period of a trial on which the primary efficacy comparisons are based, either as part of the trial or as a separate OLE trial.

Consider the following trial design in which subjects are randomized to drug or control and treated for a fixed period of time (e.g., 24 weeks); after completing the RC period of the trial, subjects may enroll in the OLE period, where all subjects receive study drug in an open-label manner.[8] The trial design shown in Diagram 2 is utilized for the following discussion and example tables and figures, as it is commonly used in chronic treatment settings.

[8] It is worth noting that there are other alternate OLE designs, which would require specific analysis considerations.

Diagram 2. Example Trial Design With an Open-Label Extension Period



2.6.2. Identify Safety Signals in Open-Label Extension Data

Open-label data may be used to evaluate unexpected safety signals and latent signals that require prolonged exposure. The following sections outline these approaches to evaluate OLE data for signal detection.

2.6.2.1. Detection of Unexpected Safety Signals

Unexpected safety signals may include signals that do not occur naturally in the population enrolled (e.g., heart failure in adolescents) or those that are not expected to occur unless exposed to drug (e.g., Stevens-Johnson Syndrome).

2.6.2.1.1. Subjects Receiving Study Drug With Potential Adverse Reactions Identified by the Review Team by System Organ Class and Preferred Term

Background and Instructions

Table 23: Subjects Receiving Study Drug With Potential Adverse Reactions is an example shell table based on MedDRA hierarchy; the granular nature of MedDRA PTs may be useful to assess for very rare AEs. The output table should inform identification of potential adverse reactions that the review team determines are very unlikely to occur naturally in the population studied or are not expected to

occur unless exposed to drug. Once a signal is identified, further characterization will be needed, and additional figures can be generated (refer to Section 2.6.3 Characterization of Safety Outcomes Over Time).

Customization

Consider using OCMQs or other custom grouping of MedDRA PTs. Depending on the trial design, output tables may need to be customized according to discussions with statistics on appropriate analyses.

Example Table

Table 23. Subjects Receiving Study Drug With Potential Adverse Reactions Identified by the Review Team by System Organ Class and Preferred Term, Pooled Analysis of Trial X, Randomized, Controlled Plus Open-Label Extension

System Organ Class Preferred Term	Drug Name[1] Dosage A N=XXX n (IR)[2] [95% CI]
SOC1	
PT1	x (y) [Y, Z]
PT2	x (y) [Y, Z]
SOC2	
PT1	x (y) [Y, Z]
PT2	x (y) [Y, Z]

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration is [e.g., X week randomized, controlled period or median and a range indicating pooled trial durations].
[1] Groups A + C + D based on Diagram 2
[2] IR = incidence rate (expressed per 100 PY), where exposure is calculated from first drug exposure until the time of an incident event for subjects that experience an event or the end of follow-up for subjects that do not experience an event.
Abbreviations: CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects receiving drug; n, number of subjects with at least one event; OLE, open-label extension, PT, preferred term; PY, person-years; SOC, system organ class.

2.6.2.2. Detection of Safety Signals With Prolonged Exposure

Prolonged exposure to a study drug may reveal rare safety signals not seen during the RC period, especially for outcomes with a longer latency time (e.g., fractures, malignancy).

- Consider including a table in an appendix of the review document using a cut-point percentage to present the original data that was reviewed to generate the adverse reaction table reviewed by the team (Refer to Optional Table Shells, Subjects Receiving Study Drug With Common Adverse Events with Incidence Rate ≥X by System Organ Class and Preferred Term (Only OLE Data) or

Subjects Receiving Study Drug With Common Adverse Events with Incidence Rate ≥X by System Organ Class and Preferred Term (All Data from At-Risk Time)).

2.6.2.2.1. Approach 1 - Subjects Receiving Study Drug With Potential Adverse Reactions Identified by the Review Team (Only OLE Data from Subjects Randomized to Drug)

Background and Instructions

Table 24: Subjects Receiving Study Drug With Potential Adverse Reactions is an example shell table based on MedDRA hierarchy; the granular nature of MedDRA PTs may be useful to assess for very rare AEs. Use this table when incorporating only OLE data from subjects randomized to drug (group C in Diagram 2).

The output table should inform assessment of AE rate(s) during long-term exposure (group C in Diagram 4) using the short-term RC period (group A in Diagram 4) incident rate(s) as reference for qualitative assessment. Remember that these are not direct comparisons given the significant differences in the populations. Once a signal is identified, further characterization will be needed, and additional figures can be generated (refer to Section 2.6.3 Characterization of Safety Outcomes Over Time).

Customization

May also consider using OCMQs or other custom grouping of MedDRA PTs. Depending on the trial design, output tables may need to be customized according to discussions with statistics on appropriate analyses.

Example Table

Table 24. Subjects Receiving Study Drug With Potential Adverse Reactions Identified by the Review Team by System Organ Class and Preferred Term, Trial X, Randomized, Controlled and Open-Label Extension Periods (Only OLE Data)

System Organ Class Preferred Term	Drug (RC)[1] N=XXX n (IR)[3] [95% CI]	Drug (OLE)[2] N=XXX n (IR)[3] [95% CI]
SOC1		
PT1	x (y) [Y, Z]	x (y) [Y, Z]
PT2	x (y) [Y, Z]	x (y) [Y, Z]

SOC2		
PT1	x (y) [Y, Z]	x (y) [Y, Z]
PT2	x (y) [Y, Z]	x (y) [Y, Z]

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration is [e.g., X week randomized, controlled period or median and a range indicating pooled trial durations].
[1] Group A based on Diagram 2
[2] Group C based on Diagram 2
[3] IR = incidence rate (expressed per 100 PY), where exposure is calculated from first drug exposure until the time of an incident event for subjects that experience an event or the end of follow-up for subjects that do not experience an event.
Abbreviations: CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; OLE, open-label extension; PT, preferred term; PY, person-years; RC, randomized, controlled; SOC, system organ class.

2.6.2.2.2. Approach 2 - Subjects Receiving Study Drug With Potential Adverse Reactions Identified by the Review Team (All Data From At-Risk Time on Drug)

Background and Instructions

Table 25: Subjects Receiving Study Drug With Potential Adverse Reactions is an example shell table based on MedDRA hierarchy; the granular nature of MedDRA PTs may be useful to assess for very rare AEs. Use this table when incorporating all data from at-risk time on drug in the analysis, including data from both the on-drug RC period and the OLE period (i.e., including all subjects receiving at least one dose of drug, groups A + C + D based on Diagram 2).

The output table should inform assessment of AE rate(s) during all at-risk time on drug (groups A + C + D based on Diagram 2) using the short-term RC period (group A in Diagram 4) incident rate(s) as reference for qualitative assessment. Remember that these are not direct comparisons given the significant differences in the populations. Once a signal is identified, further characterization will be needed, and additional figures can be generated (refer to Section 2.6.3 Characterization of Safety Outcomes Over Time).

Customization

Consider using OCMQs or other custom grouping of MedDRA PTs. Depending on the trial design, output tables may need to be customized according to discussions with statistics on appropriate analyses.

Example Table

Table 25. Subjects Receiving Study Drug With Potential Adverse Reactions Identified by the Review Team by System Organ Class and Preferred Term, Trial X, Randomized, Controlled and Open-Label Extension Periods (All Data from At-Risk Time)

System Organ Class Preferred Term	Drug (RC)[1] N=XXX n (IR)[3] [95% CI]	All Subjects Receiving Drug[2] N=XXX n (IR)[3] [95% CI]
SOC1		
PT1	x (y) [Y, Z]	x (y) [Y, Z]
PT2	x (y) [Y, Z]	x (y) [Y, Z]
SOC2		
PT1	x (y) [Y, Z]	x (y) [Y, Z]
PT2	x (y) [Y, Z]	x (y) [Y, Z]

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration is [e.g., X week randomized, controlled period or median and a range indicating pooled trial durations].
[1] Group A based on Diagram 2
[2] Groups A+C+D based on Diagram 2
[3] IR = incidence rate (expressed per 100 PY), where exposure is calculated from first drug exposure until the time of an incident event for subjects that experience an event or the end of follow-up for subjects that do not experience an event.
Abbreviations: CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; OLE, open-label extension, PT, preferred term; RC, randomized, controlled; SOC, system organ class.

2.6.3. Characterization of Safety Outcomes Over Time

Characterizing safety outcomes over time may include exploring whether there are events with notable changes in incidence rate after longer exposure to the drug.

2.6.3.1. Cumulative Incidence of [Adverse Event] Over Time With Pointwise 95% Confidence Interval

Background and Instructions

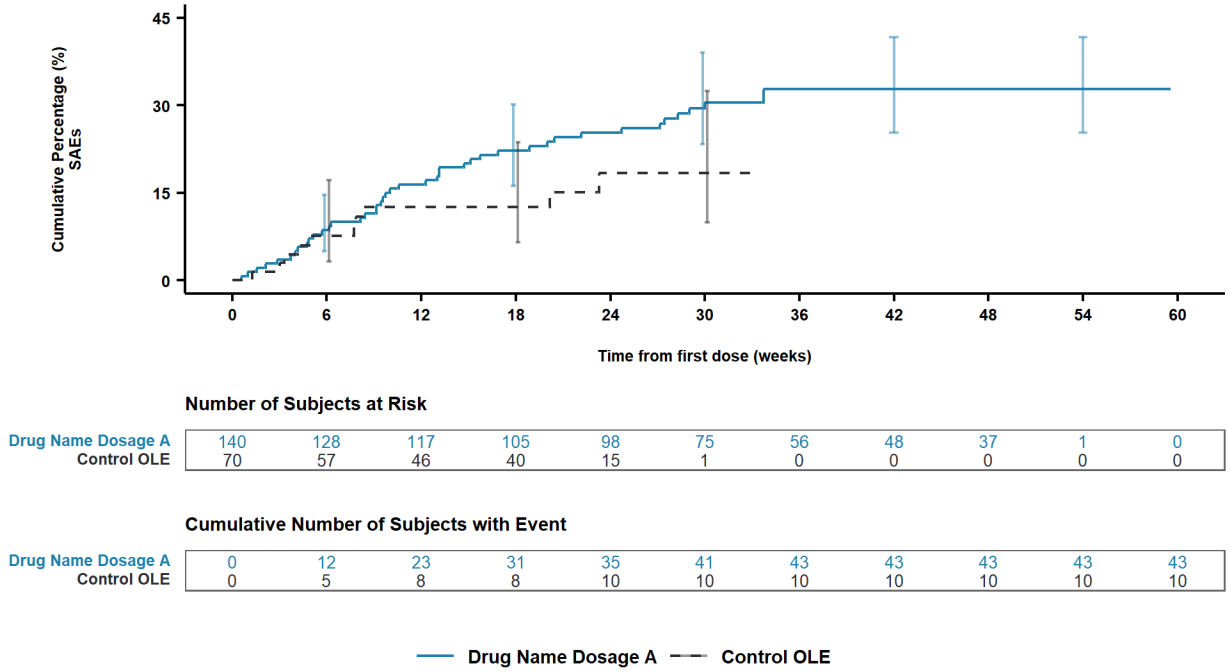
Figure 11: Kaplan-Meier Plot: Cumulative Incidence of [Adverse Event] Over Time figure depicts a K-M curve for the cumulative probability of a selected AE occurring over time along with pointwise 95% confidence intervals. The curve for the Control period ends at the end of the RC period. The presentation of data will need to be tailored to how the analysis is conducted.

Customization

N/A

Example Figure

Figure 11. Kaplan-Meier Plot: Cumulative Incidence of [Adverse Event] Over Time With Pointwise 95% Confidence Interval, Trial X, Randomized, Controlled Plus Open-Label Extension



Source: [include Applicant source, datasets and/or software tools used].
Note: This figure depicts Kaplan-Meier estimates (log-rank test) of the cumulative percentage of subjects that experience a specified AE by a given time point. AE start day was used as event time.
Note: The vertical bars shown on the plotted lines indicates the 95% confidence interval of probability of incidence at the corresponding time points.
Abbreviations: AE, adverse event; OLE, open-label extension; SAE, serious adverse event.

2.6.3.2. Rate of [Adverse Event] Over Time

Background and Instructions

Figure 12: Rate of [Adverse Event] Over Time depicts incidence rates (per 100 person years) of [adverse event] on drug, and associated 95% confidence intervals, within various time intervals. Such a presentation of the [adverse event] rate over time allows one to readily visualize and identify changes in rates over time.

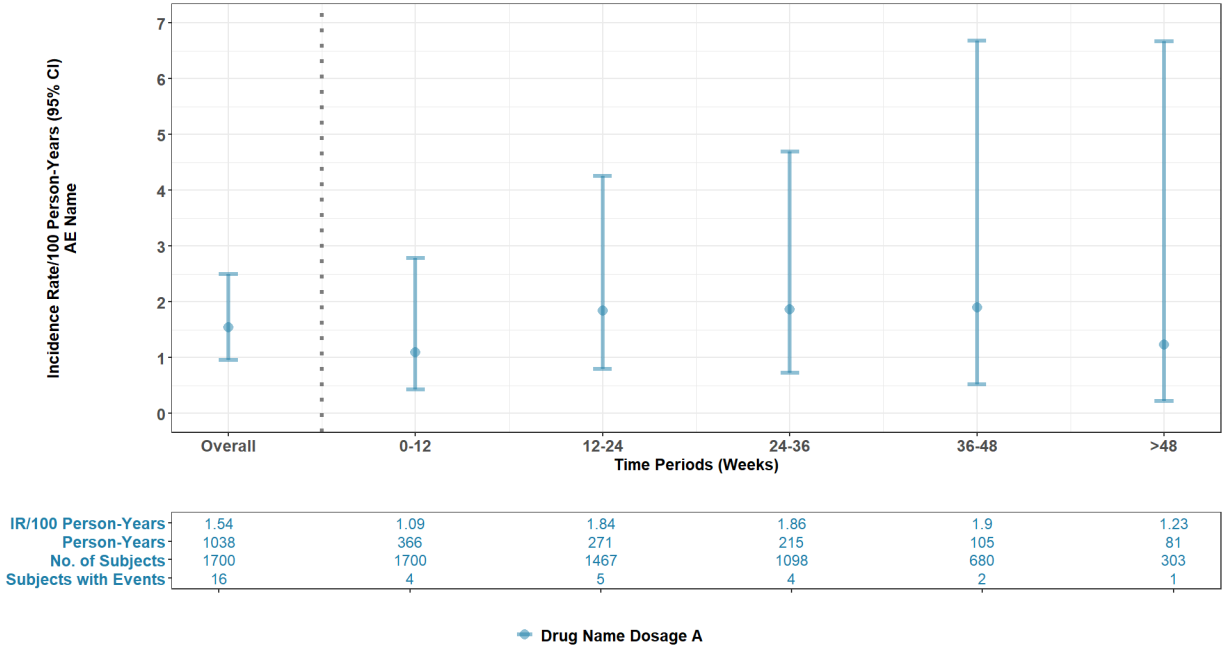
A summary of rates over time with confidence intervals should be customized to the trial setting for which it is being applied. This includes, but is not limited to, choice of time interval and whether to include exposure to treatment in subjects initially randomized to control (i.e., whether to include group D from Diagram 2) in the calculation. Time intervals should be set at relevant times for the drug development program.

Customization

Consider using alternative model-based approaches to estimate changes in rates over time with statistical input.

Example Figure

Figure 12. Rate of [Adverse Event] Over Time, Trial X, Randomized, Controlled Plus Open-Label Extension



Source: [include Applicant source, datasets and/or software tools used].
Note: The vertical bars shown indicate the 95% confidence interval of probability of incidence at the corresponding time points.
Abbreviations: AE, adverse event; CI, confidence interval.

2.6.4. Optional Table Shells

Objective table listings for common AEs from the available open-label data may be included in an appendix of the review document to present the objective data that was reviewed by the team.

2.6.4.1. Subjects Receiving Drug With Common Adverse Events with Incidence Rate ≥X by System Organ Class and Preferred Term

Background and Instructions

Table 26: Subjects Receiving Study Drug With Common Adverse Events With Incidence Rate ≥X below is an example shell table based on MedDRA hierarchy for common AEs; the granular nature of MedDRA PTs may be useful to assess for very rare AEs. The output table should inform identification of potential adverse reactions that the review team determines are very unlikely to occur naturally in the population studied or are not expected to occur unless exposed to drug.

Customization

May also consider using OCMQs or other custom grouping of MedDRA PTs. Depending on the trial design, output tables may need to be customized according to discussions with statistics on appropriate analyses.

Example Table

Table 26. Subjects Receiving Study Drug With Common Adverse Events With Incidence Rate ≥X by System Organ Class and Preferred Term, Pooled Analysis of Trial X, Randomized, Controlled Plus Open-Label Extension

System Organ Class Preferred Term	Drug Name[1] Dosage A N=XXX n (IR)[2] [95% CI]
SOC1	
PT1	x (y) [Y, Z]
PT2	x (y) [Y, Z]
SOC2	
PT1	x (y) [Y, Z]
PT2	x (y) [Y, Z]

System Organ Class Preferred Term	Drug Name[1] Dosage A N=XXX n (IR)[2] [95% CI]
SOC3	
PT1	x (y) [Y, Z]
PT2	x (y) [Y, Z]

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration is [e.g., X week randomized, controlled period or median and a range indicating pooled trial durations].
[1] Groups A + C + D based on Diagram 2
[2] IR = incidence rate (expressed per 100 PY), where exposure is calculated from first drug exposure until the time of an incident event for subjects that experience an event or the end of follow-up for subjects that do not experience an event.
Abbreviations: AE, adverse event; CI, confidence interval; IR, incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects receiving drug; n, number of subjects with at least one event; OLE, open-label extension, PT, preferred term; PY, person-years; SOC, system organ class.

2.6.4.2. Subjects Receiving Study Drug With Common Adverse Events with Incidence Rate ≥X by System Organ Class and Preferred Term (Only OLE Data)

Background and Instructions

Table 27: Subjects Receiving Study Drug With Common Adverse Events With Incidence Rate ≥X (Only OLE Data) below is an example shell table based on MedDRA hierarchy for common AEs; the granular nature of MedDRA PTs may be useful to assess for very rare AEs. Use this table when incorporating only OLE data from subjects randomized to drug (group C in Diagram 2).

The output table should inform assessment of AE rate(s) during the long-term exposure (group C in Diagram 2) using the short-term RC period (group A in Diagram 2) incident rate(s) as reference for qualitative assessment. Remember that these are not direct comparisons given the significant differences in the populations.

Customization

Consider using OCMQs or other custom grouping of MedDRA PTs. Depending on the trial design, output tables may need to be customized according to discussions with statistics on appropriate analyses.

Example Table

Table 27. Subjects Receiving Study Drug With Common Adverse Events With Incidence Rate ≥X by System Organ Class and Preferred Term, Trial X, Randomized, Controlled and Open-Label Extension Periods (Only OLE Data)

System Organ Class Preferred Term	Drug (RC)[1] N=XXX n (IR)[3] [95% CI]	Drug (OLE)[2] N=XXX n (IR)[3] [95% CI]
SOC1		
PT1	x (y) [Y, Z]	x (y) [Y, Z]
PT2	x (y) [Y, Z]	x (y) [Y, Z]
SOC2		
PT1	x (y) [Y, Z]	x (y) [Y, Z]
PT2	x (y) [Y, Z]	x (y) [Y, Z]
SOC3		
PT1	x (y) [Y, Z]	x (y) [Y, Z]
PT2	x (y) [Y, Z]	x (y) [Y, Z]

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration is [e.g., X week randomized, controlled period or median and a range indicating pooled trial durations].
[1] Group A based on Diagram 2
[2] Group C based on Diagram 2
[3] IR = incidence rate (expressed per 100 PY), where exposure is calculated from first drug exposure until the time of an incident event for subjects that experience an event or the end of follow-up for subjects that do not experience an event.
Abbreviations: AE, adverse event; CI, confidence interval; IR, incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; OLE, open-label extension, PT, preferred term; PY, person-years; RC, randomized, controlled; SOC, system organ class.

2.6.4.3. Subjects Receiving Study Drug With Common Adverse Events with Incidence Rate ≥X by System Organ Class and Preferred Term (All Data from At-Risk Time)

Background and Instructions

Table 28: Subjects Receiving Study Drug With Common Adverse Events With Incidence Rate ≥X (All Data from At-Risk Time) is an example shell table based on MedDRA hierarchy for; the granular nature of MedDRA PTs may be useful to assess for very rare AEs. Use this table when the durations of the RC and OLE periods are the same. Use this table when incorporating all data from at-risk time on drug in the analysis, including data from both the on-drug RC period and the OLE period (i.e., including all subjects receiving at least one dose of drug, groups A + C + D based on Diagram 2).

The output table should inform assessment of AE rate(s) during all at-risk time on drug (groups A + C + D based on Diagram 2) using the short-term RC period (group A in Diagram 2) incident rate(s) as reference for qualitative assessment. Remember that these are not direct comparisons given the significant differences in the populations.

Customization

May also consider using OCMQs or other custom grouping of MedDRA PTs. Depending on the trial design, output tables may need to be customized according to discussions with statistics on appropriate analyses.

Example Table

Table 28. Subjects Receiving Study Drug With Common Adverse Events With Incidence Rate ≥X by System Organ Class and Preferred Term, Trial X, Randomized, Controlled and Open-Label Extension Periods (All Data from At-Risk Time)

System Organ Class Preferred Term	Drug (RC)[1] N=XXX n (IR)[3] [95% CI]	All Subjects Receiving Drug[2] N=XXX n (IR)[3] [95% CI]
SOC1		
PT1	x (y) [Y, Z]	x (y) [Y, Z]
PT2	x (y) [Y, Z]	x (y) [Y, Z]
SOC2		
PT1	x (y) [Y, Z]	x (y) [Y, Z]
PT2	x (y) [Y, Z]	x (y) [Y, Z]
SOC3		
PT1	x (y) [Y, Z]	x (y) [Y, Z]
PT2	x (y) [Y, Z]	x (y) [Y, Z]

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration is [e.g., X week randomized, controlled period or median and a range indicating pooled trial durations].
[1] Group A based on Diagram 2
[2] Groups A+C+D based on Diagram 2
[3] IR = incidence rate (expressed per 100 PY), where exposure is calculated from first drug exposure until the time of an incident event for subjects that experience an event or the end of follow-up for subjects that do not experience an event.
Abbreviations: AE, adverse event; CI, confidence interval; IR, incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; OLE, open-label extension, PT, preferred term; RC, randomized, controlled; SOC, system organ class.

3. Expanded Safety Tables and Figures

This section provides additional presentations of data showcased in Section 2 Core Safety Tables and Figures and is composed of four subsections: Expanded Summary of Trials Analyzed, Expanded Adverse Event Analyses, Expanded Laboratory Analyses and Expanded Vital Sign Analyses.

3.1. Expanded Summary of Trials Analyzed

The figure in this section contains more in-depth analyses of the tables and figures presented in the Core section to allow drill-down as needed This section follows the same guidance, as described in Section 2.1 Summary of Trials Analyzed.

3.1.1. Time to Last Follow-Up

Background and Instructions

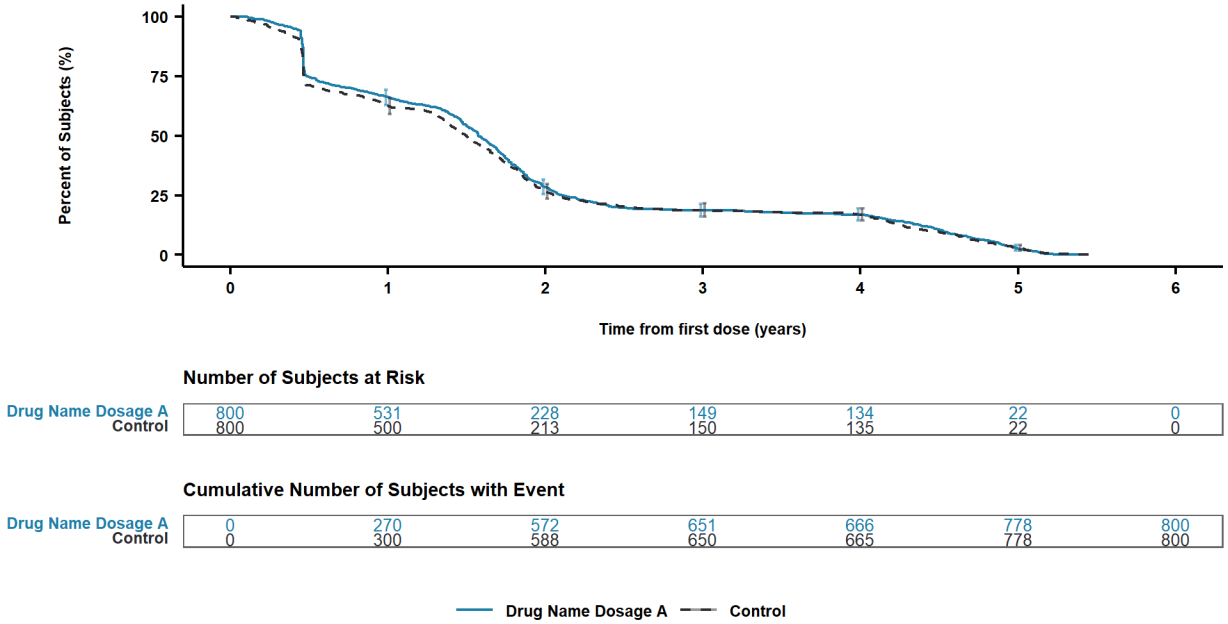
Figure 13: Kaplan Meier Plot: Time to Last Follow Up shows time to last follow-up throughout the trial. The period displayed in this figure should reflect the latest date with a record in the source dataset from study data submission.

Customization

N/A

Example Figure

Figure 13. Kaplan-Meier Plot: Time to Last Follow-Up, Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Last follow-up date defined as the last date with a record in source datasets.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Note: This figure depicts Kaplan-Meier estimates (log-rank test) of the cumulative percentage of subjects that lost follow-up by a given time point. The last recorded day was used as event time.
Note: The vertical bars shown on the plotted lines indicates the 95% confidence interval of probability of incidence at the corresponding time points.

3.2. Expanded Adverse Event Analyses

The tables in Section 3.2.1 Serious Adverse Events, Section 3.2.2 Adverse Events Leading to Treatment Discontinuation, and Section 3.2.3 General Adverse Events present either additional information or an alternate organization of the data. This section follows the same guidance, as described in Section 2.2 Adverse Event Analyses.

3.2.1. Serious Adverse Events

3.2.1.1. Subjects With Serious Adverse Events by Organ System, OND Custom Medical Queries (Narrow) and Preferred Term

Background and Instructions

Table 29: Subjects With Serious Adverse Events by Organ System presents preferred terms under each OCMQ listed in Table 11 Subjects With Serious Adverse Events by Organ System and OCMQ (Narrow), Safety Population, Pooled Analysis (or Trial X).

Customization

If deemed necessary, clinical reviewers may request CDS to add OCMQs (broad) to the table. Based on the assessment of the OCMQ results, clinical reviewers may request Table 41: Subjects With Select Narrow FDA Medical Queries from Section 4.1 Optional Adverse Event Analyses to explore the data for specific subjects.

Example Table

Table 29. Subjects With Serious Adverse Events by Organ System, OCMQ (Narrow) and Preferred Term, Safety Population, Pooled Analysis (or Trial X)

Organ System[1]	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[3,4]
Organ System 1			
OCMQ1	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
OCMQ2	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
Organ System 2			
OCMQ3	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
OCMQ4	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: SAEs classified by Applicant as [insert applicant's definition of SAE]
Note: Treatment-emergent AE defined as [definition].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Each OCMQ is aligned to a single organ system based on clinical judgment. Some OCMQs may contain terms from more than one MedDRA SOC.
[2] OCMQs include AEs that are not MedDRA PTs.
[3] Risk Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[4] Table display is ordered by the risk difference.
Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with at least one event; N, number of subjects in treatment arm,SOC, system organ class

3.2.2. Adverse Events Leading to Treatment Discontinuation

3.2.2.1. Subjects With Adverse Events Leading to Treatment Discontinuation by Organ System, OND Custom Medical Queries (Narrow) and Preferred Term

Background and Instructions

Table 30: Subjects With Adverse Events Leading to Discontinuation presents preferred terms under each OCMQ listed in Table 13: Subjects With Adverse Events Leading to Treatment Discontinuation by Organ System and OCMQ (Narrow), Safety Population, Pooled Analysis (or Trial X).

Customization

After reviewing Table 30 in the initial ST&F package, clinical reviewers may request CDS to add OCMQs (broad) to the table, if appropriate. Based on the assessment of the OCMQ results, clinical reviewers may request Table 41: Subjects With Select Narrow FDA Medical Queries from Section 4.1 Optional Adverse Event Analyses to explore the data for specific subjects.

Example Table

Table 30. Subjects With Adverse Events Leading to Treatment Discontinuation by Organ System, OCMQ (Narrow) and Preferred Term, Safety Population, Pooled Analysis (or Trial X)

Organ System[1]	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[3,4]
Organ System 1			
OCMQ1	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
Organ System 2			
OCMQ2	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)

Organ System[1] OCMQ (Narrow) Preferred Term[2]	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[3,4]
Organ System 3			
OCMQ3	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Each OCMQ is aligned to a single organ system based on clinical judgment. Some OCMQs may contain terms from more than one MedDRA SOC.
[2] OCMQs include AEs that are not MedDRA PTs.
[3] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[4] Table display is ordered by the risk difference.
Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with at least one event; N, number of subjects in treatment arm; SOC, system organ class.

3.2.3. General Adverse Events

3.2.3.1. Subjects With Adverse Events by Organ System, OND Custom Medical Queries (Narrow) and Preferred Term

Background and Instructions

Table 31: Subjects With Adverse Events by Organ System presents preferred terms under each OCMQ listed in Table 17: Incidence Rate Analysis, Safety Population, Pooled Analysis (or Trial X).

Customization

After analyzing, clinical reviewers may request to view this table for the broad OCMQs. Based on the assessment of the OCMQ results, clinical reviewers may request Table 41: Subjects With Select Narrow FDA Medical Queries from Section 4.1 Optional Adverse Event Analyses to explore the data for specific subjects.

Example Table

Table 31. Subjects With Adverse Events by Organ System, OCMQ (Narrow) and Preferred Term, Safety Population, Pooled Analysis (or Trial X)

Organ System[1]	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[3,4]
Organ System 1			
OCMQ1	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
Organ System 2			
OCMQ2	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Each OCMQ is aligned to a single organ system based on clinical judgment. Some OCMQs may contain terms from more than one MedDRA SOC.
[2] OCMQs include AEs that are not MedDRA PTs.
[3] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[4] Table display is ordered by the risk difference.
Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with at least one event; N, number of subjects in treatment arm; PT, preferred term; SOC, system organ class.

3.2.3.2. Subjects With Adverse Events by System Organ Class, Preferred Terms NOT Captured in OND Custom Medical Queries (Narrow)

Background and Instructions

Each OCMQ is composed of a listing of preferred terms that have a similar meaning to the medical concept represented by the OCMQ name. However, the OCMQs do not contain all PTs, so in addition to assessing the OCMQ results, it is important that clinical reviewers analyze either the individual PT findings provided in Table 14: Subjects With Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Analysis (or Trial X) or Table 15: Subjects With Common Adverse Events . Alternatively, clinical reviewers may choose to assess Table 32: Adverse Events by System Organ Class, Preferred Terms NOT Captured in , which presents only the PTs in the clinical trial data that are not included within any of the narrow OCMQs. Table 32 presents only the PTs in the data that are not included in any of the narrow OCMQs rather than both narrow and broad OCMQs because broad OCMQ analyses are not routinely provided within the ST&F package.

Customization

N/A

Example Table

Table 32. Subjects With Adverse Events by System Organ Class, Preferred Terms NOT Captured in OCMQs (Narrow), Safety Population, Pooled Analysis (or Trial X)

System Organ Class	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[1]
SOC1			
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
PT3	X (Y)	X (Y)	X (Y, Z)
SOC2			
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
PT3	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: AE, adverse event; CI, confidence interval; n, number of subjects with adverse event; N, number of subjects in treatment arm; PT, preferred term; SOC, system organ class.

3.2.3.3. Subjects With Adverse Events by Sex-Specific OND Custom Medical Queries (Narrow) and Preferred Term

Background and Instructions

Some OCMQs are relevant to only one sex. For instance, the Erectile Dysfunction OCMQ is relevant only to males, while the Abnormal Uterine Bleeding OCMQ is relevant only to females. Therefore, the tables that present these sex-specific OCMQs provide only the results for males or females, as appropriate, and have smaller denominators than the full safety population. Table 33: Adverse Events by Male Specific FDA Medical Query is limited to male-specific OCMQs and the male population. Table 34: Adverse Events by Female Specific FDA Medical Query is limited to female-specific OCMQs and the female population.

Customization

Clinical reviewers may request a similar table of AEs by male or female specific OCMQs (broad) from the CDS.

Example Table

Table 33. Subjects With Adverse Events by Male-Specific OCMQ (Narrow) and Preferred Term, Male Safety Population, Pooled Analysis (or Trial X)

OCMQ (Narrow) Preferred Term[1]	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[2]
Erectile dysfunction	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)
Gynecomastia	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] OCMQs include AEs that are not MedDRA PTs.
[2] Risk Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; MedDRA, Medical Dictionary for Regulatory Activities; n, number of male subjects with indicated OCMQ; N, number of subjects in treatment arm; N_s, number of male subjects with adverse event data.

Example Table

Table 34. Subjects With Adverse Events by Female-Specific OCMQ (Narrow) and Preferred Term, Female Safety Population, Pooled Analysis (or Trial X)

OCMQ (Narrow) Preferred Term[1]	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[2]
Abnormal uterine bleeding	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)

OCMQ (Narrow) Preferred Term[1]	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[2]
Amenorrhea	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)
Bacterial vaginosis	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)
Decreased menstrual bleeding	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)
Excessive menstrual bleeding	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] OCMQs include AEs that are not MedDRA PTs.
[2] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; MedDRA, Medical Dictionary for Regulatory Activities; n, number of female subjects with indicated OCMQ; N, number of subjects in treatment arm; N_s, number of female subjects with adverse event data.

3.3. Expanded Laboratory Analyses

The tables in Section 3.3.1 Laboratory Data Change Over Time from Baseline Expanded Analyses present more in-depth information from the Laboratory Data Change Over Time From Baseline Analyses (Section 2.4.2). This section follows the same guidance, as described in Section 2.4 Laboratory Analyses.

3.3.1. Laboratory Data Change Over Time From Baseline Expanded Analyses

Background and Instructions

The tables in this section provide more precise values for the data presented in Figure 6: Mean General Chemistry Data Change From Baseline Over Time .

- The *Mean Change from Baseline for General Chemistry Data Over Time by Treatment Arm* table will be generated with data for each of the following: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, glucose, calcium, magnesium, phosphate (mg/dL), protein (total), albumin, creatine phosphokinase, amylase, and lipase.
- Table 35: Mean Change From Baseline for Kidney Function Data Over Time will be generated with data for each of the following: creatinine, eGFR, and creatinine clearance.
- The *Mean Change from Baseline for Liver Biochemistry Data Over Time by Treatment Arm* table will be generated with data for each of the following: ALT, AST, ALP, TB, DB, gamma-glutamyl transpeptidase, and international normalized ratio.
- The *Mean Change from Baseline for Lipid Data Over Time by Treatment Arm* table will be generated with data for each of the following: total cholesterol, HDL, LDL, and triglycerides.
- The *Mean Change from Baseline for Hematology Data Over Time by Treatment Arm* table will be generated with data for each of the following: WBC count, hemoglobin, platelets, lymphocytes, neutrophils, eosinophils, prothrombin time, and activated partial thromboplastin.

Customization

Note that the primary analysis of interest in this table is the comparison of the mean change from baseline. Confidence intervals for individual time points can be requested.

Example Table

Table 35. Mean Change From Baseline for Kidney Function Data Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)

		Drug Name Dosage A N=XXX			Control N=XXX			
Parameter	Study Visit Time[1] (Study Day/Week/Month)	n (%) at Visit[3]	Mean	Mean Change From Baseline	n (%) at Visit[2]	Mean	Mean Change From Baseline	Difference in Mean Change (95% CI)[3]
Creatinine (mg/dL)	Baseline	X (Y)	X	N/A	X (Y)	X	N/A	N/A
	Week X	X (Y)	X	X	X (Y)	X	X	X (Y, Z)
	Week Y	X (Y)	X	X	X (Y)	X	X	X (Y, Z)
eGFR (mL/min/1.73 m^2)	Baseline	X (Y)	X	N/A	X (Y)	X	N/A	N/A
	Week X	X (Y)	X	X	X (Y)	X	X	X (Y, Z)
	Week Y	X (Y)	X	X	X (Y)	X	X	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] The time frame (e.g., by day, week, month) that corresponds best with the prespecified visit # is used as the study visit (± protocol-defined # days).
[2] n (%) at Visit refer to subjects with both baseline and postbaseline central lab data
[3] Difference in mean change is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; n, number of subjects meeting criteria; N, number of subjects in treatment arm.

3.4. Expanded Vital Sign Analyses

The tables in Section 3.4.1 Outlier Analyses present more in-depth outlier information compared to the Outlier Analyses boxplots (Section 2.5.2). This section follows the same guidance as described in Section 2.5 Vital Signs.

3.4.1. Outlier Analyses

This section contains generalized vital sign abnormality threshold cutoff criteria associated with each level. This may be used to assess the severity of abnormalities and identify important outliers. It is recommended to include the percentage of subjects with abnormality level criteria at any time during the trial and within a specific time frame. To determine this time frame, consider trial design, drug half-life, concomitant medications, or other factors that may be important for assessment.

3.4.1.1. Subjects With Maximum Postbaseline Systolic Blood Pressure by Category of Blood Pressure

Background and Instructions

Subject counts are cumulative for each abnormality threshold.

Customization

Clinical review team may customize the cutoff criteria they wish to use.

Example Table

Table 36. Subjects With Maximum Postbaseline Systolic Blood Pressure by Category of Blood Pressure, Safety Population, Pooled Analysis (or Trial X)

Systolic Blood Pressure (mm Hg)	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[1]
<90	X/Y (Z)	X/Y (Z)	X (Y, Z)
≥90	X/Y (Z)	X/Y (Z)	X (Y, Z)
≥120	X/Y (Z)	X/Y (Z)	X (Y, Z)
≥140	X/Y (Z)	X/Y (Z)	X (Y, Z)
≥160	X/Y (Z)	X/Y (Z)	X (Y, Z)
≥180	X/Y (Z)	X/Y (Z)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Note: Subject counts are cumulative for each abnormality threshold.
Abbreviations: CI, confidence interval; n, number of subjects meeting the specified criteria; N, number of subjects in treatment arm; N_s, number of subjects in treatment arm with available blood pressure data.

3.4.1.2. Subjects With Maximum Postbaseline Diastolic Blood Pressure by Category of Blood Pressure

Background and Instructions

Subject counts are cumulative for each abnormality threshold.

Customization

Clinical review team may customize the cutoff criteria they wish to use.

Example Table

Table 37. Subjects With Maximum Postbaseline Diastolic Blood Pressure by Category of Blood Pressure, Safety Population, Pooled Analysis (or Trial X)

Diastolic Blood Pressure (mm Hg)	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[1]
<60	X/Y (Z)	X/Y (Z)	X (Y, Z)
≥60	X/Y (Z)	X/Y (Z)	X (Y, Z)
≥80	X/Y (Z)	X/Y (Z)	X (Y, Z)
≥90	X/Y (Z)	X/Y (Z)	X (Y, Z)
≥110	X/Y (Z)	X/Y (Z)	X (Y, Z)
≥120	X/Y (Z)	X/Y (Z)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Note: Subject counts are cumulative for each abnormality threshold.
Abbreviations: CI, confidence interval; n, number of subjects meeting the specified criteria; N, number of subjects in treatment arm; N_s, number of subjects in treatment arm with available blood pressure data.

3.4.1.3. Subjects Meeting Specific Postbaseline Hypotension Levels

Background and Instructions

N/A

Customization

Clinical review team may customize the cutoff criteria they wish to use.

Example Table

Table 38. Subjects Meeting Specific Postbaseline Hypotension Levels, Safety Population, Pooled Analysis (or Trial X)

Blood Pressure (mm Hg)	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[1]
SBP <90	X/Y (Z)	X/Y (Z)	X (Y, Z)
DBP <60	X/Y (Z)	X/Y (Z)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; n, number of subjects meeting the specified criteria; N, number of subjects in treatment arm; N_s, number of subjects in treatment arm. with available blood pressure data; SBP, systolic blood pressure.

4. Optional Safety Tables and Figures [Available Upon Request]

This section is not provided in the initial ST&F package from the CDS, but clinical reviewers may request a table and/or figure from it throughout the integrated assessment. Nonetheless, it is at the discretion of the review team what tables and figures from this section are included in their final clinical review.

This subsection contains four modules: Optional Adverse Event Analyses (Section 4.1), Optional Subgroup Analyses (Section 4.2), Optional Laboratory Analyses (Section 4.3), and Optional Vital Sign Analyses (Section 4.4). These modules either provide additional context to the data or visualize previously given tables or figures in a different manner. If, after receiving the ST&F package, the review team wishes to receive a table and/or figure from this section, they may make the request to the CDS either during the CDS interim meeting or throughout the integrated assessment process.

4.1. Optional Adverse Event Analyses

The tables and figures in Overview of Adverse Events (Section 4.1.1), Adverse Events Leading to Treatment Discontinuation (Section 4.1.2) and General Adverse Events (Section 4.1.3) can be requested at the discretion of the review team.

4.1.1. Overview of Adverse Events

4.1.1.1. Time to Onset of [Insert AE]

Background and Instructions

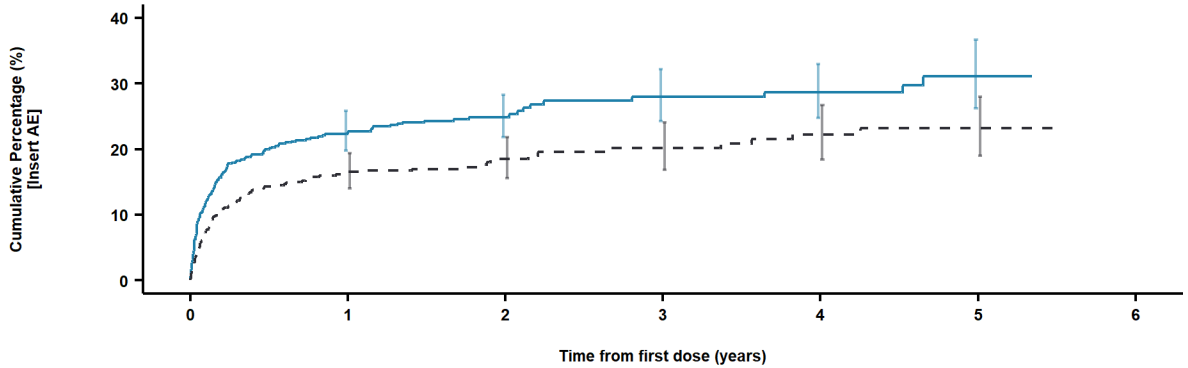
Figure 14: Kaplan Meier Plot: Time to Onset includes an example of time to onset for AEs leading to death.

Customization

Figure 14 can be created for each AE of interest, including time to onset for SAEs. The figure name should be updated to reflect the event being displayed.

Example Figure

Figure 14. Kaplan-Meier Plot: Time to Onset of [Insert AE], Safety Population, Pooled Analyses (or Trial X)



Number of Subjects at Risk

Drug Name Dosage A	800	406	168	115	104	14	0
Control	800	425	172	124	108	19	0

Cumulative Number of Subjects with Event

Drug Name Dosage A	0	173	183	189	190	192	192
Control	0	124	130	133	136	137	137

Drug Name Dosage A — Control

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Note: This figure depicts Kaplan-Meier estimates (log-rank test) of the cumulative percentage of subjects that experience an selected AE by a given time point. If a subject experienced more than one AEs, the earliest AE start day was used as event time.
Note: The vertical bars shown on the plotted lines indicates the 95% confidence interval of probability of incidence at the corresponding time points.
Abbreviations: AE, adverse event.

4.1.2. Adverse Events Leading to Treatment Discontinuation

Background and Instructions

N/A

Customization

All subject listings can be customized to have columns added or removed to display the most relevant information.

Example Table

Table 39. Listing of Subjects With Adverse Events Leading to Treatment Discontinuation, Safety Population, Pooled Analysis (or Trial X)

Treatment Arm	Unique Subject Identifier	Age	Sex	AE Day of Onset	Study Day of Last Dosage of Study Drug	MedDRA PT	Verbatim Term	Serious[1]	Severity[2]
Drug A	X	X	X	X	X	PT1	VT1	Y/N	X
Drug B	Y	X	X	X	X	PT2	VT2	Y/N	X
Drug C	Z	X	X	X	X	PT3	VT3	Y/N	X

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] SAEs classified by Applicant as [insert applicant's definition of SAE]
[2] Severity scale as defined by the protocol.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, no; PT, preferred term; SAE, serious adverse event; VT, verbatim term; Y, yes.

4.1.3. General Adverse Events

4.1.3.1. Adverse Events Occurring at ≥ X% in Drug-Treated Group and ≥ Y% More in Drug-Treated Group Than Control Group

Background and Instructions Table 40: Adverse Events Occurring at ≥X% in Drug-Treated Group provides a starting point for the adverse reactions table to be included in section 6.1 in the labeling document.

Customization

The clinical reviewer may adjust the cutoffs as deemed necessary (e.g., ≥5% in drug-treated group and ≥2% more in the drug-treated group than the control group).

Example Table

Table 40. Adverse Events Occurring at ≥X% in Drug-Treated Group and ≥Y% More in Drug-Treated Group Than Control Group, Safety Population, Pooled Analysis (or Trial X)

Preferred Term	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[1,2]
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
PT3	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[2] Table should display categories by risk difference and not by alphabetical order.
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with adverse event; N, number of subjects in treatment arm; PT, preferred term.

4.1.3.2. Listing of Subjects With Select Narrow OND Custom Medical Queries

Background and Instructions

Table 41: Listing of Subjects With Select Narrow FDA Medical Queries is an additional OCMQ table that displays subject-level data for specific subjects for the narrow OCMQs where an imbalance is noted.

Customization

All subject listings can be customized to have columns added or removed in order to display the most relevant information.

Example Table

Table 41. Listing of Subjects With Select Narrow OCMQs, Safety Population, Pooled Analysis (or Trial X)

OCMQ (Narrow)	Subject ID	Treatment Arm	MedDRA PT	Verbatim Term	Serious[1]	AE Leading to Treatment Discontinuation	Severity[2]	Study Day of Onset	Action Taken	AE Outcome
OCMQ1	Subject ID1	X	PT1	VT1	Y/N	X	X	X	X	X
	Subject ID2	X	PT1	VT1	Y/N	X	X	X	X	X
OCMQ2	Subject ID3	X	PT1	VT1	Y/N	X	X	X	X	X
	Subject ID4	X	PT1	VT1	Y/N	X	X	X	X	X

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] SAEs classified by Applicant as [insert applicant's definition of SAE]
[2] Severity scale as defined by the protocol.
Abbreviations: AE, adverse event; OCMQ; OND custom medical query; ID, identifier; MedDRA, Medical Dictionary for Regulatory Activities; N, no; PT, preferred term; VT, verbatim term; Y, yes.

4.1.3.3. Listing of Subjects With Select Broad OND Custom Medical Queries

Background and Instructions

Table 42: Listing of Subjects With Select Broad FDA Medical Queries is an additional OCMQ table that displays subject-level data for specific subjects for the broad OCMQs where an imbalance is noted.

Customization

All subject listings can be customized to have columns added or removed to display the most relevant information.

Example Table

Table 42. Listing of Subjects With Select Broad OCMQs, Safety Population, Pooled Analysis (or Trial X)

OCMQ (Broad)	Subject ID	Treatment Arm	MedDRA PT	Verbatim Term	Serious[1]	AE Leading to Treatment Discontinuation	Severity[2]	Study Day of Onset	Action Taken	AE Outcome
OCMQ1	Subject ID1	X	PT1	VT1	Y/N	X	X	X	X	X
	Subject ID2	X	PT1	VT1	Y/N	X	X	X	X	X
OCMQ2	Subject ID3	X	PT1	VT1	Y/N	X	X	X	X	X
	Subject ID4	X	PT1	VT1	Y/N	X	X	X	X	X

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Broad OCMQ analysis incorporates narrow OCMQ preferred terms to maximize sensitivity.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] SAEs classified by Applicant as [insert applicant's definition of SAE]
[2] Severity scale as defined by the protocol.
Abbreviations: AE, adverse event; OCMQ, OND custom medical query; ID, identifier; MedDRA, Medical Dictionary for Regulatory Activities; N, no; PT, preferred term; VT, verbatim term; Y, yes.

4.1.3.4. Subjects With Adverse Events by Organ System, OND Custom Medical Queries (Broad) and Preferred Term

Background and Instructions

N/A

Customization

N/A

Example Table

Table 43. Subjects With Adverse Events by Organ System, OCMQ (Broad) and Preferred Term, Safety Population, Pooled Analysis (or Trial X)

Organ System[1] OCMQ (Broad) Preferred Term[2]	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[3,4]
Organ System 1			
OCMQ1	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
OCMQ2	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
Organ System 2			
OCMQ3	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
OCMQ4	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Broad OCMQ analysis incorporates narrow OCMQ preferred terms to maximize sensitivity.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Each OCMQ is aligned to a single organ system based on clinical judgment. Some OCMQs may contain terms from more than one MedDRA SOC.
[2] OCMQs include AEs that are not MedDRA PTs.
[3] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[4] Table display is ordered by the risk difference.
Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with adverse event; N, number of subjects in treatment arm; PT, preferred term; SOC, system organ class.

4.1.3.5. Subjects With Adverse Events by Sex-Specific OND Custom Medical Queries (Broad) and Preferred Term

Background and Instructions

Some OCMQs are relevant to only one sex. For instance, the Erectile Dysfunction OCMQ is relevant only to males, while the Abnormal Uterine Bleeding OCMQ is relevant only to females. Therefore, the tables that present these sex-specific OCMQs provide only the results for males or females, as appropriate, and have smaller denominators than the full safety population. As discussed in Section 3.2.3.3 Subjects With Adverse Events by Sex-Specific OND Custom Medical Queries (Narrow) and Preferred Term, some OCMQs are

relevant to only one sex. Table 44: Adverse Events by Male Specific FDA Medical Query is limited to male-specific broad OCMQs and the male population. Table 45: Adverse Events by Female Specific FDA Medical Query is limited to female-specific broad OCMQs and the female population.

Customization

N/A

Example Table

Table 44. Subjects With Adverse Events by Male-Specific OCMQ (Broad) and Preferred Term, Male Safety Population, Pooled Analysis (or Trial X)

OCMQ (Broad) Preferred Term[1]	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[2,3]
Erectile dysfunction	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)
Gynecomastia	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Broad OCMQ analysis incorporates narrow OCMQ preferred terms to maximize sensitivity.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] OCMQs include AEs that are not MedDRA PTs.
[2] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[3] Table displays categories by risk difference.
Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom Medical query; MedDRA, Medical Dictionary for Regulatory Activities; n, number of male subjects with indicated OCMQ; N, number of subjects in treatment arm; N_s, number of male subjects with adverse event data.

Example Table

Table 45. Subjects With Adverse Events by Female-Specific OCMQ (Broad) and Preferred Term, Female Safety Population, Pooled Analysis (or Trial X)

OCMQ (Broad) Preferred Term[1]	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[2,3]
Abnormal uterine bleeding	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)
Amenorrhea	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)
Bacterial vaginosis	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)
Decreased menstrual bleeding	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)
Excessive menstrual bleeding	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT1	X/Y (Z)	X/Y (Z)	X (Y, Z)
PT2	X/Y (Z)	X/Y (Z)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Broad OCMQ analysis incorporates narrow OCMQ preferred terms to maximize sensitivity.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] OCMQs include AEs that are not MedDRA PTs.
[2] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[3] Table displays categories by risk difference.
Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; MedDRA, Medical Dictionary for Regulatory Activities; n, number of female subjects with indicated OCMQ; N, number of subjects in treatment arm; N_s, number of female subjects with adverse event data.

4.1.3.6. Subjects With Muscle Injury Algorithmic OCMQ

Background and Instructions

Table 46: Subjects With Muscle Injury Algorithmic FMQ includes all subjects with an AE of rhabdomyolysis or myoglobinuria, laboratory result of myoglobinuria, laboratory CPK level greater than 5x ULN, or the rhabdomyolysis triad of myalgia, muscular weakness, and chromaturia. More information on this algorithmic OCMQ can be found in the Muscle Injury TAG.

Customization

N/A

Example Table

Table 46. Subjects With Muscle Injury Algorithmic OCMQs, Safety Population, Pooled Analysis (or Trial X)

Algorithmic OCMQ Criterion	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[3,4]
Subjects with ≥1 algorithmic criterion	X (Y)	X (Y)	X (Y, Z)
Any muscle injury OCMQ narrow term	X (Y)	X (Y)	X (Y, Z)
Urine myoglobin > ULN	X (Y)	X (Y)	X (Y, Z)
CPK >5X ULN[1]	X (Y)	X (Y)	X (Y, Z)
Myalgia + weakness + chromaturia[2]	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used]
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] No CPK-MB/CPK >0.05 within 3 days nor CPK >ULN at baseline.
[2] [PT myalgia + PT muscular weakness + (PT myoglobin urine present or PT chromaturia)] within 7 days.
[3] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[4] Table display is ordered by the risk difference.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; OCMQ, OND custom medical query; MB, myocardial band; n, number of subjects meeting criteria; N, number of subjects in group; ULN, upper limit of normal.

4.1.3.7. Subjects With Hypoglycemia Algorithmic OCMQ

Background and Instructions

The hypoglycemia algorithmic OCMQ is intended to identify a signal of potential hypoglycemia. Table 47: Subjects With Hypoglycemia Algorithmic FMQ includes all subjects with any hypoglycemia adverse event, plasma glucose below a specified value or a combination of low glucose and adverse event terms within or without a specified time. The table displays a subgroup analysis by subjects with and without history of diabetes mellitus. Data quality of the medical history dataset may require discussion with the CDS.

If the combination of adverse event terms and plasma glucose shows a significant effect, a clinical reviewer may want to request a list of the PTs that qualified the subject.

Customization

N/A

Example Table

Table 47. Subjects With Hypoglycemia Algorithmic OCMQs, Safety Population, Pooled Analysis (or Trial X)

Population Algorithmic OCMQ Criterion	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[1]
Safety population	**X (Y)**	**X (Y)**	**X (Y, Z)**
Subjects with ≥1 algorithmic criterion	X (Y)	X (Y)	X (Y, Z)
Any hypoglycemia OCMQ narrow term	X (Y)	X (Y)	X (Y, Z)
Plasma glucose <54 mg/dL	X (Y)	X (Y)	X (Y, Z)
Hypoglycemia term[2] + plasma glucose <70 mg/dL[3]	X (Y)	X (Y)	X (Y, Z)
≥2 Hypoglycemia terms[2] + ≥2 episodes of plasma glucose <70 mg/dL	X (Y)	X (Y)	X (Y, Z)
No history of diabetes	**X (Y)**	**X (Y)**	**X (Y, Z)**
Subjects with ≥1 algorithmic criterion	X (Y)	X (Y)	X (Y, Z)
Any hypoglycemia OCMQ narrow term	X (Y)	X (Y)	X (Y, Z)
Plasma glucose <54 mg/dL	X (Y)	X (Y)	X (Y, Z)
Hypoglycemia term[2] + plasma glucose <70 mg/dL[3]	X (Y)	X (Y)	X (Y, Z)
≥2 Hypoglycemia terms[2] + ≥2 episodes of plasma glucose <70 mg/dL	X (Y)	X (Y)	X (Y, Z)

Population Algorithmic OCMQ Criterion	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[1]
History of diabetes	**X (Y)**	**X (Y)**	**X (Y, Z)**
Subjects with ≥1 algorithmic criterion	X (Y)	X (Y)	X (Y, Z)
Any hypoglycemia OCMQ narrow term	X (Y)	X (Y)	X (Y, Z)
Plasma glucose <54 mg/dL	X (Y)	X (Y)	X (Y, Z)
Hypoglycemia term[2] + plasma glucose <70 mg/dL[3]	X (Y)	X (Y)	X (Y, Z)
≥2 Hypoglycemia terms[2] + ≥2 episodes of plasma glucose <70 mg/dL	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[2] Includes any hypoglycemia OCMQ broad term that is not a hypoglycemia OCMQ narrow term or any of the following supplemental terms: accident, anxiety, asthenia, balance disorder, cold sweat, coma, confusional state, coordination abnormal, dysarthria, fall, fatigue, headache, hunger, hyperhidrosis, irritability, loss of consciousness, palpitations, road traffic accident, seizure, tremor, vision blurred, and visual impairment.
[3] Hypoglycemia term and plasma glucose level must occur within 7 days of each other.
Abbreviations: CI, confidence interval; OCMQ, OND custom medical query; n, number of subjects meeting criteria; N, number of subjects in group.

4.1.3.8. Subjects With Hyperglycemia Algorithmic OCMQ

Background and Instructions

The hyperglycemia algorithmic OCMQ is intended to identify a signal of potential hyperglycemia. Similar to the *Hypoglycemic Algorithmic OCMQ* table, this table displays a subgroup analysis of subjects with and without history of diabetes mellitus. Table 48. Subjects With Hyperglycemia Algorithmic OCMQs, Safety Population, Pooled Analysis (or Trial X) includes all subjects with any hyperglycemia adverse event, plasma glucose or HbA1c above a specific value or any new diabetes medication. Data quality of the medical history dataset may require discussion with the CDS.

Customization

N/A

Example Table

Table 48. Subjects With Hyperglycemia Algorithmic OCMQs, Safety Population, Pooled Analysis (or Trial X)

Population Algorithmic OCMQ Criterion	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[1]
Safety population	**X (Y)**	**X (Y)**	**X (Y, Z)**
Subjects with ≥1 algorithmic criterion	X (Y)	X (Y)	X (Y, Z)
Any hyperglycemia OCMQ narrow term	X (Y)	X (Y)	X (Y, Z)
Fasting plasma glucose ≥126 mg/dL	X (Y)	X (Y)	X (Y, Z)
≥2 plasma glucoses >180 mg/dL	X (Y)	X (Y)	X (Y, Z)
Any new diabetes concomitant medication	X (Y)	X (Y)	X (Y, Z)
Postbaseline HbA1c ≥6.5%	X (Y)	X (Y)	X (Y, Z)
HbA1c increase ≥0.3% with postbaseline HbA1c ≥5.7%	X (Y)	X (Y)	X (Y, Z)
Change from baseline fasting plasma glucose ≥20 mg/dL with postbaseline fasting plasma glucose >100 mg/dL	X (Y)	X (Y)	X (Y, Z)
No history of diabetes	**X (Y)**	**X (Y)**	**X (Y, Z)**
Subjects with ≥1 algorithmic criterion	X (Y)	X (Y)	X (Y, Z)
Any hyperglycemia OCMQ narrow term	X (Y)	X (Y)	X (Y, Z)
Fasting plasma glucose ≥126 mg/dL	X (Y)	X (Y)	X (Y, Z)
≥2 plasma glucoses >180 mg/dL	X (Y)	X (Y)	X (Y, Z)
Any new diabetes concomitant medication	X (Y)	X (Y)	X (Y, Z)
Postbaseline HbA1c ≥6.5%	X (Y)	X (Y)	X (Y, Z)
HbA1c increase ≥0.3% with postbaseline HbA1c ≥5.7%	X (Y)	X (Y)	X (Y, Z)
Change from baseline fasting plasma glucose ≥20 mg/dL with postbaseline fasting plasma glucose >100 mg/dL	X (Y)	X (Y)	X (Y, Z)
History of diabetes	**X (Y)**	**X (Y)**	**X (Y, Z)**
Subjects with ≥1 algorithmic criterion	X (Y)	X (Y)	X (Y, Z)
Any hyperglycemia OCMQ narrow term	X (Y)	X (Y)	X (Y, Z)
Fasting plasma glucose ≥126 mg/dL	X (Y)	X (Y)	X (Y, Z)
≥2 plasma glucoses >180 mg/dL	X (Y)	X (Y)	X (Y, Z)
Any new diabetes concomitant medication	X (Y)	X (Y)	X (Y, Z)
Postbaseline HbA1c ≥6.5%	X (Y)	X (Y)	X (Y, Z)
HbA1c increase ≥0.3% with postbaseline HbA1c ≥5.7%	X (Y)	X (Y)	X (Y, Z)
Change from baseline fasting plasma glucose ≥20 mg/dL with postbaseline fasting plasma glucose >100 mg/dL	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].

Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].

[1] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).

Abbreviations: CI, confidence interval; OCMQ, OND custom medical query; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; n, number of subjects with adverse event; N, number of subjects in treatment arm.

4.1.3.9. Subjects With Hypersensitivity Algorithmic OCMQ

Background and Instructions

The hypersensitivity algorithmic OCMQ was modeled after the MedDRA anaphylactic reactions algorithmic SMQ. Events of potential hypersensitivity can result in findings in different organ systems. Identifying overlapping, potentially related AEs from different organ systems could increase the sensitivity and specificity of identifying a systemic reaction of concern. A 7-day window was determined to be a reasonable maximum time frame between the onset of clinical manifestations of a hypersensitivity reaction.

Customization

N/A

Example Table

Table 49. Subjects With Hypersensitivity Algorithmic OCMQs, Safety Population, Pooled Analysis (or Trial X)

Algorithmic OCMQ Criterion	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[2,3]
Subjects with ≥1 algorithmic criterion[1]	X (Y)	X (Y)	X (Y, Z)
Any hypersensitivity OCMQ narrow term	X (Y)	X (Y)	X (Y, Z)
Respiratory + skin reaction	X (Y)	X (Y)	X (Y, Z)
Respiratory + systemic reaction	X (Y)	X (Y)	X (Y, Z)
Skin + systemic reaction	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Combinations of events must occur within 7 days of each other to qualify
[2] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[3] Table display is ordered by the risk difference.
Abbreviations: CI, confidence interval; OCMQ, OND custom medical query; n, number of subjects with adverse event; N, number of subjects in treatment arm.

4.2. Optional Subgroup Analyses

The tables in Section 4.2.1 Subgroup Analyses by Baseline Characteristics can be requested at the discretion of the review team.

4.2.1. Subgroup Analyses by Baseline Characteristics

4.2.1.1. Overview of Adverse Events by Demographic Subgroup

Background and Instructions

Table 50: Overview of Serious Adverse Events by Demographic Subgroup and Table 51: Overview of Adverse Events by Demographic Subgroup in this section display placeholder values for the demographic characteristics for subgroup analysis of SAEs and AEs. These placeholder values will change to reflect the values found in the clinical trial data. When CDISC-controlled terminology is used in the clinical trial data, the demographic characteristics in this table will reflect the controlled terminology.

Customization

Provide any additional potentially relevant subgroups beyond the standard demographic ones that may shed light on which subjects are most susceptible to the safety event (e.g., baseline diseases [e.g., cardiovascular disease or diabetes, or by CKD stage], concomitant medication, anthropometric characteristics [e.g., BMI]). The clinical reviewer should discuss appropriate age groups for the subgroup analysis with the CDS.

Example Tables

Table 50. Overview of Serious Adverse Events by Demographic Subgroup, Safety Population, Pooled Analysis (or Trial X)

Characteristic	Drug Name Dosage A N=XXX n/N_S (%)	Control N=XXX n/N_S (%)
Any SAE	X (Y)	X (Y)
Sex		
Male	X/Y (Z)	X/Y (Z)
Female	X/Y (Z)	X/Y (Z)

Characteristic	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)
Age group, years		
Group 1	X/Y (Z)	X/Y (Z)
Group 2	X/Y (Z)	X/Y (Z)
Group 3	X/Y (Z)	X/Y (Z)
Group 4	X/Y (Z)	X/Y (Z)
Race		
American Indian or Alaska Native	X/Y (Z)	X/Y (Z)
Asian	X/Y (Z)	X/Y (Z)
Black or African American	X/Y (Z)	X/Y (Z)
Multiple	X/Y (Z)	X/Y (Z)
Native Hawaiian or other Pacific Islander	X/Y (Z)	X/Y (Z)
White	X/Y (Z)	X/Y (Z)
Ethnicity		
Hispanic or Latino	X/Y (Z)	X/Y (Z)
Not Hispanic or Latino	X/Y (Z)	X/Y (Z)
Not reported or unknown	X/Y (Z)	X/Y (Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: SAEs classified by Applicant in [dataset].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: n, number of subjects with serious adverse event; N, number of subjects in treatment arm; N_s, total number of subjects for each specific subgroup; SAE, serious adverse event.

Table 51. Overview of Adverse Events by Demographic Subgroup, Safety Population, Pooled Analysis (or Trial X)

Characteristic	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)
Any AE	X (Y)	X (Y)
Sex		
Male	X/Y (Z)	X/Y (Z)
Female	X/Y (Z)	X/Y (Z)
Age group, years		
Group 1	X/Y (Z)	X/Y (Z)
Group 2	X/Y (Z)	X/Y (Z)
Group 3	X/Y (Z)	X/Y (Z)
Group 4	X/Y (Z)	X/Y (Z)

Characteristic	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)
Race		
American Indian or Alaska Native	X/Y (Z)	X/Y (Z)
Asian	X/Y (Z)	X/Y (Z)
Black or African American	X/Y (Z)	X/Y (Z)
Multiple	X/Y (Z)	X/Y (Z)
Native Hawaiian or other Pacific Islander	X/Y (Z)	X/Y (Z)
White	X/Y (Z)	X/Y (Z)
Ethnicity		
Hispanic or Latino	X/Y (Z)	X/Y (Z)
Not Hispanic or Latino	X/Y (Z)	X/Y (Z)
Not reported or unknown	X/Y (Z)	X/Y (Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Treatment-emergent AE defined as [definition]. MedDRA version X.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.; n, number of subjects with adverse event; N, number of subjects in treatment arm; N_s, total number of subjects for each specific subgroup.

4.3. Optional Laboratory Analyses

The tables and figures in Section 4.3.1 Shift Plots, Section 4.3.2 Last Value On-Treatment Analyses, and Section 4.3.3 Outlier Analyses can be requested at the discretion of the review team.

4.3.1. Shift Plots

4.3.1.1. Baseline vs. Maximum/Minimum Postbaseline [Insert Lab Value] by Treatment Arm

Background and Instructions

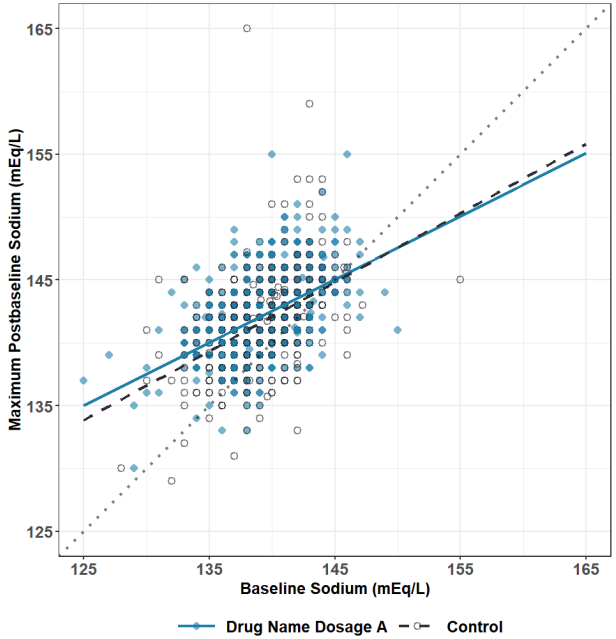
Figure 15: Baseline vs. Maximum/Minimum Postbaseline includes a plot for baseline values of one laboratory parameter compared to its maximum postbaseline. A similar figure will be generated to display baseline compared to minimum postbaseline.

Customization

Figure 15 can be generated for any laboratory parameter of interest. The figure name should be updated to reflect the event being displayed.

Example Figure

Figure 15. Baseline vs. Maximum/Minimum Postbaseline [Insert Lab Value] by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Gray dotted line = no decrease; blue line = study drug arm linear regression; gray dashed line = control arm linear regression.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].

4.3.2. Last Value On-Treatment Analyses

The “last value on-treatment” is defined as the last value for any given laboratory parameter obtained within a specific time frame. To determine this time frame, consider trial design, drug half-life, concomitant medications, or other factors that may be important for assessment. This table could include subjects who completed the trial and thus discontinued treatment per protocol, as well as subjects who discontinued treatment because of an AE. Table 52: Subjects With Last On Treatment Chemistry Value ≥ Level 2 and Table 53: Subjects With Last On Treatment Hematology Value ≥Level 2 should be generated if there are abnormalities or differences in the treatment arms in the lab data in Table 20: Subjects With Kidney Function Analyte Values Exceeding Specified Levels.

The ST&F IG contains generalized laboratory abnormality threshold cutoff criteria (e.g., level 2 or 3). However, theses thresholds can be customized during the CDS planning meeting. It is also important to discuss the appropriate time frame to include during the CDS planning meeting. Table 56: Abnormality Level Criteria for Chemistry Laboratory Results and Table 57: Abnormality Level Criteria for Hematology Laboratory Results list criteria for abnormality levels 1, 2, and 3 for chemistry and hematology, respectively, as noted in Table 52 and Table 53.

4.3.2.1. Subjects With Last On-Treatment Chemistry Value ≥ Level 2 Criteria by Treatment Arm

Background and Instructions

N/A

Customization

Abnormal threshold cutoff and time frame to be used for laboratory analysis can be customized.

Example Table

Table 52. Subjects With Last On-Treatment Chemistry Value ≥ Level 2 Criteria by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)

Parameter	Drug Name Dosage A N=XXX n/N_S (%)	Control N=XXX n/N_S (%)	Risk Difference % (95% CI)[1]
General chemistry			
Sodium, low (<130 mEq/L)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Sodium, high (>155 mEq/L)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Potassium, low (<3.4 mEq/L)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Potassium, high (>6 mEq/L)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Chloride, low (<88 mEq/L)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Chloride, high (>112 mEq/L)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Bicarbonate, low (<18 mEq/L)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Bicarbonate, high (>30 mEq/L)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Blood urea nitrogen, high (>27 mg/dL)	X/Y (Z)	X/Y (Z)	X (Y, Z)

Parameter	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[1]
Glucose, low (<54 mg/dL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Glucose, high Fasting (≥126 mg/dL) or Random (≥200 mg/dL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Calcium, low (<8 mg/dL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Calcium, high (>11 mg/dL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Magnesium, low (<1.2 mg/dL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Magnesium, high (>4 mg/dL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Phosphate, low (<2 mg/dL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Total protein, low (<5.4 g/dL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Albumin, low (<2.5 g/dL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
CPK, high (>5X ULN U/L)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Amylase, high (>1.5X ULN U/L)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Lipase, high (>1.5X ULN U/L)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Kidney function			
Creatinine, high (mg/dL) ≥2.0X baseline	X/Y (Z)	X/Y (Z)	X (Y, Z)
eGFR, low (mL/min/1.73 m^2) ≥50% decrease	X/Y (Z)	X/Y (Z)	X (Y, Z)
Liver biochemistry			
Alkaline phosphatase, high (U/L) >2.0X ULN	X/Y (Z)	X/Y (Z)	X (Y, Z)
Alanine aminotransferase, high (U/L) >5.0X ULN	X/Y (Z)	X/Y (Z)	X (Y, Z)
Aspartate aminotransferase, high (U/L) >5.0X ULN	X/Y (Z)	X/Y (Z)	X (Y, Z)
Total bilirubin, high (mg/dL) >2.0X ULN	X/Y (Z)	X/Y (Z)	X (Y, Z)
Lipids			
Total cholesterol, high (>240 mg/dL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
HDL, low (<40 mg/dL), males	X/Y (Z)	X/Y (Z)	X (Y, Z)
HDL, low (<50 mg/dL), females	X/Y (Z)	X/Y (Z)	X (Y, Z)
LDL, high (>160 mg/dL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Triglycerides, high (>300 mg/dL)	X/Y (Z)	X/Y (Z)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Last value on-treatment defined as the last value for any given laboratory parameter obtained within a specific time frame (e.g., 3 half-lives) following treatment discontinuation, regardless of reason for discontinuation.
Note: Threshold Level 2 as defined by Table 56. Abnormality Level Criteria for Chemistry Laboratory Results
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms]. (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, number of subjects meeting the specified laboratory criteria; N, number of subjects in treatment arm; N_s, total number of subjects with data available for the laboratory test of interest; ULN, upper limit of normal.

4.3.2.2. Subjects With Last On-Treatment Hematology Value ≥ Level 2 Criteria by Treatment Arm

Background and Instructions

N/A

Customization

Abnormal threshold cutoff and time frame to be used for laboratory analysis can be customized.

Example Table

Table 53. Subjects With Last On-Treatment Hematology Value ≥ Level 2 Criteria by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)

Parameter	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[1]
Complete blood count			
WBC, low (<3000 cells/μL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
WBC, high (>13000 cells/μL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Hemoglobin, >1.5 (g/dL) decrease from baseline	X/Y (Z)	X/Y (Z)	X (Y, Z)
Hemoglobin, >2 (g/dL) increase from baseline	X/Y (Z)	X/Y (Z)	X (Y, Z)
Platelets, low (<125000 cells/μL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
WBC differential			
Lymphocytes, low (<750 cells/μL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Lymphocytes, high (>10000 cells/μL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Neutrophils, low (<1000 cells/μL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Eosinophils, high (>1500 cells/μL)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Coagulation studies			
PT, high (sec) (>1.1X ULN)	X/Y (Z)	X/Y (Z)	X (Y, Z)
PTT, high (sec) (>1.21X ULN)	X/Y (Z)	X/Y (Z)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Note: Last value on-treatment defined as the last value for any given laboratory parameter obtained within a specific time frame (e.g., 3 half-lives) following treatment discontinuation, regardless of reason for discontinuation.
Note: Threshold Level 2 as defined by and Table 57. Abnormality Level Criteria for Hematology Laboratory Results.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Risk difference is shown between [treatment arms]. (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: CI, confidence interval; n, number of subjects meeting the specified laboratory criteria; N, number of subjects in treatment arm; N_s, total number of subjects with data available for the laboratory test of interest; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cell.

4.3.3. Outlier Analyses

4.3.3.1. Median and Interquartile Range for General Chemistry Data Over Time by Treatment Arm

Background and Instructions

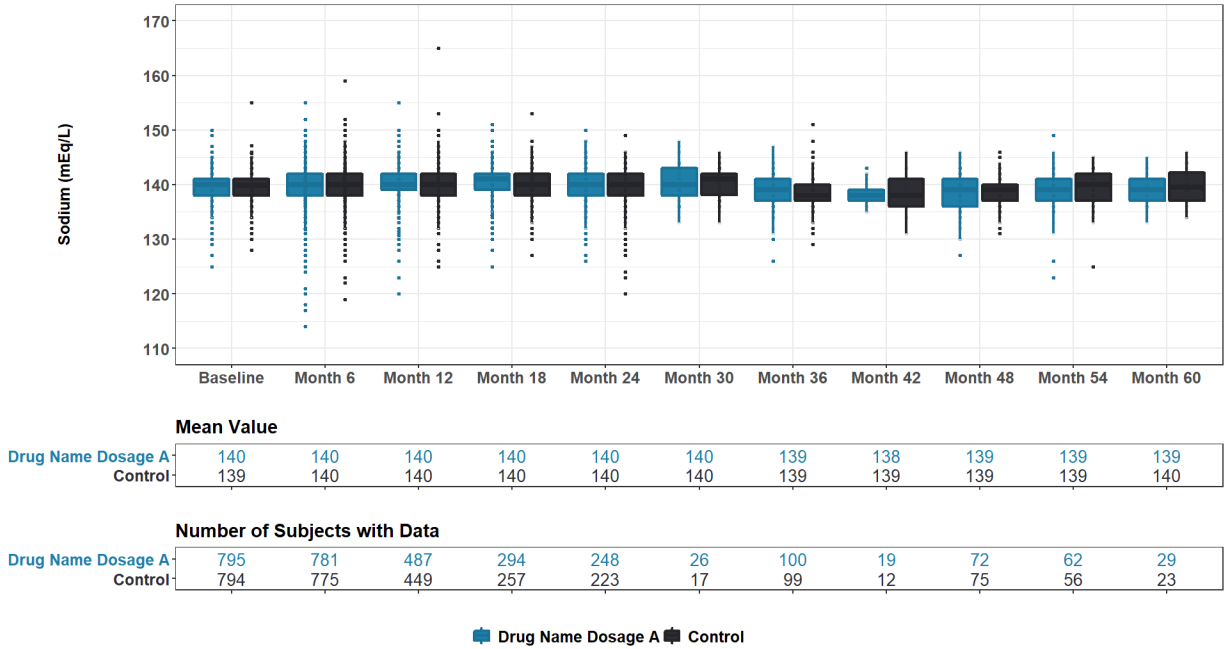
Figure 16: Median and Interquartile Range for General Chemistry Data includes an example of one of the general chemistry laboratory parameters.

Customization

This optional graph can be generated with data for each of the following: sodium, potassium, chloride, bicarbonate, glucose, calcium, magnesium, phosphate, total protein, albumin, creatine phosphokinase, amylase, and lipase. It is at the discretion of the review team which (if any) laboratory data figures are included in the final clinical review.

Example Figure

Figure 16. Median and Interquartile Range for General Chemistry Data Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers = 1.5X the interquartile range; individual outliers are those beyond this range.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].

4.3.3.2. Median and Interquartile Range for Kidney Function Data Over Time by Treatment Arm

Background and Instructions

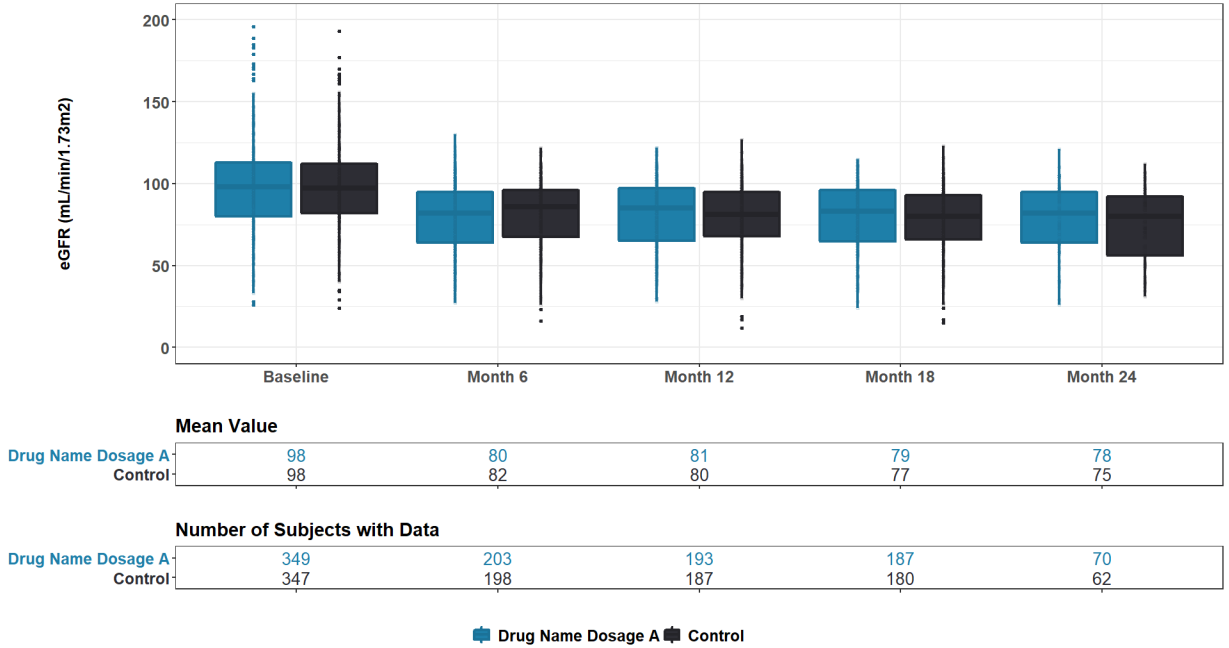
Figure 17: Median and Interquartile Range for Kidney Function Data includes an example of one of the kidney function laboratory parameters.

Customization

This optional graph can be generated with data for each of the following: creatinine and eGFR.

Example Figure

Figure 17. Median and Interquartile Range for Kidney Function Data Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers = 1.5X the interquartile range; individual outliers are those beyond this range.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: eGFR, estimated glomerular filtration rate.

4.3.3.3. Median and Interquartile Range for Liver Biochemistry Data Over Time by Treatment Arm

Background and Instructions

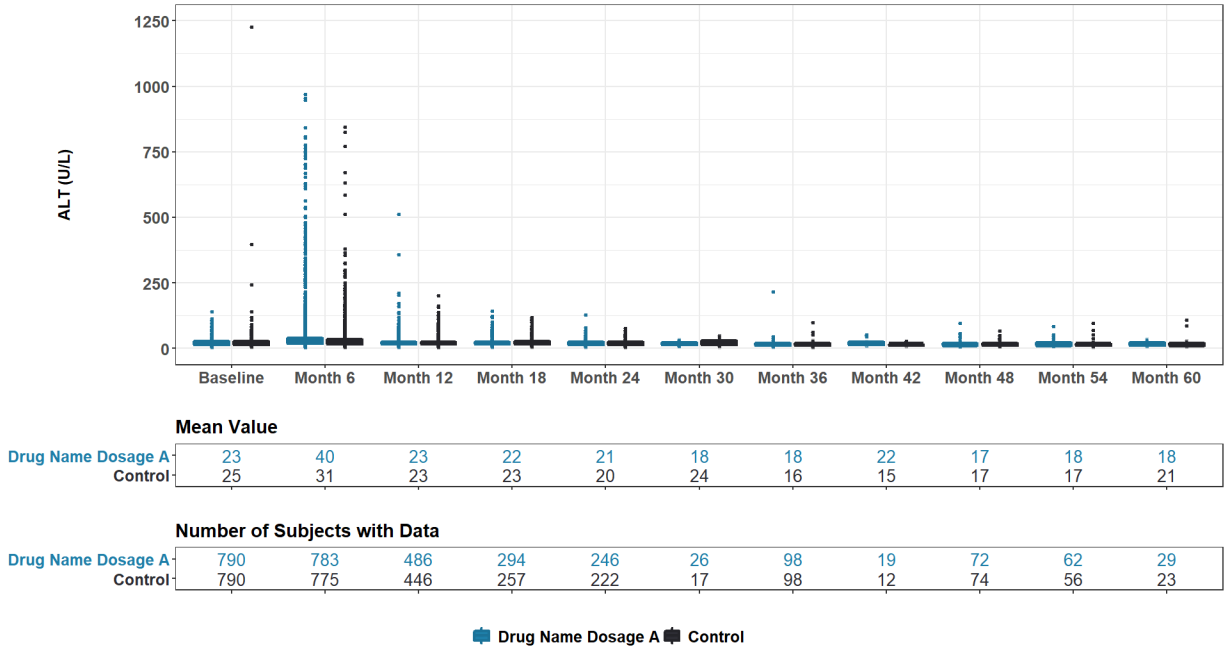
Figure 18: Median and Interquartile Range for Liver Biochemistry Data includes an example of one of the liver biochemistry laboratory parameters.

Customization

This optional graph can be generated with data for each of the following: ALT, AST, ALP, BILI, DB, gamma-glutamyl transpeptidase, and international normalized ratio.

Example Figure

Figure 18. Median and Interquartile Range for Liver Biochemistry Data Over Time by Treatment Arm, Safety Population Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers = 1.5X the interquartile range; individual outliers are those beyond this range.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: ALT, alanine aminotransferase.

4.3.3.4. Median and Interquartile Range for Lipid Data Over Time by Treatment Arm

Background and Instructions

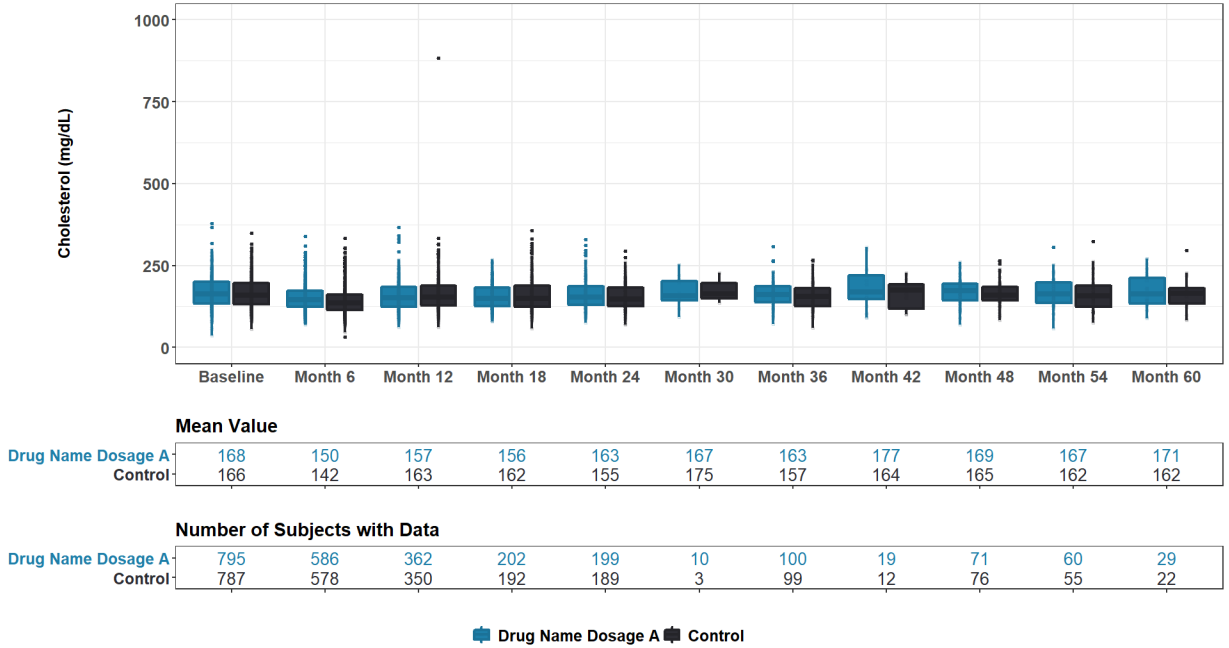
Figure 19: Median and Interquartile Range for Lipid Data includes an example of one of the lipid laboratory parameters.

Customization

This optional graph can be generated with data for each of the following: total cholesterol, HDL, LDL, and triglycerides.

Example Figure

Figure 19. Median and Interquartile Range for Lipid Data Over Time by Treatment Arm, Safety Population Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers = 1.5X the interquartile range; individual outliers are those beyond this range.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].

4.3.3.5. Median and Interquartile Range for Hematology Data Over Time by Treatment Arm

Background and Instructions

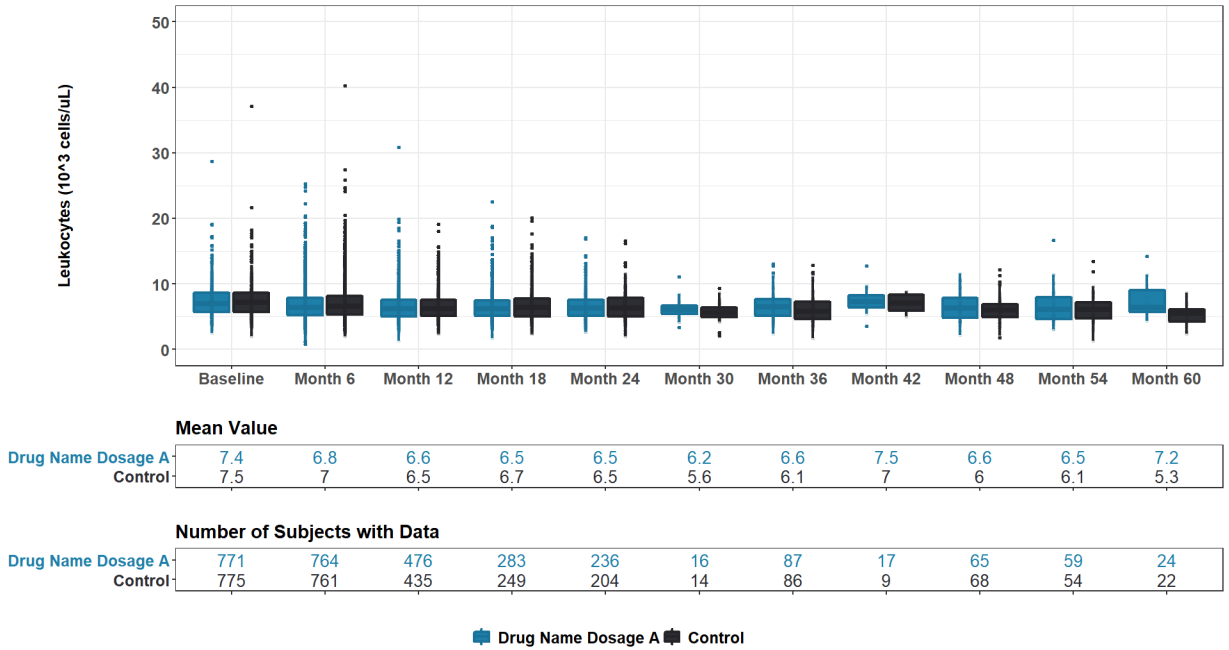
Figure 20: Median and Interquartile Range for Hematology Data includes an example of one of the hematology laboratory parameters.

Customization

This optional graph can be generated with data for each of the following: WBC count, hemoglobin, hematocrit, platelets, WBC differential (i.e., eosinophils, lymphocytes, neutrophils), prothrombin time, and partial thromboplastin time.

Example Figure

Figure 20. Median and Interquartile Range for Hematology Data Over Time by Treatment Arm, Safety Population Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers = 1.5X the interquartile range; individual outliers are those beyond this range.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].

4.3.3.6. Listing of Subjects With a Laboratory Value ≥ Level 2 Criteria

Background and Instructions

In the initial ST&F package from the CDS, clinical reviewers will receive threshold cutoff criteria associated with various levels in Table 20: Subjects With Kidney Function Analyte Values Exceeding Specified Levels. Table 54: Listing of Subjects With a Laboratory Value ≥ Level 2 provides a listing of subjects who met level 2 or 3 criteria.

Customization

The clinical reviewer may request additional tables with different level cutoffs (e.g., level 2 or 3) or specific laboratory tests. When not using pre-established laboratory grading systems, criteria from Table 56: Abnormality Level Criteria for Chemistry Laboratory Results and Table 57: Abnormality Level Criteria for Hematology Laboratory Results can be used. Similarly, graphical patient profiles may be requested for subjects of interest. All subject listings can be customized to have columns added or removed to display the most relevant information.

Example Table

Table 54. Listing of Subjects With a Laboratory Value ≥ Level 2 Criteria, Safety Population, Pooled Analysis (or Trial X)

Unique Subject Identifier	Treatment Arm	Parameter	Baseline Lab Value	Laboratory Value ≥ Level 2 Criteria	Study Day of Onset[1]
Subject ID1	X	X	X	X	X
Subject ID2	X	X	X	X	X
Subject ID3	X	X	X	X	X

Source: [include Applicant source, datasets and/or software tools used].
Note: Threshold Level 2 defined by Table 58.and Table 59
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Post randomization.
Abbreviations: ID, identifier.

4.3.3.7. Listing of Subjects With a Laboratory Value ≥ Level 2 Change From Baseline Criteria

Background and Instructions

In the initial ST&F package from CDS, clinical reviewers will receive threshold cutoff criteria associated with various levels in Table 20: Subjects With Kidney Function Analyte Values Exceeding Specified Levels. Table 55: Subjects With ≥ Level 2 Change from Baseline provides a listing of subjects who met level 2 or 3 change from baseline criteria for creatinine, eGFR, and hemoglobin, when data are available.

Customization

Clinical reviewers may request additional tables with different level cutoffs (e.g., level 2 or 3) or specific laboratory tests. When not using pre-established laboratory grading systems, criteria from Table 56: Abnormality Level Criteria for Chemistry Laboratory Results and Table 57: Abnormality Level Criteria for Hematology Laboratory Results can be used. Similarly, graphical patient profiles may be requested for subjects of interest. All subject listings can be customized to have columns added or removed to display the most relevant information.

Example Table

Table 55. Listing of Subjects With a Laboratory Value ≥ Level 2 Change From Baseline Criteria, Safety Population, Pooled Analysis (or Trial X)

Unique Subject Identifier	Treatment Arm	Parameter	Baseline Value	Laboratory Value ≥Level 2 Criteria	Change in Value	Study Day of Onset[1]
Subject ID1	X	Creatinine (mg/dL), (≥2.0X baseline)	X	X	X	X
Subject ID2	X	eGFR (mL/min/1.73 m^2), ≥50% decrease	X	X	X	X
Subject ID3	X	Hemoglobin (g/dL), (>1.5 decrease from baseline)	X	X	X	X
Subject ID4	X	Hemoglobin (g/dL), (>2 increase from baseline)	X	X	X	X

Source: [include Applicant source, datasets and/or software tools used].
Note: Threshold Level 2 as defined by Table 58.and Table 59.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[1] Post randomization.
Abbreviations: eGFR, estimated glomerular filtration rate; ID, identifier.

4.4. Optional Vital Sign Analyses

The figures in Missing and Existing Data Analysis (Section 4.4.1) and Shift Plots (Sections 4.4.2) can be requested at the discretion of the review team.

4.4.1. Missing and Existing Data Analysis

4.4.1.1. Proportion of Subjects Remaining in Trial at Each Visit by Availability of [Insert Vital Sign Value] Result

Background and Instructions

Figure 21: Proportion of Subjects Remaining in Trial at Each Visit displays the proportion of missing data for a specific vital sign result at each trial visit by trial arm. It displays the percent of subjects with the vital sign test by visit (solid bar), the percent of subjects missing the vital sign test by visit (open bar), and the percent of subjects remaining in the trial (bar height). The x-axis displays trial visits as a discrete variable rather than a continuous variable.

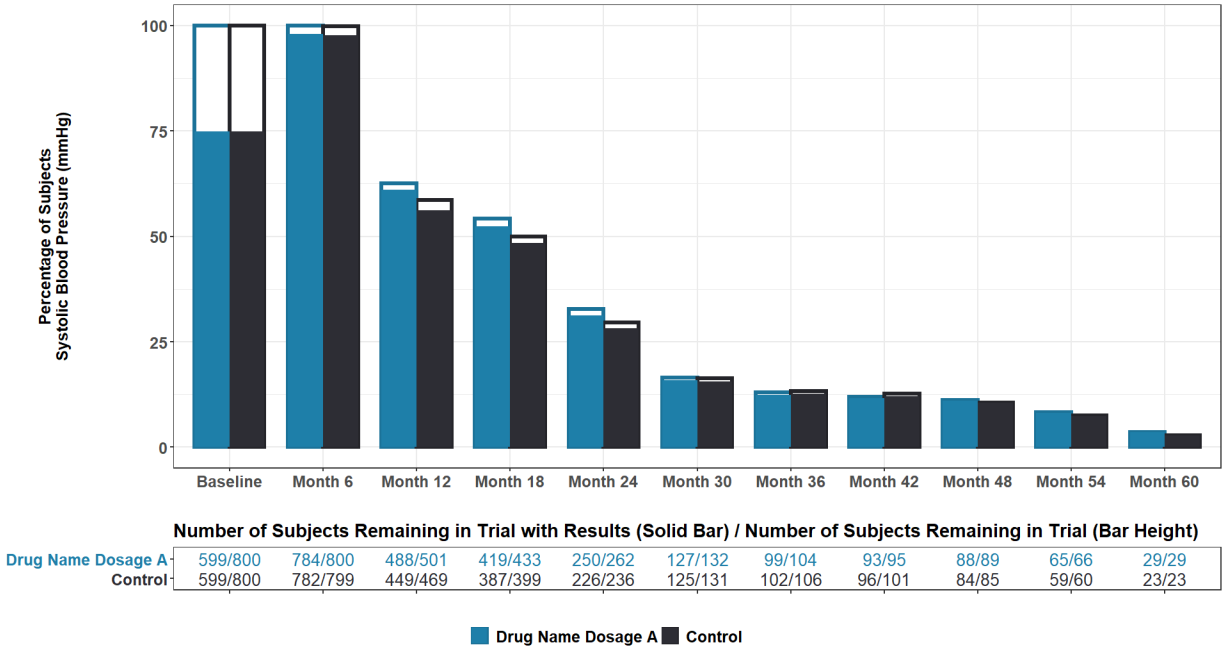
During the planning meeting with the CDS, clinical reviewers should discuss the definition of "missing" data and reflect protocol-specified trial visits. Clinical reviewers may request this figure to be displayed showing trial visits as a continuous variable. The graph depicted in Figure 21 is intended to evaluate the actual data obtained during the trial, rather than the planned trial procedures as stated in the protocol. A high proportion of missing data should signal the clinical reviewer that available data may be limited, and/or that the results might be biased such that any conclusions based on the available data might not be correct and that the data in the package should be interpreted with caution. Alternatively, the clinical reviewer may request more data from the applicant before proceeding.

Customization

Clinical reviewers should review the protocol(s) and discuss with the CDS the duration (e.g., until the end of treatment, until sometime after the end of treatment, or until the end of the trial) and population (e.g., randomized or treated) to use. Similar figures may be provided for any vitals of interest as appropriate.

Example Figure

Figure 21. Proportion of Subjects Remaining in Trial at Each Visit by Availability of [Insert Vital Sign Value] Result, Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Note: The frequency of laboratory measurements presented here is based on actual data collected.
Note: The time frame (e.g., by day, week, month) that corresponds best with the prespecified visit # is used as the study visit (± protocol-defined # days).
Note: The solid bar indicates the percent of subjects remaining in the trial with the vital sign result. The open bar indicates the percent of subjects remaining in the trial and are missing the vital sign result. The bar height indicates the percent of subjects remaining in the trial.

4.4.2. Shift Plots

4.4.2.1. Baseline vs. Maximum/Minimum Postbaseline [Insert Vital Sign Value] by Treatment Arm

Background and Instructions

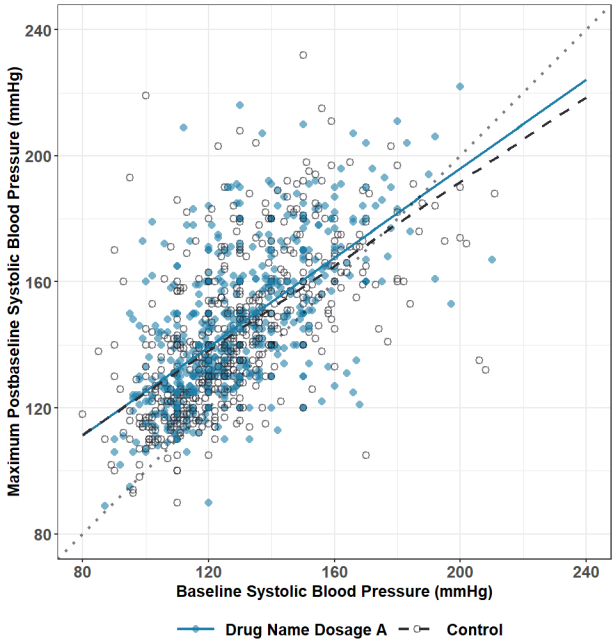
Figure 22: Baseline vs. Maximum/Minimum Postbaseline includes a plot for baseline values compared to maximum postbaseline values for one of the vital sign parameters. A similar figure will be generated to display baseline compared to minimum postbaseline.

Customization

Figure 22 can be generated for any vital sign parameter of interest. The figure name should be updated to reflect the event being displayed.

Example Figure

Figure 22. Baseline vs. Maximum/Minimum Postbaseline [Insert Vital Sign Value] by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
Note: Gray dotted line = no decrease; blue line = study drug arm linear regression; gray dashed line = control arm linear regression.
Note: Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].

5. Appendix

5.1. Reference Tables for Abnormality Level Criteria Cutoffs

5.1.1. Abnormality Level Criteria for Chemistry Laboratory Results

Selected laboratory parameters are included in the tables below.

Table 56. Abnormality Level Criteria for Chemistry Laboratory Results

Parameter	Level 1	Level 2	Level 3
General Chemistry			
Sodium, low (mEq/L)	<132	<130	<125
Sodium, high (mEq/L)	>150	>155	>160
Potassium, low (mEq/L)	<3.6	<3.4	<3.0
Potassium, high (mEq/L)	>5.5	>6	>6.5
Chloride, low (mEq/L)	<95	<88	<80
Chloride, high (mEq/L)	>108	>112	>115
Bicarbonate, low (mEq/L)	<20	<18	<15
Bicarbonate, high (mEq/L)	N/A	N/A	>30
Blood urea nitrogen, high (mg/dL)	>23	>27	>31
Glucose, low (mg/dL)	<70	<54	N/A
Glucose, high (mg/dL)			
Fasting	≥100	≥126	N/A
Random	N/A	≥200	N/A
Calcium, low (mg/dL)	<8.4	<8.0	<7.5
Calcium, high (mg/dL)	>10.5	>11.0	>12.0
Magnesium, low (mg/dL)	<1.5	<1.2	<0.9
Magnesium, high (mg/dL)	>2.3	>4.0	>7.0
Phosphate, low (mg/dL)	<2.5	<2.0	<1.4
Protein (total), low (g/dL)	<6.0	<5.4	<5.0
Albumin, low (g/dL)	<3.1	<2.5	<2.0
CPK, high (U/L)	>3 x ULN	>5 x ULN	>10 x ULN
Amylase, high (U/L)	>1.1 x ULN	>1.5 x ULN	>3.0 x ULN
Lipase, high (U/L)	>1.1 x ULN	>1.5 x ULN	>3.0 x ULN

Parameter	Level 1	Level 2	Level 3
Kidney Function			
Creatinine, increase (mg/dL)	≥1.5 x baseline	≥2.0 x baseline	≥3.0 x baseline
eGFR, decrease (ml/min/1.73m^2)	≥25% decrease	≥50% decrease	≥75% decrease
Liver Biochemistry[1]			
Alkaline phosphatase, high (U/L)	>1.5 x ULN	>2.0 x ULN	>3.0 x ULN
Alanine Aminotransferase, high (U/L)	>3.0 x ULN	>5.0 x ULN	>10.0 x ULN
Aspartate Aminotransferase, high (U/L)	>3.0 x ULN	>5.0 x ULN	>10.0 x ULN
Total Bilirubin, high (mg/dL)	>1.5 x ULN	>2.0 x ULN	>3.0 x ULN
Lipids			
Cholesterol (total), high (mg/dL)	>200	>240	>300
HDL, low (mg/dL), males	<40	<30	<20
HDL, low (mg/dL), females	<50	<40	<20
LDL, high (mg/dL)	>130	>160	>190
Triglycerides, high (mg/dL)	>150	>300	>500

Note: Provided for the purpose of identifying outliers.

[1] For specific evaluation of drug-induced liver injury, refer to Section 2.4.4 Liver Injury Screening Analyses.

Abbreviations: CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N/A, not applicable; ULN, upper limit of normal.

5.1.2. Abnormality Level Criteria for Hematology Laboratory Results

Table 57. Abnormality Level Criteria for Hematology Laboratory Results

Parameter	Level 1	Level 2	Level 3
Complete blood count			
WBC, low (x 10^9 cells/L)	<3.5	<3.0	<1.0
WBC, high (x 10^9 cells/L)	>10.8	>13.0	>15.0
Hemoglobin, decrease (g/dL)	N/A	>1.5 dec. from baseline	>2 dec. from baseline
Hemoglobin, increase (g/dL)	N/A	>2 inc. from baseline	>3 inc. from baseline
Platelets, low (x 10^9 cells/µL)	<140,000	<125,000	<100,000
Hemoglobin, low (g/dL), male	12.5-13.5	<12.5	<10.5
Hemoglobin, low (g/dL), female	11.0 – 12.0	<11	<9.5
WBC differential			
Lymphocytes, low (cells/µL)	<1000	<750	<500
Lymphocytes, high (cells/µL)	>4000	>10000	>20000
Neutrophils, low (cells/µL)	<2000	<1000	<500
Eosinophils, high (cells/µL)	>650	>1500	>5000
Coagulation studies			
PT, increase (sec)	>1.1 x ULN	>1.3 x ULN	>1.5 x ULN
PTT, increase (sec)	>1.0 x ULN	>1.21 x ULN	>1.41 x ULN

Note: Level criteria are provided for the purpose of identifying outliers.
Abbreviations: dec., decrease; inc., increase; N/A, not applicable; PT, prothro mbin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cell.

5.2. Extreme Clinical Laboratory and Vital Sign Values, Version 1.0

5.2.1. Extreme Serum, Plasma, and Whole Blood Chemistry Laboratory Values Suggestive of Laboratory Error

Table 58. Extreme Serum, Plasma, and Whole Blood Chemistry Laboratory Values Suggestive of Laboratory Error

General Chemistry Parameter	US Conventional Units: Low Threshold	US Conventional Units: High Threshold	US Conventional Units	SI Units: Low Threshold	SI Units: High Threshold	SI Units	References
Sodium (serum)	<95.0	>191	mEq/L	<95.0	>191	mmol/L	1, 6
Potassium (serum)	<1.3	>9.0	mEq/L	<1.3	>9.0	mmol/L	1
Chloride (serum)	<65.0	>138	mEq/L	<65.0	>138	mmol/L	1
Bicarbonate (serum)	<5.0	>50.0	mEq/L	<5.0	>50.0	mmol/L	2
Blood Urea Nitrogen (serum/plasma)	N/A	>200	mg/dL	N/A	>71.4	mmol/L	3
Glucose (plasma)	<10	>2700	mg/dL	<0.6	>150	mmol/L	2, 7
Total Calcium (serum)	<4.0	>20.0	mg/dL	<1.0	>5.0	mmol/L	2
Magnesium (serum)	<0.5	>15.0	mg/dL	<0.2	>6.2	mmol/L	2
Phosphate (serum)	<0.3	>45.0	mg/dL	<0.1	>14.5	mmol/L	3
Total Protein (serum)	<0.6	>90.0	g/dL	<6.0	>900	g/L	3
Albumin (serum)	<0.4	>55.0	g/dL	<4	>550	g/L	3
Total CPK (serum)	<3.0	>800,000	U/L	<3.0	>800,000	U/L	4
Amylase (serum)	N/A	>10,000	U/L	N/A	>10,000	U/L	2
Lipase (serum)	N/A	>10,000	U/L	N/A	>167	µkat/L	2
Creatinine (serum)	N/A	>80.0	mg/dL	N/A	>7072	µmol/L	5
Creatinine Clearance (serum, urine)	N/A	>200	mL/min	N/A	>3.3	mL/s	2
eGFR (serum, urine)	N/A	>200	mL/min/1.73 m2	N/A	>3.3	mL/s/1.73 m2	2
Alkaline Phosphatase (serum)	<3.0	>5000	U/L	<0.05	>83.4	µkat/L	2
Alanine Aminotransferase (serum)	N/A	>50,000	U/L	N/A	>830	µkat/L	2
Aspartate Aminotransferase (serum)	N/A	>50,000	U/L	N/A	>830	µkat/L	2
GGT (serum)	N/A	>5000	U/L	N/A	>5000	U/L	8
Total Bilirubin (serum)	N/A	>200	mg/dL	N/A	>3420	µmol/L	2

General Chemistry Parameter	US Conventional Units: Low Threshold	US Conventional Units: High Threshold	US Conventional Units	SI Units: Low Threshold	SI Units: High Threshold	SI Units	References
Total Cholesterol (serum)	<5.0	>3000	mg/dL	<0.13	>77.7	mmol/L	2
HDL (serum)	<5.0	>1000	mg/dL	<0.13	>25.9	mmol/L	2
LDL (serum)	<5.0	>2000	mg/dL	<0.13	>51.8	mmol/L	2
Triglycerides (serum)	<5.0	>3500	mg/dL	<0.13	>90.7	mmol/L	2

[1] Vogt W, Oesterle B. Extreme results in electrolyte determination [Article in German]. Wien Klin Wochenschr Suppl. 1992;192:21-27.
[2] Expert opinion.
[3] American Board of Internal Medicine Laboratory Test Reference Ranges–January 2019, Low Threshold = Lower Limit of Normal ÷ 10, High Threshold = Upper Limit of Normal x 10.
[4] Luckoor P, Salehi M, Kunadu A. Exceptionally High Creatine Kinase (CK) Levels in Multicausal and Complicated Rhabdomyolysis: A Case Report. Am J Case Rep. 2017; 18: 746–749.
[5] Persaud C, Sandesara U, Hoang V, et al. Highest Recorded Serum Creatinine. Case Rep Nephrol. 2021; 2021: 6048919.
[6] Ijaiya T, Manohar S, Lakshmi K. Therapeutic Approach to the Management of Severe Asymptomatic Hyponatremia. Case Rep Nephrol. 2021; 2021: 6048919.
[7] Guinness World Records, Highest blood sugar level, 2022.
[8] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Severity Grading In Drug Induced Liver Injury. Last Update: May 4, 2019.
Abbreviations: CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; N/A, not applicable; PT, prothrombin time; PTT, partial thromboplastin time; SI, International System; US, United States; WBC, white blood cell.

5.2.2. Extreme Serum, Plasma, and Whole Blood Hematology Laboratory Values Suggestive of Laboratory Error

Table 59. Extreme Serum, Plasma, and Whole Blood Hematology Laboratory Values Suggestive of Laboratory Error

Hematology Parameter	US Conventional Units: Low Threshold	US Conventional Units: High Threshold	US Conventional Units	SI Units: Low Threshold	SI Units: High Threshold	SI Units	References
Neutrophils (blood)	N/A	200,000	cells/µL	N/A	200,000	cells/µL	3
Lymphocytes (blood)	N/A	60,000	cells/µL	N/A	60,000	cells/µL	1
Eosinophils (blood)	N/A	20,000	cells/µL	N/A	20,000	cells/µL	1
Hemoglobin (blood)	<0.6	>30	g/dL	<6	>300	g/L	1, 2
Hematocrit (blood)	<2	>90	%	<2	>90	%	1, 2
Platelets (blood)	N/A	>5,000,000	platelets/µL	N/A	>5,000,000	platelets/µL	1
PT (plasma)	N/A	>150	seconds	N/A	>150	seconds	1
PTT (plasma)	N/A	>350	seconds	N/A	>350	seconds	1
INR (plasma)	N/A	>20	N/A	N/A	>20	N/A	1

[1] Expert opinion.
[2] Kariya T, Ito N, Kitamura T, et al. Recovery from Extreme Hemodilution (Hemoglobin Level of 0.6 g/dL) in Cadaveric Liver Transplantation. A A Case Rep. 2015 May 15; 4(10): 132–136.
[3] WB Herring, LG Smith, RI Walker, et al. Hereditary neutrophilia. Am J Med, 56 (1974), pp. 729-734.
Abbreviations: INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; SI, International System; US, United States.

5.2.3. Extreme Vital Sign Values Suggestive of Error

Table 60. Extreme Vital Sign Values Suggestive of Error

Vital Signs	Low Threshold	High Threshold	References
Pulse (beats/min)	10	600	1
Blood pressure, systolic (mmHg)	50	400	2
Blood pressure, diastolic (mmHg)	25	370	2
Respiration (breaths/min)	3	90	3
Temperature (F, C)	50° F, 10° C	120° F, 50° C	4, 5

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[2] J A Narloch, M E Brandstater. Influence of breathing technique on arterial blood pressure during heavy weightlifting. Arch Phys Med Rehabil. 1995 May;76(5):457-62.
[3] Expert opinion.
[4] Guinness Book of World Records, Lowest body temperature, 2014.
[5] Guinness Book of World Records, Highest body temperature, 1980.

5.3. Acknowledgments

The content of this integrated guide was established by the **Standard Safety Tables and Figures Working Group**:

Current members:

1. Peter Stein (Executive Sponsor)
2. Yang Veronica Pei (Project lead)
3. Bach Nhi Beasley
4. Ling Cao
5. Michelle Carey
6. Bryant Chen
7. Paul Hayashi
8. Rhonda Hearns-Stewart
9. Salman Hosain
10. Linda Jeng
11. Maria Matilde Kam
12. Gregory Levin
13. Jinzhong Liu
14. Susan Mayo
15. DeAngelo McKinley
16. Abhilasha Nair
17. Mahtab Niyyati
18. Frank Pucino
19. Alan Shapiro
20. Jeff Siegel
21. Christopher Smith
22. James Smith
23. Kim Shimy
24. Mat Soukup
25. Larissa Stabinski
26. Douglas Warfield
27. Ellen Wertheimer
28. Michael Xue
29. Qunshu Zhang
30. Jizu Zhi

Previous members:

1. Sarita Boyd
2. Anne Bunner
3. Chenoa Conley
4. Sarah Connelly
5. Susan Duke
6. Justin Earp
7. Jeffry Florian
8. Ramya Gopinath
9. Matthew Guerra
10. Kerry Jo Lee
11. Vaishali Popat
12. Robert Temple
13. Ellis Unger
14. Preeti Venkataraman
15. Frank Anania