STANDARD SAFETY TABLES AND FIGURES:

INTEGRATED GUIDE

Center for Drug Evaluation and Research (CDER)

Biomedical Informatics and Regulatory Review Science (BIRRS) Team

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Introduction

Primary clinical reviewers/medical officers use tables and figures to summarize and interpret clinical trial safety data submitted in marketing applications.

The goals of the ST&F guide are to (1) provide the standard set of safety analytic tables and figures; and (2) compile associated instructions to support reviewers as they interpret these reports and conduct their review. Additionally, if reviewers identify a safety signal in their initial analysis, they may request custom analyses as they progress in their review.

Although the clinical reviewers evaluate the standard safety analyses in this document, they are not necessarily required to be in the final clinical review. These tables and figures should not be considered all inclusive, and custom and therapeutic area specific analyses maybe needed.

All ST&F within this document initially are created independent of specific safety concerns unless earlier (presubmission) review of data or drug class issues raised particular concerns. These ST&F are examples of analyses. They may be modified based on the specific study design (e.g., to include additional treatment arms), specific safety issues, and new issues that arise during the drug development program. For example, outputs are presented for pooled analyses and include columns for different types of treatment and control arms (e.g., drug arms for multiple doses, active control, placebo). This need to be modified based on the treatment arms included and/or of particular interest. These safety analyses are exploratory in nature and confidence intervals (CIs) for the risk difference presented here are not adjusted for multiplicity.

For analyses of multiple trials, discuss with the review division, the effect of pooling different populations, interpretation of results, as well as which statistical method may be appropriate, prior to generation of such analyses. Integrated analyses of data from multiple studies may be stratified by study (e.g., with study size-adjusted percentages or rates). If there are no notable differences between trials, simple pooling of the data may be reasonable. Trials should be pooled carefully and appropriately. When studies being pooled have notable differences in their population, duration, and/or randomization ratio (e.g., 2:1, 3:1), or when dose arms are not the same across trials, a more detailed discussion on pooling methods is advisable.

Table headings[1] include the term “dosage.”[2] “Dose” refers to a specified amount of medication taken at one time. By contrast, “dosage” is the prescribed administration of a specific amount, number, and frequency of doses over a specific period of time.

Please contact ONDBiomedicalinformatics@fda.hhs.gov with comments, questions, or feedback regarding the content of this document.

[1] See the CDER Style Guide.
[2] See FDA guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products—Content and Format* (March 2010).

Standard Safety Tables and Figures

General

This section contains general information regarding the clinical trial(s) submitted to support the application, demographic, disposition, and duration of exposure tables. Outputs presented by pooled analyses also should be generated for individual registration trials.

Table 1 is an example table that includes general information for all of the trials submitted in support of the marketing application. The table should include 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 control, dose-comparison concurrent control, no treatment concurrent control, active treatment concurrent control, historical control), trial population, study endpoints, and sample size.

The primary interest is typically in the safety analysis population (i.e., all patients exposed to at least one dose of randomized treatment).

Table 1. Clinical Trials Submitted[1] 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 Patients Planned; Actual Randomized	No. of Centers and Countries
Study X NCT #	Patients with moderate to severe disease as defined by XX baseline or clinical characteristics	Control type: Randomization: Randomization ratio: Blinding: Key design features:	Drug X mg BID (N = X), XX weeks Drug Y mg BID (N = X), protocol-specified dose adjustment permitted; XX weeks. Placebo (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	YYY; ZZZ	X centers in Y countries
Study Y NCT #	Patients completing X weeks treatment or withdrawn due to treatment failure in Study X; or nonresponders after completion in studies X and Y	Control type: Randomization: Randomization ratio: Blinding: Key design features:	**Part 1** Drug X mg (N = X) Drug Y mg (N = X) Drug Z mg (N = X) **Part 2** Drug X 25 mg (N = X) Active control Y mg (N = X) Route of administration (all taken orally BID with Drug Z mg) Duration:	Long-term durability of efficacy and long-term safety	YYY; ZZZ	X centers in Y countries

Source: [include Applicant source, datasets and/or software tools used]. Provide a link to EDR for the studies included in this report.
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
Abbreviations: BID, twice daily; DB, double-blind; LTE, long-term extension; MC, multicenter; OL, open-label; PC, placebo-controlled; PG, parallel group; R, randomized; RR, randomization ratio

For Table 2, 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 were not 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, such as low-density lipoprotein cholesterol, C-reactive protein levels, kidney function, or hepatic function that could affect safety. Depending on the geographic makeup of the study, the region of participation rather than country may be included.

For trials that include older patients (e.g., Alzheimer's disease), additional geriatric 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). In addition to the standard groupings, other age groups of interest could be included. See the guidance for industry *E7 Studies in Support of Special Populations: Geriatrics, Questions and Answers* (February 2012).[3]

[3] FDA guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016)

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

Characteristic	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Placebo N = XXX n (%)	Active Control N = XXX n (%)	Total Population N = XXX n (%)
Sex, n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Male	n (%)	n (%)	n (%)	n (%)	n (%)
Female	n (%)	n (%)	n (%)	n (%)	n (%)
Age, years	**X.X (Y.Y)**	**X.X (Y.Y)**	**X.X (Y.Y)**	**X.X (Y.Y)**	**X.X (Y.Y)**
Mean (SD)	X.X (Y.Y)	X.X (Y.Y)	X.X (Y.Y)	X.X (Y.Y)	X.X (Y.Y)
Median (min, max)	X.X (Y.Y, Z.Z)	X.X (Y.Y, Z.Z)	X.X (Y.Y, Z.Z)	X.X (Y.Y, Z.Z)	X.X (Y.Y, Z.Z)
Age groups (years), n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
≥17 to <65	n (%)	n (%)	n (%)	n (%)	n (%)
≥65	n (%)	n (%)	n (%)	n (%)	n (%)
≥65 to <75	n (%)	n (%)	n (%)	n (%)	n (%)
≥75	n (%)	n (%)	n (%)	n (%)	n (%)
Race, n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
American Indian or Alaska Native Asian	n (%)	n (%)	n (%)	n (%)	n (%)
Black or African American	n (%)	n (%)	n (%)	n (%)	n (%)
Native Hawaiian or Other Pacific Islander	n (%)	n (%)	n (%)	n (%)	n (%)
White	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)
Ethnicity, n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hispanic	n (%)	n (%)	n (%)	n (%)	n (%)
Not Hispanic or Latino	n (%)	n (%)	n (%)	n (%)	n (%)
Unknown	n (%)	n (%)	n (%)	n (%)	n (%)
Country of participation, n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
United States	n (%)	n (%)	n (%)	n (%)	n (%)
Country A	n (%)	n (%)	n (%)	n (%)	n (%)
Country B	n (%)	n (%)	n (%)	n (%)	n (%)
Country C	n (%)	n (%)	n (%)	n (%)	n (%)
Country D	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)

Characteristic	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Placebo N = XXX n (%)	Active Control N = XXX n (%)	Total Population N = XXX n (%)
Clinical baseline characteristics, n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Characteristic A	n (%)	n (%)	n (%)	n (%)	n (%)
Characteristic B	n (%)	n (%)	n (%)	n (%)	n (%)
Characteristic N	n (%)	n (%)	n (%)	n (%)	n (%)

Source: [include Applicant source, datasets and/or software tools used].
[1] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: N, number of patients in treatment arm; n, number of patients with given characteristic; SD, standard deviation

Table 3 provides an example of how screening and enrollment data should be displayed. The populations should be defined as follows:

- **Screened population:** All patients screened for entry into the trial
- **Enrolled population:** All patients who signed a consent form for participation in the trial
- **Randomized population:** All patients randomized to a treatment arm; often referred to as the intention-to-treat population
- If **screening failure** data are available, provide reasons for screen failure, such as "patient noncompliance," "consent withdrawn," "inclusion/exclusion criteria not met," "other." Request breakdown of "inclusion/exclusion criteria not met" and "other," because understanding reasons for screen failure can be informative to assess the generalizability of the trial.

Table 3. Patient Screening and Enrollment, Trials A and B

Disposition	Trial A	Trial B
Patients screened	XX	XX
Screening failures	XXX (XX.X%)	XXX (XX.X%)
Inclusion/exclusion criteria not met	XXX (XX.X%)	XXX (XX.X%)
Patient noncompliance	XXX (XX.X%)	XXX (XX.X%)
Consent withdrawn	XXX (XX.X%)	XXX (XX.X%)
Other	XXX (XX.X%)	XXX (XX.X%)
Patients enrolled	XXX (XX.X%)	XXX (XX.X%)
Patients randomized	XXX (XX.X%)	XXX (XX.X%)

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

Table 4 is an example table showing all reasons reported in the study disposition dataset that should be included. Consider the following study populations:

- **Modified intention-to-treat (mITT) population:** Subset of the ITT population allowing the exclusion of some randomized patients in a justified way (e.g., patients who were deemed ineligible after randomization or certain patients who never started treatment)
- **Safety population:** All patients considered in the safety analyses who received at least one dose of the study drug in the trials submitted
- **Per-protocol population:** Only those patients who completed the treatment originally allocated and planned without major protocol violations

Table 4. Patient Disposition, Pooled Analyses[1,2]

	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Patients randomized	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**-**
ITT/mITT population[3]	n (%)	n (%)	n (%)	n (%)	-
Safety population	n (%)	n (%)	n (%)	n (%)	-
Per-protocol population	n (%)	n (%)	n (%)	n (%)	-
Discontinued study drug	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
Adverse event	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Lack of efficacy	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Protocol deviation	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Death	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Withdrawal by subject	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Other	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Discontinued study	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
Death	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Lost to follow-up	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Withdrawal by subject	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Physician decision	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Protocol deviation	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Other	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[2] [Include route of administration for all treatment arms if different ROA were used in the drug development].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; ITT, intention-to-treat; mITT, modified intention-to-treat; N, number of patients in treatment arm; n, number of patients in specified population or group

Customization

Consider adding metrics such as dose intensity and relative dose intensity as appropriate (e.g., for oncology trials):

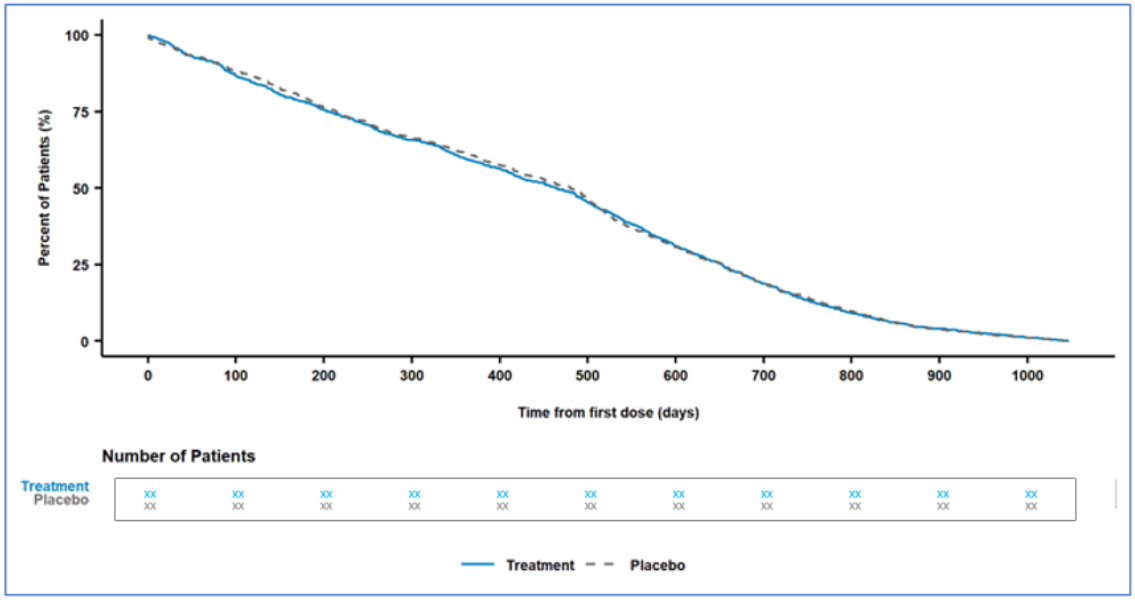
- **Dose intensity** is the total amount of drug given in a fixed unit of time (usually 1 week), thus is a function of dose and frequency of administration.
- **Relative dose intensity (RDI)** is the ratio of "delivered" to the "planned" dose intensity and can be expressed as a percentage. An RDI of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

Table 5. Duration of Treatment Exposure, Safety Population, Pooled Analyses[1]

Parameter	Drug Name Dosage X N = XXX	Drug Name Dosage Y N = XXX	Active Control N = XXX	Placebo N = XXX	Risk Difference (%) (95% CI)[2]
Duration of treatment, weeks (or months, or days, or cycles)					
Mean (SD)	X (Y)	X (Y)	X (Y)	X (Y)	X (Y, Z)
Median (min, max)	X (Y, Z)	X (Y, Z)	X (Y, Z)	X (Y, Z)	X (Y, Z)
Interquartile range	X -Y	X -Y	X -Y	X -Y	X
Total exposure (person years)	X (Y)	X (Y)	X (Y)	X (Y)	X (Y, Z)
Patients treated, by duration, n (%)					
Any duration (at least 1 dose)	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
<1 month	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
≥1 month	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
≥3 months	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
≥6 months	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
≥12 months	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Duration = [e.g., X-week double-blind treatment period or median and a range indicating pooled trial durations].
[2] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with given treatment duration; NA, not applicable; SD, standard deviation

Figure 1. Time to Permanent Discontinuation of Study Drug,[1] Safety Population, Pooled Analyses

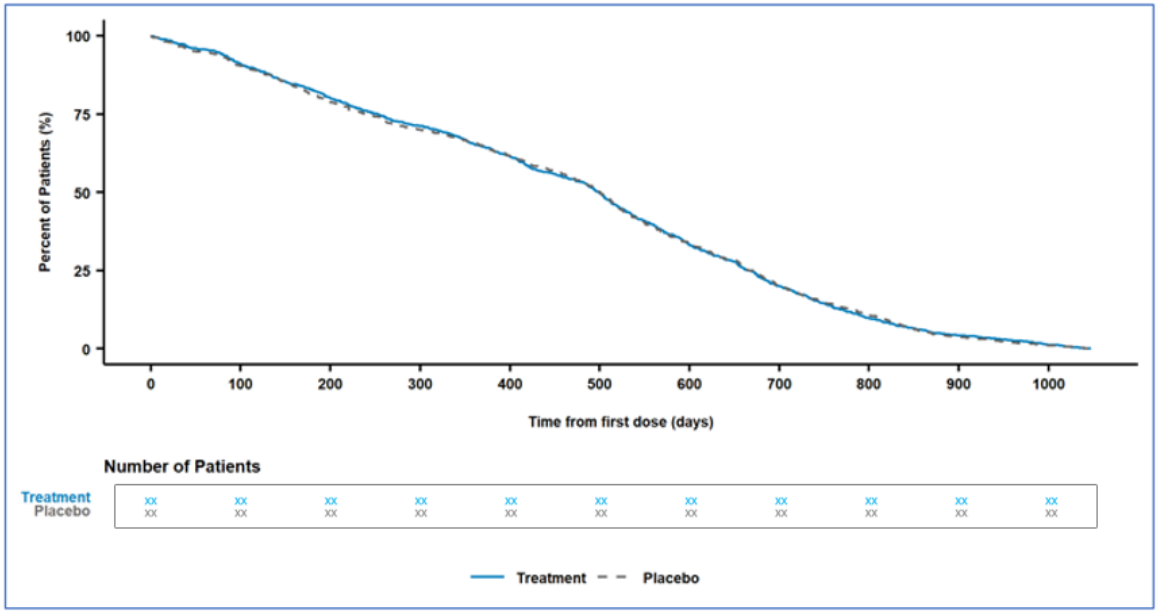


Source: [include source dataset(s) and tools used].
[1] Defined as the duration of time from first dose to last dose of study agent for each patient, regardless of the reason for study agent discontinuation.

Customization

A similar figure for time to subjects discontinuation from the study may be produced. If there is a significant differential discontinuation between arms, consider further evaluation such as exposure-adjusted analysis for adverse events (AEs).

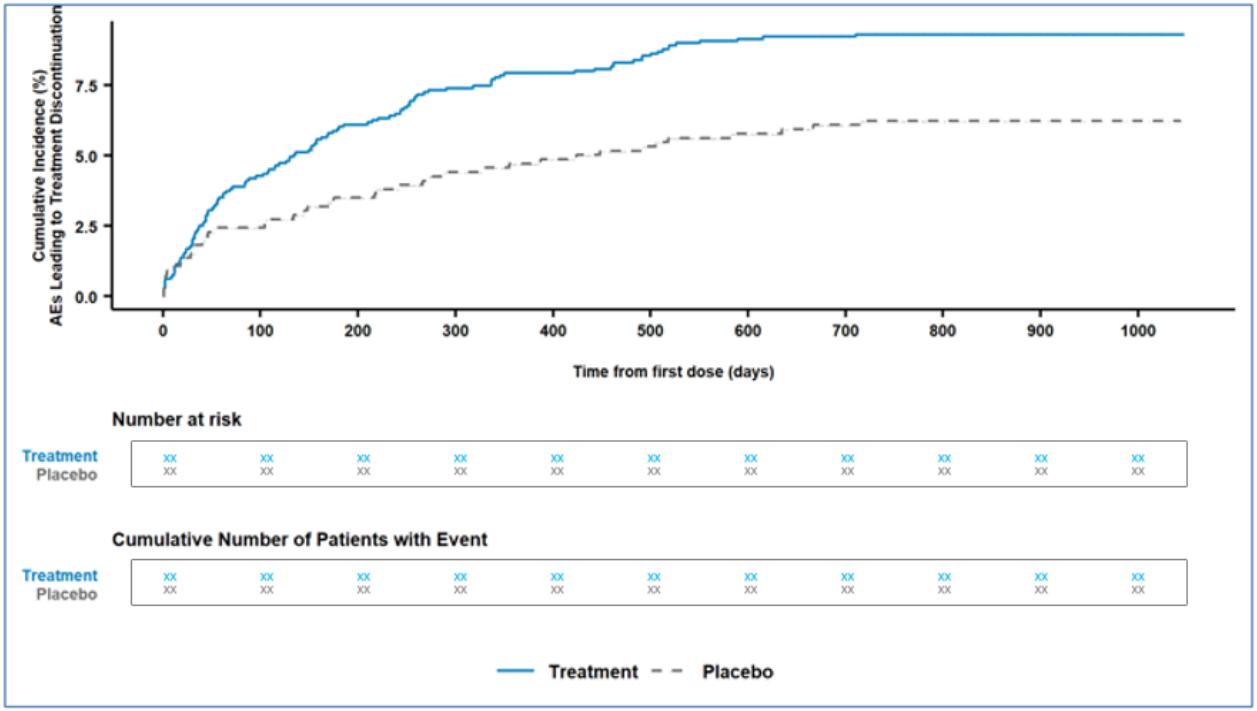
Figure 2. Time to Last Follow Up,[1] Safety Population, Pooled Analyses



Source: [include source dataset(s) and/or tools used].
[1] Last follow-up date was defined as the last date with a record in source datasets.

Figure 3 shows time to AEs leading to treatment discontinuation throughout the trial. This figure shows a time to event analysis of adverse events that lead to treatment discontinuation by treatment arm. The time period displayed in this figure should be the treatment period as specified by the protocol and not the follow-up period, because an AE cannot lead to treatment discontinuation if the treatment is already discontinued based on the protocol.

Figure 3. Time to Adverse Event Leading to Treatment Discontinuation, Safety Population, Trial X



Source: [include source dataset(s) and tools used].

Customization

If there is an adverse event with very low incidence, a cumulative incidence plot (CIP) may be a better representation compared to a KM plot. A KM plot considers remaining patients in the study and cumulative incidence over time represents actual occurrence; therefore, one can see when the events occurred and get an accurate estimate of the incidence by treatment group.

Adverse Event Analyses

This section provides an analysis of AEs, including serious AEs (SAEs), AEs leading to discontinuation, and AEs of special interest (AESIs). In addition, analyses are also presented by FDA Medical Query (FMQ) arranged by System Organ Class (SOC). All AE tables and figures in this document present treatment-emergent adverse events (TEAEs) as a default.

The FMQs are standardized groupings of related Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs), categorized as either narrow or broad, that have been developed by FDA reviewers to facilitate safety signal detection in the premarket safety database. Narrow terms indicate a high degree of certainty that the FMQ concept occurred, while broad terms should be considered more exploratory or hypothesis generating. Preferred terms can appear within more than one FMQ. For instance, the PT Cerebral Hemorrhage occurs in the narrow category for both the FMQs Hemorrhage and Stroke-TIA. Therefore, to avoid double counting of adverse events, the results of different FMQs should not be added together. For tables that include FMQs, all FMQs should be run. In general, PTs are ordered by decreasing risk difference (RD). In displays of FMQ data, tables are arranged by SOC; if there are multiple FMQs within the SOC, FMQs are ordered by decreasing RD. For further analyses, including analyses by PT, refer to the Standard Expanded Safety Tables and Figures.

Adverse event tables should be produced for pooled analyses, individual registration trials, and any other trials of interest of the reviewer. Consider exposure-adjusted incidence rates (EAIRs) (number of subjects or number of events divided by the total person years/cycles) as appropriate. These situations include substantially different treatment or trial duration, differential discontinuation between arms, or relatively rare AESIs being evaluated.

Table 6 shows an overview of AEs and includes incidence of SAEs based on individual components of the SAE criteria.

Table 6. Overview of Adverse Events,[1] Safety Population, Pooled Analyses[2]

Event	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
SAE	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
SAEs with fatal outcome	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Life-threatening SAEs	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SAEs requiring hospitalization	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SAEs resulting in substantial disruption of normal life functions	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Congenital anomaly or birth defect	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Other	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
AE leading to permanent discontinuation of study drug	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**

Event	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
AE leading to dose modification of study drug	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
AE leading to interruption of study drug	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
AE leading to reduction of study drug	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
AE leading to dose delay of study drug	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Other	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Any AE[4]	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
Severe	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Moderate	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Mild	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

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

[1] Treatment-emergent AE defined as [definition]. MedDRA version X.

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

[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).

[4] Severity as assessed by the investigator

Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

Serious Adverse Events

This section describes serious AEs, which are defined as any untoward medical occurrence that, at any dose results in death, is life-threatening, requires 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, jeopardize the patient and require medical or surgical intervention to prevent one of the outcomes listed above.

All deaths that occurred in the development program, excluding those deaths considered to be an effectiveness clinical trial outcome, should be included, without regard to investigator or Applicant judgment about causality.

Customization

A KM plot for deaths (if numerous) may be helpful. Consider requesting a similar table that displays results by individual trials of large size, if the population studied is considered to be at high risk, or for trials that include a large number of deaths.

Table 7. Deaths, Safety Population, Pooled Analyses[1]

Deaths	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[2]
Total deaths	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
Cause of death 1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Cause of death 2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Treatment-emergent deaths[3]	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
Cause of death 1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Cause of death 2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Nontreatment-emergent deaths[4]	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
Cause of death 1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Cause of death 2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Cause of death 3	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[2] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[3] Treatment-emergent AE defined as [definition]. MedDRA version X.
[4] Defined as [(e.g., deaths beyond the protocol-defined treatment-emergent adverse event period in the same trial or deaths from other trials with drug)].
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event

Table 8 provides a list of all patient deaths from the adverse event as well as disposition datasets (AEs with outcome death from adverse events datasets, and patients who died due to natural causes and are only listed in the disposition datasets). Summarize deaths in a table as appropriate. The study day of death below shows date of death, not date of onset of SAE leading to death.

Table 8. All Individual Patient Deaths, Safety Population, Pooled Analyses[1]

Study Arm	Patient ID	Age/ Gender	Dosage	Dosing Duration (Days)	Study Day of Death	Cause of Death	
						MedDRA Preferred Term	Verbatim Term
Drug X	X	X/Y	X mg	X	X	PT1	VT1
Placebo	X	X/Y	X mg	X	X	PT2	VT2

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

Table 9. Patients With Serious Adverse Events[1] by System Organ Class and Preferred Term, Safety Population, Pooled Analyses[2]

System Organ Class Preferred Term	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Any SAE	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
SOC1	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT3	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SOC2	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT3	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires 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.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SAE, serious adverse event; SOC, System Organ Class

Table 10 provides a list of SAEs by SOC and FMQ (narrow). Refer to Table 34 to view the specific preferred terms under each FMQ.

Customization

A similar table of SAE by SOC and FMQ (broad) can be generated if desired.

Table 10. Patients With Serious Adverse Events[1] by System Organ Class and FDA Medical Query (Narrow), Safety Population, Pooled Analyses[2]

System Organ Class[4] FMQ (Narrow)	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
SOC1					
FMQ1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SOC2					
FMQ3	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ4	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires 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.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[4] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain preferred terms from more than one SOC.
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, System Organ Class

See Table 34 for the specific preferred terms under each FMQ.

Customization

A similar table of FMQ (broad) leading to treatment discontinuation may be generated if desired.

Table 11. Patients with FDA Medical Query (Narrow) Leading to Treatment Discontinuation, Safety Population, Pooled Analyses[1]

System Organ Class[3] FMQ (Narrow)	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[2]
Patients with at least one AE leading to discontinuation	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
SOC1	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
FMQ1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SOC2	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
FMQ3	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ4	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[2] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[3] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain preferred terms from more than one SOC.
Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA Medical Query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, System Organ Class

See Table 43 for discontinuation by SOC, FMQ (narrow), and the specific preferred terms for these FMQs.

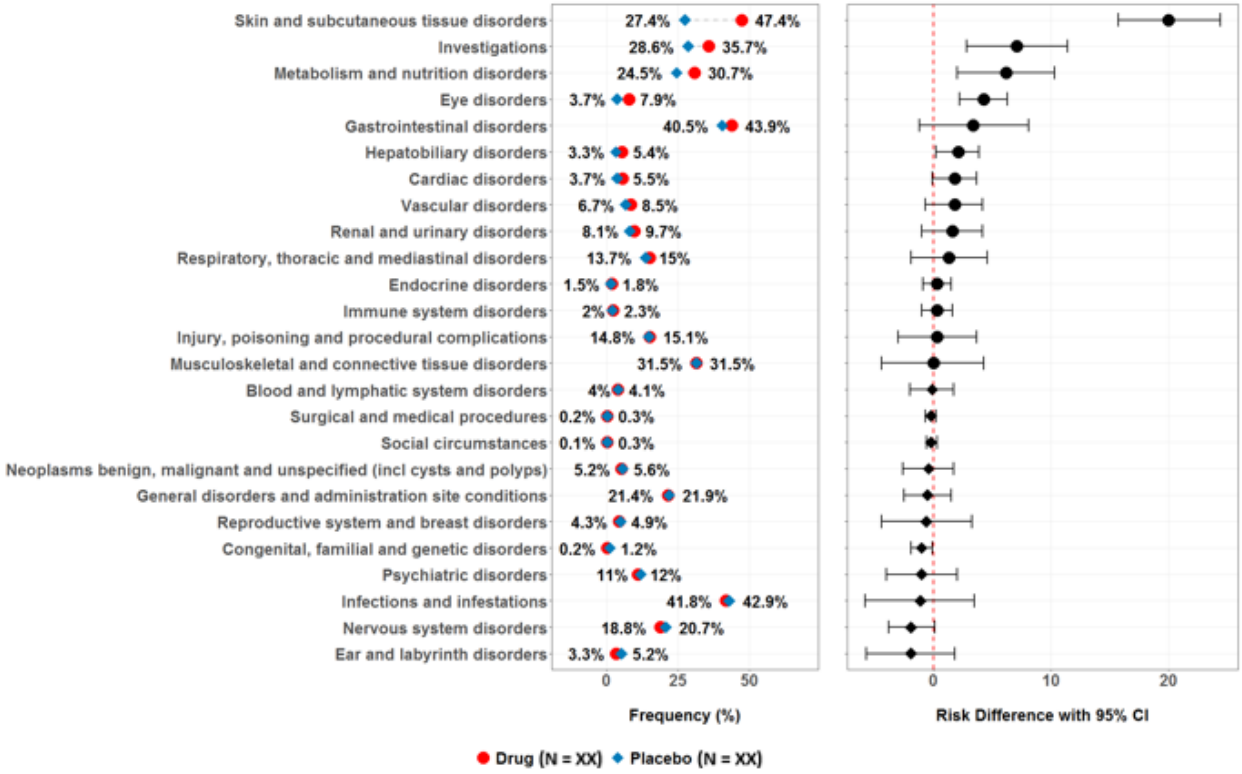
Table 12. Patients With Adverse Events[1] Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Pooled Analyses[2]

System Organ Class Preferred Term	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Patients with at least one AE leading to discontinuation	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
SOC1	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT3	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SOC2	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT3	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent adverse event defined as [definition]. MedDRA version X.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with at least one event; PT, preferred term; SOC, System Organ Class

Treatment-Emergent Adverse Events

Figure 4. Patients With Adverse Events[1] by System Organ Class, Safety Population, Pooled Analyses



Source: [include source dataset(s) and software tools used].
[1] Treatment-emergent adverse event defined as [definition].
Abbreviation: CI, confidence interval

Table 13 is useful for analyses of common TEAEs. After analyzing Table 13, please refer to Table 36 to view entire table of adverse events and to support product labeling Section 6.1 “Adverse Reactions—Clinical Studies Experience.”

Table 13. Patients With Common Adverse Events[1] Occurring at ≥X% Frequency, Safety Population, Pooled Analyses[2]

Preferred Term[3]	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[4,5]
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT3	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

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

For Table 14, it's important to review the entire table and then decide the appropriate cutoff. For example, >5%, >2%, or >1% frequency may be an appropriate cutoff or none, depending on the data presented. Refer to Table 33 to view specific preferred terms under each FMQ by SOC.

Table 14. Patients With Adverse Events[1] by System Organ Class and FDA Medical Query, Safety Population, Pooled Analyses[2]

	Narrow FMQs				Broad FMQs			
System Organ Class[4] FMQ	**Drug Name N = XXX n (%)**	**Active Control N = XXX n (%)**	**Placebo N = XXX n (%)**	**Risk Difference (%) (95% CI)[3]**	**Drug Name N = XXX n (%)**	**Active Control N = XXX n (%)**	**Placebo N = XXX n (%)**	**Risk Difference (%) (95% CI)[3]**
SOC1								
FMQ1	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ3	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
SOC2								
FMQ1	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ3	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
SOC3								
FMQ1	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ3	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent adverse event defined as [definition]. MedDRA version X.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo)
[4] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with at least one event; SOC, System Organ Class

Some FMQs are relevant to only one sex. For instance, the Erectile Dysfunction FMQ is relevant only to males while the Abnormal Uterine Bleeding FMQ is relevant only to females. Therefore, the tables that present these sex-specific FMQs (Tables 15 to 18) provide only the results for males or females, as appropriate, and have smaller denominators than the full safety population.

Table 15. Patients With Adverse Events by Male-Specific FDA Medical Query (Narrow)[1] and Preferred Term, Male Safety Population, Pooled Analyses[2]

FMQ (Narrow) Preferred Term	Drug A Dosage X N = XXX n (%)	Drug A Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Erectile Dysfunction	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Gynecomastia	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent adverse event defined as [definition]. MedDRA version X.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with at least one event; PT, preferred term

Table 16. Patients With Adverse Events by Male-Specific FDA Medical Query (Broad)[1] and Preferred Term, Male Safety Population, Pooled Analyses[2]

FMQ (Broad) Preferred Term	Drug A Dosage X N = XXX n (%)	Drug A Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3,4]
Erectile Dysfunction	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Gynecomastia	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent adverse event defined as [definition]. MedDRA version X.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[4] Table displays categories by risk difference.
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with at least one event; PT, preferred term

Table 17. Patients With Adverse Events by Female-Specific FDA Medical Query (Narrow)[1] and Preferred Term, Female Safety Population, Pooled Analyses[2]

FMQ (Narrow) Preferred Term	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Abnormal Uterine Bleeding	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Amenorrhea	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Bacterial Vaginosis	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

FMQ (Narrow) Preferred Term	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Decreased Menstrual Bleeding	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

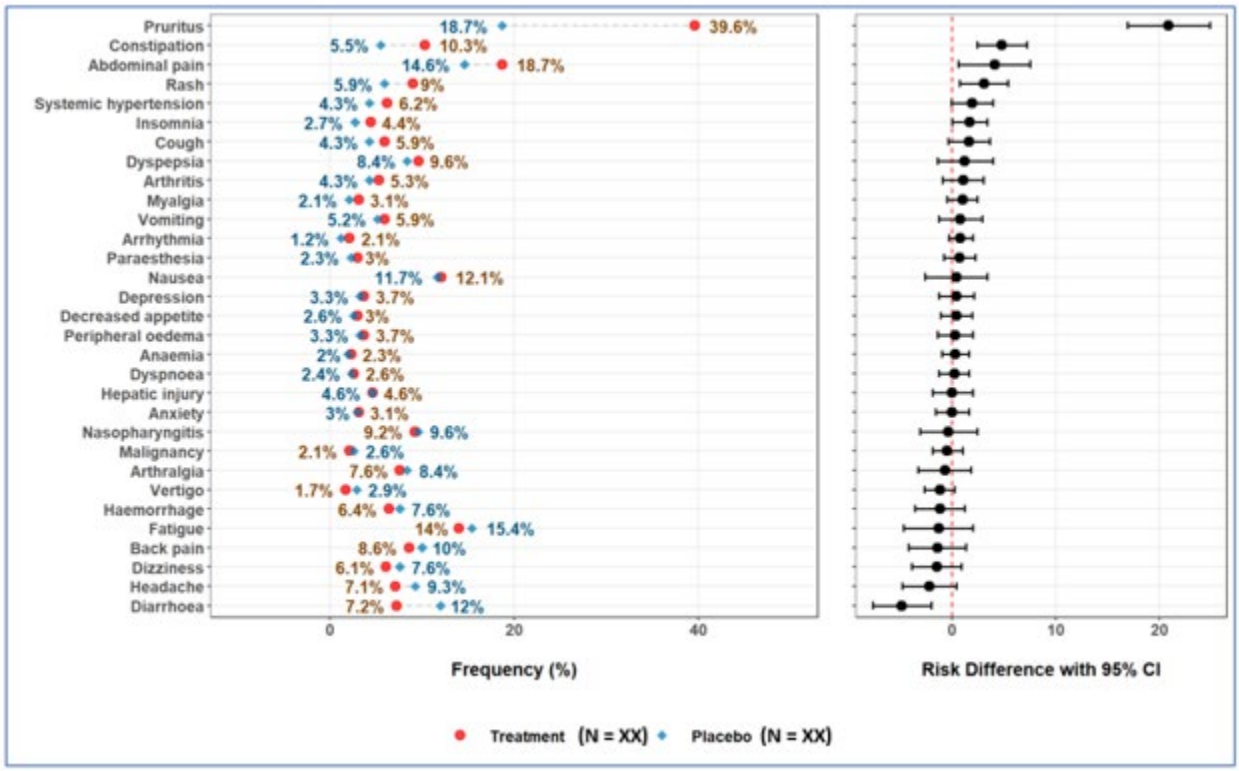
Source: [include Applicant source, datasets and/or software tools used].
[1] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[2] Treatment-emergent adverse event defined as [definition]. MedDRA version X.
[3] Difference is shown between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

Table 18. Patients With Adverse Events by Female-Specific FDA Medical Query (Broad)[1] and Preferred Term, Female Safety Population, Pooled Analyses[2]

FMQ (Broad) Preferred Term	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3,4]
Abnormal Uterine Bleeding	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Amenorrhea	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Bacterial Vaginosis	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Decreased Menstrual Bleeding	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[2] Treatment-emergent adverse event defined as [definition]. MedDRA version X.
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[4] Table displays categories by risk difference.
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term

Figure 5. Patients With Adverse Events[1] ≥X% in Any Treatment Arm by FDA Medical Query (Narrow), Safety Population, Trial X



Source: [include Applicant source, datasets and/or software tools used].
Abbreviations: FMQ, FDA Medical Query; N, number of patients in treatment arm

Algorithmic FMQs are an important step forward in signal detection, as these include data from not only the AE dataset, but also the laboratory, concomitant medications and the medical history datasets. They also evaluates temporal relationships as appropriate. Four algorithmic FMQs have been developed so far, and are presented below. Note that algorithmic FMQs are still in development and will be updated as more experience is gained by using them in NDA/BLA safety evaluations.

Table 19 shows n (%) of patients picked up by the algorithmic FMQs. Refer to Tables 39 to 42 for details on each criteria that make up the algorithm.

Table 19. Patients With Algorithmic FDA Medical Query, Safety Population, Pooled Analysis (or Trial X)

Algorithmic FMQ	Drug Name Dosage X N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Hypersensitivity	n (%)	n (%)	n (%)
Hyperglycemia	n (%)	n (%)	n (%)
Hypoglycemia	n (%)	n (%)	n (%)
Rhabdomyolysis and other muscle injury	n (%)	n (%)	n (%)

Source: [include Applicant source, datasets and/or software tools used].
Abbreviations: FMQ, FDA Medical Query; N, number of patients in treatment arm; n, number of patients with adverse event

Adverse Events of Special Interest

A protocol specified definition for AESI should be discussed with the review division at milestone meetings including the Type C ISS safety meeting.

The information described in Table 20 may vary depending on the AE and may combine observations across different datasets to provide a complete picture of the AE (e.g., laboratory and adverse event datasets). In some cases, AESIs are not defined based on only MedDRA terms and instead are based on a targeted query or adjudicated results (e.g., major adverse cardiovascular event).

Table 20. Adverse Events of Special Interest Assessment, Safety Population, Pooled Analysis (or Trial X)[1]

AESI Assessment	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[2]
AE grouping related to AESI[3]	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Maximum severity[3]					
Severe	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Moderate	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Mild	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Serious[3]	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Deaths	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Resulting in discontinuation	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Relatedness[4]	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Laboratory Assessment[5]	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[2] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[3] Use FMQ grouping if appropriate.
[4] As determined by investigator.
[5] Include relevant laboratory results as appropriate for AESI evaluation.
Abbreviations: AESI, adverse event of special interest; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event

Subgroup Analyses by Baseline Characteristics

The benefit-risk profile of an investigational drug product may differ across subgroups of patients who share certain baseline characteristics. “Subgroup analysis” refers to evaluation of treatment effects for a specific safety or efficacy endpoint within a specific study population that share certain baseline characteristics. The main aim of conducting subgroup analyses during the safety review is to assess for potential differences in safety among different categories of the study population and identify subgroups that are more vulnerable to certain adverse drug effects (e.g., high rate of certain AEs in females compared to males).

Documenting findings of safety by demographic subgroups (sex, age, race, and ethnicity) is required under Food and Drug Administration Safety and Innovation Act Section 907. An example of an overview of adverse events by demographic subgroup is shown in Table 22.

Customization

- Specify the **AE/SAE terms** for which subgroup incidences should be provided. This may be AEs of special interest or FMQs or specific AE PTs which were found to be notably higher in the study drug treatment arm. Subgroup analyses can also be provided for imbalances in safety laboratory analyte measurements meeting Level 2 increases or decreases (e.g., increase in alanine aminotransferase, or decreases in estimated glomerular filtration rate (eGFR). The list of AE/FMQs for subgroup analysis should be focused on only relevant AE/FMQs—given the large number of subgroups routinely evaluated (i.e., requesting subgroup analyses on a large number of AEs/FMQs without specific rationale for the inclusion of particular AE/FMQs, is not usually appropriate).
- Provide any additional **potentially relevant subgroups** beyond the standard demographic ones that may shed light on which patients are most susceptible to the safety event (e.g., subgroups by baseline diseases [e.g., cardiovascular disease or diabetes, or by CKD stage], or by concomitant medication, or by anthropometric characteristics [e.g., body mass index]).
- In addition to subgroup analyses examining AE incidence by subgroup factors (as shown below), analyses examining the baseline characteristics of the group of patients in whom the event occurred (vs the overall population of patients) can be helpful. Such analyses may provide insight into susceptibility factors for the safety event. For example, compared to the overall study population are patients with the event older, more likely to be male or more likely to be female, have a more frequent medical history of particular diseases, etc. Such an analysis is only useful when there are sufficient patients with the event to make the characterization of these patients compared to the overall population reasonably robust.

Table 21. Overview of Serious Adverse Events[1] by Demographic Subgroup, Safety Population, Pooled Analysis (or Trial X)

Characteristic	Treatment Arm N = XXX [n/N_S (%)]	Placebo N = XXX [n/N_S (%)]
Any SAE, n (%)	**n (%)**	**n (%)**
Sex, n (%)		
Male	n/N_S (%)	n/N_S (%)
Female	n/N_S (%)	n/N_S (%)
Age group, years, n (%)		
Group 1	n/N_S (%)	n/N_S (%)
Group 2	n/N_S (%)	n/N_S (%)
Group 3	n/N_S (%)	n/N_S (%)
Group 4	n/N_S (%)	n/N_S (%)
Race, n (%)		
American Indian or Alaska Native	n/N_S (%)	n/N_S (%)
Black or African American	n/N_S (%)	n/N_S (%)
Multiple	n/N_S (%)	n/N_S (%)
White	n/N_S (%)	n/N_S (%)
Asian	n/N_S (%)	n/N_S (%)
Native Hawaiian or Other Pacific Islander	n/N_S (%)	n/N_S (%)

Characteristic	Treatment Arm N = XXX [n/N_s (%)]	Placebo N = XXX [n/N_s (%)]
Ethnicity, n (%)		
Hispanic or Latino	n/N_s (%)	n/N_s (%)
Not Hispanic or Latino	n/N_s (%)	n/N_s (%)
Not reported or unknown	n/N_s (%)	n/N_s (%)

Source: [include Applicant source, datasets and/or software tools used].
[1] Defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires 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.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup; SAE, serious adverse event

Table 22. Overview of Adverse Events[1] by Demographic Subgroup, Safety Population, Pooled Analysis (or Trial X)

Characteristic	Treatment Arm N = XXX [n/N_s (%)]	Placebo N = XXX [n/N_s (%)]
Any AE, n (%)	n (%)	n (%)
Sex, n (%)		
Male	n/N_s (%)	n/N_s (%)
Female	n/N_s (%)	n/N_s (%)
Age group, years, n (%)		
Group 1	n/N_s (%)	n/N_s (%)
Group 2	n/N_s (%)	n/N_s (%)
Group 3	n/N_s (%)	n/N_s (%)
Group 4	n/N_s (%)	n/N_s (%)
Race, n (%)		
American Indian or Alaska Native	n/N_s (%)	n/N_s (%)
Black or African American	n/N_s (%)	n/N_s (%)
Multiple	n/N_s (%)	n/N_s (%)
White	n/N_s (%)	n/N_s (%)
Asian	n/N_s (%)	n/N_s (%)
Native Hawaiian or Other Pacific Islander	n/N_s (%)	n/N_s (%)
Ethnicity, n (%)		
Hispanic or Latino	n/N_s (%)	n/N_s (%)
Not Hispanic or Latino	n/N_s (%)	n/N_s (%)
Not reported or unknown	n/N_s (%)	n/N_s (%)

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent adverse event defined as [definition]. MedDRA version X.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities.; N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup

Customization

To further evaluate individual potential safety signals, consider additional subgroup analyses (e.g., application specific AESIs) that explore effects of shared characteristics (e.g., FMQ or PT by demographic subgroups as shown in table below). Consider customizing the table to conduct subgroup analyses using other baseline characteristics (e.g., weight, body mass index, eGFR).

Table 23. Patients With XXX [insert FDA Medical Query/Preferred Term of Interest] by Demographic Subgroups, Safety Population, Pooled Analysis (or Trial X)

Characteristic	Treatment Arm N = XXX [n/N_s (%)]	Placebo N = XXX [n/N_s (%)]
Any [insert FMQ/PT of Interest], n (%)	n (%)	n (%)
Sex, n (%)		
Male	n/N_s (%)	n/N_s (%)
Female	n/N_s (%)	n/N_s (%)
Age group, years, n (%)		
Group 1	n/N_s (%)	n/N_s (%)
Group 2	n/N_s (%)	n/N_s (%)
Group 3	n/N_s (%)	n/N_s (%)
Group 4	n/N_s (%)	n/N_s (%)
Race, n (%)		
American Indian or Alaska Native	n/N_s (%)	n/N_s (%)
Black or African American	n/N_s (%)	n/N_s (%)
Multiple	n/N_s (%)	n/N_s (%)
White	n/N_s (%)	n/N_s (%)
Asian	n/N_s (%)	n/N_s (%)
Native Hawaiian or Other Pacific Islander	n/N_s (%)	n/N_s (%)
Ethnicity, n (%)		
Hispanic or Latino	n/N_s (%)	n/N_s (%)
Not Hispanic or Latino	n/N_s (%)	n/N_s (%)
Not reported or unknown	n/N_s (%)	n/N_s (%)

Source: [include Applicant source, datasets and/or software tools used].
Abbreviations: N, number of patients in treatment arm; N_s, total number of patients for each specific subgroup; n, number of patients with adverse event; PT, preferred term

Laboratory Analyses

The following standard safety tables and figures are intended for routine safety analyses of laboratory parameters for new drug and biologic applications. 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, specific outlier criteria, and last value on-treatment analyses, are provided in Standard Expanded Safety Tables and Figures section.

Customization

Visualizations of the figures should be edited, as necessary (e.g., placing a break in the y-axis where appropriate if extreme outliers result in a compressed display of the data).

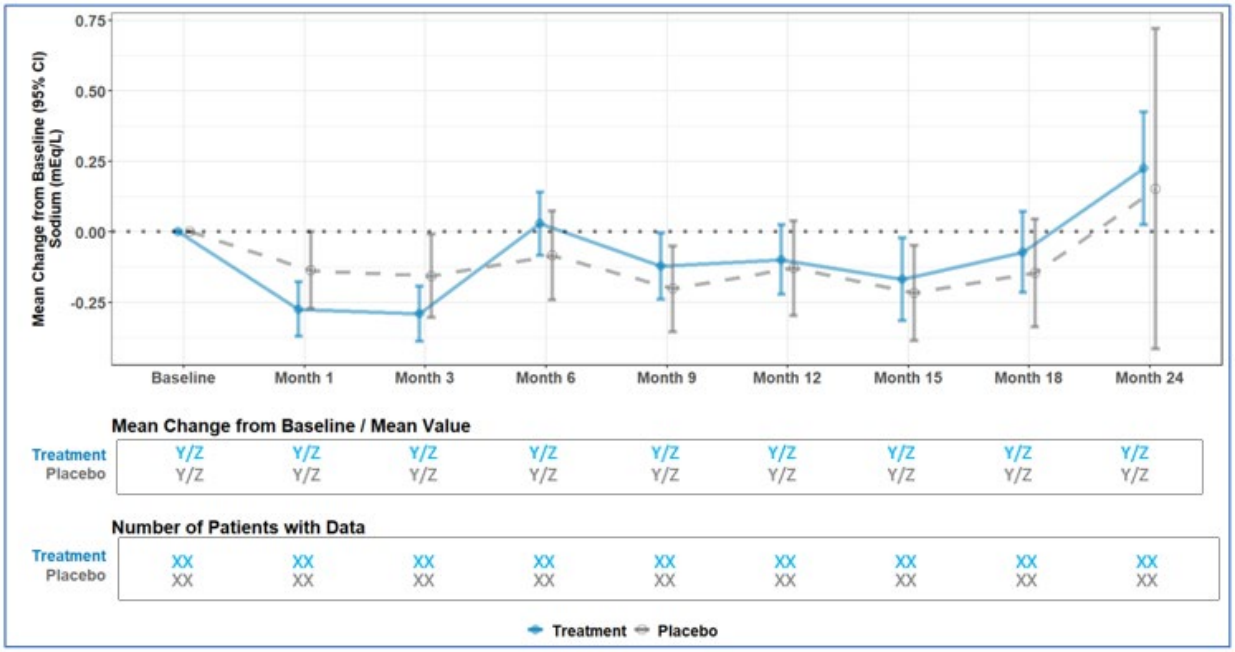
Laboratory Data Change Over Time From Baseline Analyses

The following tables and figures are provided as example displays of mean changes in laboratory values over time and are presented in clinically relevant groupings. Specifically, mean laboratory data change from baseline over timeline charts are presented below. The median, interquartile range, and outlier boxplot graphs and/or the mean laboratory data change from baseline over time tables are also helpful presentations of the data. These tables provide

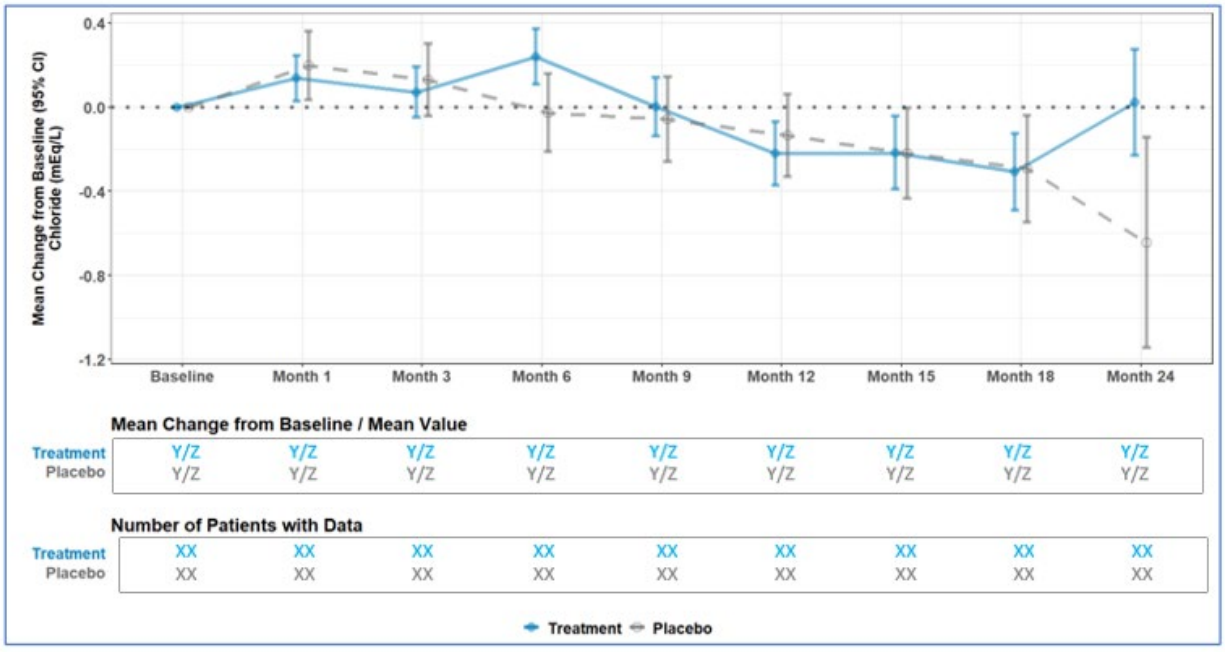
the mean change from baseline laboratory data over time as well as the percent change from baseline laboratory data over time.

Note: Mean laboratory change from baseline graphs show population level means, so when only 5 to 10% of subjects remain in the trial, the data should be truncated. When only 5 to 10% subjects remain in the trial, the characteristics of the subjects in the trial may not reflect the randomization and the visual presentation of sparse data can present noise in the data, which can be misleading. All data can be presented in the median, interquartile range, and outlier analyses boxplots.

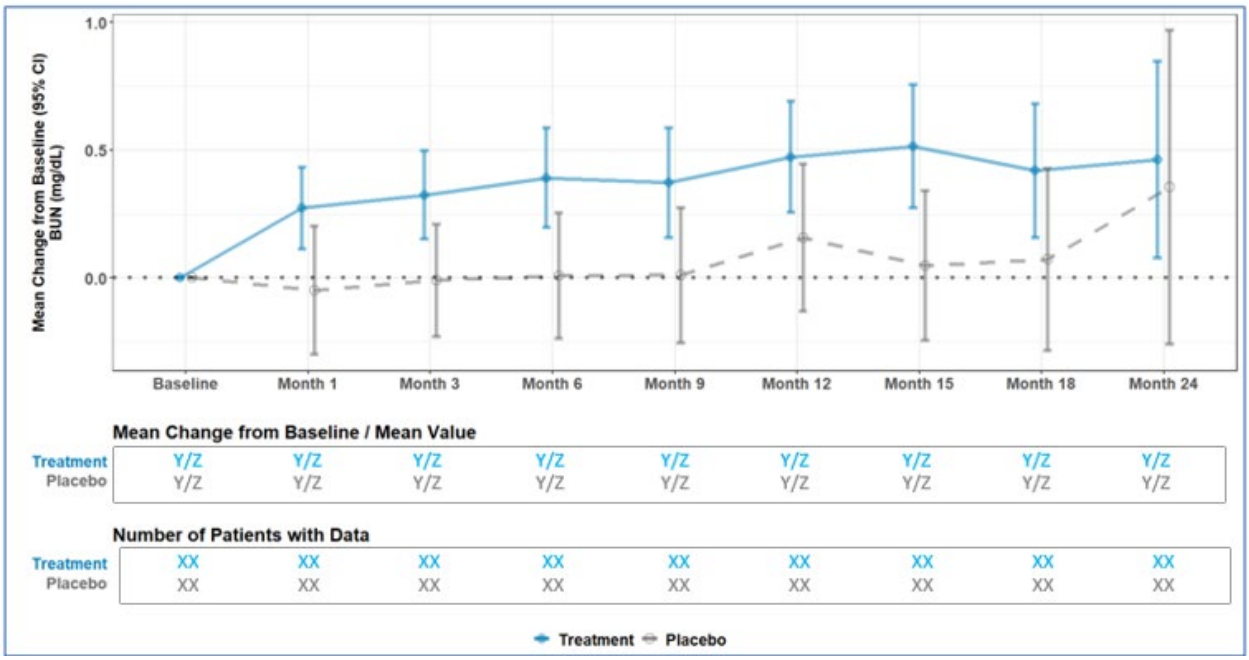
Figure 6. Mean Laboratory (Chemistry) Data Change From Baseline Over Time, Safety Population, Pooled Analyses

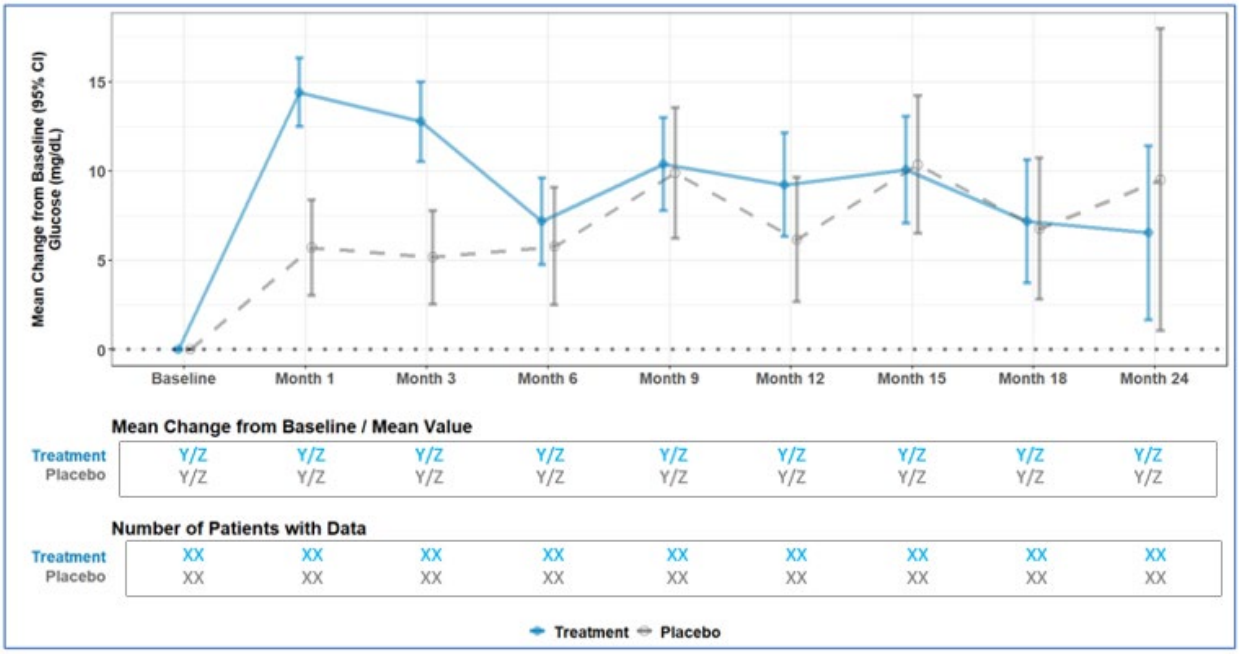


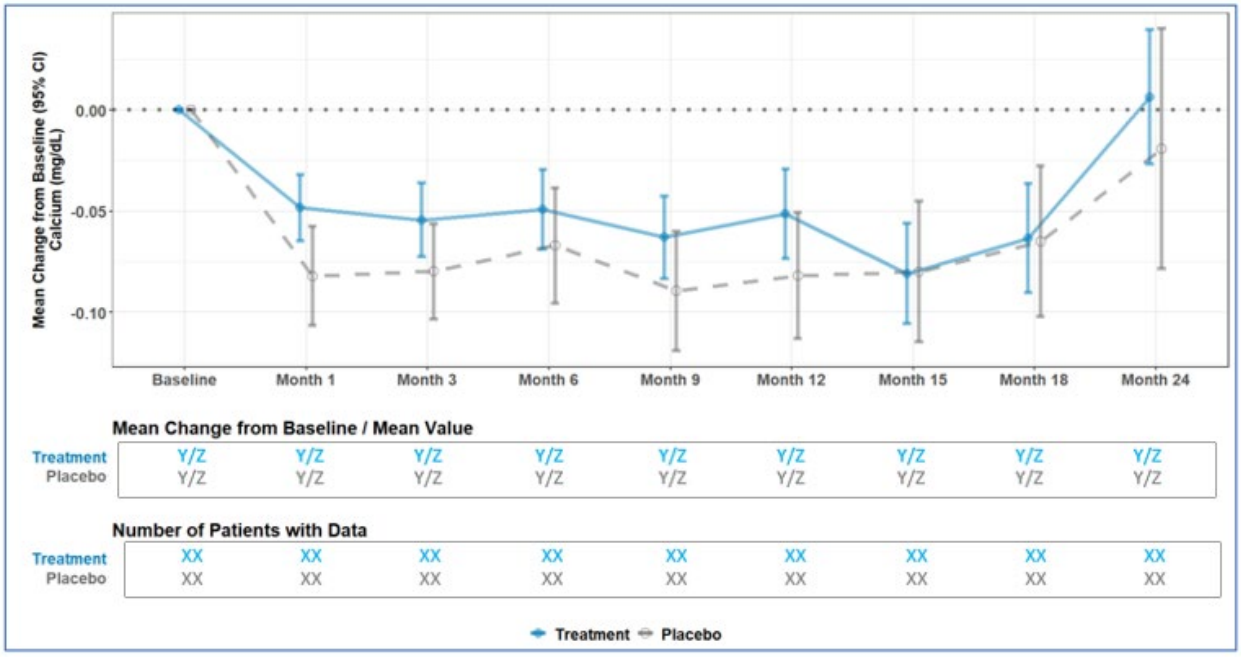

Mean Change from Baseline (95% CI)
Potassium (mEq/L)
0.10
0.05
0.00
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo

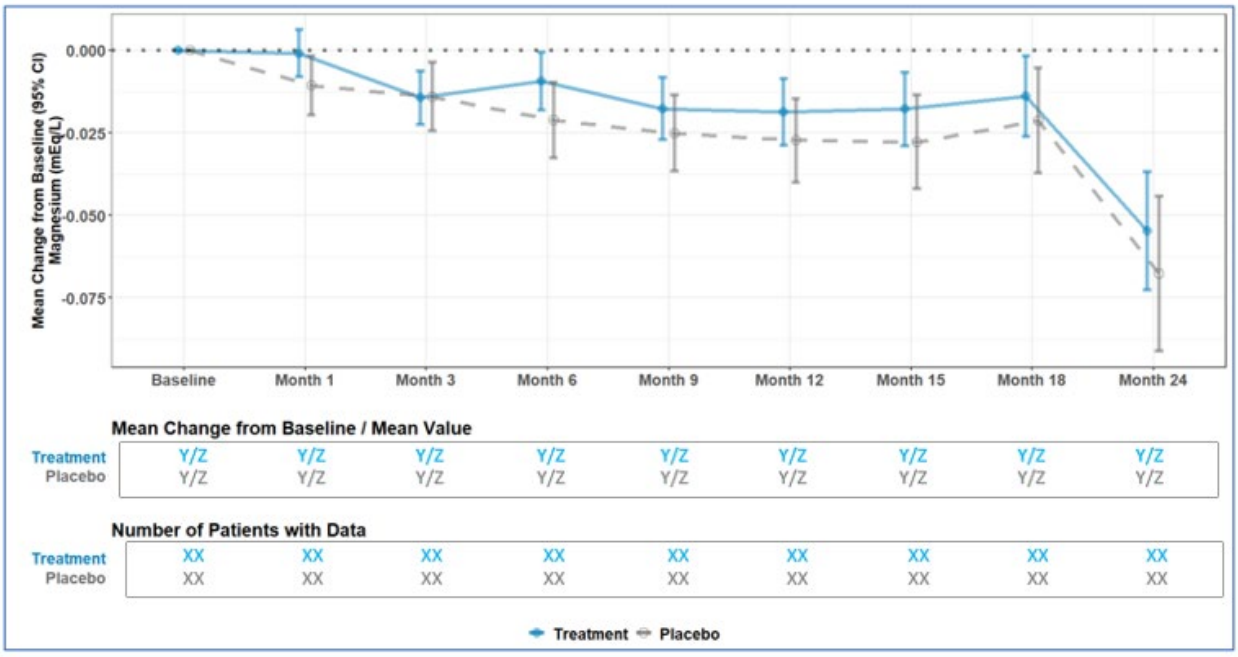

Mean Change from Baseline (95% CI)
Chloride (mEq/L)
0.4
0.0
-0.4
-0.8
-1.2
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo

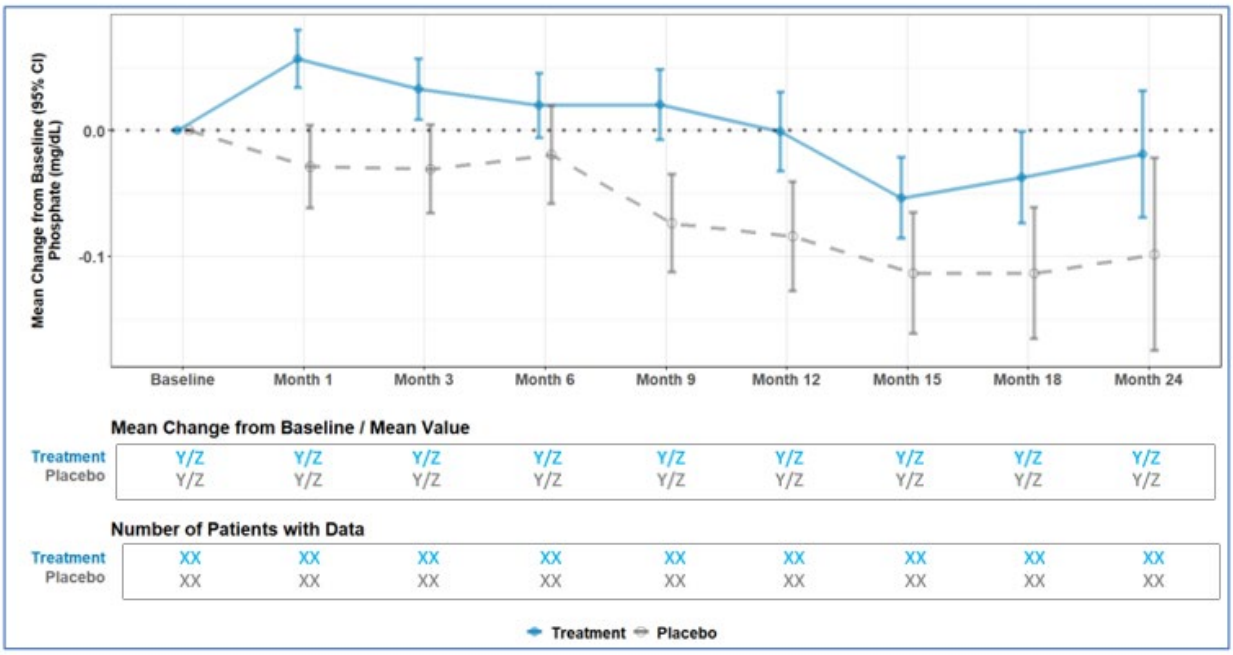

Mean Change from Baseline (95% CI)
Bicarbonate (mEq/L)
0.50
0.25
0.00
-0.25
-0.50
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo

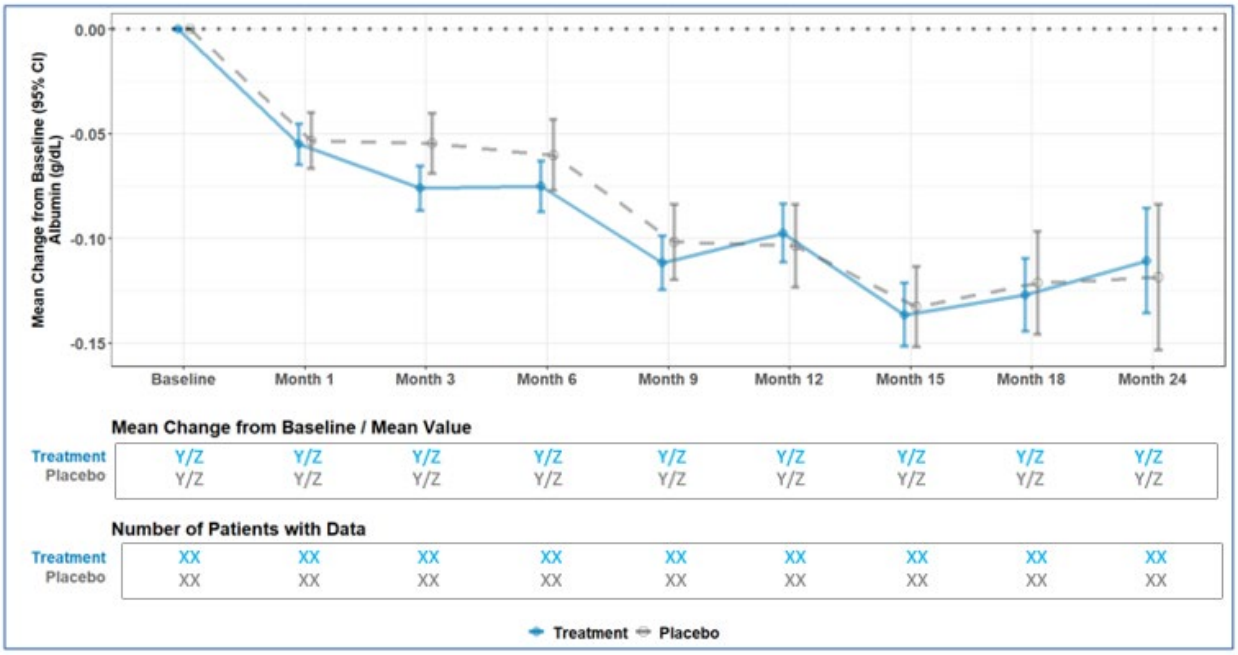

Mean Change from Baseline (95% CI)
BUN (mg/dL)
1.0
0.5
0.0
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo

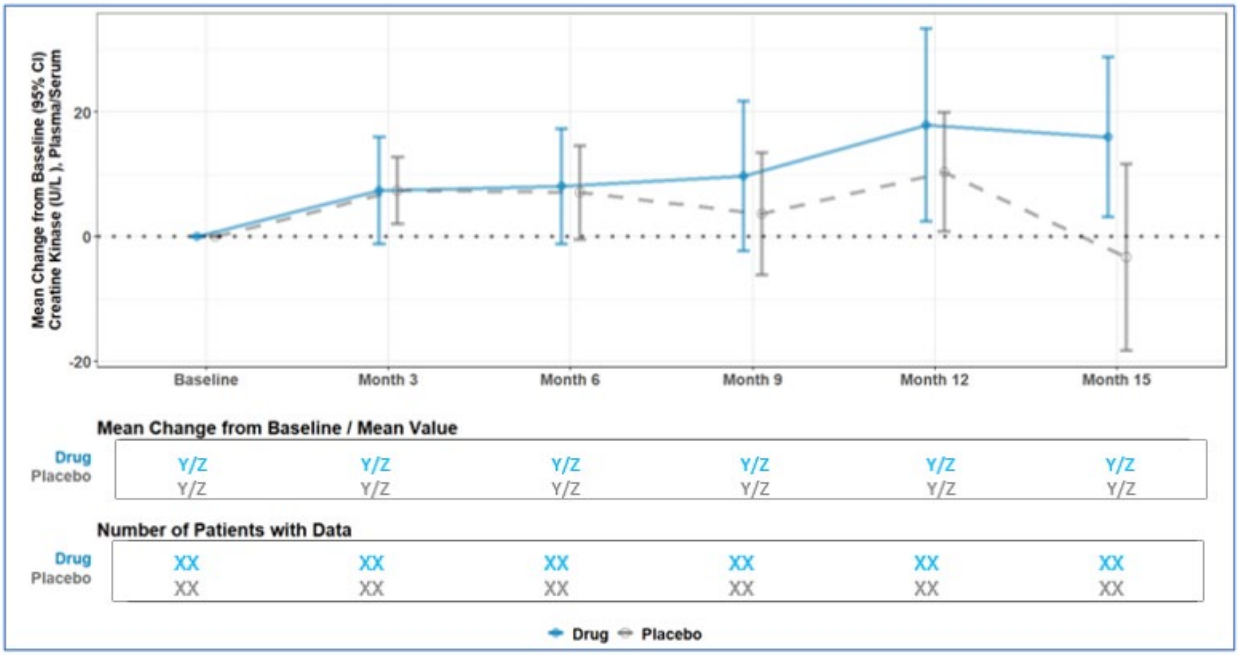

Mean Change from Baseline (95% CI)
Glucose (mg/dL)
15
10
5
0
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo

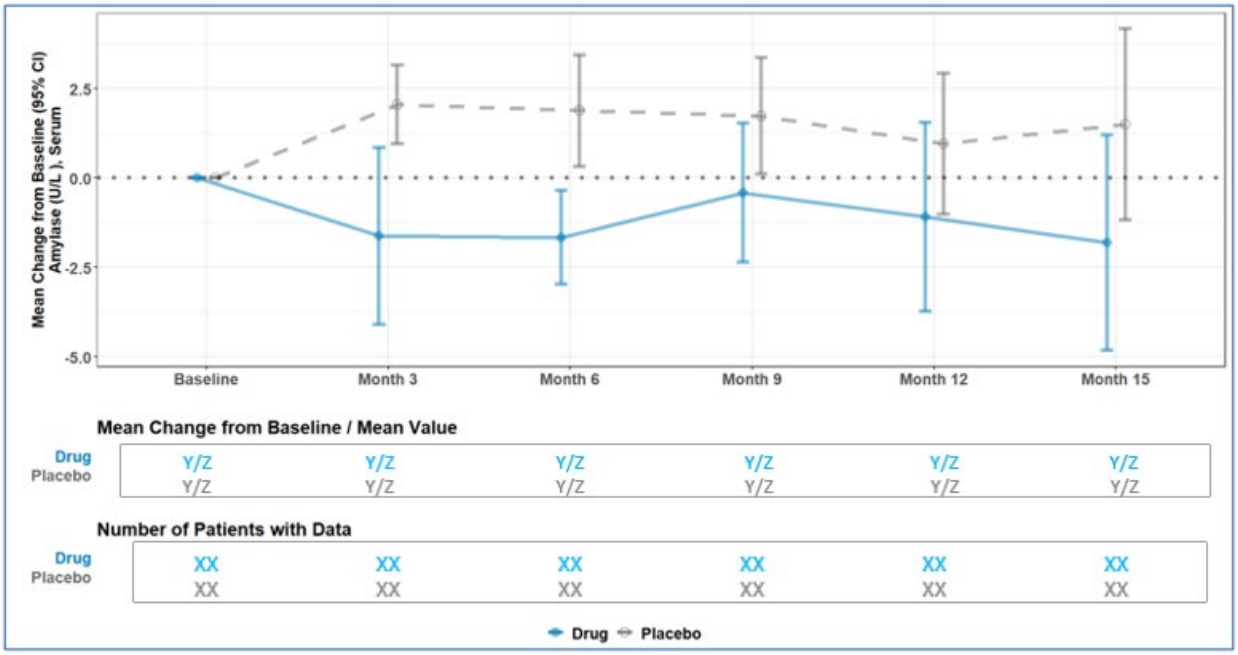

Mean Change from Baseline (95% CI)
Calcium (mg/dL)
0.00
-0.05
-0.10
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo

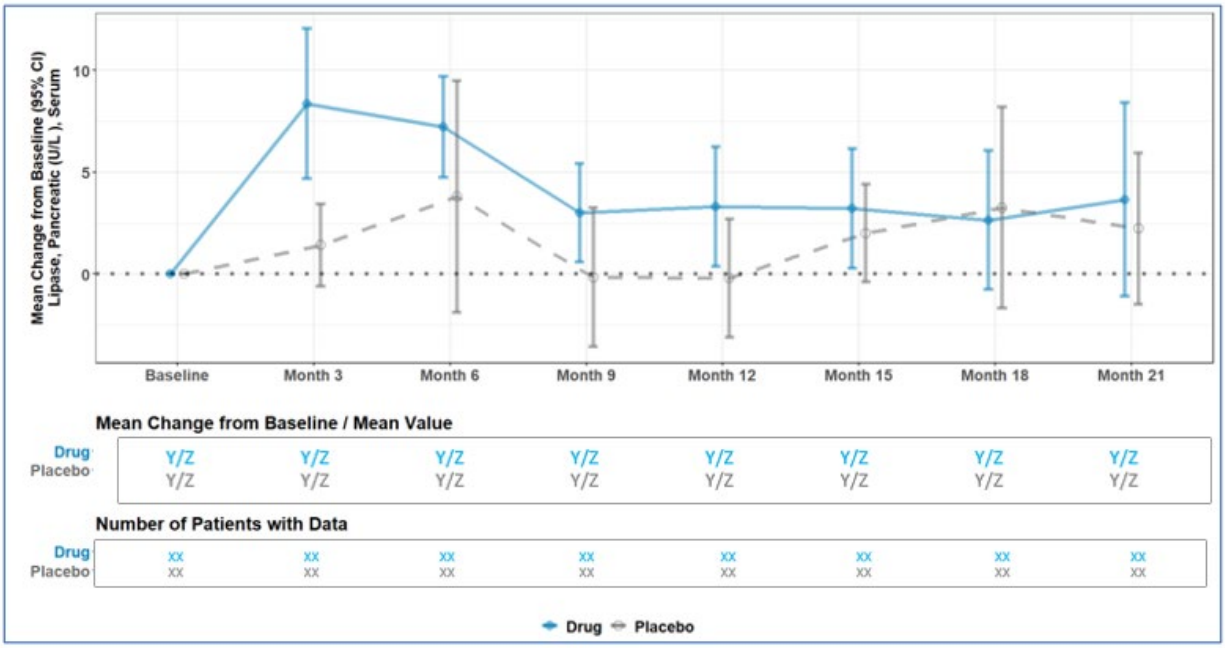

Mean Change from Baseline (95% CI)
Magnesium (mEq/L)
0.000
-0.025
-0.050
-0.075
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo


Mean Change from Baseline (95% CI)
Phosphate (mg/dL)
0.0
-0.1
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo


Mean Change from Baseline (95% CI) Albumin (g/dL)
0.00
-0.05
-0.10
-0.15
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo

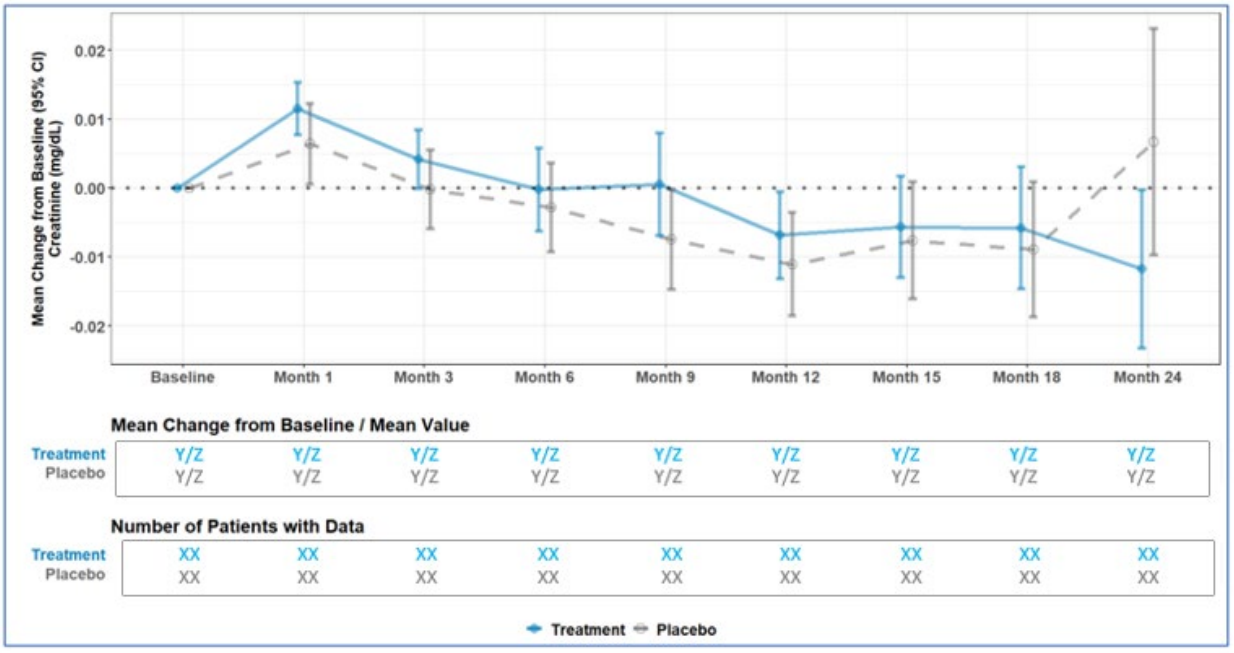

Mean Change from Baseline (95% CI) Creatine Kinase (U/L), Plasma/Serum
20
0
-20
Baseline
Month 3
Month 6
Month 9
Month 12
Month 15
Mean Change from Baseline / Mean Value
Drug Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Drug XX XX XX XX XX XX
Placebo XX XX XX XX XX XX
Drug
Placebo

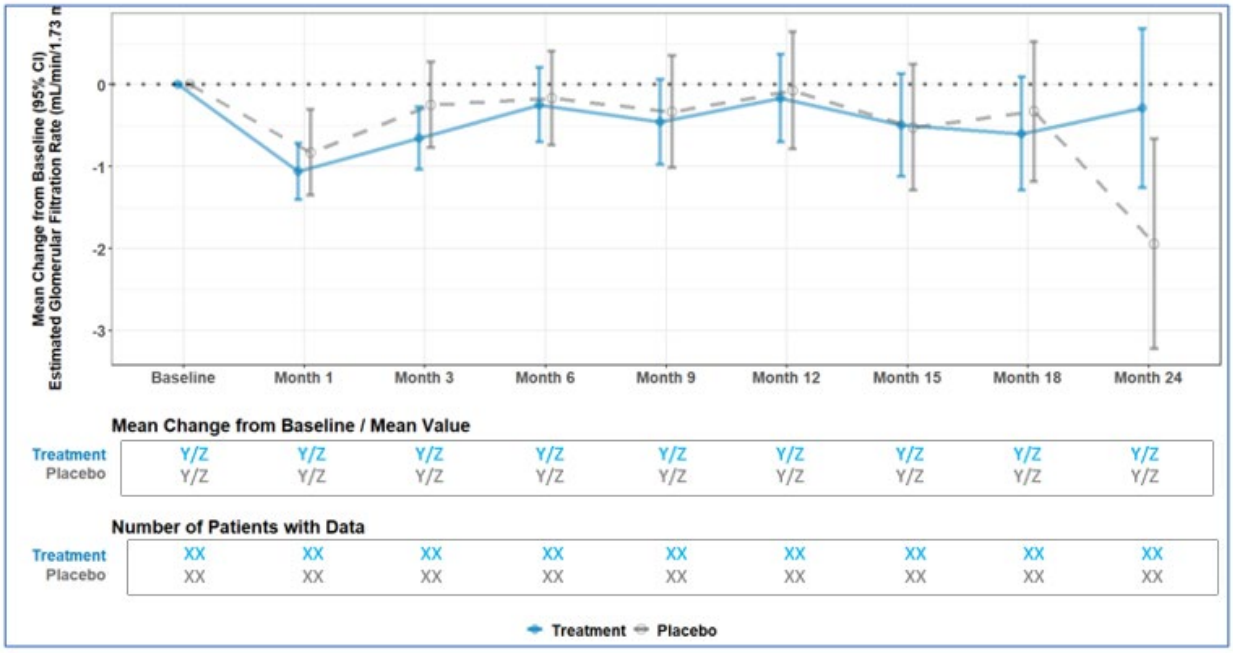




Source: [include Applicant source, datasets and/or software tools used].
Note: Results are provided from baseline until <5 to 10% of randomized population remains in study to avoid presentation of noise in data due to very small number of patients remaining in the trial

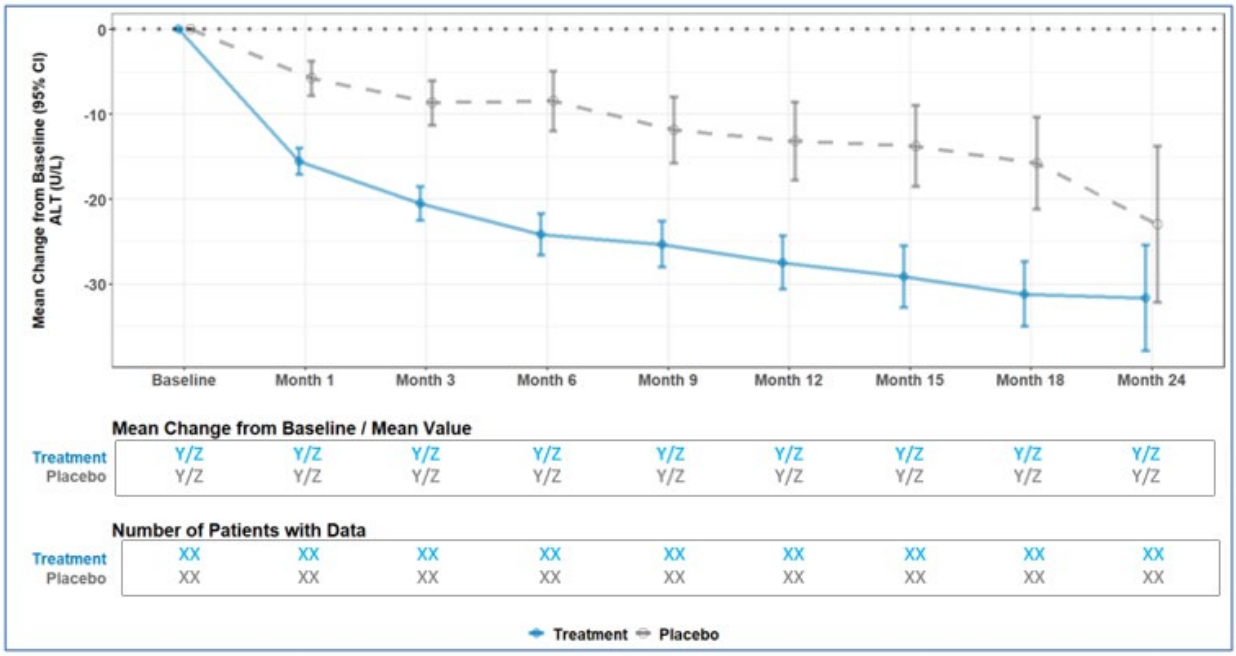
Figure 7. Mean Laboratory (Kidney Function) Data Change From Baseline Over Time, Safety Population, Pooled Analyses

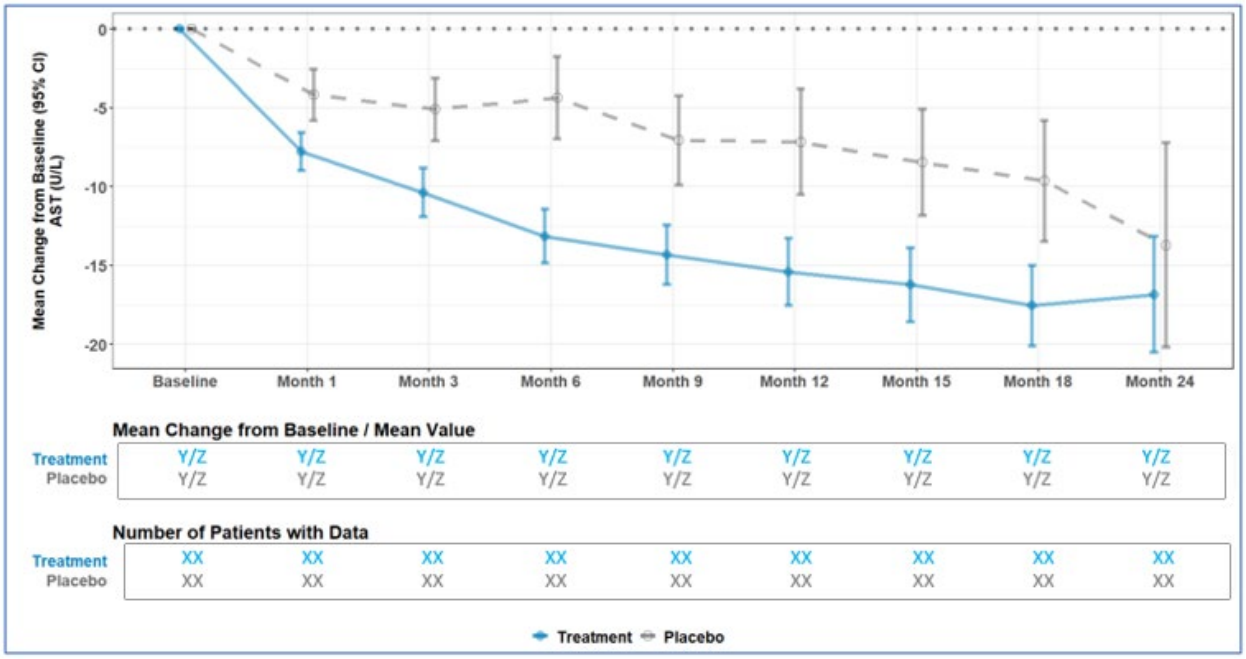


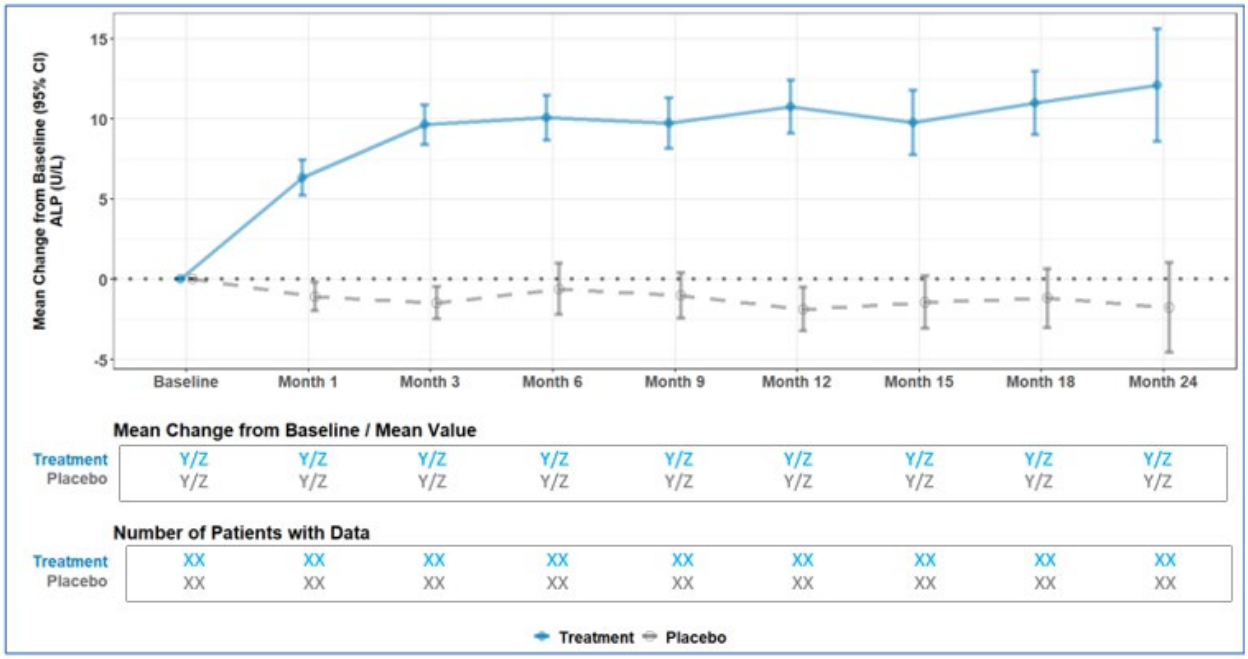


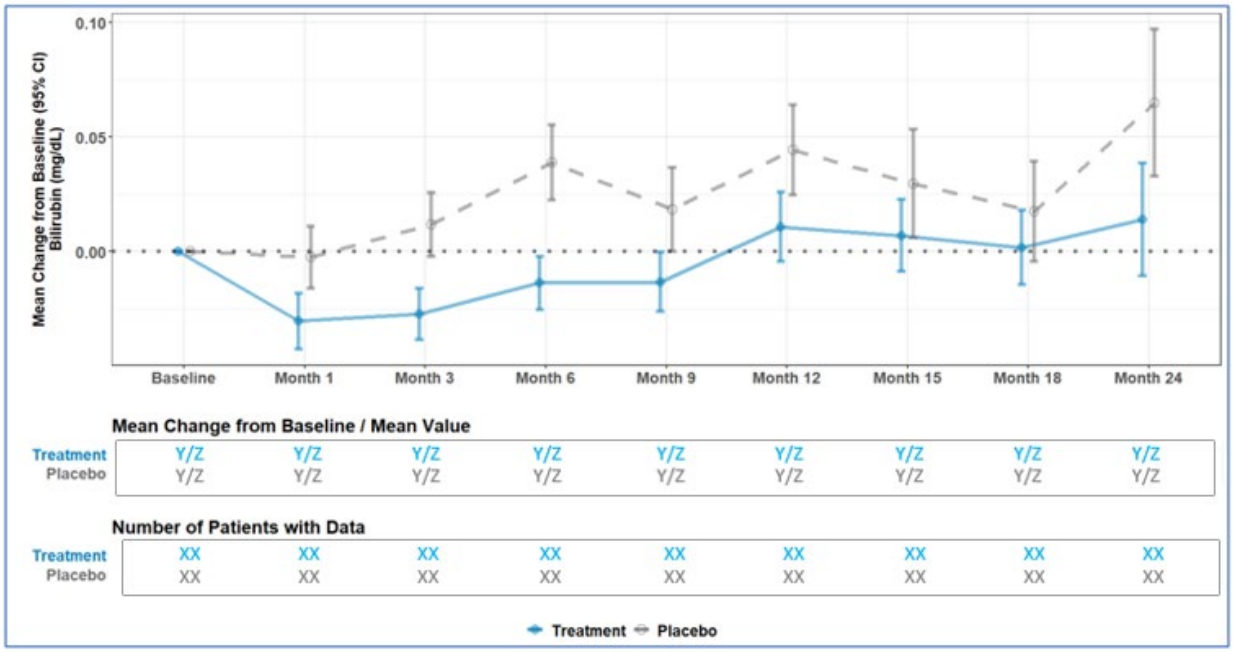
Source: [include source dataset(s)]; software: R
Note: Results are provided from baseline until <5 to 10% of randomized population remains in study to avoid presentation of noise in data due to very small number of patients remaining in the trial

Figure 8. Mean Laboratory (Liver Biochemistry) Data Change From Baseline Over Time, Safety Population, Pooled Analyses

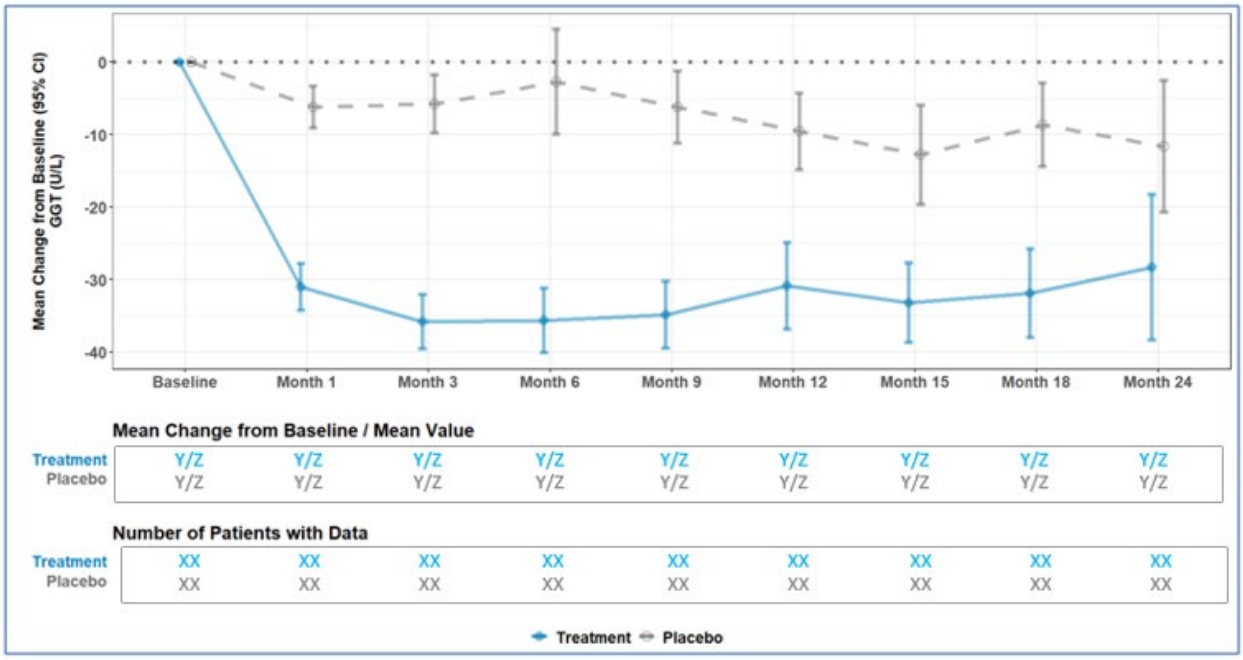


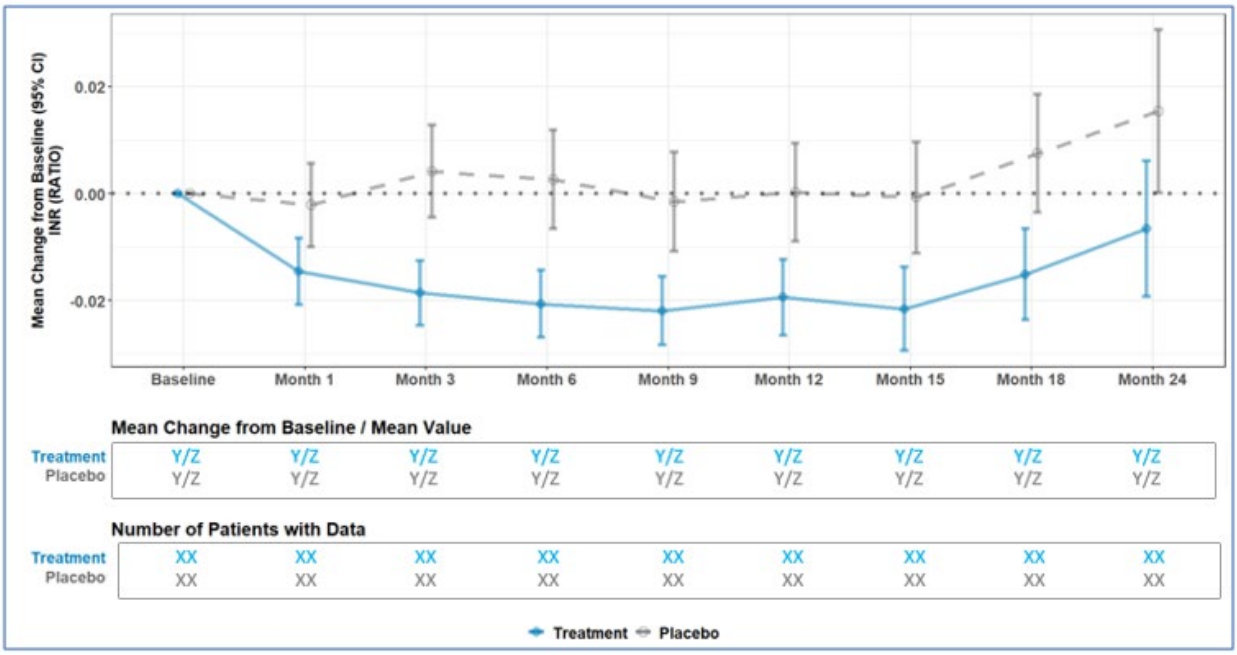



Mean Change from Baseline (95% CI)
ALP (U/L)
15
10
5
0
-5
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo


Mean Change from Baseline (95% CI)
Bilirubin (mg/dL)
0.10
0.05
0.00
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo

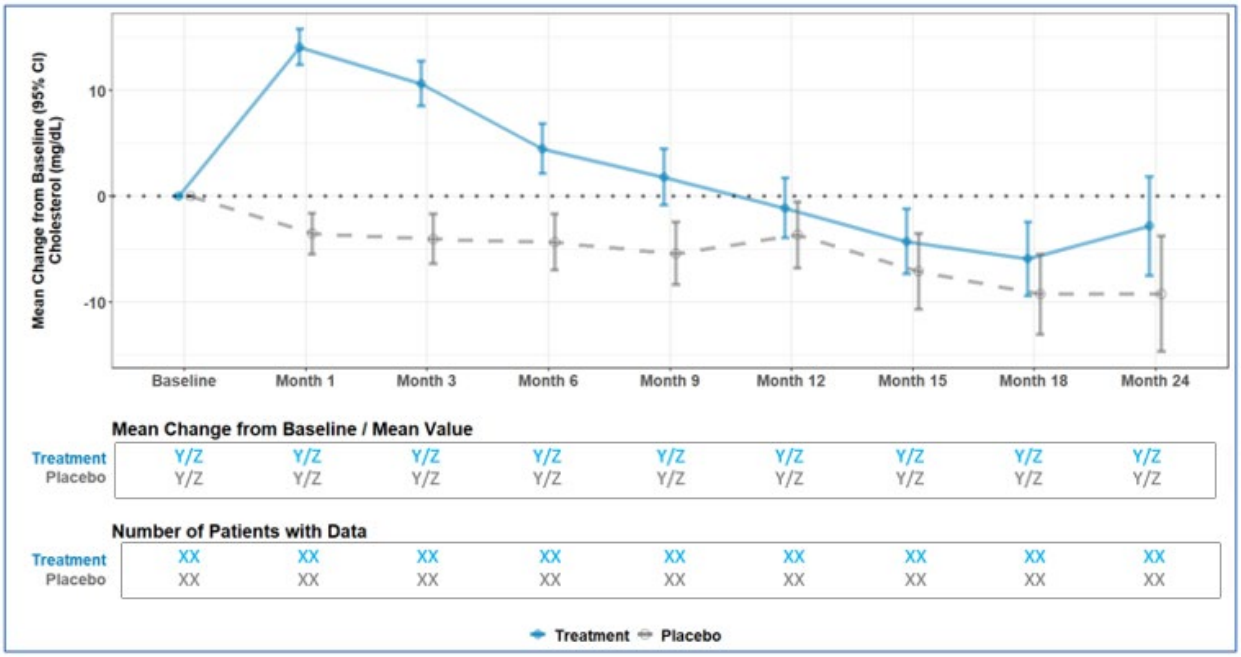

Mean Change from Baseline (95% CI)
Direct Bilirubin (mg/dL)
0.02
0.01
0.00
-0.01
-0.02
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo

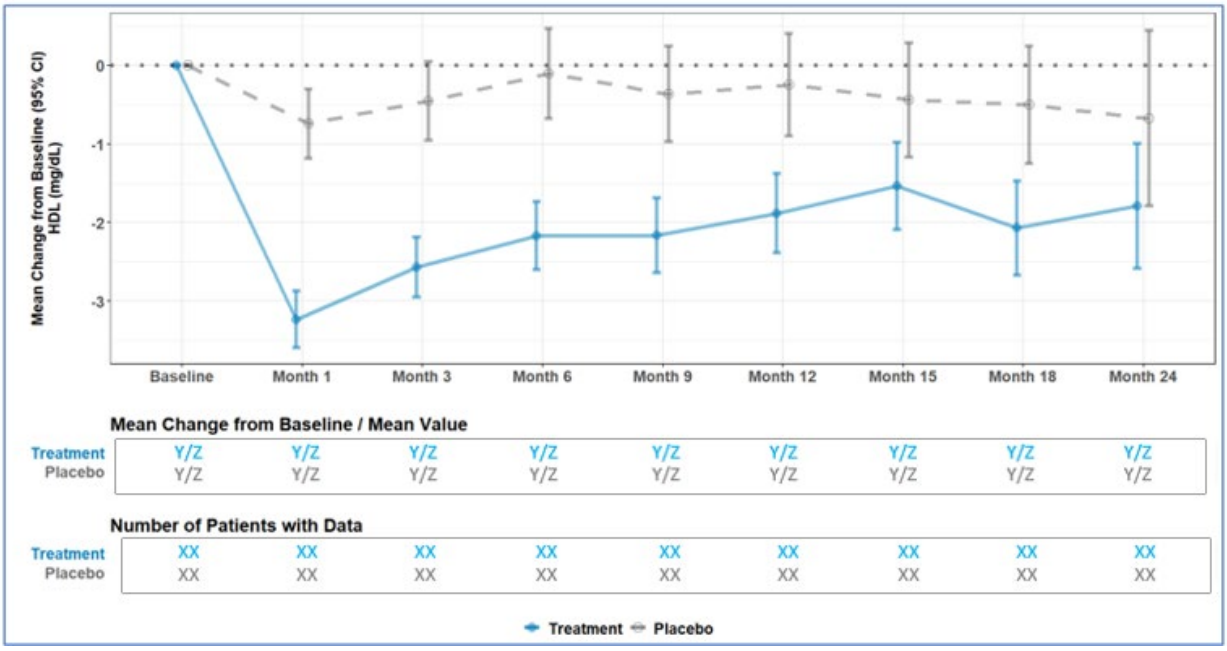

Mean Change from Baseline (95% CI)
GGT (U/L)
0
-10
-20
-30
-40
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo

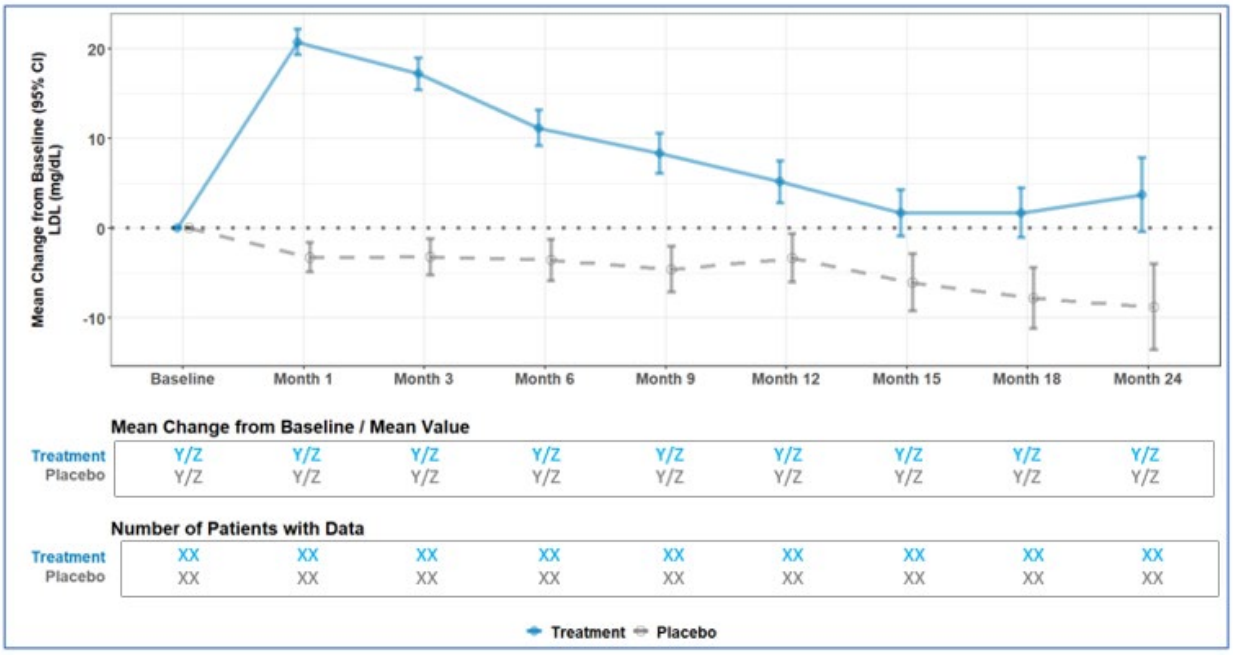


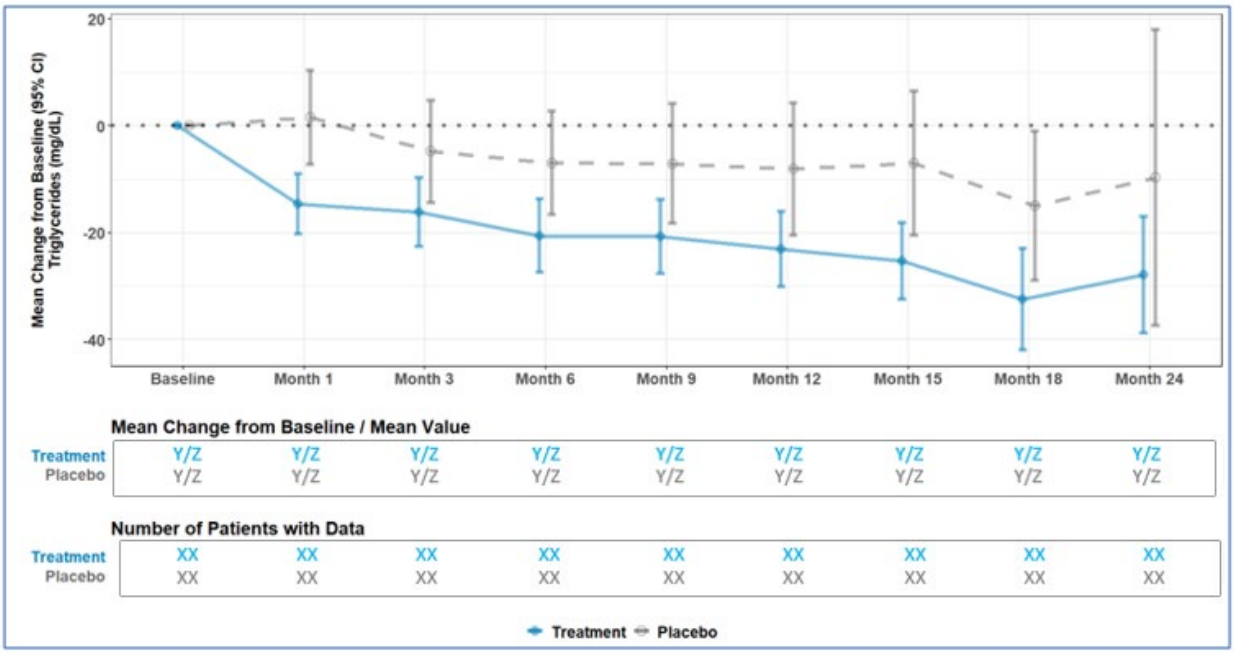
Source: [include Applicant source, datasets and/or software tools used].
Note: Results are provided from baseline until <5 to 10% of randomized population remains in study to avoid presentation of noise in data due to very small number of patients remaining in the trial

Figure 9. Mean Laboratory (Lipids) Data Change From Baseline Over Time, Safety Population, Pooled Analyses



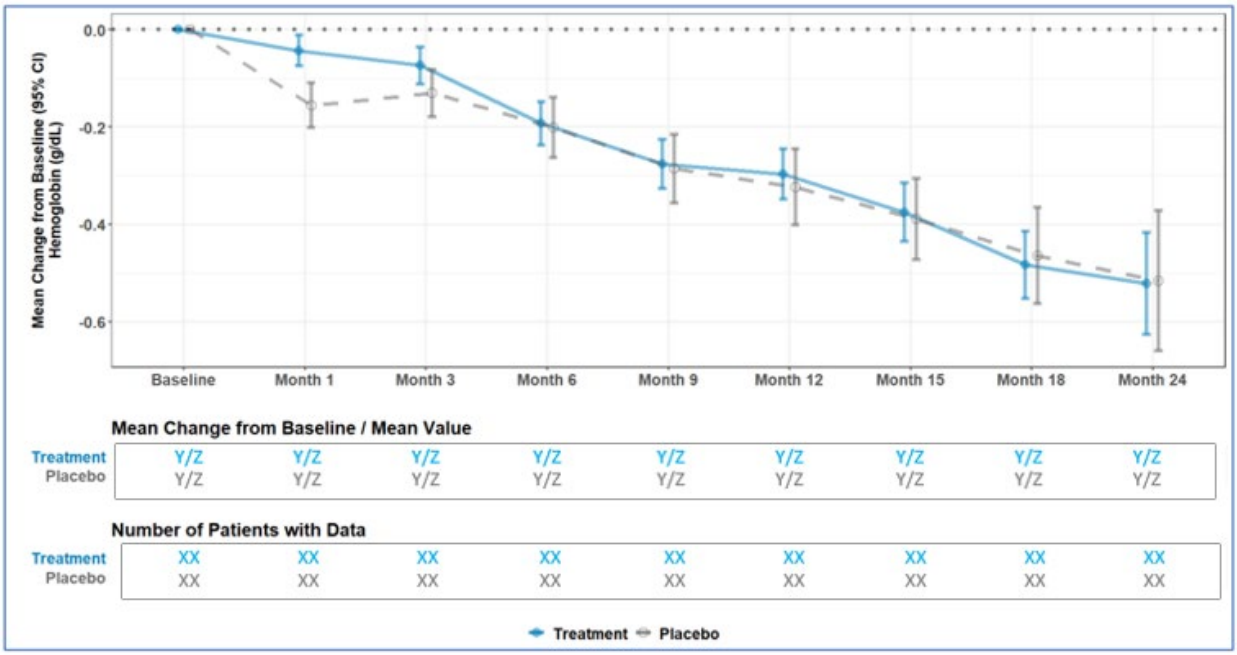


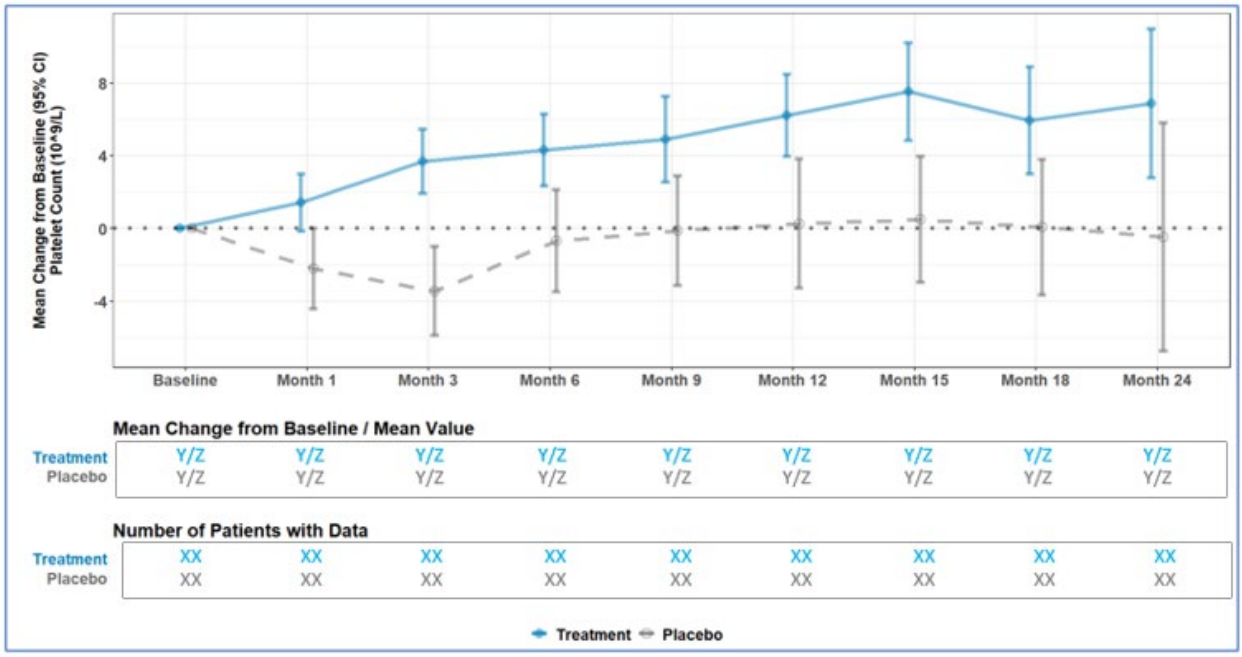


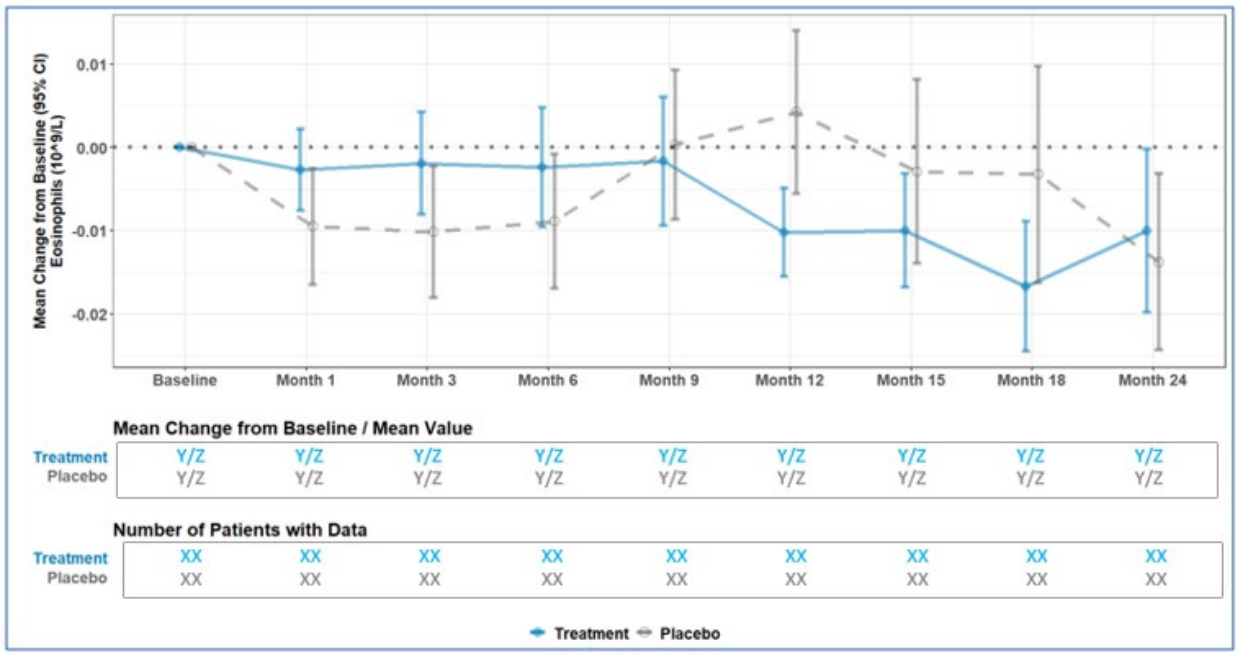


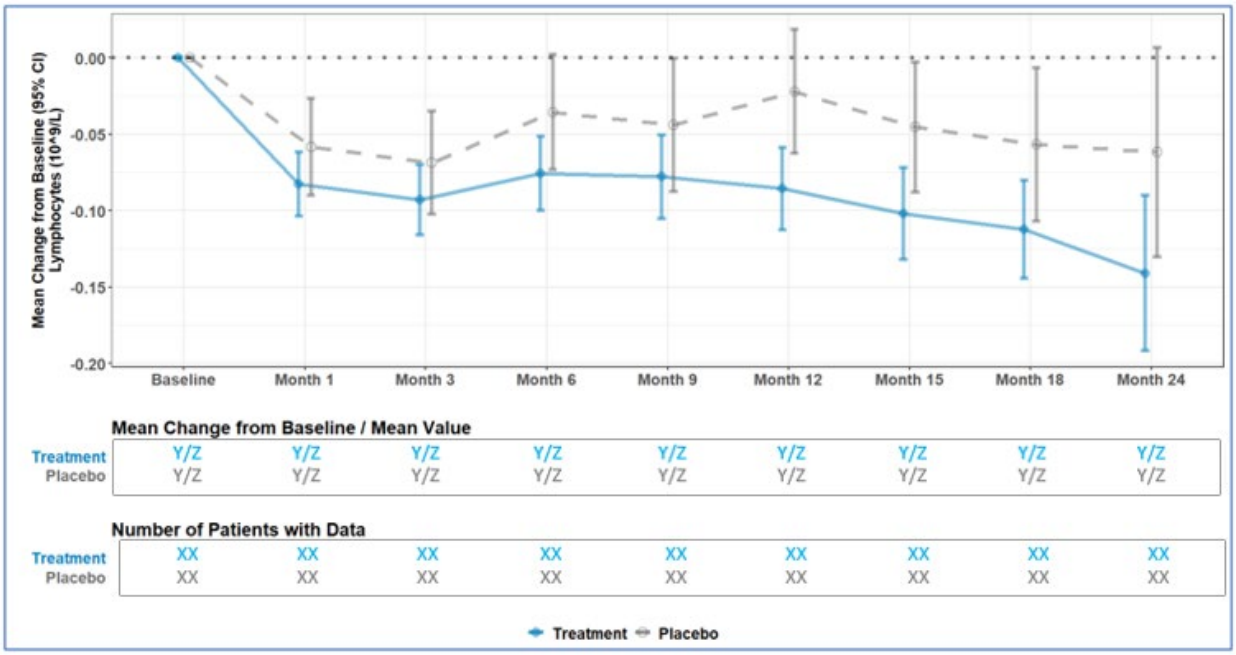
Source: [include Applicant source, datasets and/or software tools used].
Note: Results are provided from baseline until <5 to 10% of randomized population remains in study to avoid presentation of noise in data due to very small number of patients remaining in the trial

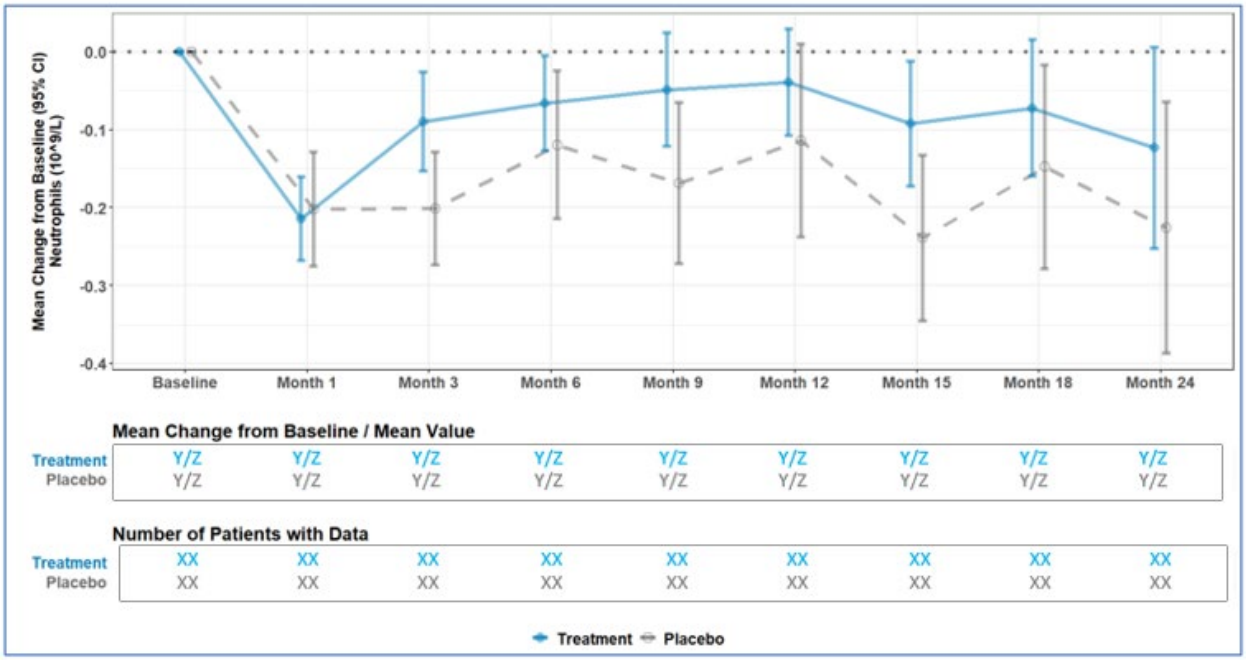
Figure 10. Mean Laboratory (Hematology) Data Change From Baseline Over Time, Safety Population, Pooled Analyses




Mean Change from Baseline (95% CI)
Platelet Count (10^9/L)
8
4
0
-4
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo


Mean Change from Baseline (95% CI)
Eosinophils (10^9/L)
0.01
0.00
-0.01
-0.02
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo


Mean Change from Baseline (95% CI) Lymphocytes (10^9/L)
0.00
-0.05
-0.10
-0.15
-0.20
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo


Mean Change from Baseline (95% CI) Neutrophils (10^9/L)
0.0
-0.1
-0.2
-0.3
-0.4
Baseline
Month 1
Month 3
Month 6
Month 9
Month 12
Month 15
Month 18
Month 24
Mean Change from Baseline / Mean Value
Treatment Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Placebo Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z Y/Z
Number of Patients with Data
Treatment XX XX XX XX XX XX XX XX XX
Placebo XX XX XX XX XX XX XX XX XX
Treatment
Placebo

Source: [include Applicant source, datasets and/or software tools used].
Note: Results are provided from baseline until <5 to 10% of randomized population remains in study to avoid presentation of noise in data due to very small number of patients remaining in the trial

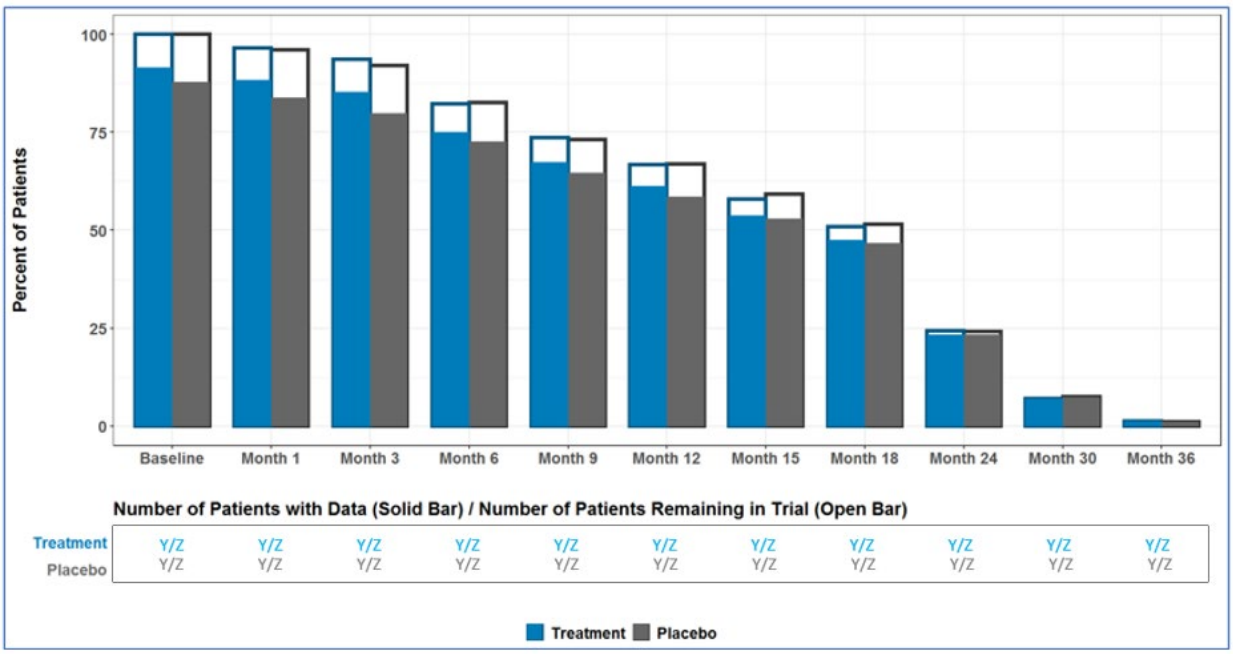
Missing and Existing Data Analysis

Figure 11 displays the proportion of missing data by study arm. It displays proportion of patients who had liver function laboratory tests by visit (solid bar), and % of patients remaining in the trial (open bar). The x-axis displays study visits as a discrete variable rather than a continuous variable. This graph should evaluate the actual data obtained during the trial rather than the planned study procedures as stated in the protocol.

A high proportion of missing data should signal 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 should interpret the data in this package with caution.

The following graph should be provided for alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, gamma-glutamyl transferase, international normalized ratio, serum creatinine, and estimated glomerular filtration rate (if available). As appropriate, similar figures also should be provided for any analyte/vitals of interest (e.g., blood pressure, white blood cells, body mass index).

Figure 11. Proportion of Patients Remaining With Missing and Existing Laboratory Data Records, Safety Population, Trial X



Source: [include Applicant source, datasets and/or software tools used].
Note: The frequency of laboratory measurements presented here is based on actual data collected.
Note: The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit # is used as the study visit (+/- protocol-defined # days).

Outlier Analyses

This section contains generalized laboratory abnormality threshold cutoff criteria associated with each level. This may be used to assess the severity of abnormalities and identify important outliers. If a review division or therapeutic area has prespecified cutoff criteria they wish to leverage, those should be used. This could be discussed at the pre-NDA/BLA planning meeting or the Type C ISS meeting. Additionally, it is also important to use the Meeting to discuss which timeframe is appropriate to include. It is recommended to include the percentage of patients with abnormality level criteria at any time during the trial and within a specific timeframe (e.g., 3 or 5 half-lives) following treatment intervention discontinuation.

In certain populations where an established grading system already exists, such as for patients with human immunodeficiency virus (e.g., “NIH 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 please refer to Table 59 and Table 60.

For a tabular presentation of abnormality level criteria for laboratory results, last value on-treatment analyses of interest, and/or a listing of all treatment arm patients with a laboratory value meeting ≥ Level 2 criteria, please refer to Table 59 and Table 60.

If notable differences are observed among the treatment arms through Table 24 through Table 28, provide Table 52, and Table 53 to evaluate last value on-treatment as a percentage of patients with abnormality level criteria within a specific timeframe (e.g., 3 half-lives) following treatment intervention discontinuation.

Customization

Clearly note any prespecified cutoff criteria and timeframe used in laboratory analysis.

Table 24. Patients With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels,[1] Safety Population, Pooled Analyses[2]

	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Sodium, low (mEq/L)				
Level 1 (<132)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<130)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<125)	n (%)	n (%)	n (%)	X (Y, Z)
Sodium, high (mEq/L)				
Level 1 (>150)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>155)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>160)	n (%)	n (%)	n (%)	X (Y, Z)
Potassium, low (mEq/L)				
Level 1 (<3.6)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<3.4)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<3.0)	n (%)	n (%)	n (%)	X (Y, Z)
Potassium, high (mEq/L)				
Level 1 (>5.5)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>6.0)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>6.5)	n (%)	n (%)	n (%)	X (Y, Z)
Chloride, low (mEq/L)				
Level 1 (<95)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<88)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<80)	n (%)	n (%)	n (%)	X (Y, Z)
Chloride, high (mEq/L)				
Level 1 (>108)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>112)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>115)	n (%)	n (%)	n (%)	X (Y, Z)
Bicarbonate, low (mEq/L)				
Level 1 (<20)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<18)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<15)	n (%)	n (%)	n (%)	X (Y, Z)
Bicarbonate, high (mEq/L)				
Level 3 (>30)	n (%)	n (%)	n (%)	X (Y, Z)

	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Blood Urea Nitrogen, high (mg/dL)				
Level 1 (>23)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>27)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>31)	n (%)	n (%)	n (%)	X (Y, Z)
Glucose, low (mg/dL)				
Level 1 (<70)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<54)	n (%)	n (%)	n (%)	X (Y, Z)
Glucose, high (mg/dL)				
Level 1 (fasting ≥100)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (fasting ≥126 or random glucose ≥200)	n (%)	n (%)	n (%)	X (Y, Z)
Calcium, low (mg/dL)				
Level 1 (<8.4)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<8.0)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<7.5)	n (%)	n (%)	n (%)	X (Y, Z)
Calcium, high (mg/dL)				
Level 1 (>10.5)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>11.0)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>12.0)	n (%)	n (%)	n (%)	X (Y, Z)
Magnesium, low (mg/dL)				
Level 1 (<1.5)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<1.2)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<0.9)	n (%)	n (%)	n (%)	X (Y, Z)
Magnesium, high (mg/dL)				
Level 1 (>2.3)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>4.0)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>7.0)	n (%)	n (%)	n (%)	X (Y, Z)
Phosphate, low (mg/dL)				
Level 1 (<2.5)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<2.0)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<1.4)	n (%)	n (%)	n (%)	X (Y, Z)
Protein, total, low (g/dL)				
Level 1 (<6.0)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<5.4)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<5.0)	n (%)	n (%)	n (%)	X (Y, Z)

	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Albumin, low (g/dL)				
Level 1 (<3.1)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<2.5)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<2.0)	n (%)	n (%)	n (%)	X (Y, Z)
CPK, high (U/L)				
Level 1 (>3 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>5 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>10 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Amylase, high (U/L)				
Level 1 (>1.1 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>1.5 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>3.0 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Lipase, high (U/L)				
Level 1 (>1.1 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>1.5 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>3.0 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Threshold Levels 1, 2, and 3 as defined by Table 59.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of patients in treatment arm; n, number of patients meeting criteria; ULN, upper limit of normal

Table 25. Patients With One or More Kidney Function Analyte Values Exceeding Specified Levels,[1] Safety Population, Pooled Analyses[2]

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

Source: [include Applicant source, datasets and/or software tools used].
[1] Threshold Levels 1, 2, and 3 as defined by Table 59.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria

Table 26. Patients With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels,[1,2] Safety Population, Pooled Analyses[3]

	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[4]
Alkaline phosphatase, high (U/L)				
Level 1 (>1.5 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>2.0 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>3.0 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Alanine aminotransferase, high (U/L)				
Level 1 (>3.0 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>5.0 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>10.0 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Aspartate aminotransferase, high (U/L)				
Level 1 (>3.0 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>5.0 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>10.0 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)

	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[4]
Bilirubin, total, high (mg/dL)				
Level 1 (>1.5 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>2.0 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>3.0 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Threshold Levels 1, 2, and 3 as defined by Table 59.
[2] For specific evaluation of drug-induced liver injury, refer to Drug-Induced Livery Injury (DILI) Screening section.
[3] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[4] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; ULN, upper limit of normal

Table 27. Patients With One or More Lipids Analyte Values Exceeding Specified Levels,[1] Safety Population, Pooled Analyses[2]

	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Cholesterol, total, high (mg/dL)				
Level 1 (>200)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>210)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>225)	n (%)	n (%)	n (%)	X (Y, Z)
HDL, males, low (mg/dL)				
Level 1 (<40)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<30)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<20)	n (%)	n (%)	n (%)	X (Y, Z)
HDL, females, low (mg/dL)				
Level 1 (<50)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<40)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<20)	n (%)	n (%)	n (%)	X (Y, Z)
LDL, high (mg/dL)				
Level 1 (>130)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>160)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>190)	n (%)	n (%)	n (%)	X (Y, Z)

	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Triglycerides, high (mg/dL)				
Level 1 (>150)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>300)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>500)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Threshold Levels 1, 2, and 3 as defined by Table 59.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of patients in treatment arm; n, number of patients meeting criteria

Table 28. Patients With One or More Hematology Analyte Values Exceeding Specified Levels,[1] Safety Population, Pooled Analyses[2]

	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Complete Blood Count				
WBC, low (cells/µL)				
Level 1 (<3500)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<3000)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<1000)	n (%)	n (%)	n (%)	X (Y, Z)
WBC, high (cells/µL)				
Level 1 (>10,800)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>13,000)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>15,000)	n (%)	n (%)	n (%)	X (Y, Z)
Hemoglobin, low (g/dL)				
Level 2 (>1.5 dec. from baseline)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>2 dec. from baseline)	n (%)	n (%)	n (%)	X (Y, Z)
Hemoglobin, high (g/dL)				
Level 2 (>2 g/dl inc. from baseline)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>3 g/dl inc. from baseline)	n (%)	n (%)	n (%)	X (Y, Z)
Hemoglobin, male (g/dL)				
Level 2 (<12.5 g/dL)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<10.5 g/dL)	n (%)	n (%)	n (%)	X (Y, Z)
Hemoglobin, female (g/dL)				
Level 2 (<11 g/dL)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<9.5 g/dL)	n (%)	n (%)	n (%)	X (Y, Z)

	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Platelets, low (cells/µL)				
Level 1 (<140,000)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<125,000)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<100,000)	n (%)	n (%)	n (%)	X (Y, Z)
WBC Differential				
Lymphocytes, low (cells/µL)				
Level 1 (<1000)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<750)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<500)	n (%)	n (%)	n (%)	X (Y, Z)
Lymphocytes, high (cells/µL)				
Level 1 (>4000)				
Level 2 (>10000)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>20000)	n (%)	n (%)	n (%)	X (Y, Z)
Neutrophils, low (cells/µL)				
Level 1 (<2000)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (<1000)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (<500)	n (%)	n (%)	n (%)	X (Y, Z)
Eosinophils, high (cells/µL)				
Level 1 (>650)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>1500)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>5000)	n (%)	n (%)	n (%)	X (Y, Z)
Coagulation Studies				
PT, high (sec)				
Level 1 (>1.1 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>1.3 x UL)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>1.5 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
PTT, high (sec)				
Level 1 (>1.0 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (>1.21 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (>1.41 x ULN)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Threshold Levels 1, 2, and 3 as defined by Table 60.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cells

Drug-Induced Liver Injury Screening Analyses

This section is comprised of four default screening analyses:Missing and Existing Data Analysis; hepatocellular drug-induced liver injury (DILI) screening plots; cholestatic DILI screening plot; and comparison of patients with maximal treatment-emergent liver test abnormalities.

Customization

If these screening analyses do not indicate a potential signal for DILI (e.g., no cases in the Hy's Law, cholestasis, or Temple's Corollary quadrants), then a potential for significant DILI with the study drug is unlikely. In this case, further analyses may not be needed.

Conversely, if there are one or more cases outside the left lower quadrant and/or an increase in such cases in the treatment arm, then the following is recommended:

- Generate follow-on/custom analyses that may provide additional evidence of potential DILI, especially when the trial involves patients with underlying liver disease, where abnormal baseline liver biochemistries and natural disease progression may complicate the analysis for DILI.

Missing and Existing Data Analysis

Refer to the missing and existing data analysis section for missing data analysis for liver-related laboratory parameter. Missing data analysis can be provided for: alanine aminotransferase (ALT); aspartate aminotransferase (AST); alkaline phosphatase (ALP); total bilirubin (TB); gamma-glutamyl transferase; and international normalized ratio.

Hepatocellular Drug-Induced Liver Injury Screening Plot(s)

Figure 12 is intended to quickly identify cases of possible serious hepatocellular DILI. In the default plot, each patient is plotted based on their maximum **postbaseline** TB (y-axis) and transaminase (ALT or AST, whichever is higher). Each value is expressed as multiples of ULN on logarithmic scales. Dashed lines in this plot represent TB and transaminase cutoffs of 2 x ULN and 3 x ULN (default), respectively and are based on Hy's Law criteria (see bullet 1 below).

The main purpose of this plot is to identify patients 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% mortality risk. Hy's Law cases may only constitute a small fraction of all patients 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 post marketing safety.

We recommend interpretation of this screening plot using a 4-quadrant approach:

1. The **right upper quadrant** represents potential Hy's Law cases that may carry an increased risk of DILI-related fatality. For purposes of this plot, potential Hy's Law cases are defined as **any** postbaseline TB elevation to ≥2 x upper limit of normal (ULN) occurring on or within 30 days after a postbaseline ALT or AST (transaminases) elevation to ≥3 x ULN **and** concurrent ALP is <2 x ULN. These patients should be identified in the graph with a red

circle. Patients may be plotted in the right upper quadrant based on maximum postbaseline TB and AST or ALT but should **not** be identified as a potential Hy's Law case (not circled) if the elevations did not occur within the prespecified time frame (i.e., within 30 days) **and/or** the concurrent ALP level was ≥2 x ULN (see below for list of Hy's law criteria). This analysis can 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 patient characteristics.

True Hy's Law cases have the following:[4,5]

- Predominant hepatocellular injury, as shown by ≥3 x elevations above the ULN of ALT or AST in conjunction with TB elevation to ≥2 x ULN, representing sufficient loss of hepatic cells to interfere with bilirubin excretion, as indicated by elevation of serum TB to 2 x ULN. In general, such a finding represents damage to one-third to one-half of liver cells, posing a significant risk of liver failure. Patients with pretreatment elevation of liver enzymes may show elevations of these indicators relative to their baseline values.
- Absence of cholestatic injury as indicated with a normal or only modestly elevated ALP level. Cases with elevated ALP at or above 2 x ULN are not circled as potential Hy's Law cases in the hepatocellular DILI screening plot.
- Exclusion of other causes of increased aminotransferase(s) and TB, such as viral hepatitis, preexisting or acute liver disease, or another drug capable of causing the observed liver injury.

2. The **right lower quadrant** represents Temple's Corollary. Patients in this quadrant have ALT and/or AST ≥3 x ULN but there is no accompanying TB elevation or jaundice. These cases do not themselves indicate a high risk of fatal liver injury but represent potential DILI cases of significance. It is important to consider these cases as potential DILI in a clinical trial setting because many may have discontinued the study drug due to transaminase elevations and therefore did not progress to TB elevations meeting Hy's Law criteria. On the other hand, it may be reassuring if many cases in Temple's Corollary remained on therapy without the development of Hy's Law cases because it would suggest the injury does not progress to jaundice despite continued drug exposure.
3. The **left upper quadrant** represents cholestasis where jaundice occurs with no or minimal hepatocellular injury (ALT and AST less than 3 x ULN). These cases typically do not carry as high a risk of fatality but can represent potentially significant DILI. Certain drugs can be associated with predominant cholestatic injury that leads to an increased risk for serious liver adverse outcomes such as vanishing bile duct syndrome. Patients with advanced liver disease or cirrhosis may be particularly prone to severe outcomes after any liver injury including cholestatic DILI.
4. The **left lower quadrant** indicates those cases where the risk of severe DILI is low.

Customization

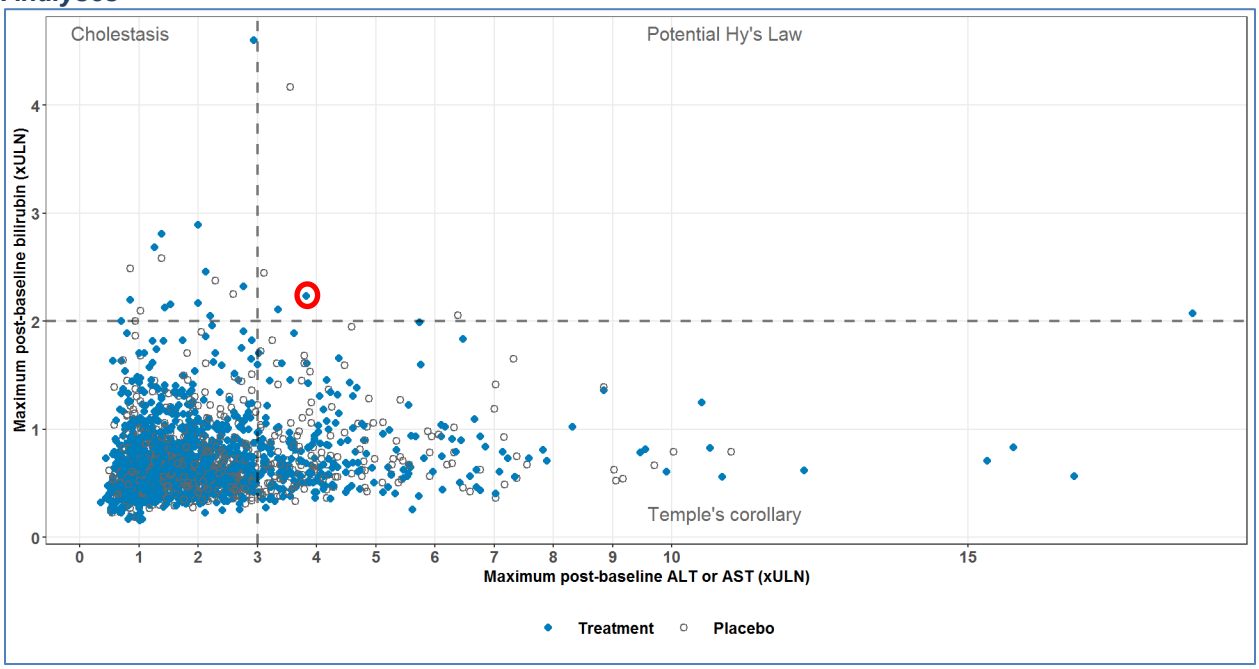
The reported ULNs may vary between laboratory sites; therefore, the default graph displays AST or ALT normalized to the reported ULNs. A similar graph displaying the measured values of liver biochemistry tests rather than normalized values can be helpful but should note that a cutoff line depicting 3 x ULN for transaminases should not be drawn due to the variations in

[4] See FDA guidance for industry *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* (July 2009)
[5] CIOMS: Drug-Induced Liver Injury, available at: https://cioms.ch/publications/product/drug-induced-liver-injury/

reported normal ranges. This analysis can 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 patient characteristics.

In studies that enroll patients with abnormal baseline liver biochemistry values (i.e., elevated baseline AST, ALT, ALP), an additional series of plots can be generated using other reference limits: (1) multiples of baseline values (e.g., ALP 2 x baseline or ALT 3 x 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. In patients with elevated baseline transaminase values, who show improvements in their transaminase levels and in essence, establish a new lower “baseline” during the trial consider using the new lower transaminase values in subsequent assessment for potential DILI “baseline” (i.e., DILI assessment in patients who normalize their transaminase levels after initiation of study drug should use normal range cutoffs rather than multiples of baseline in potential DILI assessment).

Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses



Source: [include Applicant source, datasets and/or software tools used].
Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2 x ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3 x ULN, and ALP <2 x ULN (note ALP values are not circled). All patients with at least one postbaseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal

Cholestatic Drug-Induced Liver Injury Screening Plot

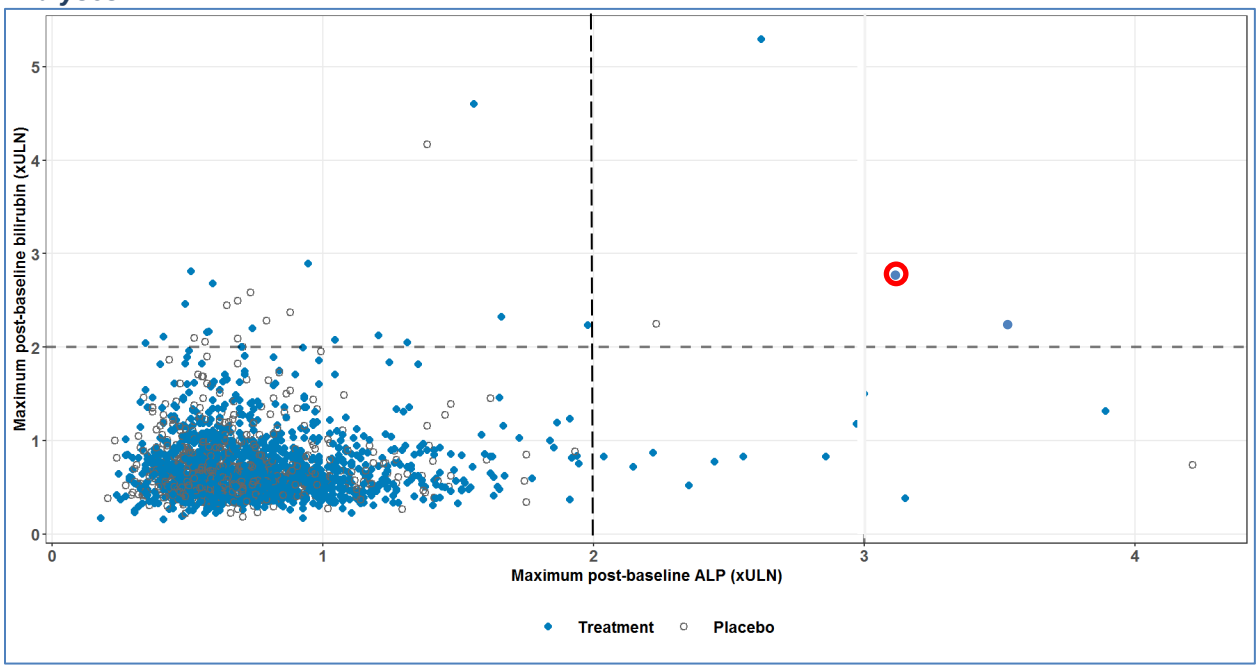
While ALP elevations can be from other sources (e.g., bone), significant ALP elevation in the setting of hepatic dysfunction (e.g., jaundice) may suggest cholestatic DILI. The cholestatic screening plot (Figure 13) is analogous to the hepatocellular screening plot (Figure 12). Maximum postbaseline TB is plotted against maximum postbaseline ALP rather than ALT or

AST. The quadrants are similarly defined by TB ≥2 x ULN, but the ALP cutoff is ≥2 x ULN as the default. Red circled cases in the right upper quadrant indicates patients who had their maximum bilirubin within 30 days (default) of ALP becoming >2 x 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, DILI case in the right upper quadrant do not carry the 10% mortality risk of a Hy's Law case. Nevertheless, the combination of ALP ≥2 x ULN and jaundice is concerning for cholestatic injury deserving exploration. Similar to the hepatocellular screening plot (evaluation of drug-induced serious hepatotoxicity, or eDISH), 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, this plot can be produced using another timeframe (e.g., 45 days or 60 days) and alternative cutoffs for TB and ALP levels.

Figure 13. Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses



Source: [include Applicant source, datasets and/or software tools used].
Each data point represents a patient 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 2 x ULN within 30 days after postbaseline ALP became equal to or exceeding 2 x ULN.
Abbreviations: ALP, alkaline phosphatase; ULN, upper limit of normal

Comparison of Patients With Maximal Treatment-Emergent Liver Test Abnormalities

Tables 29 and 30 are intended to demonstrate potential imbalances in the proportion of patients who are found in each quadrant of concern between study arms using maximum treatment-emergency liver test abnormalities. The table helps differentiate potential DILI cases in the active group versus the comparator group. If there are proportionately more cases in the active

group, concern for a DILI issue is heightened. A similar table can be generated for the cholestatic liver injury screening plot if there is concern.

If the proportions of missing data shown in Table 29 or Table 30 are high, then the available data may be misleading and should be interpreted with caution.

Table 29. Patients in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses

Quadrant	Drug Name N = XXX n (%)	Placebo N = XXX n (%)
Potential Hy's Law (right upper)		
Cholestasis (left upper)		
Temple's corollary (right lower)		
Total		

Source: [include Applicant source, datasets and/or software tools used]
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria

Table 30. Patients in Each Quadrant for Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses

Quadrant	Drug Name N = XXX n (%)	Placebo N = XXX n (%)
Bilirubin ≥2 x ULN and ALP ≥2 x ULN (right upper)		
Bilirubin ≥2 x ULN and ALP <2 x ULN (left upper)		
Bilirubin <2 x ULN and ALP ≥2 x ULN (right lower)		
Total		

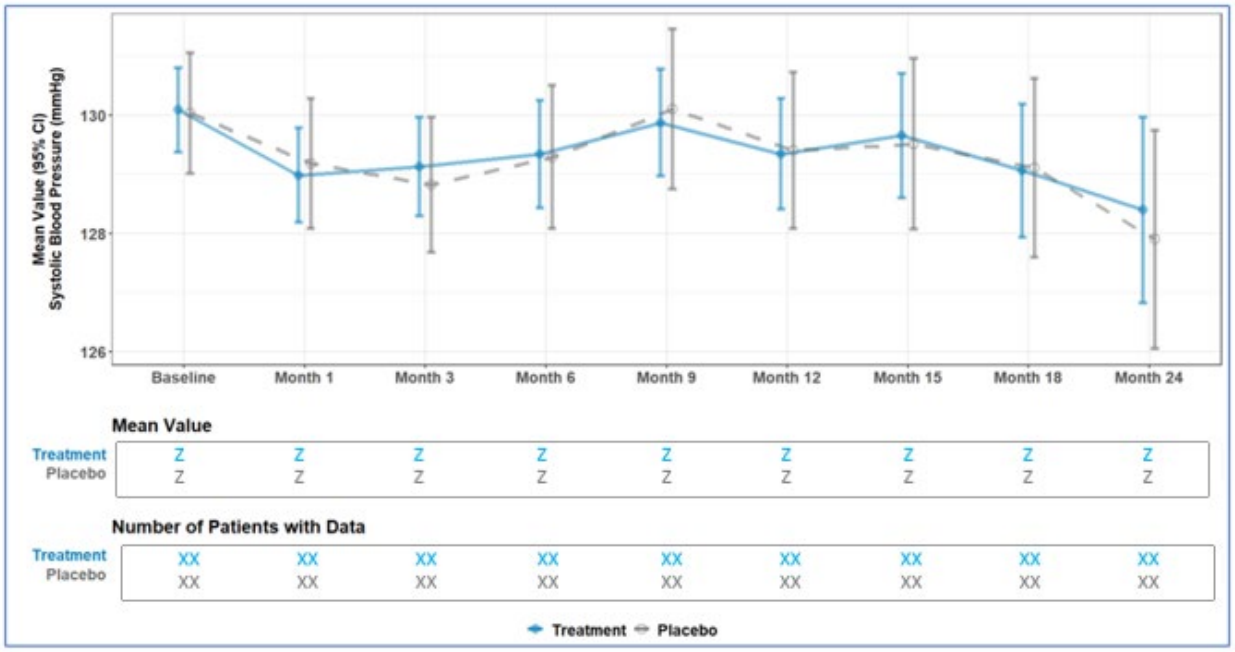
Source: [include Applicant source, datasets and/or software tools used].
Abbreviations: ALP, alkaline phosphatase; N, number of patients in treatment arm; n, number of patients meeting criteria; ULN, upper limit of normal

Vital Signs

The following standard tables and figures are intended for routine safety analyses of vital signs for new drug and biologic applications that do not present special concerns. If the study agent is believed to significantly alter vital signs, additional analyses may be required, such as an assessment of the proportion of patients with changes in blood pressure medication or shift tables. For additional information, please refer to the draft guidance for industry *Assessment of Pressor Effects of Drugs.*[6]

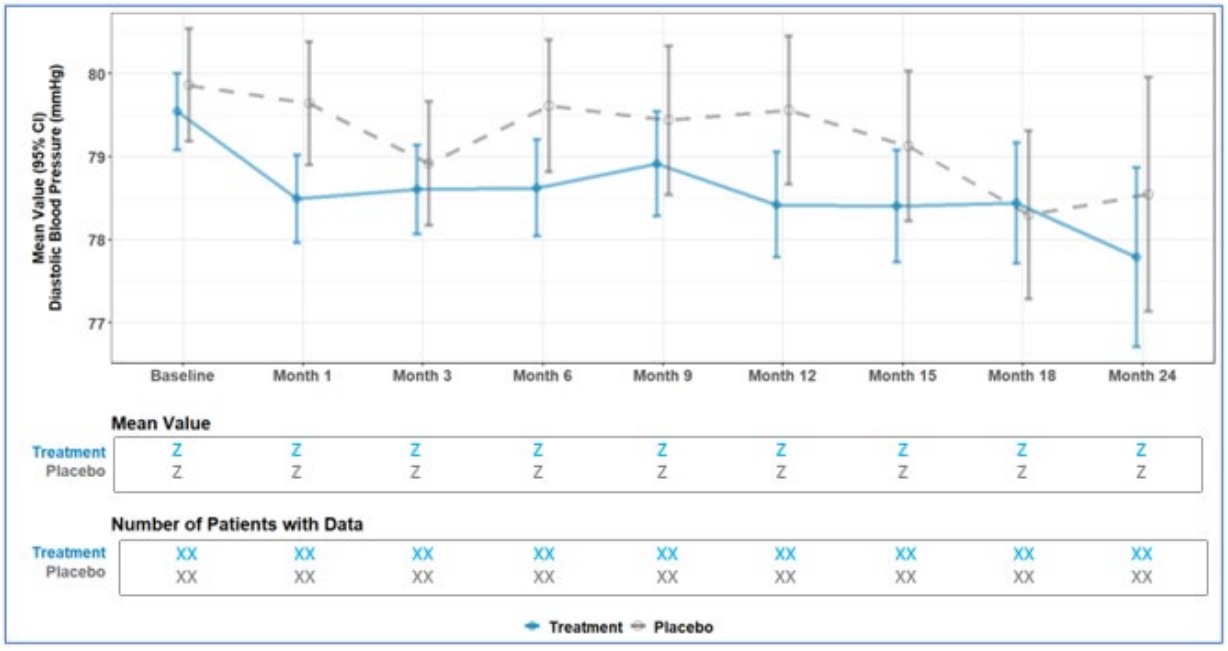
[6] FDA draft guidance for industry *Assessment of Pressor Effects of Drugs* (February 2022)

Figure 14. Mean and 95% Confidence Interval of Systolic Blood Pressure Over Time by Treatment Arm, Safety Population, Trial X



Source: [include Applicant source, datasets and/or software tools used].
Vertical bars show 95% CIs.
Abbreviations: BUD, budesonide; CI, confidence interval

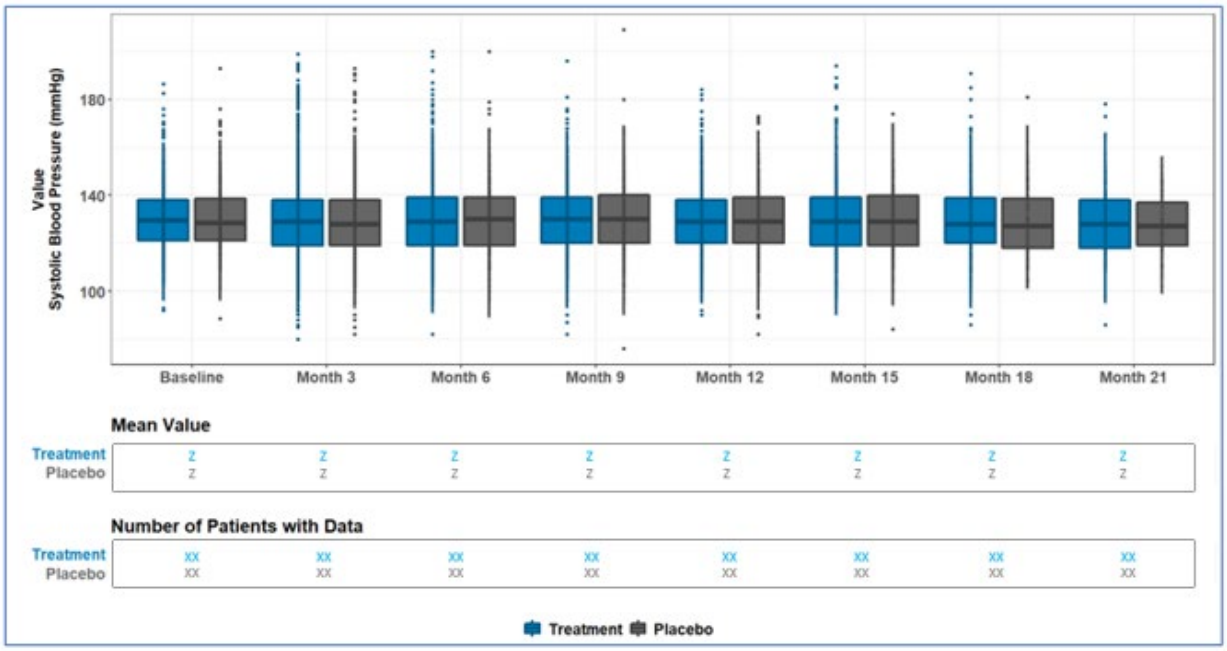
Figure 15. Mean and 95% Confidence Interval of Diastolic Blood Pressure Over Time by Treatment Arm, Safety Population, Trial X



Source: [include Applicant source, datasets and/or software tools used].
Vertical bars show 95% CIs.
Abbreviations: BUD, budesonide; CI, confidence interval

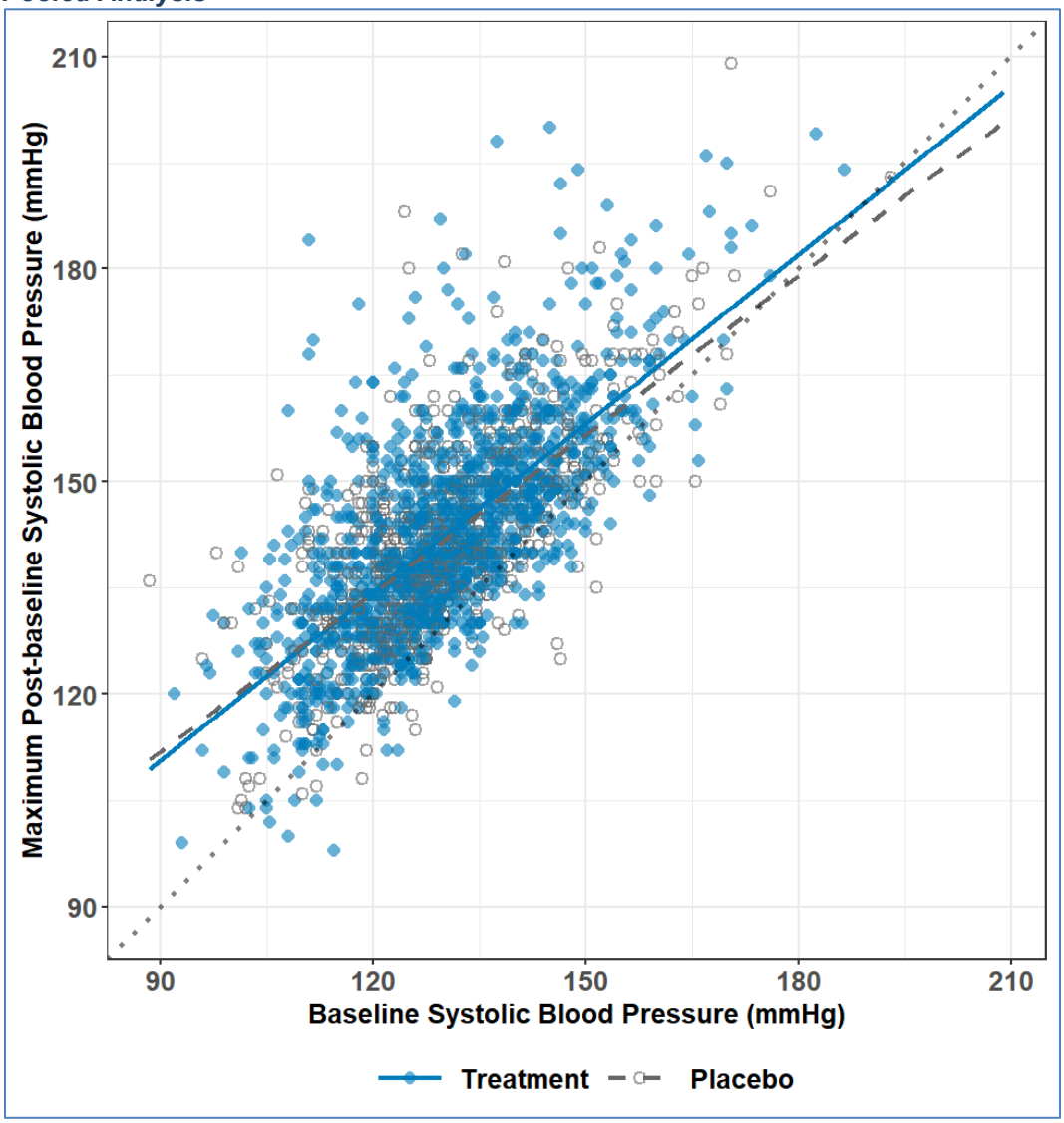
For the display of blood pressure data, if there are three or more treatment arms, do not request the Median and Interquartile Range boxplots, to avoid very busy and difficult to interpret plots.

Figure 16. Median Interquartile Range of Systolic Blood Pressure Over Time by Treatment Arm,[1] Safety Population, Pooled Analysis



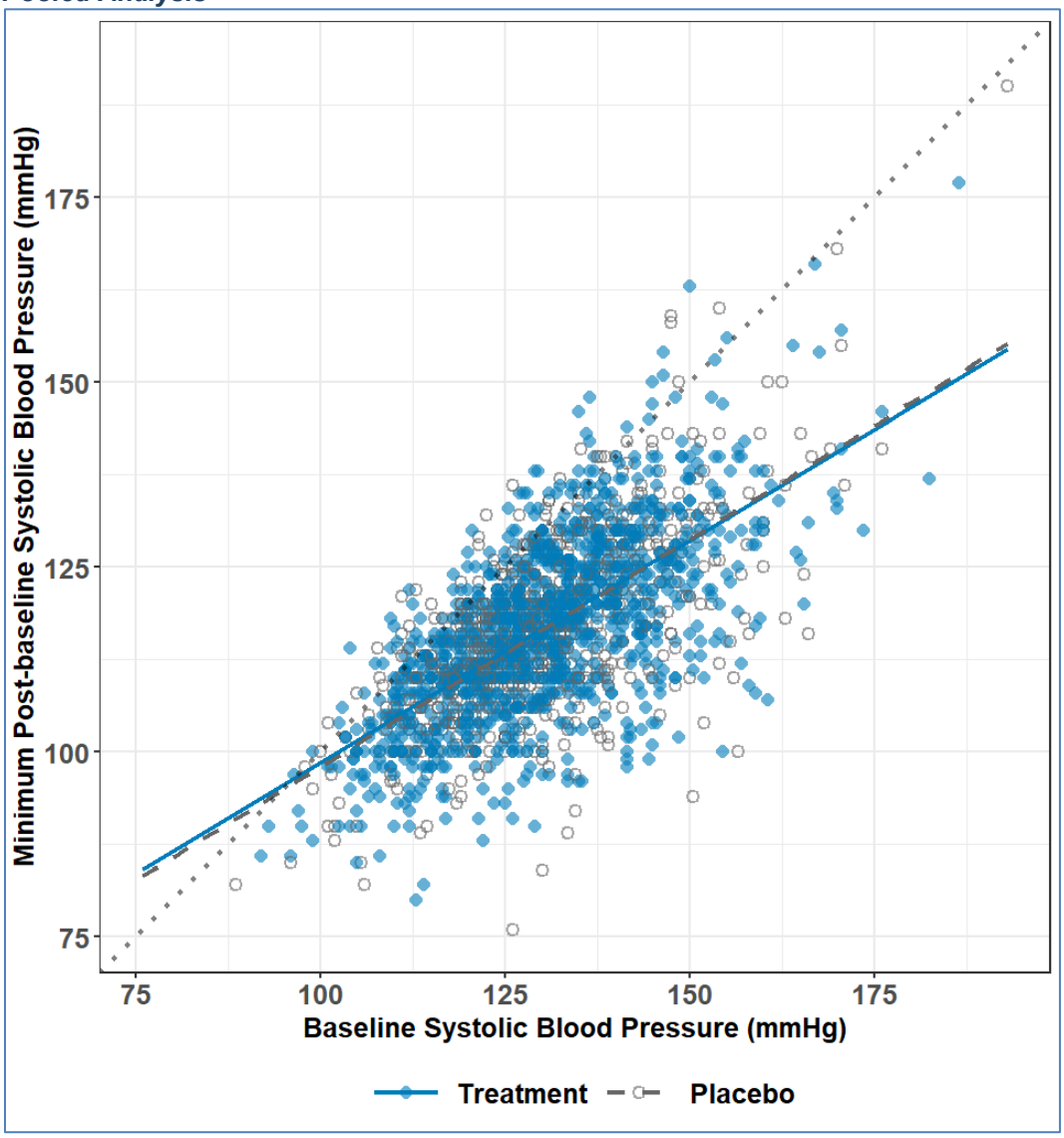
Source: [include Applicant source, datasets and/or software tools used].
[1] Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers =1.5x the interquartile range; individual outliers are those beyond this range.

Figure 17. Baseline vs. Maximum Systolic Blood Pressure by Treatment Arm,[1] Safety Population, Pooled Analysis



Source: [include Applicant source, datasets and/or software tools used].
[1] Gray dotted line = no increase; blue line = treatment linear regression; gray dashed line = placebo linear regression.

Figure 18. Baseline vs. Minimum Systolic Blood Pressure by Treatment Arm,[1] Safety Population, Pooled Analysis



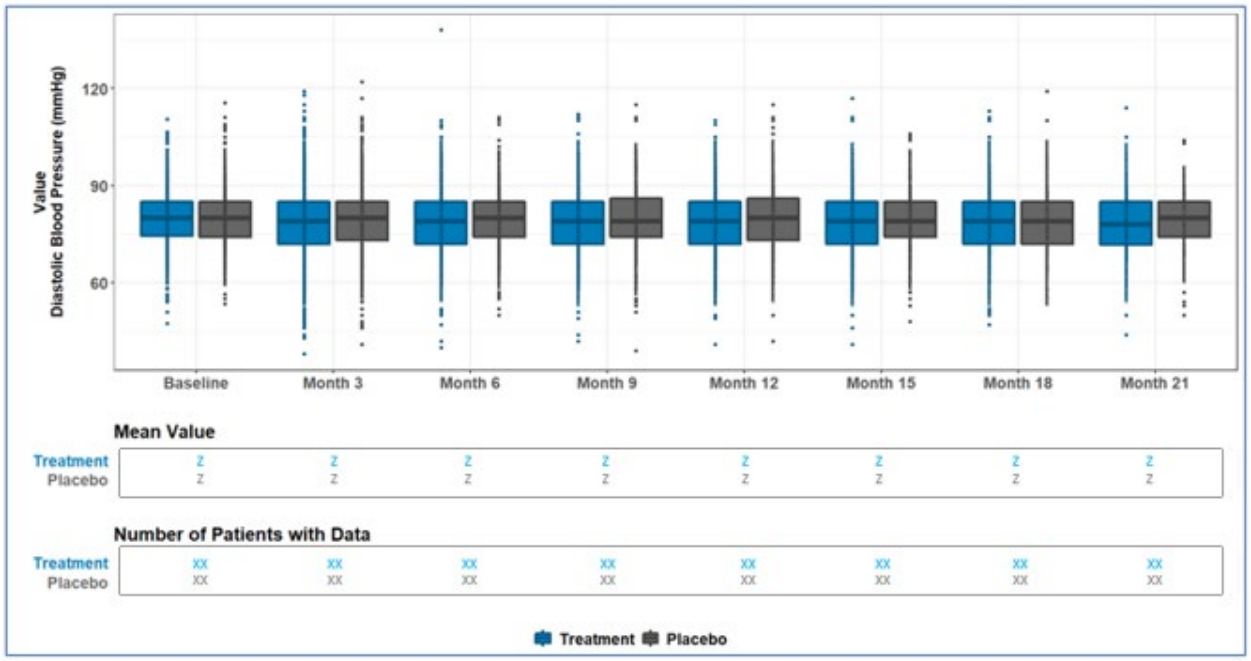
Source: [include Applicant source, datasets and/or software tools used].
[1] Gray dotted line = no decrease; blue line = treatment linear regression; gray dashed line = placebo linear regression.

Table 31. Percentage of Patients With Maximum Systolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Pooled Analysis

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

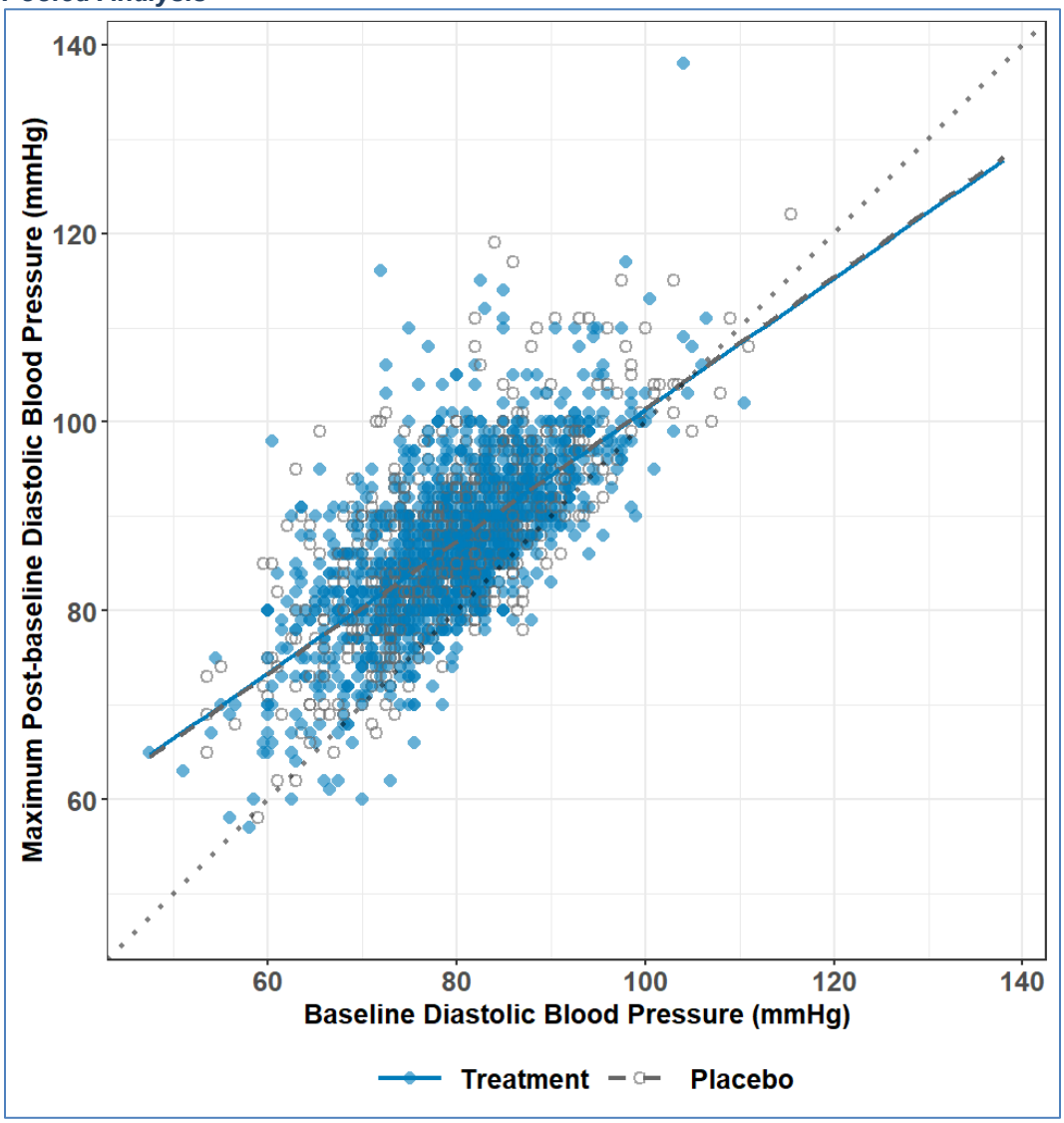
Source: [include Applicant source, datasets and/or software tools used].
[1] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: N, number of patients in treatment arm with available blood pressure data; n, number of patients with indicated blood pressure

Figure 19. Median and Interquartile Range of Diastolic Blood Pressure Over Time by Treatment Arm,[1] Safety Population, Pooled Analysis



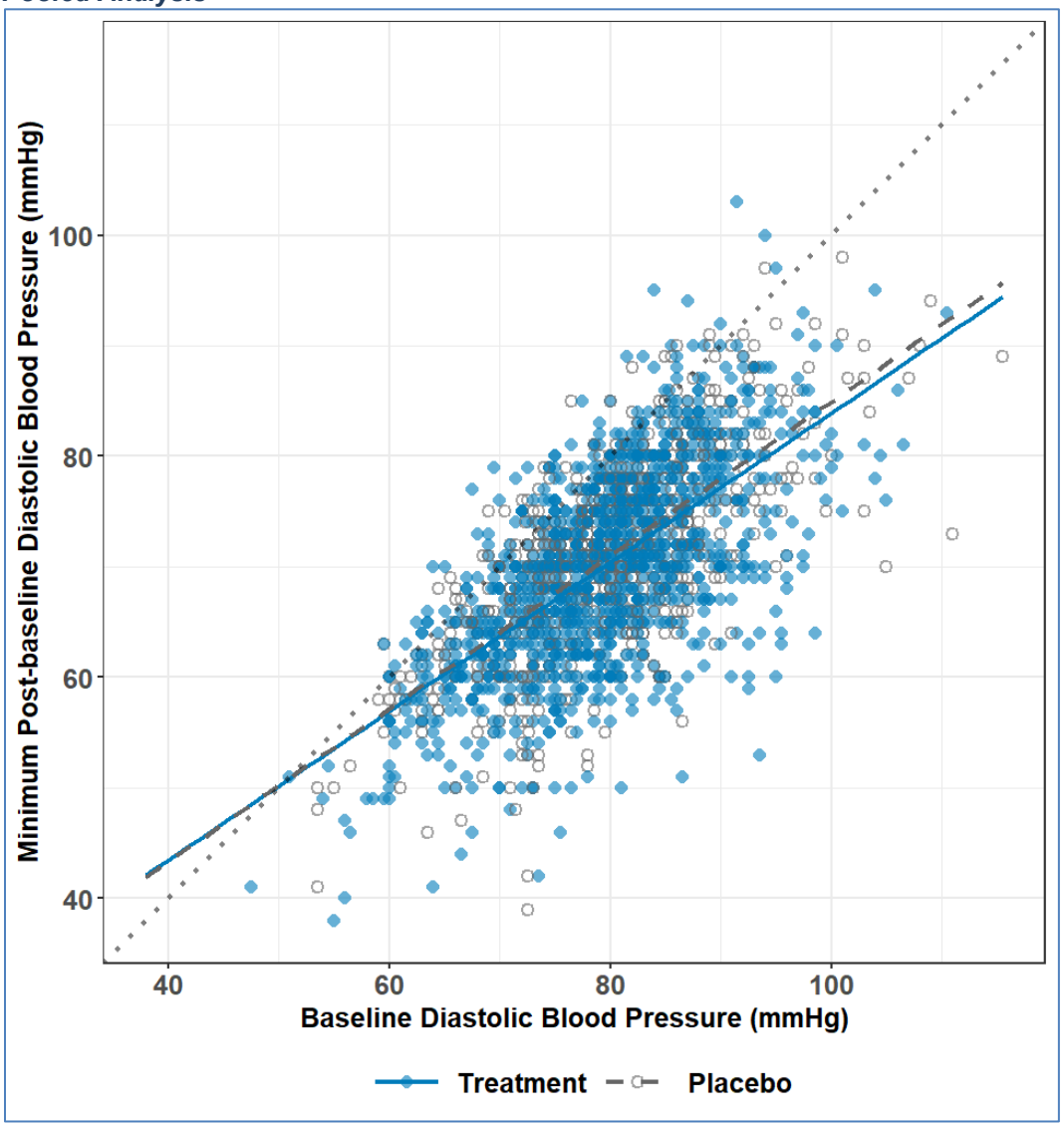
Source: [include Applicant source, datasets and/or software tools used].
[1] Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers =1.5 X the interquartile range; individual points are those beyond this range.

Figure 20. Baseline vs. Maximum Diastolic Blood Pressure by Treatment Arm,[1] Safety Population, Pooled Analysis



Source: [include Applicant source, datasets and/or software tools used].
[1] Gray dotted line = no increase; blue line = treatment linear regression; gray dashed line = placebo linear regression.

Figure 21. Baseline vs. Minimum Diastolic Blood Pressure by Treatment Arm,[1] Safety Population, Pooled Analysis



Source: [include Applicant source, datasets and/or software tools used].
[1] Gray dotted line = no decrease; blue line = treatment linear regression; gray dashed line = placebo linear regression.

Table 32. Percentage of Patients With Maximum Diastolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Pooled Analysis

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

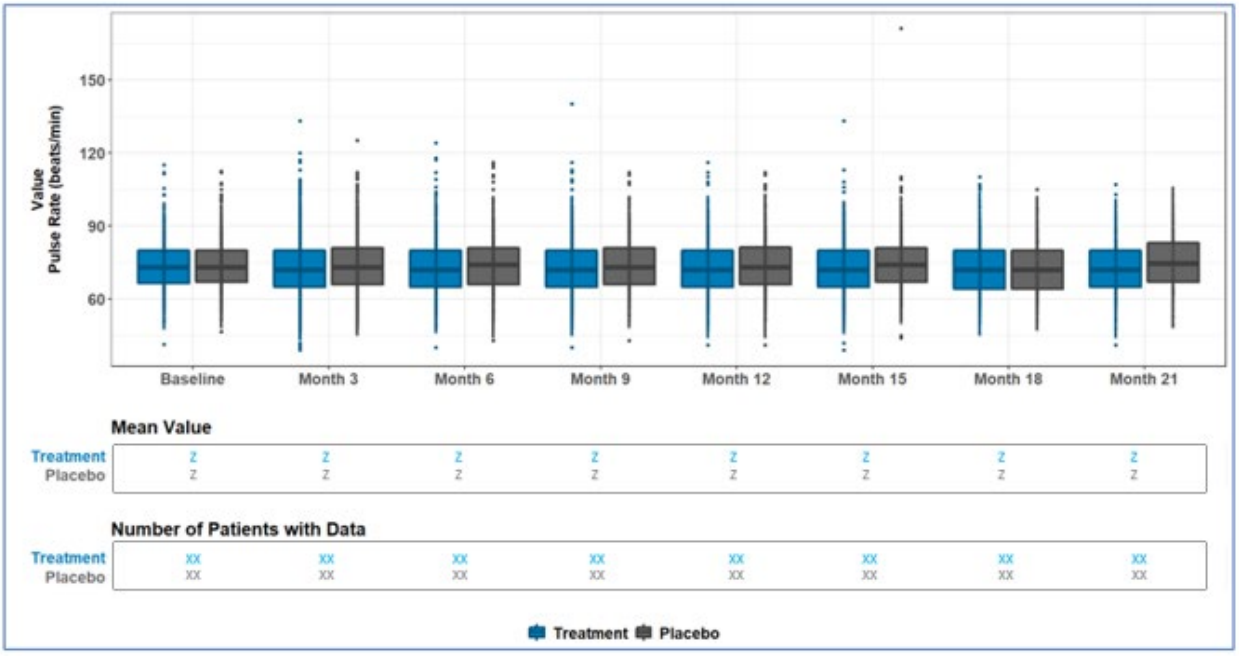
Source: [include Applicant source, datasets and/or software tools used].
[1] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; n, number of patients with indicated blood pressure; N, number of patients in treatment arm with available blood pressure data

Table 33. Percentage of Patients Meeting Specific Hypotension Levels Postbaseline, Safety Population, Pooled Analysis

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

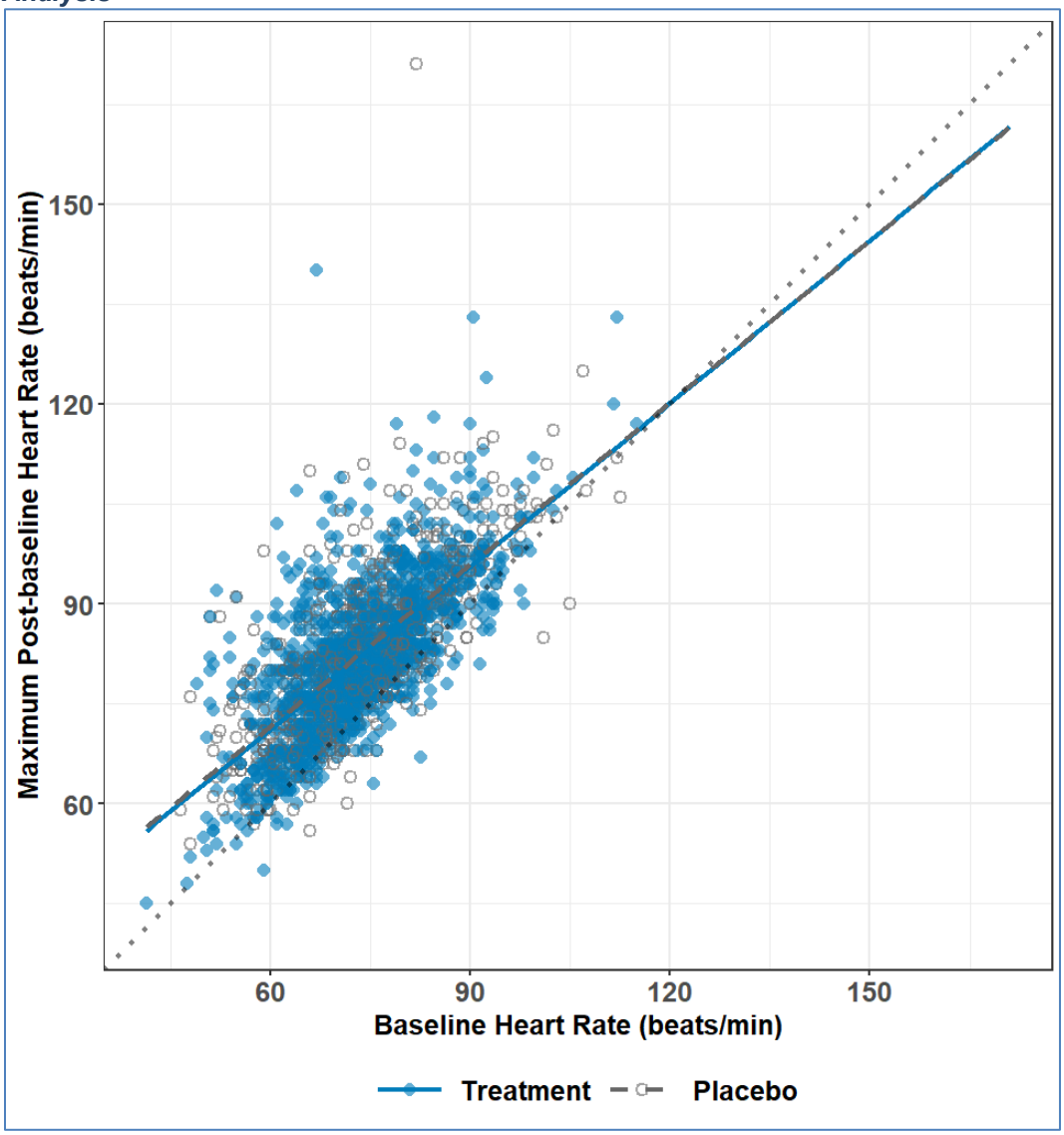
Source: [include Applicant source, datasets and/or software tools used].
[1] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; N, number of patients in treatment arm with available blood pressure data; n, number of patients with indicated blood pressure

Figure 22. Median and Interquartile Range of Pulse Rate Over Time by Treatment Arm,[1] Safety Population, Pooled Analysis



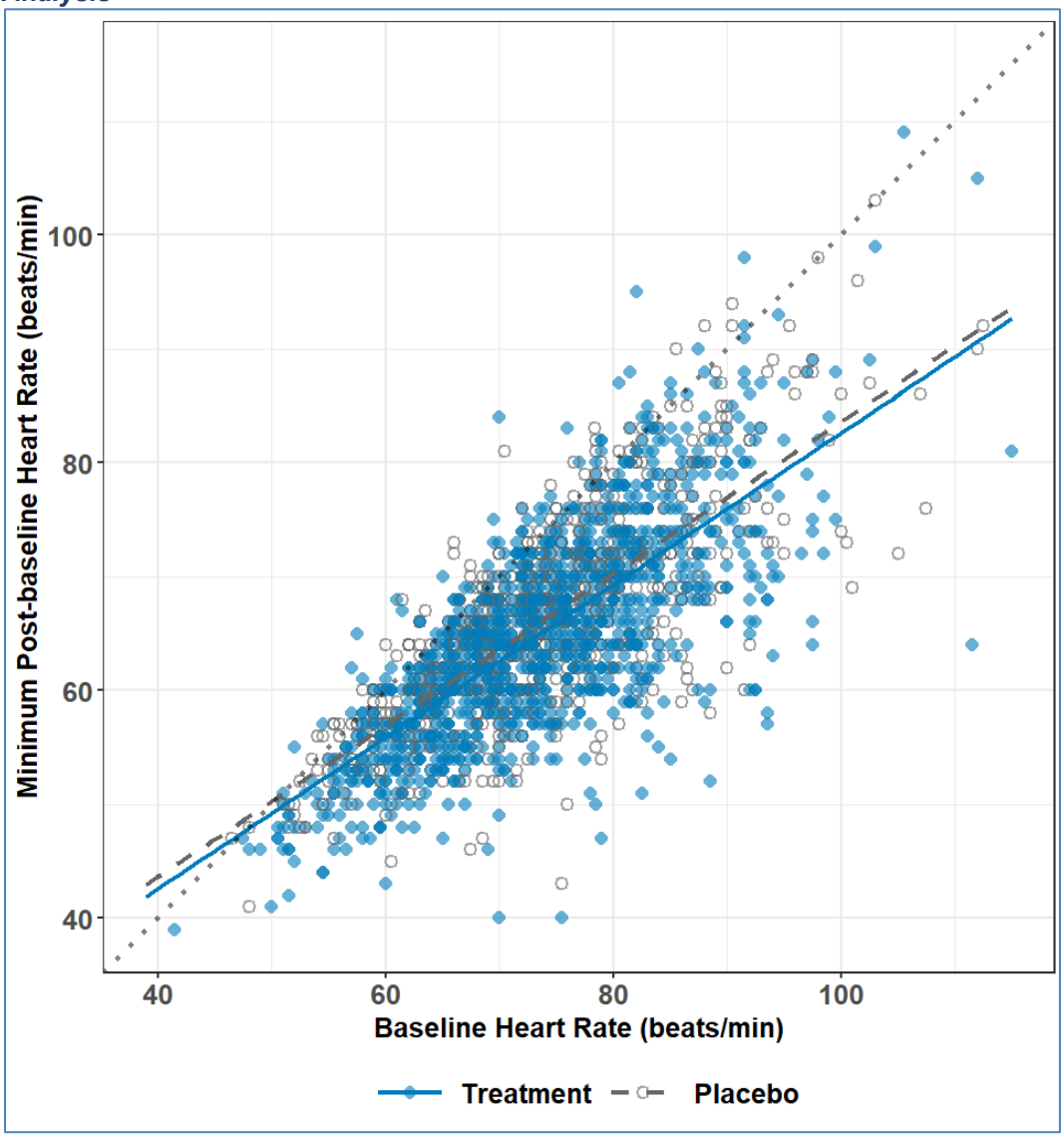
Source: [include Applicant source, datasets and/or software tools used].
[1] Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers =1.5x the interquartile range; individual outliers are those beyond this range.

Figure 23. Baseline vs. Maximum Pulse Rate by Treatment Arm,[1] Safety Population, Pooled Analysis



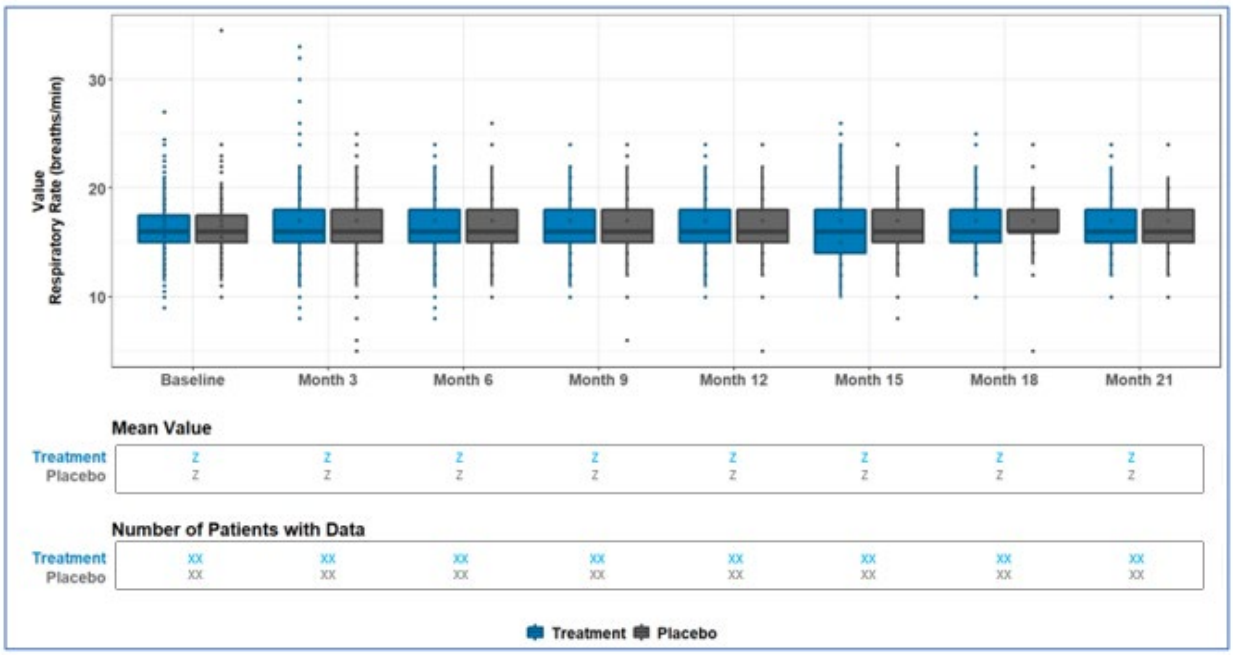
Source: [include Applicant source, datasets and/or software tools used].
[1] Gray dotted line = no increase; blue line = treatment linear regression; grey dashed line = placebo linear regression.

Figure 24. Baseline vs. Minimum Pulse Rate by Treatment Arm,[1] Safety Population, Pooled Analysis



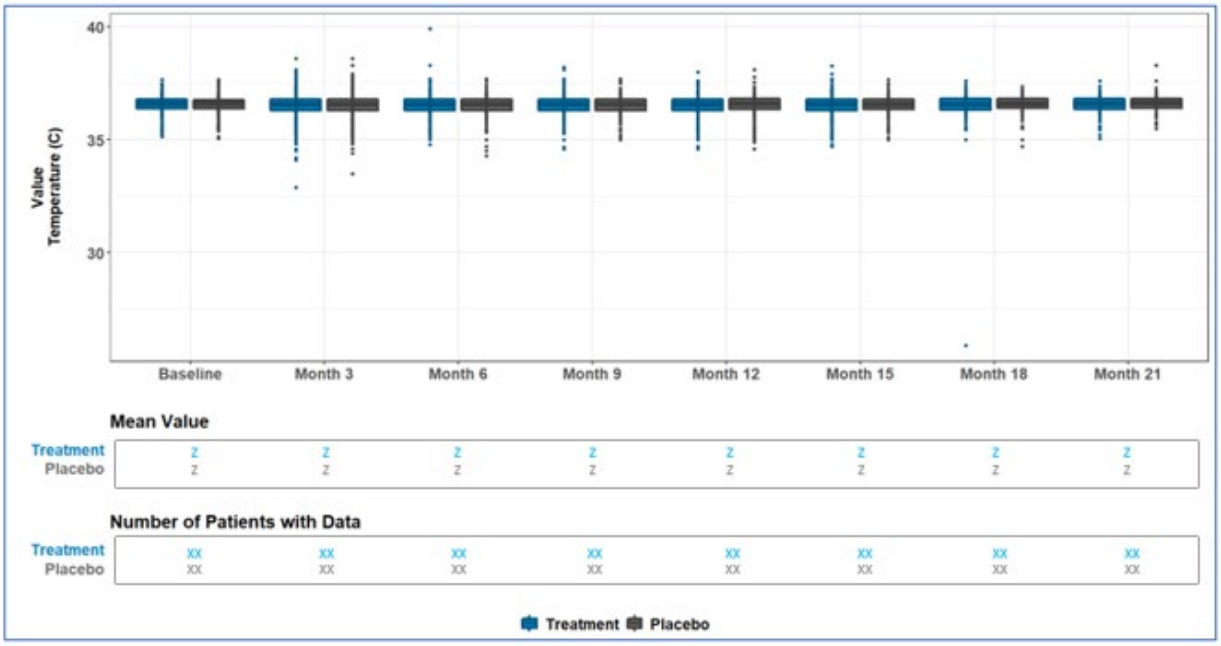
Source: [include Applicant source, datasets and/or software tools used].
[1] Gray dotted line = no decrease; blue line = treatment linear regression; grey dashed line = placebo linear regression.

Figure 25. Median and Interquartile Range of Respiratory Rate Over Time by Treatment Arm,[1] Safety Population, Pooled Analysis



Source: [include Applicant source, datasets and/or software tools used].
[1] 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.

Figure 26. Median and Interquartile Range of Body Temperature Over Time by Treatment Arm,[1] Safety Population, Pooled Analysis



Source: [include Applicant source, datasets and/or software tools used].
[1] 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.

Standard Expanded Safety Tables and Figures

This section provides additional presentations of data showcased earlier and is comprised of two subsections: expanded adverse event analyses and expanded laboratory analyses.

Expanded Adverse Event Analyses

The tables in Sections serious adverse events and adverse events present either additional information or an alternate organization of the data. This section follows the same guidance, as described in the adverse events section.

Serious Adverse Events

Table 34 presents preferred terms under each FMQ in Table 10.

Customization

If deemed necessary, add FMQ (broad) to the table.

Table 34. Patients With Serious Adverse Events[1] by System Organ Class, FDA Medical Query (Narrow) and Preferred Term, Safety Population, Pooled Analysis (or Trial X)[2]

System Organ Class[5] FMQ (Narrow)[3]	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[4,6]
SOC1					
FMQ1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SOC2					
FMQ1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1]Defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires 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.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Treatment-emergent adverse event defined as [definition].
[4] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[5] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
[6] Table display is ordered by the risk difference.
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; N, number of patients in treatment arm; n, number of patients with at least one event; PT, preferred term; SOC, System Organ Class

Adverse Events

Table 35. Patients With Adverse Events[1] by System Organ Class, Safety Population, Pooled Analysis (or Trial X)[2]

System Organ Class	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3,4]
Blood and lymphatic system	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Cardiac disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Ear and labyrinth disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Endocrine disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Eye disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Gastrointestinal disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Hepatobiliary disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Immune system disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Infections and infestations	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Injury, poisoning and procedural complications	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent adverse event defined as [definition].
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[4] Table display is ordered by the risk difference.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event

For a graphical presentation of Table 35, see Figure 4.

Table 36 presents entire table of adverse events, while Table 13 shows common AEs.

Table 36. Patients With Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Analysis (or Trial X)[1]

System Organ Class Preferred Term[2]		Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3,4]
SOC1	**n (%)**	**n (%)**	**n (%)**	**n (%)**		**X (Y, Z)**
PT1	n (%)	n (%)	n (%)	n (%)		X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)		X (Y, Z)
PT3	n (%)	n (%)	n (%)	n (%)		X (Y, Z)
SOC2	**n (%)**	**n (%)**	**n (%)**	**n (%)**		**X (Y, Z)**
PT1	n (%)	n (%)	n (%)	n (%)		X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)		X (Y, Z)
PT3	n (%)	n (%)	n (%)	n (%)		X (Y, Z)

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

Table 37. Patients With Adverse Events by System Organ Class, FDA Medical Query (Narrow)[1] and Preferred Term, Safety Population, Pooled Analysis (or Trial X)[2]

System Organ Class[4] FMQ (Narrow) Preferred Term	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3,5]
SOC1					
FMQ1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SOC2					
FMQ2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent adverse event defined as [definition]. MedDRA version X.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[4] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
[5] Table display is ordered by the risk difference.
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; MedDRA, Medical Dictionary for Regulatory Activities.; N, number of patients in treatment arm; n, number of patients with at least one event; PT, preferred term; SOC, System Organ Class

Table 38. Patients With Adverse Events by System Organ Class, FDA Medical Query (Broad)[1] and Preferred Term, Safety Population, Pooled Analysis (or Trial X)[2]

System Organ Class[4] FMQ (Broad) Preferred Term	**Drug Name Dosage X** **N = XXX** **n (%)**	**Drug Name Dosage Y** **N = XXX** **n (%)**	**Active Control** **N = XXX** **n (%)**	**Placebo** **N = XXX** **n (%)**	**Risk Difference (%)** **(95% CI)**[3,5]
SOC1					
FMQ1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	*n (%)*	n (%)	n (%)	X (Y, Z)
PT2	n (%)	*n (%)*	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	*n (%)*	n (%)	n (%)	*X (Y, Z)*
PT1	n (%)	*n (%)*	n (%)	n (%)	X (Y, Z)
PT2	n (%)	*n (%)*	n (%)	n (%)	X (Y, Z)
SOC2					
FMQ3	n (%)	*n (%)*	n (%)	n (%)	*X (Y, Z)*
PT1	n (%)	*n (%)*	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ4	n (%)	n (%)	n (%)	n (%)	*X (Y, Z)*
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[2] Treatment-emergent adverse event defined as [definition]. MedDRA version X.
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage X vs. Placebo.
[4] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
[5] Table display is ordered by the risk difference.
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, System Organ Class

Table 39. Patients With Rhabdomyolysis and Other Muscle Injury Algorithmic FDA Medical Query, Safety Population, Pooled Analysis (or Trial X)

Algorithmic FMQ Criterion	**Drug Name Dose X** **N = XXX** **N (%)**	**Drug Name Dose Y** **N = XXX** **N (%)**	**Control** **N = XXX** **N (%)**	**Risk Difference (%)** **(95% CI)**[1,4]
Patients with ≥1 Algorithmic Criterion	n(%)	n(%)	n(%)	X (Y, Z)
Any Rhabdomyolysis FMQ Narrow	n(%)	n(%)	n(%)	X (Y, Z)
Urine myoglobin > ULN	n(%)	n(%)	n(%)	X (Y, Z)
CPK >5 x ULN[2]	n(%)	n(%)	n(%)	X (Y, Z)
Myalgia + Weakness + Chromaturia[3]	n(%)	n(%)	n(%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Difference is shown between [treatment arms].
[2] NO CPK-MB/CPK >0.05 within 3 days NOR CPK > ULN at baseline.
[3] [PT Myalgia + PT Muscular Weakness + (PT Myoglobin Urine Present OR PT Chromaturia)] within 7 days.
[4] Table display is ordered by the risk difference.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; FMQ, FDA Medical Query; N, number of patients in group; n, number of patients meeting criteria; PT, preferred term, ULN, upper limit of normal

Table 40. Patients With Hypoglycemia Algorithmic FDA Medical Query, Safety Population, Pooled Analysis (or Trial X)

Population Algorithmic FMQ Criterion	Drug Name Dosage X N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[1]
Safety Population	n(%)	n(%)	
Patients with ≥ 1 Algorithmic Criterion	n(%)	n(%)	X (Y, Z)
Any Hypoglycemia FMQ Narrow Term	n(%)	n(%)	X (Y, Z)
Plasma Glucose < 54 mg/dL	n(%)	n(%)	X (Y, Z)
Hypoglycemia Term[2] + Plasma Glucose < 70 mg/dL[3]	n(%)	n(%)	X (Y, Z)
≥ 2 Hypoglycemia Terms[2] + ≥ 2 Episodes of Plasma Glucose < 70 mg/dL	n(%)	n(%)	X (Y, Z)
No History of Diabetes	n(%)	n(%)	
Patients with ≥ 1 Algorithmic Criterion	n(%)	n(%)	X (Y, Z)
Any Hypoglycemia FMQ Narrow Term	n(%)	n(%)	X (Y, Z)
Plasma Glucose < 54 mg/dL	n(%)	n(%)	X (Y, Z)
Hypoglycemia Term[2] + Plasma Glucose < 70 mg/dL[3]	n(%)	n(%)	X (Y, Z)
≥ 2 Hypoglycemia Terms[2] + ≥ 2 Episodes of Plasma Glucose < 70 mg/dL	n(%)	n(%)	X (Y, Z)
History of Diabetes	n(%)	n(%)	
Patients with ≥ 1 Algorithmic Criterion	n(%)	n(%)	X (Y, Z)
Any Hypoglycemia FMQ Narrow Term	n(%)	n(%)	X (Y, Z)
Plasma Glucose < 54 mg/dL	n(%)	n(%)	X (Y, Z)
Hypoglycemia Term[2] + Plasma Glucose < 70 mg/dL[3]	n(%)	n(%)	X (Y, Z)
≥ 2 Hypoglycemia Terms[2] + ≥ 2 Episodes of Plasma Glucose < 70 mg/dL	n(%)	n(%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Difference is shown between [treatment arms].
[2] Includes any Hypoglycemia FMQ Broad term that is not a Hypoglycemia FMQ 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; FMQ, FDA Medical Query; N, number of patients in group; n, number of patients meeting criteria; PT, preferred term

Table 41. Patients With Hyperglycemia Algorithmic FDA Medical Query, Safety Population, Pooled Analysis (or Trial X)

Population Algorithmic FMQ Criterion	Drug Name Dosage X N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[1]
Safety Population	n(%)	n(%)	
Patients with ≥ 1 Algorithmic Criterion	n(%)	n(%)	X (Y, Z)
Any Hyperglycemia FMQ Narrow term	n(%)	n(%)	X (Y, Z)
Fasting Plasma Glucose ≥ 126 mg/dL	n(%)	n(%)	X (Y, Z)
≥ 2 Plasma Glucoses > 180 mg/dL	n(%)	n(%)	X (Y, Z)
Any New Diabetes Concomitant Medication	n(%)	n(%)	X (Y, Z)
Post Baseline HbA1c ≥ 6.5%	n(%)	n(%)	X (Y, Z)
HbA1c Increase ≥ 0.3% with Post Baseline HbA1c ≥ 5.7%	n(%)	n(%)	X (Y, Z)
Change from Baseline Fasting Plasma Glucose ≥ 20 mg/dL with Post Baseline Fasting Plasma Glucose > 100 mg/dL	n(%)	n(%)	X (Y, Z)

Population Algorithmic FMQ Criterion	Drug Name Dosage X N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[1]
No History of Diabetes	n(%)	n(%)	
Patients with ≥ 1 Algorithmic Criterion	n(%)	n(%)	X (Y, Z)
Any Hyperglycemia FMQ Narrow term	n(%)	n(%)	X (Y, Z)
Fasting plasma glucose ≥ 126 mg/dL	n(%)	n(%)	X (Y, Z)
≥ 2 Plasma Glucoses > 180 mg/dL	n(%)	n(%)	X (Y, Z)
Any New Diabetes Concomitant Medication	n(%)	n(%)	X (Y, Z)
Post Baseline HbA1c ≥ 6.5%	n(%)	n(%)	X (Y, Z)
HbA1c Increase ≥ 0.3% with Post Baseline HbA1c ≥ 5.7%	n(%)	n(%)	X (Y, Z)
Change from Baseline Fasting Plasma Glucose ≥ 20 mg/dL with Post Baseline Fasting Plasma Glucose > 100 mg/dL	n(%)	n(%)	X (Y, Z)
History of Diabetes	n(%)	n(%)	
Patients with ≥ 1 Algorithmic Criterion	n(%)	n(%)	X (Y, Z)
Any Hyperglycemia FMQ Narrow term	n(%)	n(%)	X (Y, Z)
Fasting plasma glucose ≥ 126 mg/dL	n(%)	n(%)	X (Y, Z)
≥ 2 Plasma Glucoses > 180 mg/dL	n(%)	n(%)	X (Y, Z)
Any New Diabetes Concomitant Medication	n(%)	n(%)	X (Y, Z)
Post Baseline HbA1c ≥ 6.5%	n(%)	n(%)	X (Y, Z)
HbA1c Increase ≥ 0.3% with Post Baseline HbA1c ≥ 5.7%	n(%)	n(%)	X (Y, Z)
Change from Baseline Fasting Plasma Glucose ≥ 20 mg/dL with Post Baseline Fasting Plasma Glucose > 100 mg/dL	n(%)	n(%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Difference is shown between [treatment arms].
[2] Table display is ordered by the risk difference.
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; N, number of patients in treatment arm; n, number of patients with adverse event

Table 42. Patients With Algorithmic Hypersensitivity FDA Medical Query, Safety Population, Trial X

Algorithmic FMQ Criterion	Drug Name Dose X N = XX n(%)	Drug Name Dose Y N = XX n(%)	Active Control N = XX n(%)	Risk Difference (95% CI)[1,3]
Patients with ≥1 Algorithmic Criterion [2]	n(%)	n(%)	n(%)	X (Y, Z)
Any hypersensitivity FMQ narrow term	n(%)	n(%)	n(%)	X (Y, Z)
Respiratory + Skin Reaction	n(%)	n(%)	n(%)	X (Y, Z)
Respiratory + Systemic Reaction	n(%)	n(%)	n(%)	X (Y, Z)
Skin + Systemic Reaction	n(%)	n(%)	n(%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Difference is shown between [treatment arms].
[2] Combinations of events must occur within 7 days of each other to qualify
[3] Table display is ordered by the risk difference.
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; N, number of patients in treatment arm; n, number of patients with adverse event

Customization

After reviewing Table 39 in the initial ST&F package, add FMQ (broad) to the table if appropriate.

Table 43. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class, FDA Medical Query (Narrow)[1] and Preferred Term, Safety Population, Pooled Analyses[2]

System Organ Class[4] FMQ (Narrow) Preferred Term	**Drug Name Dosage X** **N = XXX** **n (%)**	**Drug Name Dosage Y** **N = XXX** **n (%)**	**Active Control** **N = XXX** **n (%)**	**Placebo** **N = XXX** **n (%)**	**Risk Difference (%) (95% CI)**[3,5]
SOC1	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
FMQ1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	*X (Y, Z)*
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SOC2	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
FMQ2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT3	n (%)	n (%)	n (%)	n (%)	*X (Y, Z)*
PT4	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SOC3	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
FMQ2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT5	n (%)	n (%)	n (%)	n (%)	*X (Y, Z)*
PT6	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent AE defined as [definition]. MedDRA version.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[4] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
[5] Table display is ordered by the risk difference.
Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA Medical Query; MedDRA, Medical Dictionary for Regulatory Activities.; N, number of patients in treatment arm; n, number of patients with at least one event;[1] PT, preferred term; SOC, System Organ Class

Table 44. Listing of Patients With Adverse Events[1] Leading to Treatment Discontinuation From Study Drug, Safety Population, Pooled Analysis[2]

Study Arm	Patient ID	Dosage	MedDRA Preferred Term	Verbatim Term	SAE[3]	AE Day of Onset/Stop	Study Day of Last Dosage of Study Drug	Day of Discontinuation From Study or Day of Study Completion	Investigator's Assessment of Relatedness[4]
Drug A	X	X mg	PT1	VT1	Y/N	X / Y	X	X	Y/N
	Y	X mg	PT2	VT2	Y/N	X / Y	X	X	Y/N
	Z	X mg	PT3	VT3	Y/N	X / Y	X	X	Y/N

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent AE defined as [definition]. MedDRA version X.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] SAEs classified by Applicant in [dataset].
[4] Reported per Applicant's system (e.g., Y/N, 5-point scale).
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event

Expanded Laboratory Analyses

Laboratory Data Change Over Time From Baseline Expanded Analyses

Table 45 provides more precise values for the data presented in Figure 6.

Table 45. Mean Change From Baseline for General Chemistry Data Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)

Parameter	Study Visit time[1] (Study Day/Week/Month)	Treatment Arm (N = X)			Control Arm (N = X)			Difference in Mean Change (95% CI)[2]
		n (%) at Visit	Mean (95% CI)	Mean Change From Baseline (95% CI)	n (%) at Visit	Mean (95% CI)	Mean Change From Baseline (95% CI)	
Sodium (mEq/L)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Potassium (mEq/L)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)

Parameter	Study Visit time[1] (Study Day/Week/Month)	Treatment Arm (N = X)			Control Arm (N = X)			Difference in Mean Change (95% CI)[2]
		n (%) at Visit	Mean (95% CI)	Mean Change From Baseline (95% CI)	n (%) at Visit	Mean (95% CI)	Mean Change From Baseline (95% CI)	
Chloride (mEq/L)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Bicarbonate (mEq/L)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Blood urea nitrogen (mg/dL)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Glucose (mg/dL)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Calcium (mg/dL)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Magnesium (mg/dL)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Phosphate (mg/dL)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Protein (total) (g/dL)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Albumin (g/dL)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
CPK (U/L)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)

Parameter	Study Visit time[1] (Study Day/Week/Month)	Treatment Arm (N = X)			Control Arm (N = X)			Difference in Mean Change (95% CI)[2]
		n (%) at Visit	Mean (95% CI)	Mean Change From Baseline (95% CI)	n (%) at Visit	Mean (95% CI)	Mean Change From Baseline (95% CI)	
Amylase (U/L)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Lipase (U/L)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit # is used as the study visit (+/- protocol-defined # days).
[2] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria

Table 46 provides more precise values for the data presented in Figure 7.

Table 46. Mean Change From Baseline for Kidney Function Data Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)

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

Source: [include Applicant source, datasets and/or software tools used].
[1] The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit # is used as the study visit (+/- protocol-defined # days).
[2] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria

Table 47 provides more precise values for Figure 8,

Table 47. Mean Change From Baseline for Liver Biochemistry[1] Data Over Time by Treatment Arm, Safety Population, Pooled Analyses

		Treatment Arm (N = X)			Control Arm (N = X)			
Parameter	**Study Visit Time[2] (Study Day/Week/Month)**	**n (%) at Visit**	**Mean (95% CI)**	**Mean Change From Baseline (95% CI)**	**n (%) at Visit**	**Mean (95% CI)**	**Mean Change From Baseline (95% CI)**	**Difference in Mean Change (95% CI)[3]**
Alkaline phosphatase (U/L)	Baseline	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week X	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week Y	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
Alanine aminotransferase (U/L)	Baseline	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week X	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week Y	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
Aspartate aminotransferase (U/L)	Baseline	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week X	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week Y	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
Bilirubin (total) (mg/dL)	Baseline	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week X	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week Y	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
INR (ratio)	Baseline	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week X	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week Y	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
GGT (U/L)	Baseline	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week X	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week Y	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] For specific evaluation of drug-induced liver injury, refer to Drug-Induced Liver Injury Screening Analyses
[2] The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit # is used as the study visit (+/- protocol-defined # days).
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; GGT, gamma-glutamyl transferase; INR, international normalized ratio; N, number of patients in treatment arm; n, number of patients meeting criteria

Table 48 provides more precise values for the data presented in Figure 9.

Table 48. Mean Change From Baseline for Lipid Data Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)

Parameter	Study Visit Time[1] (Study Day/Week/Month)	Treatment Arm (N = X)			Control Arm (N = X)			Difference in Mean Change (95% CI)[2]
		n (%) at Visit	Mean (95% CI)	Mean Change From Baseline (95% CI)	n (%) at Visit	Mean (95% CI)	Mean Change From Baseline (95% CI)	
Cholesterol (total), (mg/dL)	Baseline	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week X	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week Y	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
HDL (mg/dL)	Baseline	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week X	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week Y	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
LDL, high (mg/dL)	Baseline	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week X	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week Y	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
Triglycerides (mg/dL)	Baseline	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week X	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)
	Week Y	n (%)	X(Y,Z)	X(Y,Z)	n (%)	X(Y,Z)	X(Y,Z)	X(Y,Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit # is used as the study visit (+/- protocol-defined # days).
[2] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of patients in treatment arm; n, number of patients meeting criteria

Table 49 provides more precise values for the data presented in Figure 10.

Table 49. Mean Change From Baseline for Hematology Data Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)

Parameter	Study Visit Time[1] (Study Day/Week/Month)	Treatment Arm (N = X)			Control Arm (N = X)			Difference in Mean Change (95% CI)[2]
		n (%) at Visit	Mean (95% CI)	Mean Change From Baseline (95% CI)	n (%) at Visit	Mean (95% CI)	Mean Change From Baseline (95% CI)	
Complete Blood Count								
WBC (cells/μL)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Hemoglobin (g/dL)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Platelets (cells/μL)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
WBC Differential								
Lymphocytes (cells/μL)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Neutrophils (cells/μL)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Eosinophils (cells/μL)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Coagulation Studies								
PT (sec)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)

Parameter	Study Visit Time[1] (Study Day/Week/Month)	Treatment Arm (N = X)			Control Arm (N = X)			Difference in Mean Change (95% CI)[2]
		n (%) at Visit	Mean (95% CI)	Mean Change From Baseline (95% CI)	n (%) at Visit	Mean (95% CI)	Mean Change From Baseline (95% CI)	
PTT (sec)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)

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

[1] The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit # is used as the study visit (+/- protocol-defined # days).

[2] Difference is shown between [treatment arms]. (E.g., Difference is shown between Drug Name dosage X vs. placebo).

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cells

Outlier Criteria and Analyses

Customization

Tables with different level cutoffs (e.g., Levels 2 or 3) can be produced if desired. When not using pre-established laboratory grading systems, criteria from Tables 59 and 60 can be used. Similarly, Graphical Patient Profiles may also be requested for patients of interest.

Table 50. Listing of Patients With a Laboratory Value ≥ Level 2 Criteria,[1] Safety Population, Pooled Analysis[2]

USUBJID	Treatment Arm	Parameter	Baseline Lab Value	Laboratory Value Meeting Level 2 Criteria	Study Day[3]

Source: [include Applicant source, datasets and/or software tools used].
[1] Threshold Level 2 as defined by Table 59.and Table 60
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Postrandomization.
Abbreviation: USUBJID, unique subject identifier

Table 51. Listing of Patients With a Laboratory Value ≥ Level 2 Change From Baseline Criteria,[1] Safety Population, Pooled Analysis[2]

USUBJID	Treatment Arm	Parameter	Baseline Value	Qualifying Value	Change in Value	Study Day[3]
		Creatinine (mg/dL), (≥2.0 x baseline)				
		eGFR (ml/min/1.73m^2), ≥50% decrease				
		Hemoglobin (g/dL), (>1.5 decrease from baseline)				
		Hemoglobin (g/dL), (>2 increase from baseline)				

Source: [include Applicant source, datasets and/or software tools used].
[1] Threshold Level 2 as defined by Table 59 and Table 60.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Postrandomization.
Abbreviations: eGFR, estimated glomerular filtration rate; USUBJID, unique subject identifier

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 timeframe (e.g., 3 half-lives) following treatment intervention discontinuation, regardless of reason for discontinuation. This table could include patients who completed the trial and thus discontinued treatment per protocol as well as patients who discontinued treatment because of an adverse event.

If notable differences are observed among the treatment arms in the laboratory data analysis, it is recommended to evaluate the percentage of patients with abnormality level criteria at any time during the trial and within a specific timeframe (e.g., 3 half-lives) following treatment intervention discontinuation.

Tables 59 and 60 list abnormality Levels 1, 2, and 3 criteria for chemistry and hematology, respectively, as noted in Tables 52 and 53.

Table 52. Patients With Last On-Treatment[1] Chemistry Value ⩾ Level 2 Criteria[2] by Treatment Arm, Safety Population, Pooled Analyses[3]

Parameter	Drug Name N = XXX n (%)	Control N = XXX n (%)	Risk Difference (%) (95% CI)[4]
General Chemistry			
Sodium, low (<130mEq/L)	n (%)	n (%)	X (Y, Z)
Sodium, high (>155 mEq/L)	n (%)	n (%)	X (Y, Z)
Potassium, low (<3.4 mEq/L)	n (%)	n (%)	X (Y, Z)
Potassium, high (>6 mEq/L)	n (%)	n (%)	X (Y, Z)
Chloride, low (<88 mEq/L)	n (%)	n (%)	X (Y, Z)
Chloride, high (>112 mEq/L)	n (%)	n (%)	X (Y, Z)
Bicarbonate, low (<18 mEq/L)	n (%)	n (%)	X (Y, Z)
Bicarbonate, high (>30 mEq/L)	n (%)	n (%)	X (Y, Z)
Blood urea nitrogen, high (>27 mg/dL)	n (%)	n (%)	X (Y, Z)
Glucose, low (<54 mg/dL)	n (%)	n (%)	X (Y, Z)
Glucose, high Fasting (≥126 mg/dL) or Random (≥200 mg/dL)	n (%)	n (%)	X (Y, Z)
Calcium, low (<8 mg/dL)	n (%)	n (%)	X (Y, Z)
Calcium, high (>11 mg/dL)	n (%)	n (%)	X (Y, Z)
Magnesium, low (<1.2 mg/dL)	n (%)	n (%)	X (Y, Z)
Magnesium, high (>4 mg/dL)	n (%)	n (%)	X (Y, Z)
Phosphate, low (<2 mg/dL)	n (%)	n (%)	X (Y, Z)
Protein (total), low (<5.4 g/dL)	n (%)	n (%)	X (Y, Z)
Albumin, low (<2.5 g/dL)	n (%)	n (%)	X (Y, Z)
CPK, high (>5 x ULN U/L)	n (%)	n (%)	X (Y, Z)
Amylase, high (>1.5 x ULN U/L)	n (%)	n (%)	X (Y, Z)
Lipase, high (>1.5 x ULN U/L)	n (%)	n (%)	X (Y, Z)
Kidney Function			
Creatinine, high (mg/dL) ≥2.0 x baseline	n (%)	n (%)	X (Y, Z)
eGFR, low (ml/min/1.73m^2) ≥50% decrease	n (%)	n (%)	X (Y, Z)

Parameter	Drug Name N = XXX n (%)	Control N = XXX n (%)	Risk Difference (%) (95% CI)[4]
Liver Biochemistry[3]			
Alkaline phosphatase, high (U/L) >2.0 x ULN	n (%)	n (%)	X (Y, Z)
Alanine Aminotransferase, high (U/L) >5.0 x ULN	n (%)	n (%)	X (Y, Z)
Aspartate Aminotransferase, high (U/L) >5.0 x ULN	n (%)	n (%)	X (Y, Z)
Bilirubin (total), high (mg/dL) >2.0 x ULN	n (%)	n (%)	X (Y, Z)
Lipids			
Cholesterol (total), high (>240 mg/dL)	n (%)	n (%)	X (Y, Z)
HDL, low (<40 mg/dL), males	n (%)	n (%)	X (Y, Z)
HDL, low (<50 mg/dL), females	n (%)	n (%)	X (Y, Z)
LDL, high (>160 mg/dL)	n (%)	n (%)	X (Y, Z)
Triglycerides, high (>300 mg/dL)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Last value on-treatment defined as the last value for any given laboratory parameter obtained within a specific timeframe (e.g., 3 half-lives) following treatment intervention discontinuation, regardless of reason for discontinuation.
[2] Threshold Level 2 as defined by Table 59.
[3] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[4] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X 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 patients in treatment arm; n, number of patients meeting criteria; ULN, upper limit of normal

Table 53. Patients With Last On-Treatment[1] Hematology Value ≥ Level 2 Criteria[2] by Treatment Arm, Safety Population, Pooled Analyses[3]

Parameter	Drug Name N = XXX n (%)	Active Control N = XXX n (%)	Risk Difference (%) (95% CI)[4,]
Complete Blood Count			
WBC, low (<3000 cells/µL)	n (%)	n (%)	X (Y, Z)
WBC, high (>13,000 cells/µL)	n (%)	n (%)	X (Y, Z)
Hemoglobin, >1.5 (g/dL) decrease from baseline	n (%)	n (%)	X (Y, Z)
Hemoglobin, >2 (g/dL) increase from baseline	n (%)	n (%)	X (Y, Z)
Platelets, low (<125,000 cells/µL)	n (%)	n (%)	X (Y, Z)
WBC Differential			
Lymphocytes, low (<750 cells/µL)	n (%)	n (%)	X (Y, Z)
Lymphocytes, high (>10000 cells/µL)	n (%)	n (%)	X (Y, Z)
Neutrophils, low (<1000 cells/µL)	n (%)	n (%)	X (Y, Z)
Eosinophils, high (>1500 cells/µL)	n (%)	n (%)	X (Y, Z)
Coagulation Studies			
PT, high (sec) (>1.1 x ULN)	n (%)	n (%)	X (Y, Z)
PTT, high (sec) (>1.21 x ULN)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Last value on-treatment defined as the last value for any given laboratory parameter obtained within a specific timeframe (e.g., 3 half-lives) following treatment intervention discontinuation, regardless of reason for discontinuation.
[2] Threshold Level 2 as defined by and Table 60.
[3] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[4] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cells

Optional Safety Tables and Figures

The optional safety tables and figures on the following pages contain two modules: (1) optional adverse event analyses tables, and (2) optional laboratory and vital sign data distribution over time figures. These modules either provide additional context to the data or visualize previously given tables/figures in a different manner.

Optional Adverse Event Analyses Tables

Exposure-Adjusted Analyses

Exposure-adjusted analyses should be evaluated in situations where comparing crude incidence rate of AEs may not accurately represent true risks. These situations include:

- When there is substantially different treatment or trial duration among treatment arms (Patients are exposed to a study treatment for a longer duration are expected to have higher chance of experiencing the AE)
- Differential discontinuation between arms
- Longer studies, e.g., a study of two years or longer duration
- Drug development program where the studies differ in length, where per patient year display can help enable comparisons of event rates across studies of different durations.

Table 54. Exposure-Adjusted Incidence Rate Analysis, Safety Population, Pooled Analyses (or Trial X)

Preferred Term	Drug Name Dosage X PY[1]=xxx.x EAIR (Per 100 PY)	Placebo PY[1]=xxx.x EAIR (Per 100 PY)	Risk Difference (95% CI)[2,3]
PT1	EAIR (per 100 PY)	EAIR (per 100 PY)	X (Y, Z)
PT2	EAIR (per 100 PY)	EAIR (per 100 PY)	X (Y, Z)
PT3	EAIR (per 100 PY)	EAIR (per 100 PY)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Treatment-emergent AE defined as [definition]. MedDRA version X. An asterisk (*) indicates a grouped term.
[1] Indicate method used to calculate the patient years.
[2] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[3] Table display is ordered by the risk difference.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate; N, number of patients in treatment arm; n, number of patients with AE; PT, preferred term; PY, patient years

For this table, the method used to determine patient years should be explained in the footnote.

Exposure-adjusted event rate analysis may be presented if appropriate. The denominator for each AE is not the overall exposure; it is the “adjusted” exposure omitting exposure post the occurrence of the AE. Therefore, the patient years in the top of the column is not the actual denominator for each row. Top of the column includes the overall patient years (sum of all exposures of the randomized population per treatment group).

Relatedness Analyses

The limitation of assigning drug relatedness during the premarket phase of the drug development should be noted, as the extensive safety profile of the drug is not available early in the development. Therefore, a table of AEs with drug relationship as assessed by the investigator may have limited utility, given the difficulty of assigning drug relationship. However, it provides an additional input in safety evaluation, as it reflects the clinical assessment of the investigator at the point of care. It is helpful to assess drug relationship by evaluating imbalances across treatment arms in incidence.

Table 55. Patients With Adverse Events[1] Assessed by Investigator as Treatment-Related Occurring at X% Frequency, Safety Population, Pooled Analyses (or Trial X)[2]

Preferred Term	Drug Name Dosage X N=XXX n (%)	Drug Name Dosage Y N=XXX n (%)	Active Control N=XXX n (%)	Placebo N=XXX n (%)	Risk Difference (%) (95% CI)[3,4]
Any treatment-related AE	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT3	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent AE is defined as [definition].
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[4] Table display is ordered by the risk difference.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term

Additional FMQ Tables

Additional FMQ tables (Tables 56 and 57) display subject-level data for specific patients for the FMQs where an imbalance is noted.

Table 56. Selected Narrow FDA Medical Queries[1], Safety Population, Pooled Analyses (or Trial X)[2]

FMQ Patient ID	Age	MedDRA PT	Verbatim Term	Serious	AE Discontinuation	Severity	Study Day of Onset	Action Taken	Outcome
FMQ1 (Drug)									
Patient ID1									
Patient ID2									
FMQ1 (Control)									
Patient ID1									
Patient ID2									
FMQ2 (Drug)									
Patient ID1									
Patient ID2									
FMQ2 (Control)									
Patient ID1									
Patient ID2									

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent AE defined as [definition].
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
Abbreviations: AE, adverse event; FMQ; FDA Medical Query; PT, preferred term

Table 57. Selected Broad FDA Medical Queries[1], Safety Population, Pooled Analyses (or Trial X)[2]

FMQ Patient ID	Age	MedDRA PT	Verbatim Term	Serious	AE Discontinuation	Severity	Study Day of Onset	Action Taken	Outcome
FMQ1 (Drug)									
Patient ID1									
Patient ID2									
FMQ1 (Control)									
Patient ID1									
Patient ID2									
FMQ2 (Drug)									
Patient ID1									
Patient ID2									

FMQ Patient ID	Age	MedDRA PT	Verbatim Term	Serious	AE Discontinuation	Severity	Study Day of Onset	Action Taken	Outcome
FMQ2 (Control)									
Patient ID1									
Patient ID2									

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent AE defined as [definition].
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
Abbreviations: AE, adverse event; FMQ, FDA Medical Query; PT, preferred term

Adverse Event Analyses to Inform Adverse Reaction Table

Customization

Adjust the cutoffs, as deemed necessary (e.g., ≥5% in drug-treated group and ≥2% more in the drug-treated group than the placebo-treated group). Any refinements to this table may be discussed during the Type C ISS meeting, pre-NDA meeting or other interactions with the review division.

Table 58. Patients With Adverse Events[1] Occurring at ≥X% in Drug-Treated Group and ≥Y% More in Drug-Treated Group Than Placebo-Treated Group, More Often in Treatment, Safety Population, Pooled Analyses (or Trial X)[2]

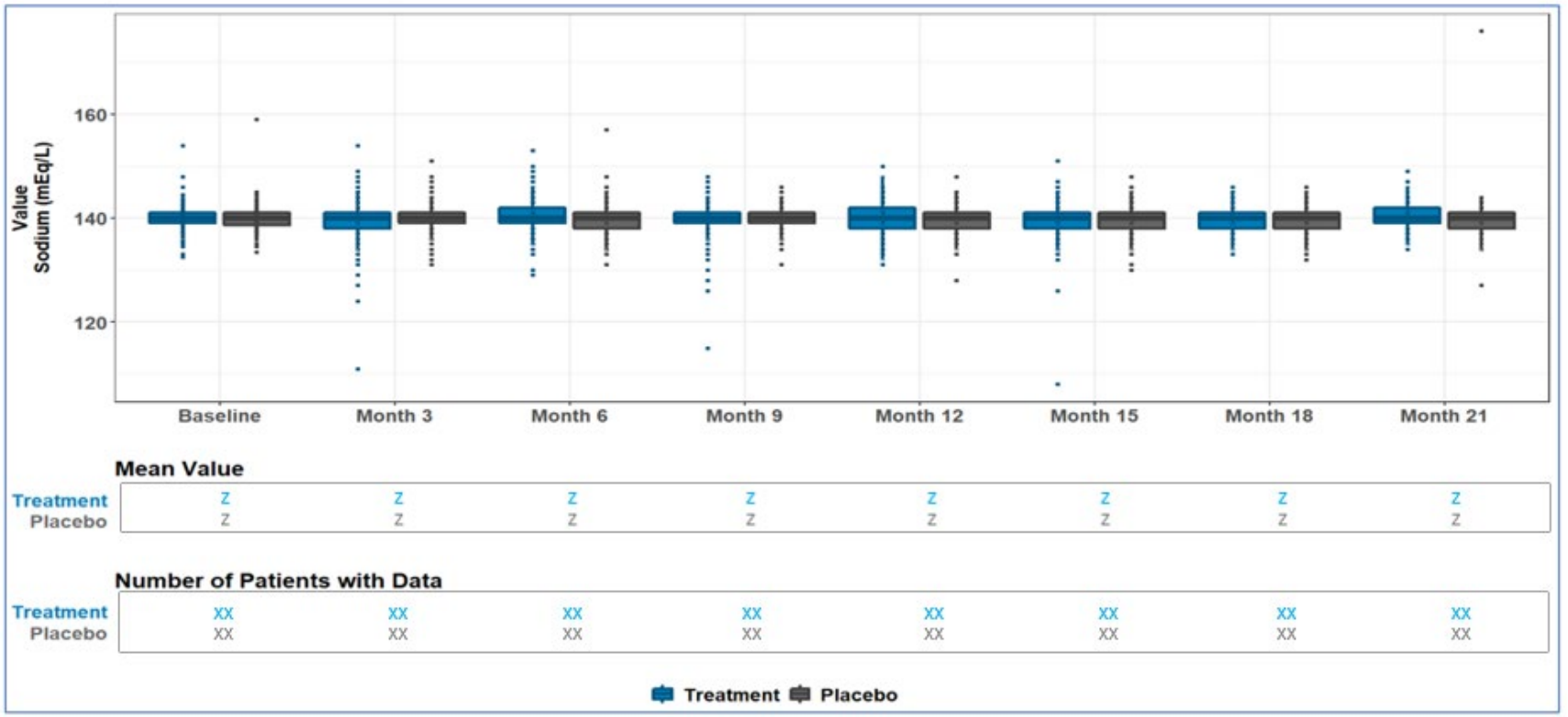
Preferred Term	Drug Name Dosage X N=XXX n (%)	Drug Name Dosage Y N=XXX n (%)	Active Control N=XXX n (%)	Placebo N=XXX n (%)	Risk Difference (%) (95% CI)[3,4]
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT3	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

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

Optional Laboratory and Vital Sign Data Distribution Over Time Figures

The optional graphs on the following pages can be generated with data for each of the following: sodium, potassium, chloride, bicarbonate, glucose, calcium, magnesium, phosphate, total protein, albumin, creatine phosphokinase, amylase, lipase, etc.

Figure 27. Median and Interquartile Range[1] for Sodium Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)[2]



Baseline	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X
Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X
Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X

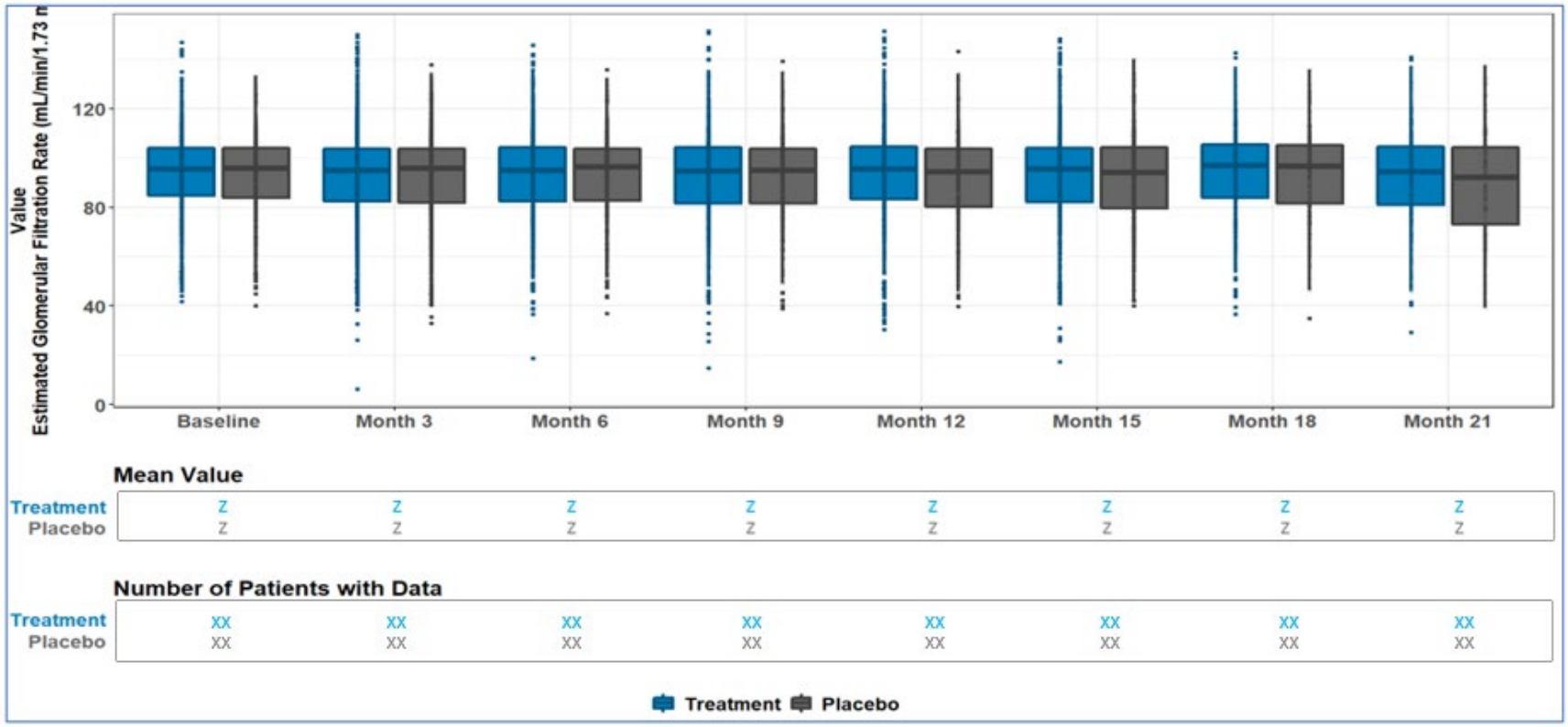
Source: [include Applicant source, datasets and/or software tools used].

[1] Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers = 1.5 X the interquartile range; individual outliers are those beyond this range.

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

Figure 28 includes an example of one of the kidney function laboratory parameters. This graph can be generated with data for each of the following: creatinine and eGFR.

Figure 28. Median and Interquartile Range[1] of Estimated Glomerular Filtration Rate (eGFR) Over Time by Treatment Arm, Safety Population, Pooled Analyses (or Trial X)[2]



Baseline	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X
Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X
Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X

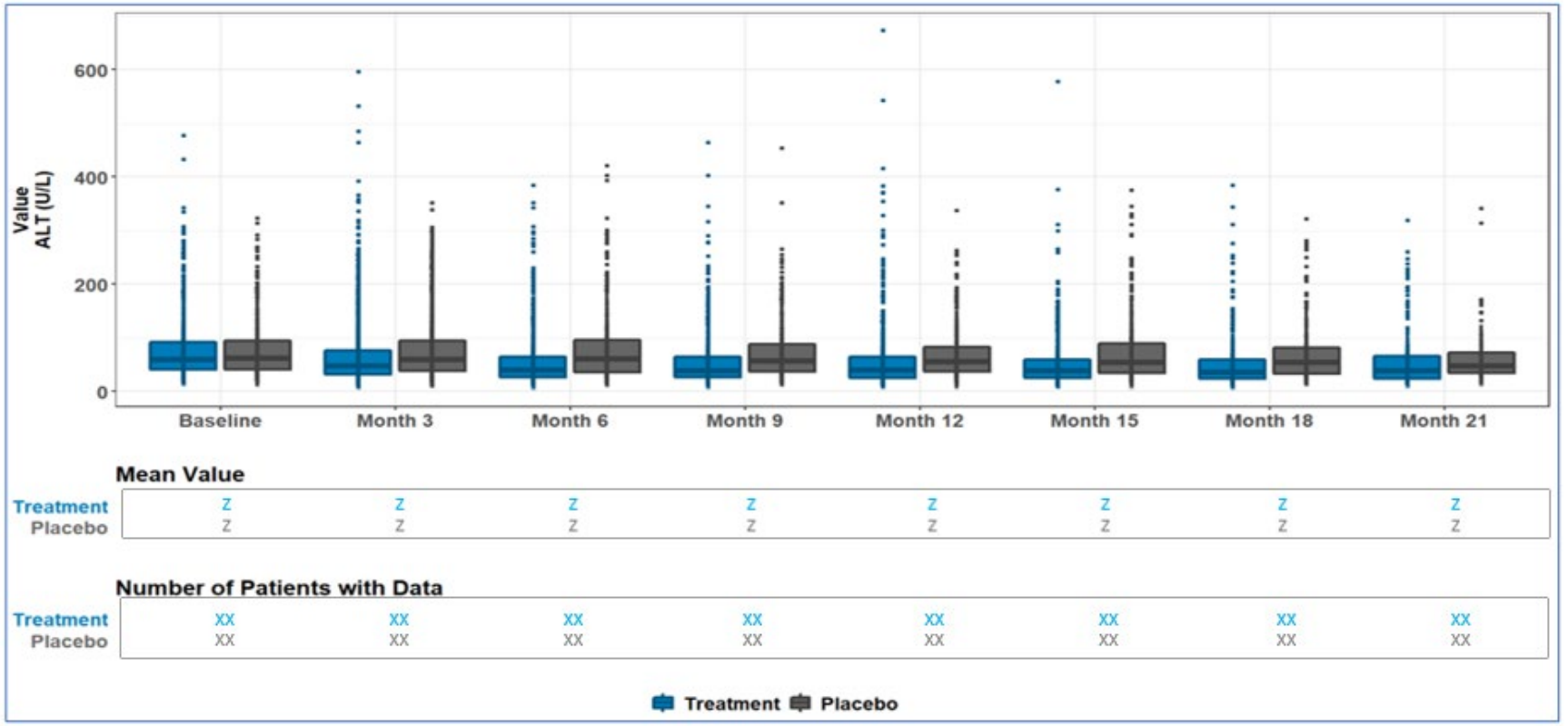
Source: [include Applicant source, datasets and/or software tools used].:

[1] Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers = 1.5 X the interquartile range; individual outliers are those beyond this range.

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

Figure 29 includes an example of one of the liver biochemistry laboratory parameters. This graph can be generated with data for each of the following: ALP, ALT, AST, and TB.

Figure 29. Median and Interquartile Range[1] of Alanine Aminotransferase Over Time by Treatment Arm, Safety Population Pooled Analyses (or Trial X)[2]

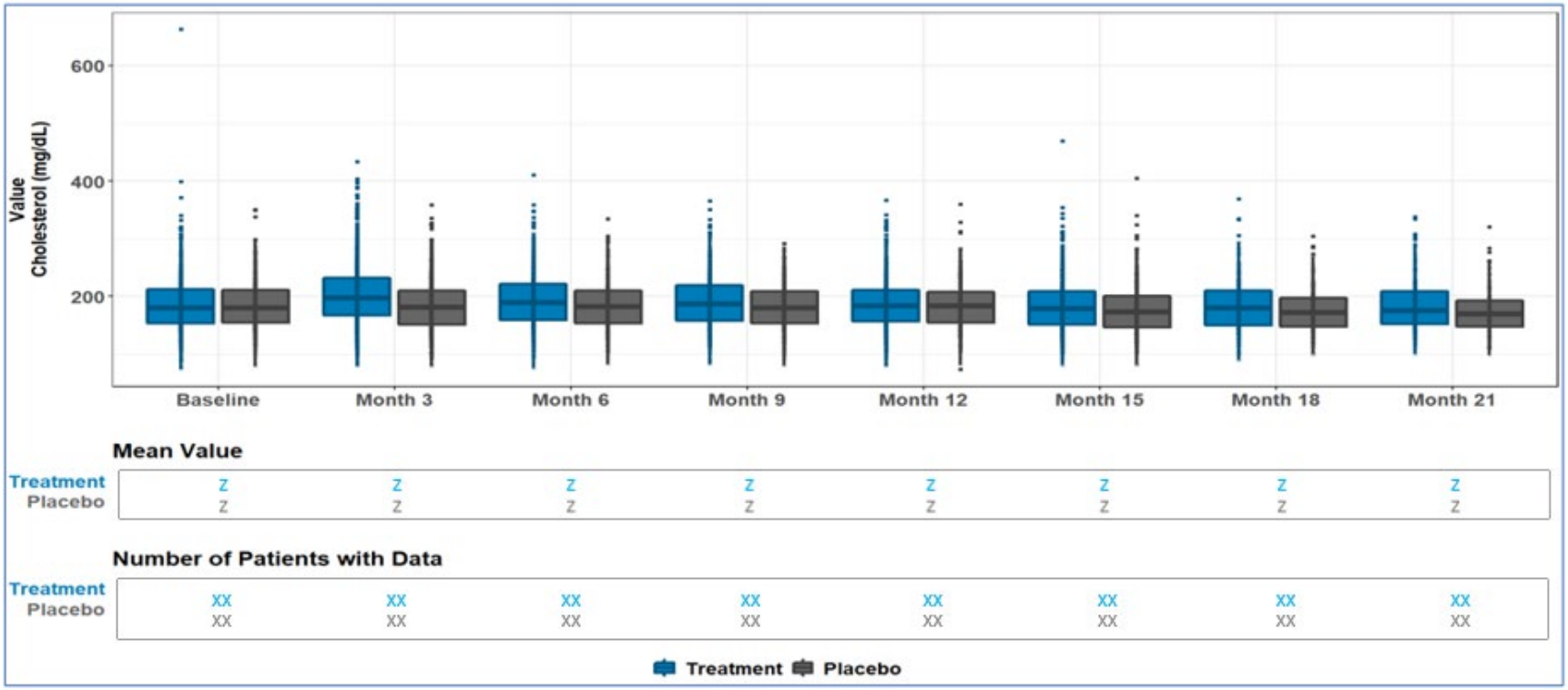


Baseline	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X
Drug N = X Control N = X	Drug N = X Control N = X	Drug N = X Control N = X	Drug N = X Control N = X	Drug N = X Control N = X	Drug N = X Control N = X	Drug N = X Control N = X	Drug N = X Control N = X	Drug N = X Control N = X	Drug N = X Control N = X	Drug N = X Control N = X

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

Figure 30 includes an example of one of the Lipid laboratory parameters. This graph can be generated with data for each of the following: Total cholesterol, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), and Triglycerides (TG).

Figure 30. Median and Interquartile Range[1] of Total Cholesterol Over Time by Treatment Arm, Safety Population, Pooled Analyses (or Trial X)[2]



Baseline	**Study Visit X**	**Study Visit X**	**Study Visit X**	**Study Visit X**	**Study Visit X**	**Study Visit X**	**Study Visit X**	**Study Visit X**	**Study Visit X**	**Study Visit X**
Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X
Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X

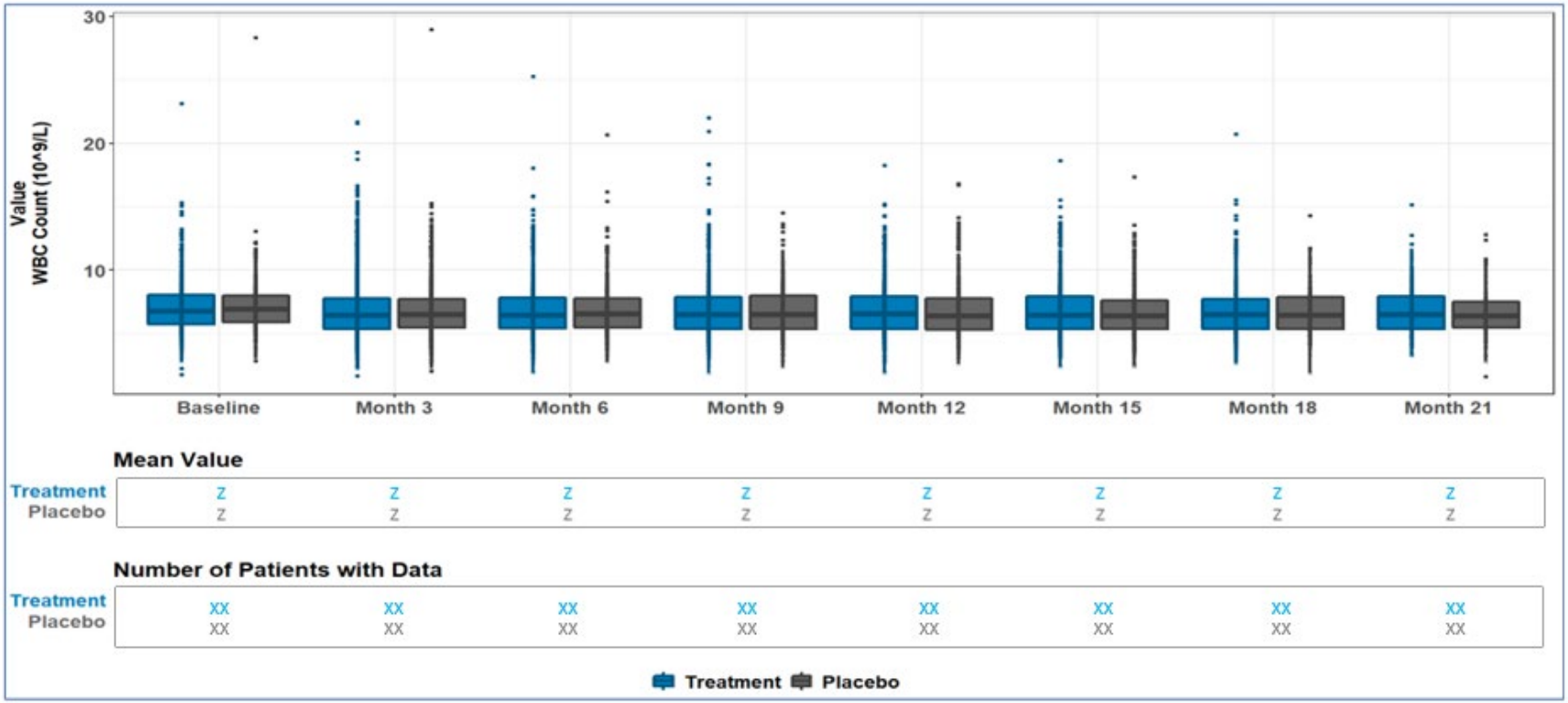
Source: [include Applicant source, datasets and/or software tools used].:

[1] Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers = 1.5 X the interquartile range; individual outliers are those beyond this range.

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

Figure 31 includes an example of one of the hematology laboratory parameters. This graph can be generated with data for each of the following: white blood cell (WBC) count, hemoglobin, hematocrit, platelets, WBC differential (i.e., eosinophils, lymphocytes, neutrophils), prothrombin time, and partial thromboplastin time.

Figure 31. Median and Interquartile Range[1] of White Blood Cell Count Over Time by Treatment Arm, Safety Population, Pooled Analyses (or Trial X)[2]



Baseline	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X	Study Visit X
Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X	Drug N = X
Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X	Control N = X

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

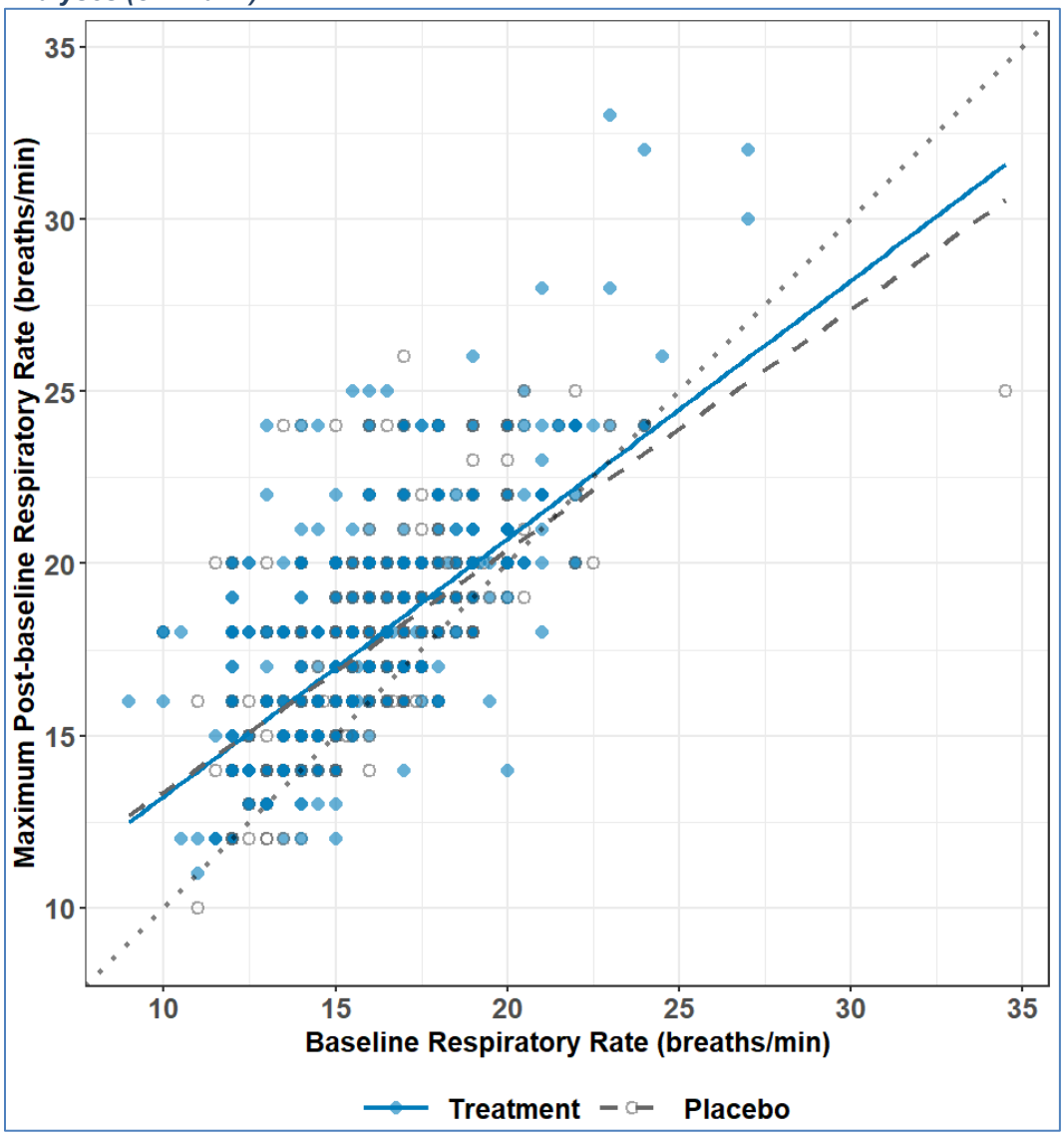
[1] Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers = 1.5 X the interquartile range; individual outliers are those beyond this range.

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

Abbreviation: WBC, white blood cell

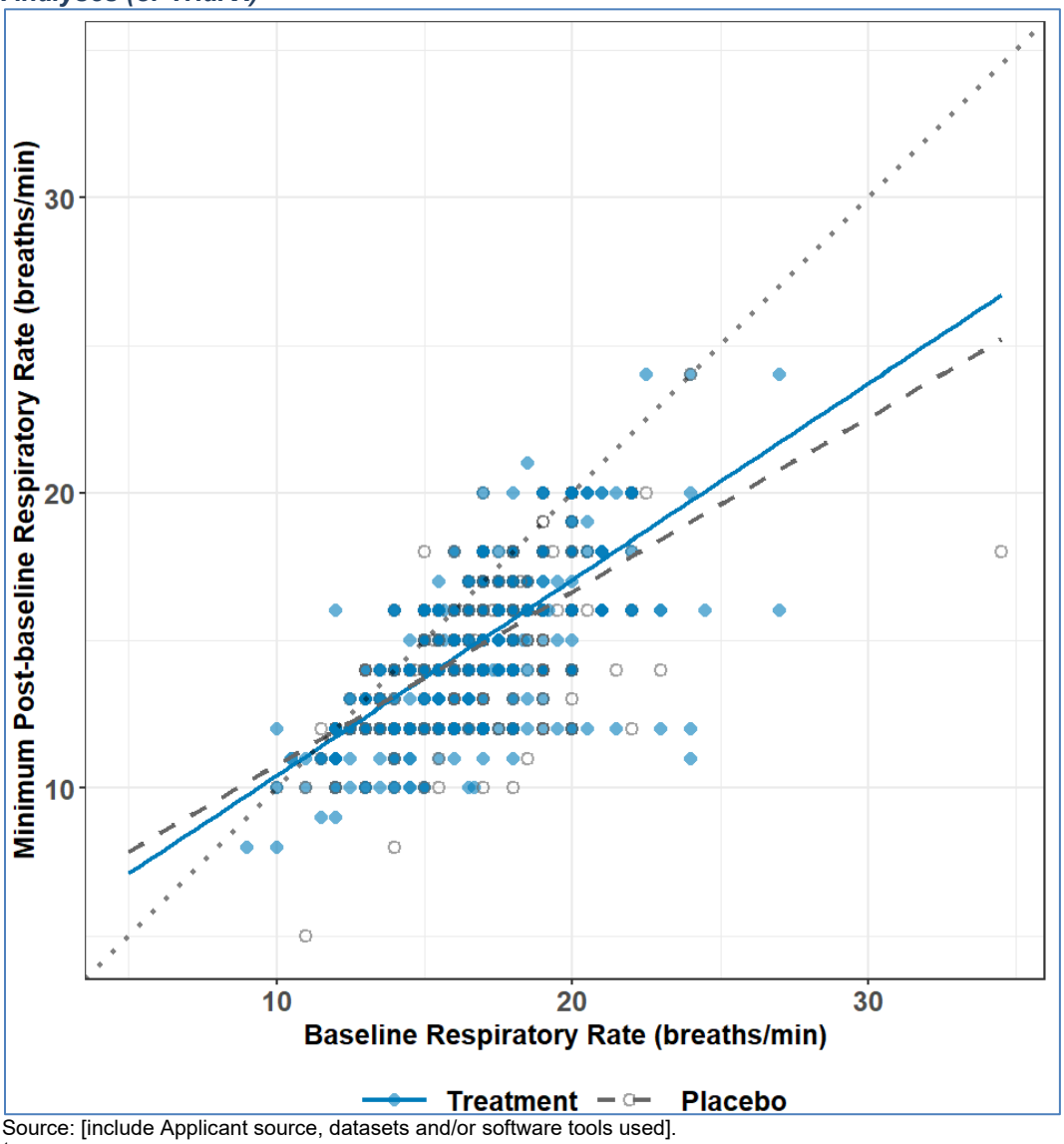
The following figures can be presented as optional figures for the vital sign data representation if there is a concern about changes in respiratory rate and temperature with the IP administration.

Figure 32. Baseline vs. Maximum Respiratory Rate by Treatment Arm,[1] Safety Population, Pooled Analyses (or Trial X)



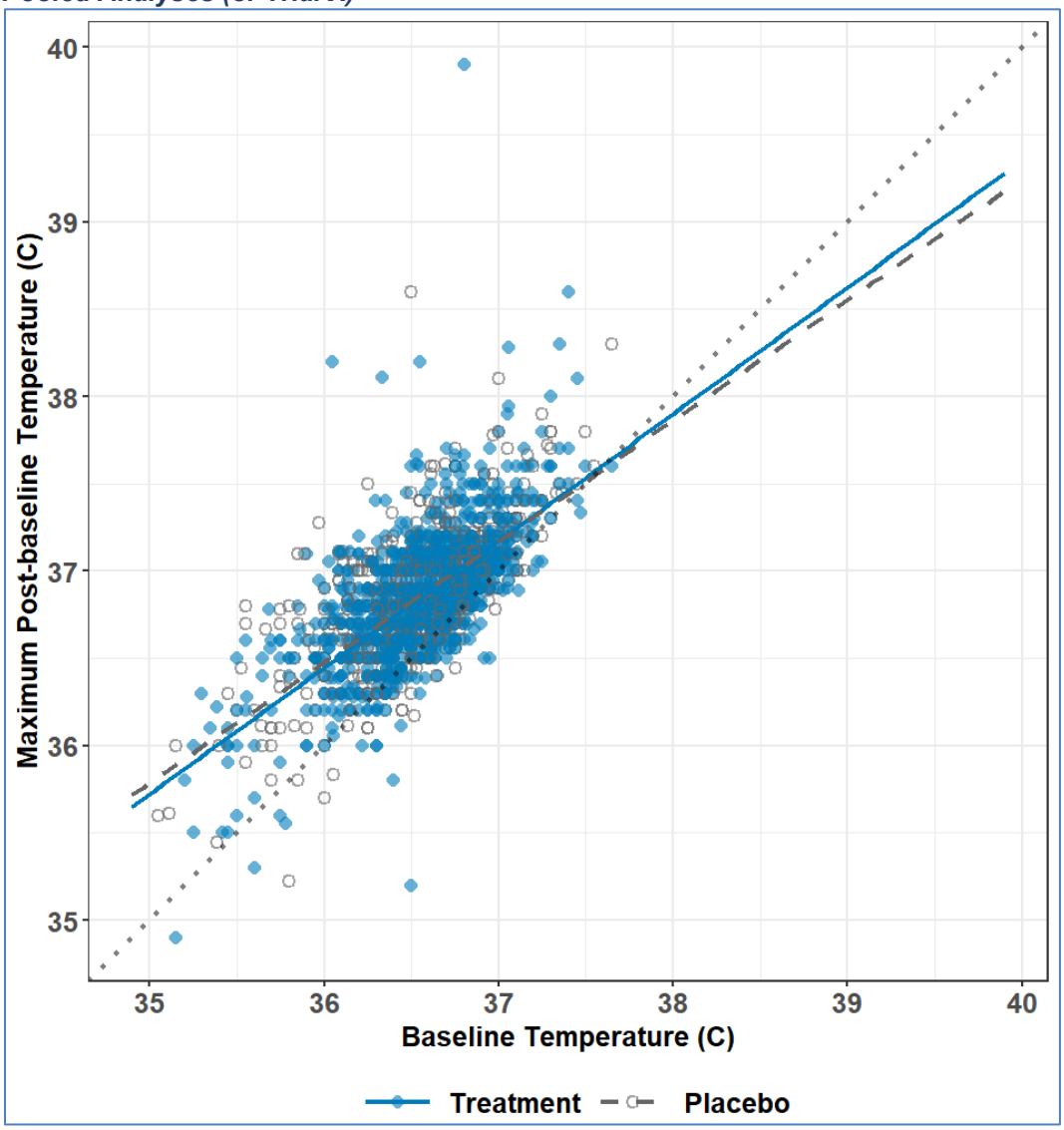
Source: [include Applicant source, datasets and/or software tools used].
[1] Gray dotted line = no increase; blue line = treatment linear regression; gray dashed line = placebo linear regression.

Figure 33. Baseline vs. Minimum Respiratory Rate by Treatment Arm,[1] Safety Population, Pooled Analyses (or Trial X)



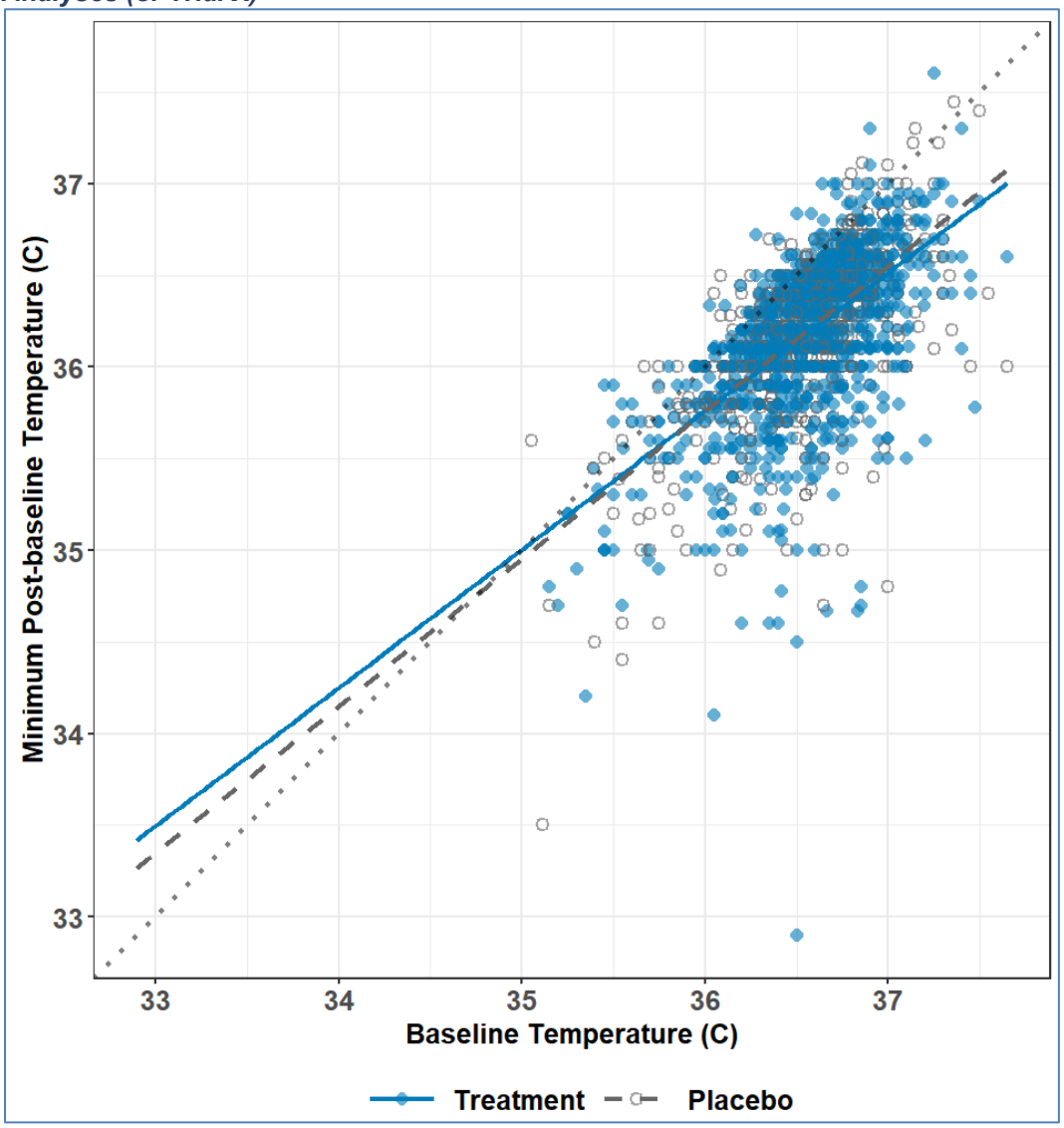
Source: [include Applicant source, datasets and/or software tools used].
[1] Gray dotted line = no decrease; blue line = treatment linear regression; grey dashed line = placebo linear regression.

Figure 34. Baseline vs. Maximum Body Temperature by Treatment Arm,[1] Safety Population, Pooled Analyses (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
[1] Gray dotted line = no increase; blue line = treatment linear regression; gray dashed line = placebo linear regression.

Figure 35. Baseline vs. Minimum Body Temperature by Treatment Arm,[1] Safety Population, Pooled Analyses (or Trial X)



Source: [include Applicant source, datasets and/or software tools used].
[1] Gray dotted line = no decrease; blue line = treatment linear regression; gray dashed line = placebo linear regression.

Appendix

The Appendix contains tables that may be leveraged as a reference for abnormality level criteria cutoffs.

Reference Tables for Abnormality Level Criteria Cutoffs

Tables 59 and 60 list abnormality Levels 1, 2, and 3 criteria for chemistry and hematology, respectively, as noted in Tables 24 to 28 and Tables 50 to 52.

Table 59. Abnormality Level Criteria[1] 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	
Glucose, high (mg/dL)			
Fasting or	≥100	≥126	
Random	N/A	≥200	
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
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[2]			
Alkaline phosphatase, high (U/L)	>1.5 x ULN	>2.0 x ULN	>3.0 x ULN
Alanine Aminotransferase, high	>3.0 x ULN	>5.0 x ULN	>10.0 x ULN
Aspartate Aminotransferase, high	>3.0 x ULN	>5.0 x ULN	>10.0 x ULN
Bilirubin (total) (mg/dL)	>1.5 x ULN	>2.0 x ULN	>3.0 x ULN

Parameter	Level 1	Level 2	Level 3
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

[1] Provided for the purpose of identifying outliers.
[2] For specific evaluation of drug-induced liver injury, refer to Drug-Induced Liver Injury Screening Analyses
Abbreviations: CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ULN, upper limit of normal

Table 60. Abnormality Level Criteria1 for Hematology Laboratory Results

Parameter	Level 1	Level 2	Level 3
Complete Blood Count			
WBC, low (cells/µL)	<3500	<3000	<1000
WBC, high (cells/µL)	>10,800	>13,000	>15,000
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 (cells/µL)	<140,000	<125,000	<100,000
Hemoglobin, male (g/dL)	12.5-13.5	<12.5	<10.5
Hemoglobin, female (g/dL)	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

[1] Provided for the purpose of identifying outliers.
Abbreviations: PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cell; ULN, Upper Limit of Normal

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Mahtab Niyyati

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