U.S. FOOD & DRUG ADMINISTRATION

STANDARD SAFETY TABLES AND FIGURES:

MUSCLE INJURY TARGETED ANALYSIS GUIDE

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

Center for Drug Evaluation and Research (CDER)
Biomedical Informatics and Regulatory Review Science Team (BIRRS)

Version 1.2

Version Date: April 2025

Table of Contents

Table of Tables

Table of Figures

1. Introduction

Clinical reviewers use tables and figures to investigate potential safety findings in marketing applications and present clinical safety data in their reviews. The goal of the Standard Safety Tables and Figures Muscle Injury Targeted Analysis Guide (TAG) is to provide additional analyses to further investigate a potential muscle injury signal identified during the initial clinical safety review or when muscle injury is an adverse event of special interest (AESI). The muscle injury TAG is generated upon request by the clinical reviewer.

Targeted analyses are provided for exploratory purposes and are not meant to be exhaustive. Additional custom analyses not included in the TAG to further characterize the potential for muscle injury may also be requested. The determination of which tables and figures for inclusion in the clinical safety review is at the discretion of the clinical reviewer.

1.1. Background

Skeletal muscle injury results in the release of intracellular contents into the circulation[1] and has multiple causes, including trauma, prolonged immobilization, marked exertion, hyperthermia, infection, toxins, and drugs. Rhabdomyolysis is considered a severe manifestation of this type of injury, although there are no consensus criteria that provide a specific creatine phosphokinase (CPK) level required for this diagnosis. Commonly cited thresholds in the literature are a CPK elevation of at least five to ten times the upper limit of normal that is followed by a rapid decrease in CPK to normal levels with resolution of the inciting event.[2,3] Other thresholds that have been cited are CPK levels of 1,000 or 5,000 U/L, although it is possible for patients to have levels above 100,000 U/L.[4] If clinical reviewers observe a muscle injury signal, they will need to determine whether to characterize the syndrome as rhabdomyolysis based on their analysis of all of the data.

This guide includes an OND Custom Medical Query (OCMQ) for muscle injury, which has an algorithmic component. OCMQs combine similar adverse event (AE) terms to promote safety signal detection during the analysis of clinical trial data. The algorithmic component contained in this and other OCMQs is designed to leverage information such as the laboratory, concomitant medication, medical history, and temporal

---

[1] Zimmerman, JL and MC Shen, 2013, Rhabdomyolysis, Chest, 144(3):1058-1065.
[2] Zutt, R, AJ van der Kooi, GE Linthorst, RJ Wanders, and M de Visser, 2014, Rhabdomyolysis: review of the literature, Neuromuscul Disord, 24(8):651-659.
[3] Chavez, LO, M Leon, S Einav, and J Varon, 2016, Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice, Crit Care, 20(1):135.
[4] Heard, H and J Barker, 2016, Recognizing, diagnosing, and treating rhabdomyolysis, Jaapa, 29(5):29-32.

information in addition to the AE data to identify events that may not have been captured during clinical trials. The Muscle Injury algorithmic OCMQs includes all subjects with an AE of rhabdomyolysis or myoglobinuria, laboratory result of myoglobinuria, laboratory CPK level greater than five times the upper limit of normal, and those who experience the rhabdomyolysis triad of myalgia, muscular weakness, and chromaturia.

2. Screening Analyses

This section includes screening tables from the Standard Safety Tables & Figures Integrated Guide (ST&F IG) for AE analyses that pertain to muscle injury from the to facilitate the review of all pertinent analyses in one document. Only the portions of the tables and figures that are relevant to muscle injury are included.

2.1. Muscle Injury AE Analyses

Example Table

Table 1. Subjects With AEs[1] by Muscle Injury Narrow OCMQs and Preferred Term, Safety Population, Pooled Analysis (or Trial X)[2]

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

Source: Extract of Table 31 - Subjects with AEs by Organ System, OND Custom Medical Query (Narrow) and Preferred Term within the ST&F Integrated Guide.
[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 of pooled trial durations].
[3] OCMQs include AEs that are not MedDRA PTs.
[4] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[5] Table display is ordered by risk difference.
Abbreviations: CI, confidence interval; OCMQ, OND Custom Medical Query; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with at least one event; N, number of subjects in treatment arm; PT, preferred term.

For Table 2: Subjects With AEs by Muscle Injury Broad OCMQs and Preferred Term, the Broad OCMQs includes both Broad and Narrow PTs.

Example Table

Table 2. Subjects With AEs[1] by Muscle Injury Broad[2] OCMQs and Preferred Term, Safety Population, Pooled Analysis (or Trial X)[3]

OCMQ (Broad) Preferred Term[4]	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[5,6]
Muscle Injury (Broad)	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
PT3	X (Y)	X (Y)	X (Y, Z)

Source: Extract of Table 43 - Subjects with AEs by Organ System, OND Custom Medical Query (Broad) and Preferred Term within the ST&F Integrated Guide.
[1] Treatment-emergent AE defined as [definition]. MedDRA version X.
[2] Broad OCMQ analysis incorporates Narrow OCMQ preferred terms to maximize sensitivity.
[3] Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[4] OCMQs include AEs that are not MedDRA PTs.
[5] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[6] Table display is ordered by risk difference.
Abbreviations: CI, confidence interval; OCMQ, OND Custom Medical Query; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with AE; N, number of subjects in treatment arm; PT, preferred term.

2.2. Laboratory Analyses

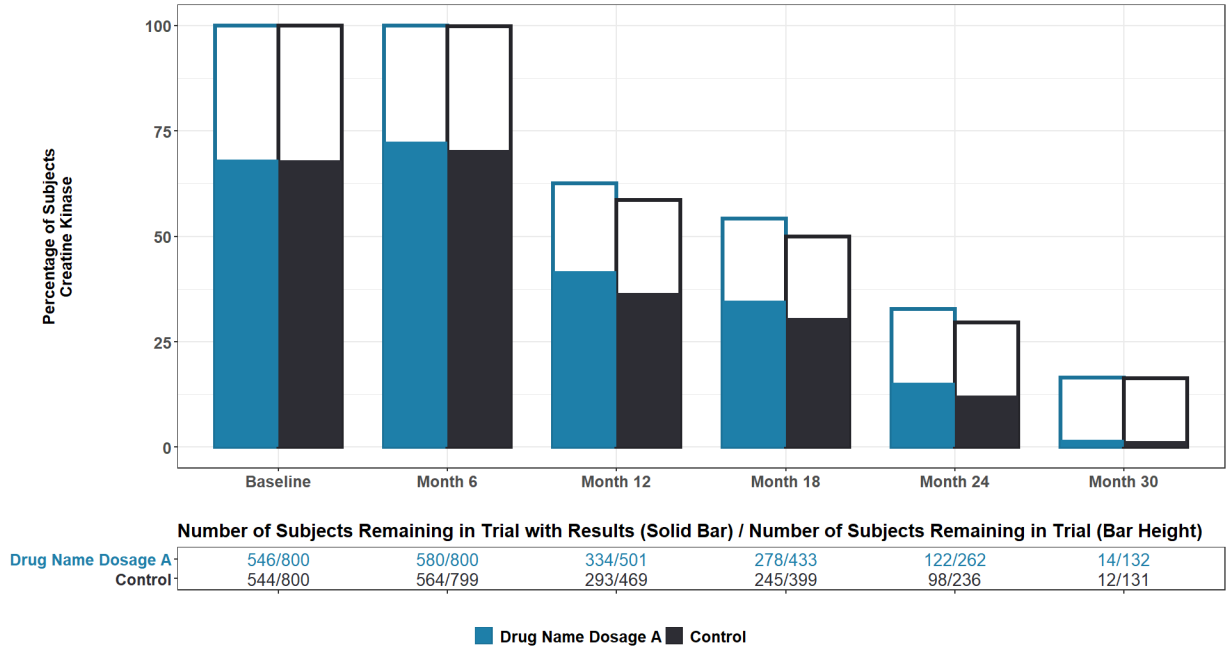
This section includes screening tables and figures of muscle injury laboratory abnormalities (e.g., CPK) from the Laboratory Analysis module in the ST&F IG to facilitate review of all pertinent analyses in one package.

The existing and missing data analysis in Figure 1: Proportion of Subjects Remaining in Trial at Each Visit by Availability of CPK Result displays the proportion of existing and missing data by study arm. A high proportion of missing data suggests that available data is limited, and that the data presented in this package should be interpreted with caution. Alternatively, the reviewer may ask the sponsor to address missing data in the application before continuing with analyses.

Figure 1 displays the proportion of subjects with CPK data by visit (solid bar) and the percentage of subjects remaining in the trial (open bar). This graph should evaluate the actual data obtained during the trial, rather than the planned study procedures as stated in the protocol.

Example Figure

Figure 1. Proportion of Subjects Remaining in Trial at Each Visit by Availability of CPK Result, Safety Population, Pooled Analysis (or Trial X)[1]



Source: Extract of Figure 5 - Proportion of Subjects Remaining in Trial at Each Visit by Availability of [Insert Lab Value] Result within the ST&F Integrated Guide.
[1] Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Note: The frequency of laboratory measurements presented here is based on actual data collected.
Note: The time frame (e.g., by day, week, month) that corresponds best with the prespecified visit # is used as the trial visit (±protocol-defined # days).
Note: The solid bar indicates the percent of subjects remaining in the trial with the laboratory result. The open bar indicates the percent of subjects remaining in the trial who are missing the laboratory result. The bar height indicates the percent of subjects remaining in the trial.
Abbreviations: CPK, creatine phosphokinase.

Example Table

Table 3. Mean Change From Baseline in CPK Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)[1]

		Drug Name Dosage A N=XXX			Control N=XXX			
Parameter	Study Visit[2] (Study Day, Week, or Month)	n (%) at Visit[3]	Mean	Mean Change From Baseline	n (%) at Visit[3]	Mean	Mean Change From Baseline	Difference in Mean Change (95% CI)[4]
CPK (U/L)	Baseline	X (Y)	X	N/A	X (Y)	X	N/A	N/A
	Week X	X (Y)	X	X	X (Y)	X	X	X (Y, Z)
	Week Y	X (Y)	X	X	X (Y)	X	X	X (Y, Z)
	Week Z	X (Y)	X	X	X (Y)	X	X	X (Y, Z)

Source: Extract of Table 35 - Mean Change from Baseline for Kidney Function Over Time by Treatment Arm within the ST&F Integrated Guide.

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

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

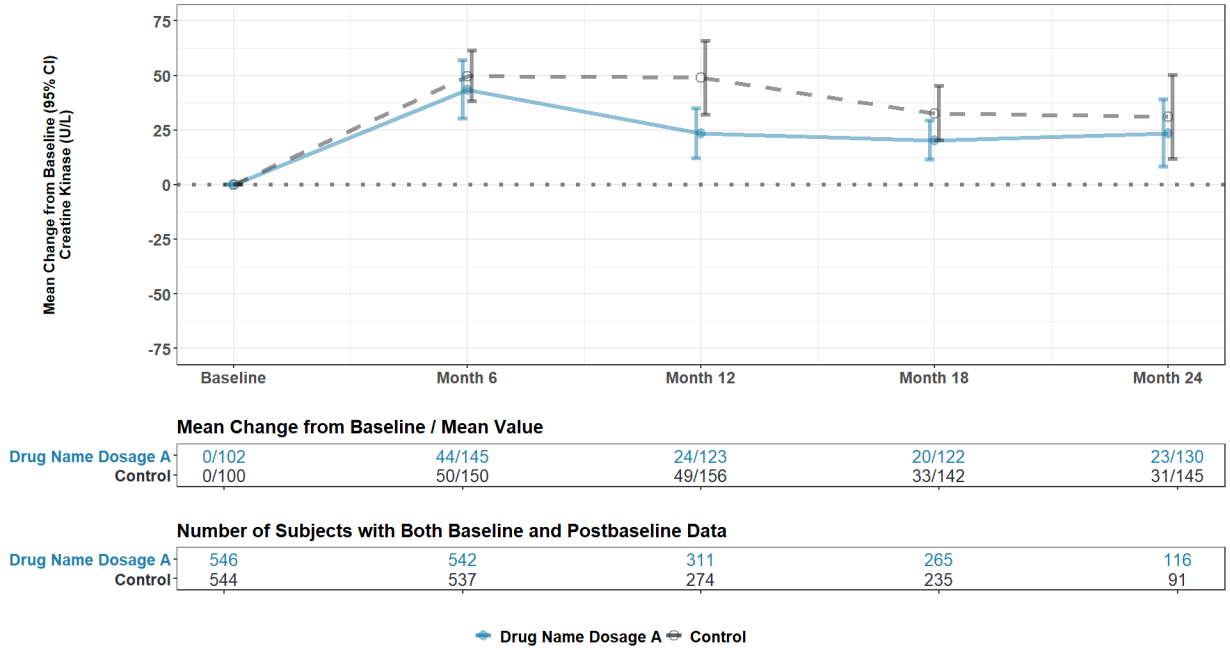
[3] n (%) at Visit refers to subjects with both baseline and postbaseline central lab data

[4] Difference in mean change is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; n, number of subjects meeting criteria; N, number of subjects in treatment arm.

Example Figure

Figure 2. Mean Change From Baseline in CPK Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)[1]



Source: Extract of Figure 6 - Mean General Chemistry Data Change From Baseline Over Time by Treatment Arm within the ST&F Integrated Guide.
[1] Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Note: If a timepoint is reached where there are only a few subjects remaining in the trial (e.g., less than 5%), consideration should be made to truncate this graph as the results would not be considered a reliable indicator of the true mean.
Note: Laboratory results obtained during unscheduled trial visits that occur outside of a protocol-specified visit window are in the data for the nearest protocol-specified visit.
Note: Subjects with both baseline and postbaseline data available are included in the mean change from baseline calculations at each visit. The number of subjects reflects only those included in the mean change from baseline calculations, rather than the total number of subjects.
Note: The vertical bars shown on the plotted lines indicates the 95% confidence interval of the mean change at the corresponding time points.
Note: Only central laboratory data were used for the plot.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase.

Table 4: Subjects With One or More CPK Values Exceeding Specified Levels provides abnormality criteria for the purpose of identifying outliers.

Example Table

Table 4. Subjects With One or More CPK Values Exceeding Specified Levels,[1] Safety Population, Pooled Analysis (or Trial X)[2]

Parameter	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[3]
CPK, high (U/L)			
Level 1 (>3x ULN)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 2 (>5x ULN)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 3 (>10x ULN)	X/Y (Z)	X/Y (Z)	X (Y, Z)

Source: Example Table 20 - Subjects with Kidney Function Analyte Values Exceeding Specified Levels within the ST&F Integrated Guide.
[1] Threshold Levels 1, 2, and 3 as defined by example Table 56 - Abnormality Level Criteria for Chemistry Laboratory Results within the ST&F Integrated Guide.
[2] Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[3] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Note: Subject counts are cumulative for each abnormality threshold.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; n, number of subjects meeting the specified laboratory criteria; N, number of subjects in treatment arm; N_s, total number of subjects with data available for the laboratory test of interest.

For Table 5: Subjects With Last On-Treatment CPK ≥ Level 2 Criteria the "last on-treatment value" is defined as the last value for any given laboratory parameter obtained within a specific timeframe (e.g., 1 to 3 half-lives) following treatment discontinuation, regardless of the reason for discontinuation. Therefore, this table includes subjects who completed the trial and thus discontinued treatment per protocol as well as subjects who discontinued treatment for other reasons. This presentation can be helpful when a study drug is causing laboratory abnormalities but the effect is diminished because multiple values are being obtained when subjects are no longer receiving the study drug.

Example Table

Table 5. Subjects With Last On-Treatment[1] CPK ≥ Level 2 Criteria[2] by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)[3]

Parameter	Drug Name Dosage A N=XXX n/N_s (%)	Control Arm N=XXX n/N_s (%)	Risk Difference % (95% CI)[4]
CPK, high (U/L) >5x ULN	X/Y (Z)	X/Y (Z)	X (Y, Z)

Source: Extract of Table 52 - Subjects with Last On-Treatment Chemistry Value ≥ Level 2 Criteria by Treatment Arm within the ST&F Integrated Guide.
[1] Last value on-treatment defined as the last value for any given laboratory parameter obtained within a specific time frame (e.g., three half-lives) following treatment discontinuation, regardless of reason for discontinuation.
[2] Threshold Level 2 as defined by example Table 56. Abnormality Level Criteria for Chemistry Laboratory Results within the ST&F Integrated Guide.
[3] Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[4] Risk difference is shown between [treatment arms]. (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; n, number of subjects meeting the specified laboratory criteria; N, number of subjects in treatment arm; N_s, total number of subjects with data available for the CPK laboratory test; ULN, upper limit of normal.

Example Table

Table 6. Subjects With Muscle Injury Algorithmic OCMQs, Safety Population, Pooled Analysis (or Trial X)[1]

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

Source: Table 47 – Subjects with Muscle Injury algorithmic OCMQ, Safety Population within the ST&F Integrated Guide.

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

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

[3] Table display is ordered by the risk difference.

[4] No CPK-MB/CPK >0.05 within 3 days nor CPK > ULN at baseline.

[5] [PT myalgia + PT muscular weakness + (PT myoglobin urine present or PT chromaturia)] within 7 days.

Abbreviations CI, confidence interval; CPK, creatine phosphokinase; OCMQ, OND Custom Medical Query; MB, myocardial band; n, number of subjects meeting criteria; N, number of subjects in group; PT, preferred term; ULN, upper limit of normal.

3. Targeted Analyses

Several targeted analyses are provided in this section to further explore a potential muscle injury safety signals identified in the ST&F IG.

3.1. Muscle Injury AE Analyses

Table 7: Subjects With Medically Important Outcomes Related to Muscle Injury Narrow OCMQs, is intended to assess severity of Muscle Injury AEs between active and control arms. Table 7 displays the Preferred terms within the Muscle Injury Narrow OCMQ category that result in outcomes that are serious, fatal, or result in drug discontinuation.

Example Table

Table 7. Subjects With Medically Important Outcomes Related to Muscle Injury Narrow OCMQs, Safety Population, Pooled Analysis (or Trial X)[1]

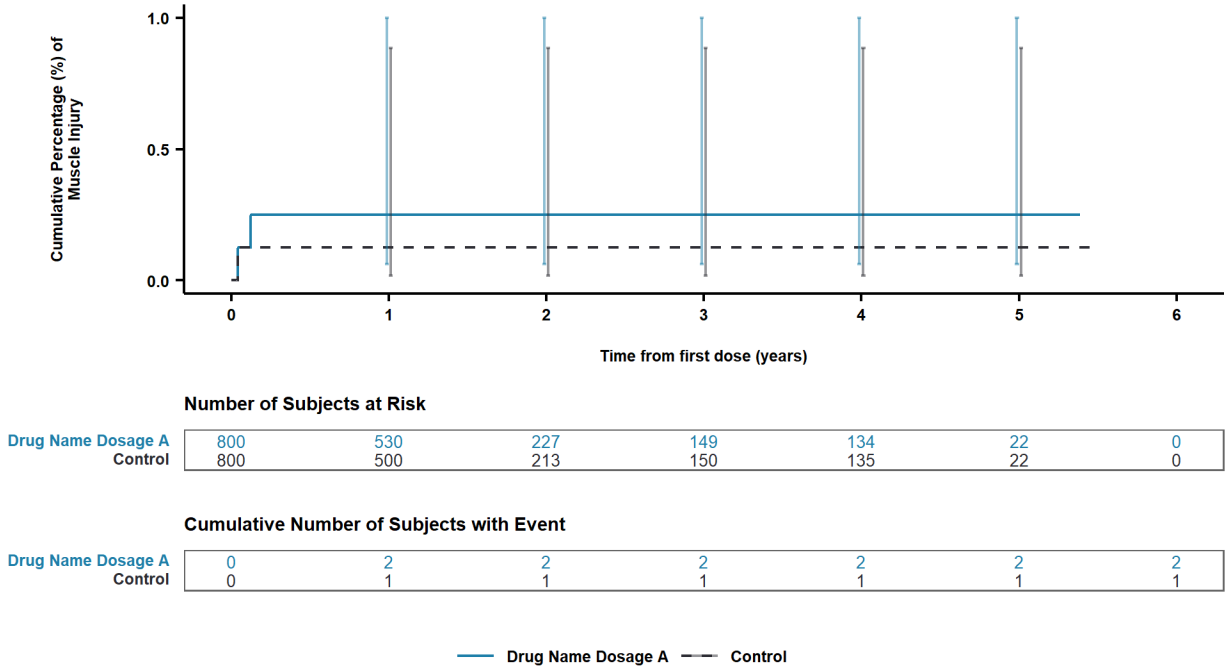
Adverse Event Category Preferred Term[2]	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[5]
Any Narrow OCMQ SAEs[3]	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
Any Narrow OCMQ AEs leading to death[4]	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)
Any Narrow OCMQ AE with outcome of drug discontinuation	X (Y)	X (Y)	X (Y, Z)
PT1	X (Y)	X (Y)	X (Y, Z)
PT2	X (Y)	X (Y)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
[2] OCMQs include AEs that are not MedDRA PTs.
[3] SAEs classified by Applicant as [insert Applicant's definition of SAE].
[4] Death events as defined in the ADAE dataset.
[5] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Abbreviations: ADAE, adverse event analysis dataset; AE, adverse event; CI, confidence interval; OCMQ, OND Custom Medical Query, PT, preferred term; SAE, serious adverse event, n, number of subjects with at least one event; N, number of subjects in treatment arm.

Figure 3: Time to Onset of Muscle Injury displays the time to muscle injury onset by treatment arm as defined by the Muscle Injury Narrow OCMQs. An additional graph may be requested from the CDS to display time to muscle injury-related SAEs or time to discontinuation of study drug due to muscle injury if there are a substantial number of such terms (e.g., >10).

Example Figure

Figure 3. Kaplan-Meier Plot: Time to Onset of Muscle Injury,[1] Safety Population, Pooled Analysis (or Trial X)[2]



Source: [include Applicant source, datasets and/or software tools used].
[1] Muscle injury onset defined as the first occurrence for a subject of an AE in the Muscle Injury Narrow OCMQs.
[2] Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Note: The vertical bars shown on the plotted lines indicates the 95% confidence interval of probability of incidence at the corresponding time points.
Note: This figure depicts Kaplan-Meier estimates of the cumulative percentage of subjects that experience the AE being assessed by a given time point. If a subject experienced multiple AEs qualifying for this display, the earliest AE start day was used as the event time.
Note: The vertical bars shown on the plotted lines indicates the 95% confidence interval of probability of incidence at the corresponding time points.
Abbreviations: AE, adverse event; OCMQ, OND Custom Medical Query.

In Table 8: Action Taken With Study Drug for Muscle Injury Narrow OCMQs, actions such as interruption or reduction in dosing generally indicate more concern by the investigator about the AE than if there was no change in dosing, and drug withdrawal generally indicates the most concern.

Example Table

Table 8. Action Taken With Study Drug for Muscle Injury Narrow OCMQ Term, Safety Population, Pooled Analysis (or Trial X)[1,2]

Action Taken With Study Drug for Narrow OCMQ Term	Drug Name Dosage A N=XXX n (%)	Control Arm N=XXX n (%)	Risk Difference % (95% CI)[4,5]
Drug withdrawn	X (Y)	X (Y)	X (Y, Z)
Drug interrupted[3]	X (Y)	X (Y)	X (Y, Z)
Dose reduced	X (Y)	X (Y)	X (Y, Z)
Dose not changed	X (Y)	X (Y)	X (Y, Z)
Dose increased	X (Y)	X (Y)	X (Y, Z)
Not applicable	X (Y)	X (Y)	X (Y, Z)
Unknown	X (Y)	X (Y)	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 of pooled trial durations].
[2] Subjects may be counted more than once.
[3] Subject-level analyses may be necessary as reported term(s) may include subjects in whom the study drug was temporarily held or discontinued the study drug permanently.
[4] Risk difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
[5] Table display is ordered by the risk difference.
Abbreviations: CI, confidence interval; OCMQ, OND Custom Medical Query, n, number of subjects with at least one action taken; N, number of subjects in treatment arm.

Comparison of the line listing with the baseline characteristics of the trial in Table 9: Individual Baseline Characteristics of Subjects in Treatment Arm With Muscle Injury may indicate whether there are potential subject risk factors that increase the likelihood of muscle injury following exposure to the investigational product. However, caution should be used when interpreting the results of a limited number of cases, and a table comparing trial arms for the occurrence of muscle injury across multiple subgroups is not routinely provided as the total number of muscle injury cases in a trial is generally expected to be low (i.e., less than 10). However, when there are a substantial number of cases, the clinical reviewer may wish to request a summary table from the CDS that compares the occurrence of muscle injury across treatment arms based on various characteristics such as age, sex, weight, and race.

Example Table

Table 9. Individual Baseline Characteristics of Subjects in Treatment Arm With Muscle Injury,[1] Safety Population, Pooled Analysis (or Trial X)[2]

Subject ID	Age (yrs)	Sex	Weight (kg)	Race	Ethnicity	Country of Participation
X	X	X	X	X	X	X
Y	X	X	X	X	X	X
Z	X	X	X	X	X	X

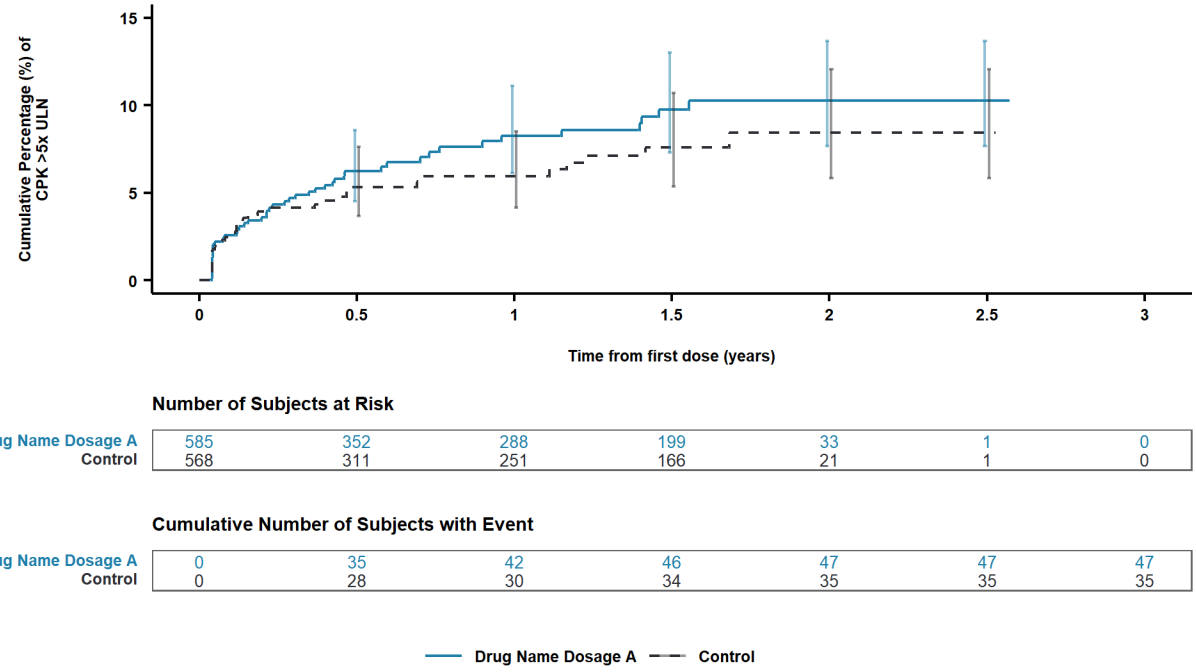
Source: [include Applicant source, datasets and/or software tools used].
[1] Defined by the Muscle Injury algorithmic OCMQ provided in Section 4.1.
[2] Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: ID, identifier.

3.2. Laboratory Analyses

Additional figures may be appropriate to follow-up potential signals, such as the cumulative incidence of muscle injury as defined by the Muscle Injury algorithmic OCMQs.

Example Figure

Figure 4. Kaplan-Meier Plot: Cumulative Incidence of CPK >5x ULN, Safety Population, Pooled Analysis (or Trial X)[1]



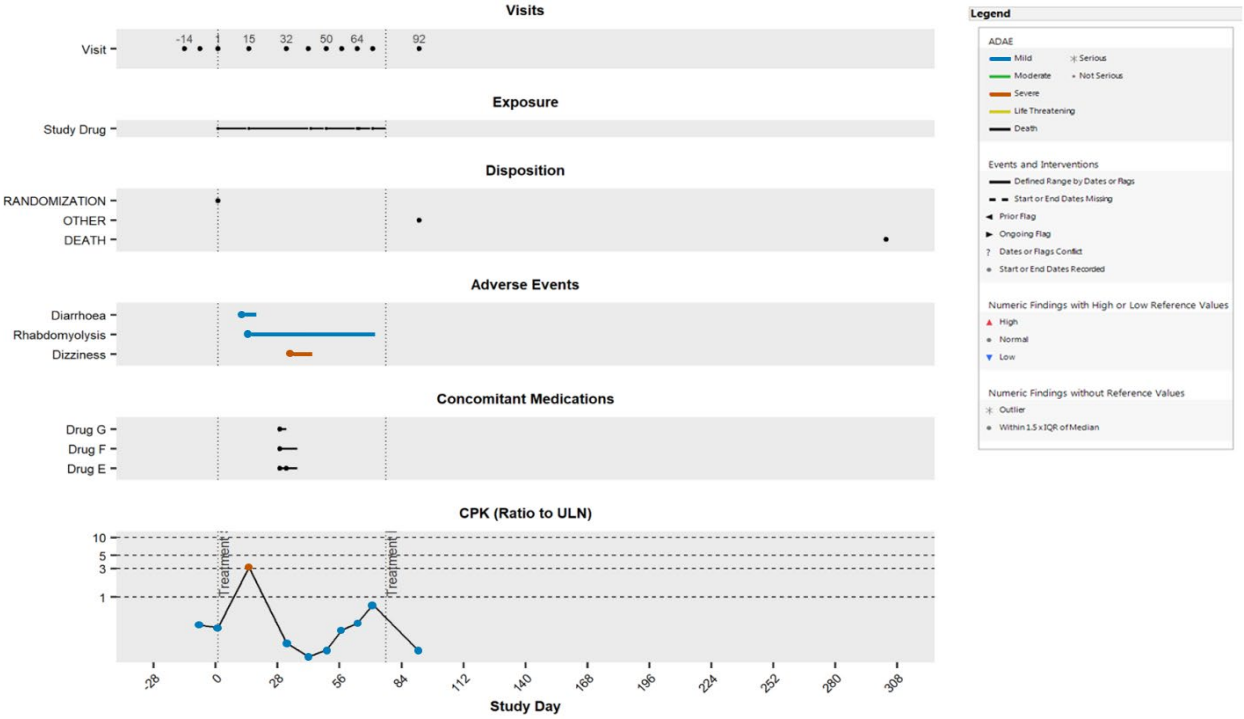
Source: [include Applicant source, datasets and/or software tools used].
[1] Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Note: This figure depicts Kaplan-Meier estimates of the cumulative percentage of subjects that experience a CPK >5x ULN by a given time point.
Note: The vertical bars shown on the plotted lines indicates the 95% confidence interval of probability of incidence at the corresponding time points.
Abbreviations: CPK, creatine phosphokinase; ULN, upper limit of normal.

3.3. Patient-Level Analyses – Graphical Patient Profile

A graphical patient profile (GPP) displays subject-level data over time to provide an overview of a subject's course by combining drug exposure, AEs, concomitant therapies, and relevant lab values. Note that not all subjects will need a GPP. The clinical reviewer should work with the CDS to identify appropriate subjects for this type of display. For instance, a GPP may be helpful for all subjects who experienced muscle injury during the trial based on the Muscle Injury algorithmic OCMQs, or for only a subset of subjects who received the investigational drug.

Example Figure

Figure 5. Graphical Patient Profile of Subject XXX



Source: Include source dataset(s) and tools used.
Abbreviations: ADAE, adverse event analysis dataset; CPK, creatine phosphokinase, ULN, upper limit of normal.

4. Appendix

4.1. Muscle Injury Algorithmic OCMQ Description

The Muscle Injury algorithmic OCMQs includes subjects with an AE of myoglobinuria, laboratory result of elevated myoglobin in the urine, laboratory CPK result greater than five times the ULN, and those who experience the rhabdomyolysis triad of myalgia, muscular weakness, and chromaturia.[2] The individual components of the triad are required to occur within 7 days of each other to help ensure that they are related to the same underlying event. Subjects with elevated CPK levels at baseline are excluded from qualifying for the algorithm based on laboratory CPK levels in order to minimize false positive muscle injury diagnoses caused by other underlying muscle inflammatory disorders. Similarly, subjects with CPK-MB levels greater than 5 percent of the total CPK are excluded due to the likelihood of a cardiac cause for the CPK elevation.[4] References in the literature state that the CPK should rapidly return to near normal values following resolution of the inciting event, but do not provide specific definitions for what should constitute “rapid” or “near normal.” The intent of requiring rapid resolution is to exclude chronic muscle disorders. However, given the absence of a standardized definition in the literature for rapid resolution and the absence of routinely captured information in the clinical trial data regarding the timing of inciting event resolution, no requirement regarding the rapidity of CPK resolution was specified in the algorithm. Therefore, subjects qualify for the algorithm if they meet any of the following criteria:

1. Any Muscle Injury OCMQ Narrow term
2. Urine myoglobin > ULN
3. CPK >5x ULN and no (CPK-MB/CPK > 0.05 within 3 days or CPK > ULN at baseline)
4. [PT myalgia + PT muscular weakness + (PT myoglobin urine present or PT chromaturia)] within 7 days