U.S. FOOD & DRUG ADMINISTRATION

STANDARD SAFETY TABLES AND FIGURES:

KIDNEY INJURY

TARGETED ANALYSIS GUIDE

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

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Version 1.2

Version Date: April 2025

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1. Introduction

Clinical reviewers use tables and figures to summarize and interpret clinical trial data submitted in marketing applications. The goal of the Standard Safety Tables and Figures Kidney Injury Targeted Analysis Guide (TAG) is to provide more in-depth analyses to investigate a potential kidney injury signal or when kidney injury is an adverse event of special interest (AESI). The kidney 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 kidney 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

Analyses of kidney function may detect acute kidney injury (AKI) or the development or progression of chronic kidney disease (CKD). If a potential safety signal is detected, there should be further evaluation of the timecourse and persistence of changes in kidney function.

It is important to note that creatinine, while commonly used, lacks both sensitivity and specificity as a biomarker for kidney injury. Measurement of glomerular filtration rate using exogenous markers (e.g., inulin, iothalamate, iohexol) provides a more accurate assessment of renal function than estimating equations, but this is not commonly done in clinical practice. Estimation of renal function using a contemporary and widely accepted equation is usually sufficient. In this TAG estimated GFR (eGFR) will be calculated using the equations[1] specified in Section 4.2 Estimated Glomerular Filtration Rate Equations. It is acceptable to use another equation (e.g., Modification of Diet in Renal Disease [MDRD]) if one was specified for a particular program. If children transition to adulthood during the trial, the equation used to calculate eGFR should remain consistent for the duration of their participation in the trial.

Additional analyses may be needed to understand the risk of kidney injury in the following situations:

- Populations with unusual muscle mass (e.g., muscular dystrophy) or muscle mass that is changing over the course of the trial (e.g., intensive care unit [ICU] populations) for which creatinine-based assessments may not provide an accurate or reliable measure of kidney function.
- Populations with pre-existing kidney disease or those prone to frequent variations in kidney function (e.g., heart failure).

[1] Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to calculate eGFR for adults (≥ 18 years old), and the Schwartz equation (2009) for children ages ≥1 to <18 years

- The pattern of drug-induced kidney injury is not manifested as an early decline in kidney function.
- The drug impacts serum creatinine without causing changes in kidney function (e.g., through altering the secretion of creatinine by the kidney tubules).

Additional analyses may include:

- Subgroup analyses based on risk factors for AKI (e.g., by baseline kidney function when a substantial portion of the trial population has CKD, age, use of angiotensin converting enzyme [ACE] inhibitors/angiotensin receptor blockers [ARB]/diuretics).
- Other laboratory data relevant to the evaluation of kidney function or kidney injury (e.g., quantitative proteinuria or albuminuria data, or cystatin C).[2]
- Other signs that might suggest a mechanism for a signal, such as concurrent decreases in blood pressure and albuminuria that could indicate a hemodynamic effect.

In some cases, it may be necessary to further analyze subject narrative information (e.g., demographics and clinical characteristics and/or use of concomitant medications, comorbidities that increase the risk of kidney injury, associated adverse events [AE] and/or frequency, timing, and duration of kidney injury events) to assess causality.

[2] Although blood urea nitrogen (BUN) varies inversely with kidney function, it is a less useful indicator than serum creatinine or eGFR because BUN can change independently of kidney function. The two main reasons are: (1) the rate of urea production is not constant (e.g., production increases with high-protein diet, hemorrhage, trauma, or glucocorticoids, and decreases with a low-protein diet or liver disease); and (2) filtered urea is passively reabsorbed by the kidney, leading to a rise in BUN that is disproportionate to the change in kidney function in some clinical situations (e.g., volume depletion). It is therefore not recommended that changes in BUN be used to detect changes in kidney function or kidney injury.

2. Screening Analyses

2.1. Adverse Event Analyses

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

Example Table

Table 1. Subjects with Adverse Events[1] by AKI 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]
Acute Kidney 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)

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: AKI, acute kidney injury; CI, confidence interval; OCMQ, OND Custom Medical Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; PT, preferred term.

For Table 2: Subjects With Adverse Events by AKI Broad OCMQs and Preferred Term, Safety Population, Pooled Analysis (or Trial X), the Broad OCMQs includes both Broad and Narrow PTs.

Example Table

Table 2. Subjects With Adverse Events[1] by AKI 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]
Acute Kidney 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)

Source: Extract of Table 43 - Subjects with AEs by Organ System, OCMQ 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:; AKI, acute kidney injury; CI, confidence interval; OCMQ, OND Custom Medical Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term.

2.2. Laboratory Analyses

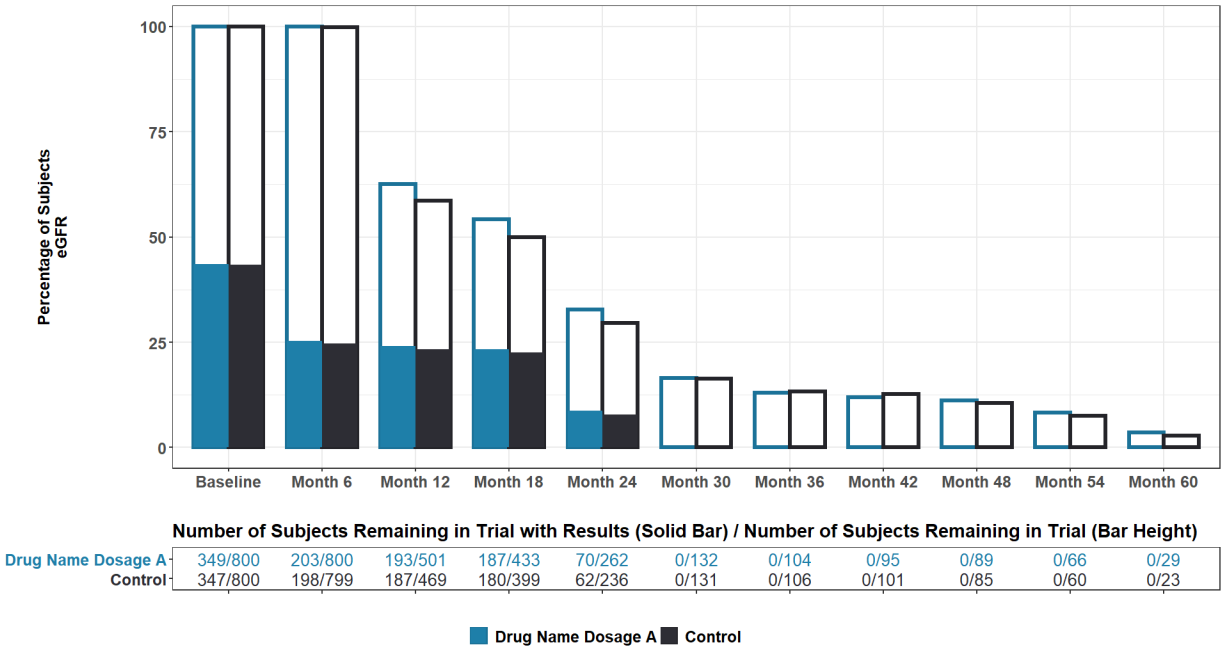
This section includes screening tables and figures of kidney laboratory abnormalities (e.g., creatinine, eGFR) from the Laboratory Analysis module in the ST&F IG to facilitate review of all pertinent analyses in one package.

The existing and missing data analysis shown in Figure 1: Proportion of Subjects Remaining in Trial at Each Visit by Avaliability of eGFR 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 who had kidney function laboratory tests by visit (solid bar), and the percent of subjects remaining in the trial (open bar). This graph should evaluate the actual data obtained at study-defined planned visits during the trial. Include separate figures for serum creatinine, eGFR, and other markers of kidney function or injury (e.g., cystatin C, quantitative measures of proteinuria or albuminuria) if collected.

Example Figure

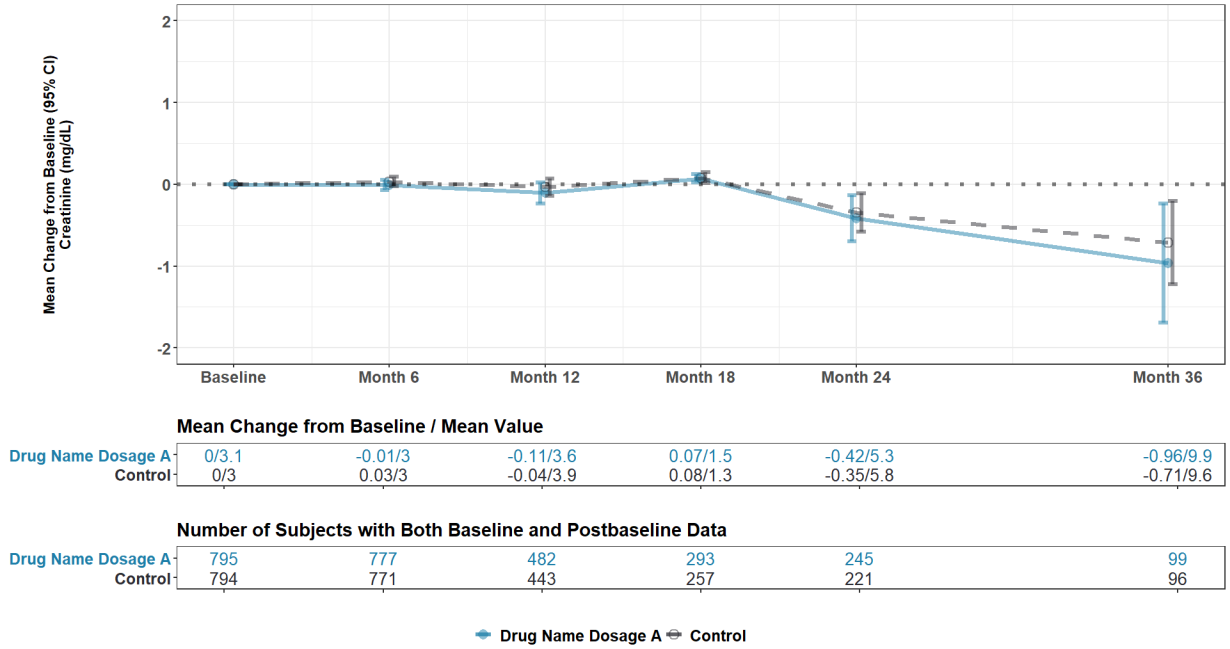
Figure 1. Proportion of Subjects Remaining in Trial at Each Visit by Availability of eGFR Result, Safety Population, Pooled Analysis (or Trial X)[1]



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 timeframe (e.g., by day, week, month) that corresponds best with the pre-specified visit # is used as the study visit (+/- protocol-defined # days).
Note: The solid bar indicates the percent of subjects remaining in the trial with the laboratory result. The open bar indicates the percent of subjects remaining in the trial and are missing the laboratory result. The bar height indicates the percent of subjects remaining in the trial.
Abbreviations: eGFR, estimated glomerular filtration rate.

Example Figure

Figure 2. Mean Change From Baseline in Kidney Function Data 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: 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.

Example Table

Table 3. Mean Change From Baseline in Kidney Function Analyte Values 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 Time[2] (Study Day/Week/Month)	n (%) at Visit	Mean	Mean Change From Baseline	n (%) at Visit[3]	Mean	Mean Change From Baseline	Difference in Mean Change (95% CI)[4]
Creatinine (mg/dL)	Baseline	X (Y)	X	N/A	X (Y)	X	N/A	N/A
	Week X	X (Y)	X	X	X (Y)	X	X	X (Y,Z)
	Week Y	X (Y)	X	X	X (Y)	X	X	X (Y,Z)
eGFR (ml/min/1.73m^2)	Baseline	X (Y)	X	N/A	X (Y)	X	N/A	N/A
	Week X	X (Y)	X	X	X (Y)	X	X	X (Y,Z)
	Week Y	X (Y)	X	X	X (Y)	X	X	X (Y,Z)

Source: 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 time frame (e.g., by day, week, month) that corresponds best with the prespecified visit # is used as the study visit (± protocol-defined # days).
[3] n (%) at Visit refer 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; eGFR, estimated glomerular filtration rate; N, number of subjects in treatment arm; n, number of subjects meeting criteria.

Table 4: Subjects With Kidney Function Analyte Values Exceeding Specified Baseline Levels provides abnormality criteria for the purpose of identifying outliers.

Example Table

Table 4. Subjects With Kidney Function Analyte Values Exceeding Specified Baseline 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]
Creatinine, high (mg/dL)			
Level 1 (≥1.5 x baseline)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 2 (≥2.0 x baseline)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 3 (≥3.0 x baseline)	X/Y (Z)	X/Y (Z)	X (Y, Z)
eGFR, low (mL/min/1.73m^2)			
Level 1 (≥25% decrease from baseline)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 2 (≥50% decrease from baseline)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 3 (≥75% decrease from baseline)	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: Subjects counts are cumulative for each abnormality threshold.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of subjects in treatment arm; N_s, total number of subjects with data available for the laboratory test of interest; n, number of subjects meeting the specified laboratory criteria.

Table 5: Listing of Subjects with a Creatinine or eGFR Laboratory Value ≥ Level 2 Change From Baseline Criteria provides subject-level data for subjects who meet Level 2 or greater criteria. Depending on the number of subjects and level of concern, the reviewer may request narratives for these subjects from the Applicant.

Example Table

Table 5. Listing of Subjects with a Creatinine or eGFR Laboratory Value ≥ Level 2 Change From Baseline Criteria,[1] Safety Population, Pooled Analysis (or Trial X)[2]

Unique Subject Identifier	Treatment Arm	Parameter	Baseline Value	Laboratory Value ≥Level 2 Criteria	Change in Value	Study Day of Onset[3]
Subject ID1	X	Creatinine (mg/dL), (≥2.0 x baseline)	X	X	X	X
Subject ID2	X	eGFR (ml/min/1.73m^2), ≥50% decrease	X	X	X	X

Source: Extract of Table 55 - Listing of Subjects With a Laboratory Value ≥ Level 2 Change From Baseline Criteria
[1] Threshold Level 2 as defined by 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] Post-randomization.
Abbreviations: eGFR, estimated glomerular filtration rate.

For Table 6: Subjects With Last On-Treatment Creatinine and eGFR Value by Level Criteria by Treatment Arm, 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 if a study drug causes laboratory abnormalities but the effect is diminished because multiple labs are obtained when subjects are no longer receiving the study drug.

Example Table

Table 6. Subjects With Last On-Treatment[1] Creatinine and eGFR Value[2] by Level Criteria by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)[3]

Parameter	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[4]
Creatinine, high (mg/dL) ≥1.5 x baseline	X/Y (Z)	X/Y (Z)	X (Y,Z)
Creatinine, high (mg/dL) ≥2.0 x baseline	X/Y (Z)	X/Y (Z)	X (Y,Z)
eGFR, low (ml/min/1.73m^2) ≥25% decrease	X/Y (Z)	X/Y (Z)	X (Y,Z)
eGFR, low (ml/min/1.73m^2) ≥50% decrease	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; eGFR, estimated glomerular filtration rate; n, number of subjects meeting the specified laboratory criteria; N, number of subjects in treatment arm; N_s, total number of subjects with data available for the laboratory test of interest.

3. Targeted Analyses

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

3.1. Analyses of Kidney Injury Adverse Events

The AE analyses in this guide are presented using the AKI OND Custom Medical Query (OCMQ). In some cases, other grouping strategies such as custom queries, Standardised MedDRA Queries (SMQs), or MedDRA hierarchy may be appropriate.

Table 7: Subjects With Medically Important Outcomes Related to AKI Narrow OCMQs and Table 8: Subjects With Medically Important Outcomes Related to AKI Broad OCMQs are intended to assess severity of AKI AEs between active and control arms. These tables display the Preferred terms within the AKI OCMQ category that result in outcomes that are serious, fatal, or result in drug discontinuation . Refer to Section 4 Appendix for additional tables to explore the data at the subject level.

Example Table

Table 7. Subjects With Medically Important Outcomes Related to AKI 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 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 AEs 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 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 from 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; 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.

Example Table

Table 8. Subjects With Medically Important Outcomes Related to AKI Broad OCMQs, Safety Population, Pooled Analysis (or Trial X)[1]

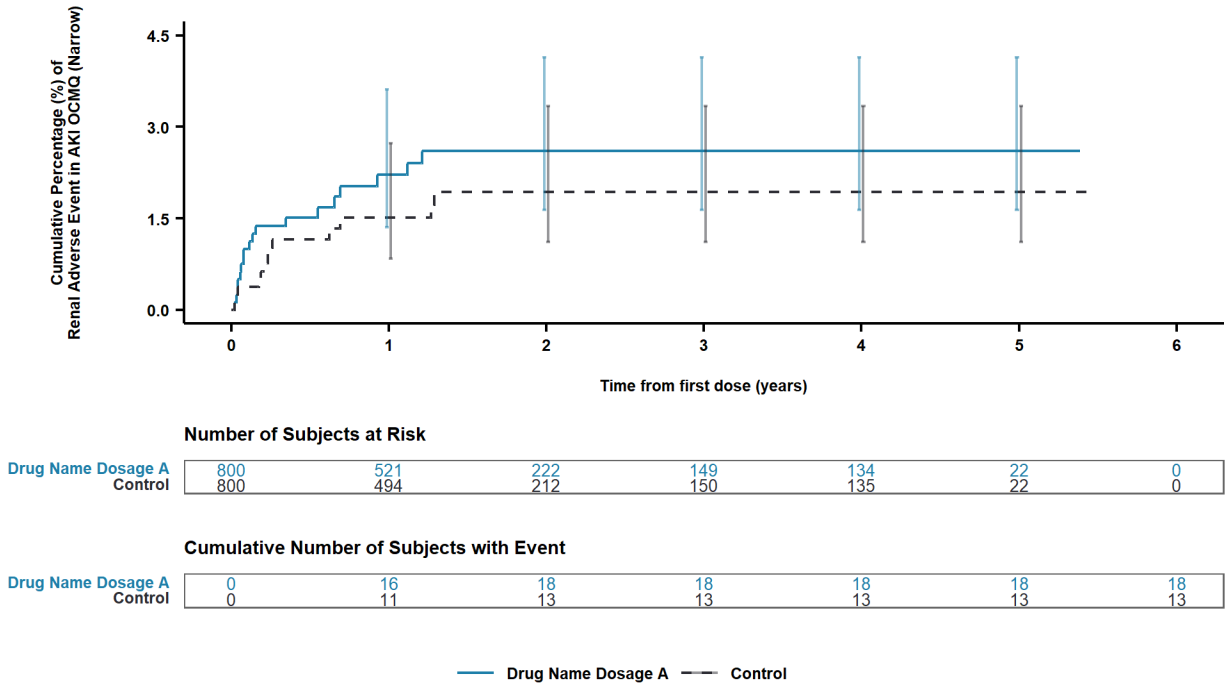
Adverse Event Category Preferred Term[2]	Drug Name Dosage A N=XXX n (%)	Control N=XXX n (%)	Risk Difference % (95% CI)[5]
Any Broad OCMQ SAEs[3]	X (Y)	X (Y)	X (Y,Z)
PT1	X (Y)	X (Y)	X (Y,Z)
PT2	X (Y)	X (Y)	X (Y,Z)
Any Broad OCMQ AEs leading to death[4]	X (Y)	X (Y)	X (Y,Z)
PT1	X (Y)	X (Y)	X (Y,Z)
PT2	X (Y)	X (Y)	X (Y,Z)
Any Broad 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: Kaplan-Meier Plot: Time to Onset of Kidney Adverse Event in AKI OCMQs (Narrow) displays the time to kidney adverse event onset by treatment arm as defined by the Kidney Injury Narrow OCMQs. An additional graph may be requested from the CDS to display time to kidney injury-related SAEs or time to discontinuation of study drug due to kidney injury if there are a substantial number of such terms (e.g., >10).

Example Figure

Figure 3. Kaplan-Meier Plot: Time to Onset of Kidney Adverse Event in AKI OCMQs (Narrow)[1], Safety Population, Pooled Analysis (or Trial X)[2]



Source: [include Applicant source, datasets and/or software tools used].
[1] Kidney Injury onset defined as the first occurrence for a subject of an AE in the Kidney 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.
Abbreviations: AKI, acute kidney injury; OCMQ, OND Custom Medical Query.

Table 9: Action Taken With Drug Due to Adverse Event in AKI OCMQs (Narrow) is intended to compare the proportion of subjects who had an action taken due to AKI OCMQ AEs. The reviewer may consider further analyses to evaluate subjects who completed the study, discontinued the study, or were lost to follow-up.

Example Table

Table 9. Action Taken With Drug Due to Adverse Event in AKI OCMQs (Narrow), 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 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 have been counted in more than one category (i.e., a subject could have multiple adverse events with different actions taken with the drug)
[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: AKI, acute kidney injury; CI, confidence interval; OCMQ, OND Medical Query; N, number of subjects in treatment arm; n, number of subjects with at least one action taken.

3.2. Laboratory Analyses

The following analyses may be performed to further explore changes in kidney laboratory studies over time. Analyses may explore a single laboratory value or show a trend over time. Note that variability could be present in populations with variable kidney function (e.g., heart failure). In general, if trials collect other markers of kidney function or injury (e.g., cystatin C, quantitative measures of proteinuria or albuminuria), these data should also be analyzed.

Analysis comparing change relative to last known value may be more helpful than comparisons to baseline to assess short-term changes reflective of acute kidney injury or drug-induced kidney injury. Comparisons with baseline do not differentiate between acute and chronic injury; additional analyses may be necessary to follow up potential signals and to assess reversibility.

3.2.1. eGFR and Serum Creatinine

Example Table

Table 10. Subjects With Kidney Function Analyte Values Exceeding Last Known Value, Safety Population, Pooled Analysis (or Trial X)[1]

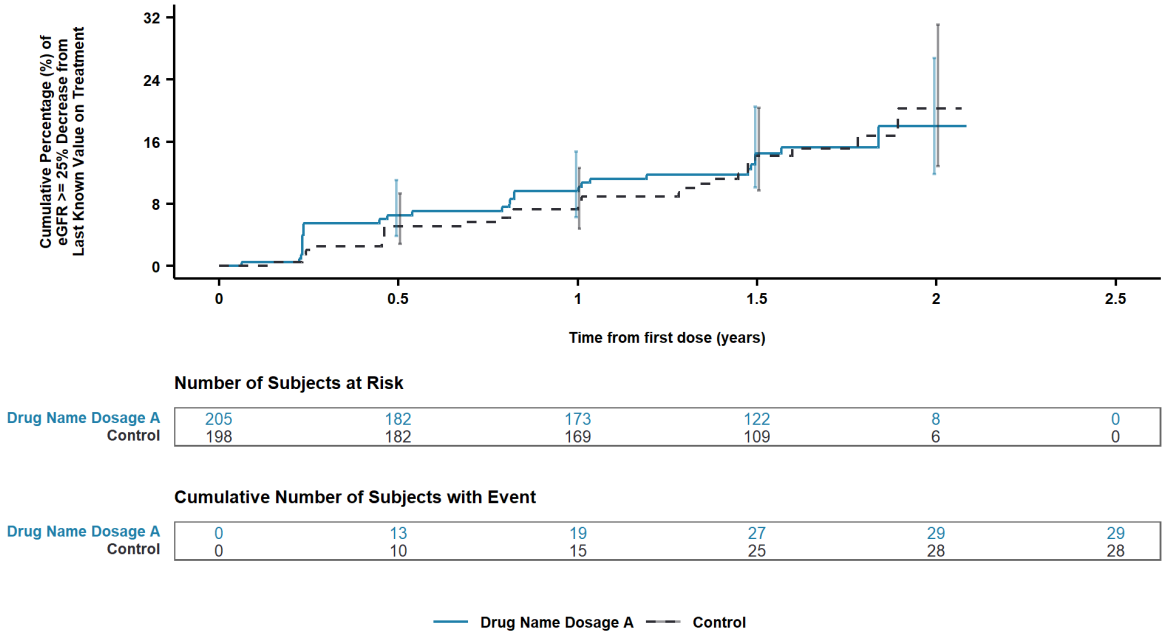
Parameter	Drug Name Dosage A N=XXX n/N_s (%)	Control N=XXX n/N_s (%)	Risk Difference % (95% CI)[2]
Creatinine, high (mg/dL)			
Level 1 (≥1.5 x last known value)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 2 (≥2.0 x last known value)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 3 (≥3.0 x last known value)	X/Y (Z)	X/Y (Z)	X (Y, Z)
eGFR, low (mL/min/1.73m^2)			
Level 1 (≥25% decrease from last known value)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 2 (≥50% decrease from last known value)	X/Y (Z)	X/Y (Z)	X (Y, Z)
Level 3 (≥75% decrease from last known value)	X/Y (Z)	X/Y (Z)	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] Risk Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name Dosage A vs. Control).
Note: Subjects counts are cumulative for each abnormality threshold.

Figure 4: Time to Onset of eGFR ≥25% Decrease From Last Known Value on Treatment, Any Time Post-Randomization shows the cumulative incidence of eGFR decrease from last known value. An imbalance between study arms would contribute toward evidence of potential kidney injury.

Example Figure

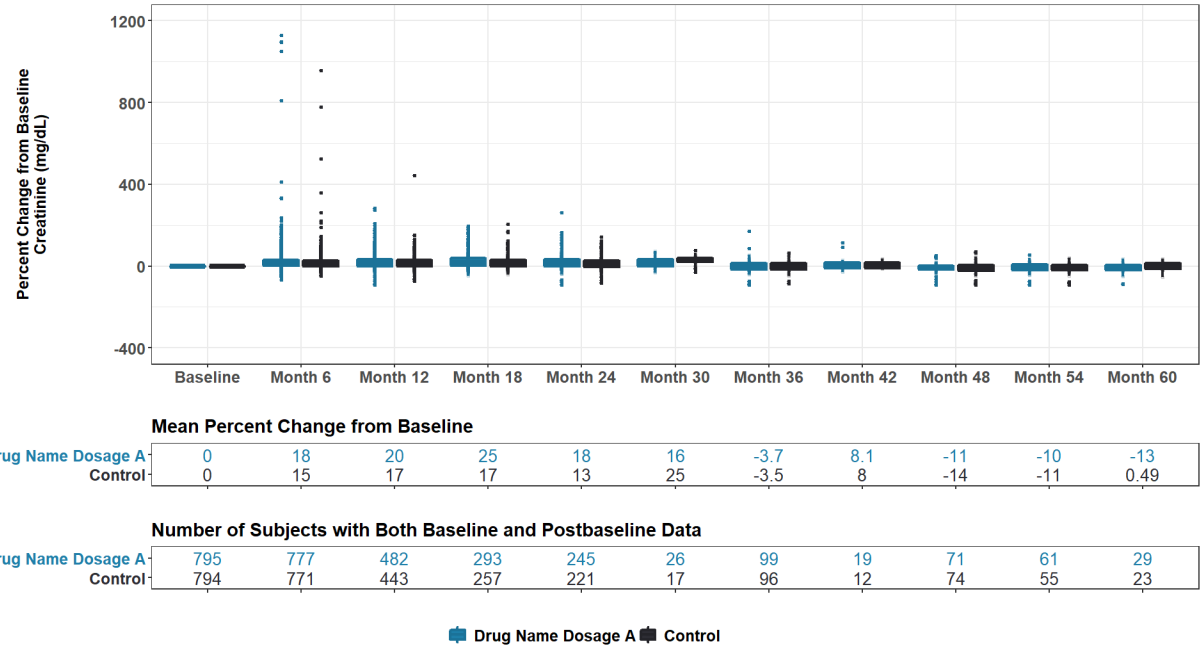
Figure 4. Time to Onset of eGFR ≥25% Decrease From Last Known Value on Treatment, Any Time Post-Randomization, Safety Population, Pooled Analysis (or Trial X)[1]



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: The vertical bars shown on the plotted lines indicates the 95% confidence interval of probability of incidence at the corresponding time points.Abbreviations: eGFR, estimated glomerular filtration rate.

Example Figure

Figure 5. Percent Change From Baseline[1] in Serum Creatinine[2] Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)[3]



Mean Percent Change from Baseline

	Baseline	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60
Drug Name Dosage A	0	18	20	25	18	16	-3.7	8.1	-11	-10	-13
Control	0	15	17	17	13	25	-3.5	8	-14	-11	0.49

Number of Subjects with Both Baseline and Postbaseline Data

	Baseline	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60
Drug Name Dosage A	795	777	482	293	245	26	99	19	71	61	29
Control	794	771	443	257	221	17	96	12	74	55	23

Drug Name Dosage A Control

Source: [include Applicant source, datasets and/or software tools used].
[1] Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5x the interquartile range; individual points are outliers beyond this range.
[2] If multiple values (scheduled and unscheduled) are associated with a subject for a visit, the worst value obtained (i.e., maximum increase in creatinine) is displayed at the prespecified scheduled visit.
[3] Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].

3.2.2. Subjects That Discontinue Treatment

Table 11: Subjects That Discontinue Treatment Because of Kidney Adverse Event and Associated Last Kidney Laboratory Values by Treatment Arm lists the subjects that discontinued treatment because of kidney dysfunction (per the AE dataset) and their associated last on-treatment lab values. For ease of review, sort/organize this table by trial, treatment, eGFR decrease, study day, and unique subject ID. The reviewer might want to examine the narratives and/or Case Report Forms (CRFs) for these subjects.

Example Table

Table 11. Subjects That Discontinue Treatment Because of Kidney Adverse Event and Associated Last Kidney Laboratory Values by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)[1]

Unique Subject Identifer	Treatment Arm	Last Value				
		eGFR % Change	Last eGFR (mL/min/1.73m^2)	S_{Cr} Fold Change From Baseline	Last S_{Cr} (mg/dL)	Last Study Day
Subject ID1	X	X	X	X	X	X

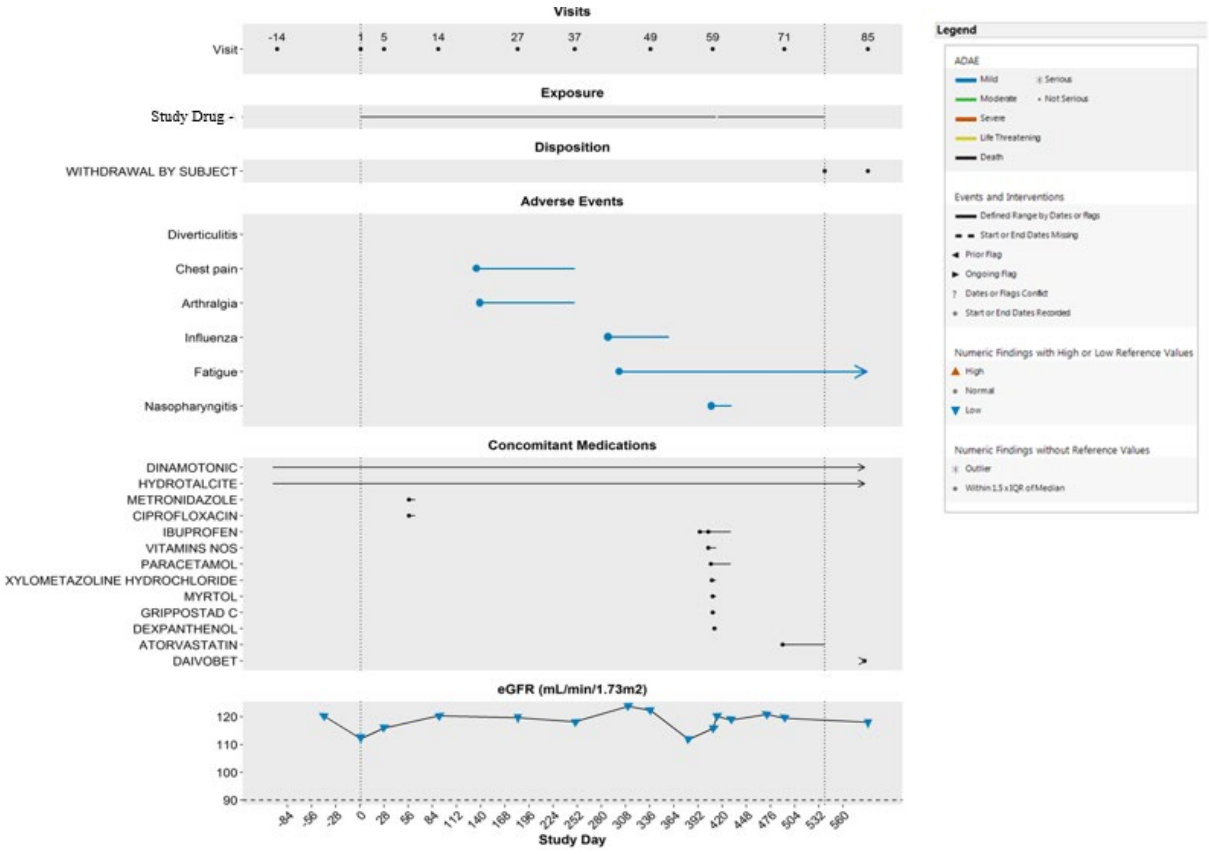
Source: [include Applicant source, datasets and/or software tools used].
[1] Duration = [e.g., X-week double-blind treatment period or median and a range of pooled trial durations].
Abbreviations: eGFR, estimated glomerular filtration rate; S_{Cr}, standardized serum creatinine.

3.3. Subject-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 kidney injury during the trial based on the Kidney Injury OCMQs, or for only a subset of subjects who received the investigational drug.

Example Figure

Figure 6. Graphical Patient Profile, Subject XXX



Source: [include Applicant source, datasets and/or software tools used].
Abbreviations: ADAE, adverse events analysis dataset; eGFR, estimated glomerular filtration rate.

4. Appendix

4.1. Additional Adverse Event Tables

If one or more OCMQs or individual PTs appear to have a meaningful increase in frequency in the investigational arm(s), Table 12: Subjects That Discontinue Treatment Because of Kidney Adverse Event and Associated Last Kidney Laboratory Values by Treatment Arm and Table 13: Listing of Subjects with AKI Narrow OCMQs enable further investigation.

Example Table

Table 12. Listing of Subjects with AKI Narrow OCMQs[1], Safety Population, Pooled Analysis (or Trial X)[2]

Unique Subject Identifier	Treatment Arm	MedDRA PT	Verbatim Term	Serious[3]	Severity[4]	Study Day of Event	Last Day of Study Drug Dosing	Action Taken	Outcome
Subject ID1	X	PT1	VT1	Y/N	X	X	X	X	X

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 of pooled trial durations].
[3] SAEs classified by Applicant as [insert Applicant's definition of SAE]
[4] Severity scale as defined by the protocol.
Abbreviations: AKI, acute kidney injury; AE, adverse event; OCMQ; OND Custom Medical Query; PT, preferred term; MedDRA, Medical Dictionary for Regulatory Activities; N, no; PT, preferred term; VT, verbatim term; Y, yes.

Example Table

Table 13. List of Subjects with AKI Broad OCMQs[1], Safety Population, Pooled Analysis (or Trial X)[2]

Unique Subject Identifier	Treatment Arm	MedDRA PT	Verbatim Term	Serious[3]	Severity[4]	Study Day of Event	Last Day of Study Drug Dosing	Action Taken	Outcome
Subject ID1	X	PT1	VT1	Y/N	X	X	X	X	X

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 of pooled trial durations].
[3] SAEs classified by Applicant as [insert Applicant's definition of SAE]
[4] Severity scale as defined by the protocol.
Abbreviations: AKI, acute kidney injury; AE, adverse event; OCMQ, OND Custom Medical Query; ID, identifier; PT, preferred term; MedDRA, Medical Dictionary for Regulatory Activities; N, no; PT, preferred term; VT, verbatim term; Y, yes.

4.2. Estimated Glomerular Filtration Rate Equations

Table 14. Estimated Glomerular Filtration Rate Equations

Age Range	Equations
Adults (≥18 years)	CKD-EPI creatinine equation: eGFR = 141 x $\min(S_{Cr}/\kappa, 1)^{\alpha}$ x $\max(S_{Cr}/\kappa, 1)^{-1.209}$ x 0.993^{age} x 1.018 [if female] x 1.159 [if Black]
Children (≥1 and <18 years)*	Schwartz equation (2009): eGFR = 0.413 x [serum creatinine (mg/dL) / height (cm)]
Children (<1 years)	No applicable eGFR equation; use serum creatinine by age cutoffs

Source: [include Applicant source, datasets and/or software tools used].
Equation abbreviations/units: eGFR = mL/min/1.73m^2,S_{Cr} = mg/dL, κ = 0.7 (females) or 0.9 (males),α = -0.329 (females) or -0.411 (males), min = indicates the minimum of S_{Cr}/κ or 1, max = indicates the maximum of S_{Cr}/κ or 1, age = years
* If a subject is enrolled prior to 18 years of age, the Schwartz equation should be used for the duration of the study even if the subject turns 18 years old during the study.
Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; S_{Cr}, serum creatinine.