General Guidance*

- If condition is addressed on Appendix III tables, follow specific guidance. This general guidance only applies to abnormalities without specific guidance in the Toxicity Management Section of the protocol.
General Guidance*

*If condition is addressed on Appendix III tables, follow specific guidance. This general guidance only applies to abnormalities without specific guidance in the Toxicity Management Section of the protocol.

± At Week 0 (study enrollment), consult the CMC for guidance regarding follow up and ongoing study product administration.

Any grade 3 clinical or laboratory AE observed prior to Week 5 will prompt consultation with the CMC prior to any injectable dosing.

Grade 3±

Related? NO

Consult the CMC for management

YES

Hold study product AND consult the CMC

Re-evaluate

≤ Grade 2 documented within 4 weeks?

YES

Continue study product

STOP study product. Participant will transition to Step 3

NO

Injectable phase

STOP study product. Participant will NOT transition to Step 2. Follow participant annually until 3 years from Enrollment date (see Protocol Appendix ID and Section 5.3.1 of SSP)

Oral phase

If same Grade 3 AE recurs at any time, consult CMC for further management

Strengthened text:

- Grade 3 ±
- Related?
- Yes: Hold study product AND consult the CMC
- No: Consult the CMC for management
- Re-evaluate
- ≤ Grade 2 documented within 4 weeks?
  - Yes: Continue study product
  - No: STOP study product.
  - Injectable phase: Participant will transition to Step 3
  - Oral phase: STOP study product. Participant will NOT transition to Step 2. Follow participant annually until 3 years from Enrollment date (see Protocol Appendix ID and Section 5.3.1 of SSP)
- If same Grade 3 AE recurs at any time, consult CMC for further management

*General Guidance*
**General Guidance***

Any grade 4 clinical or laboratory AE observed prior to Week 5 will prompt consultation with the CMC prior to any injectable dosing.

- **Grade 4 ±**
  - Hold study product AND consult the CMC
  - If in consultation with CMC study product is resumed, and same Grade 4 AE recurs at any time
  - Follow CMC guidance, but in general:
    - Related to study product?
      - **YES**
        - Injection phase
        - Stop study product. Participant will transition to Step 3
        - Participant will NOT transition to Step 2. Follow participant annually until 3 years from Enrollment date
      - **NO**
        - Oral phase
        - Permanently discontinue study product.

*If condition is addressed on Appendix III tables, follow specific guidance
± At Week 0 (study enrollment), consult the CMC for guidance regarding follow up and ongoing study product administration
Specified Toxicities
Nausea, Vomiting, and Diarrhea*

Grade 1 or 2
Continue study product

Grade ≥ 3
Related?

Hold study product Consult CMC

Is the AE Grade ≤ 2 within 7 days?

YES
Continue study product

NO
Consult the CMC for guidance

NO
Consult the CMC for guidance

*For all grade levels, treat symptomatically
Specified Toxicities

ALT

Oral Phase (Step 1)

Grade ≥ 3

STOP study product.
Participant will NOT transition to Step 2.
Follow participant annually until 3 years from Enrollment date

Please note: All cases should be reported to the CMC. Participants will be followed with weekly ALT assessment until they return to ≤ Grade 1

If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.

- Cases of CK abnormality, presumed to be exercise induced, ≥ Grade 3 accompanied by ALT ≤ Grade 3 should be reported to the CMC for adjudication of further management and administration of study product.
- Grade 4 ALT elevation will always prompt permanent discontinuation of study product.
- Report as an EAE any abnormality of ALT > 3x ULN AND total bilirubin > 2x ULN (both occurring at the same time)
Specified Toxicities

ALT

Injection Phase (Step 2)

Grade ≥ 2

Inform the CMC

Please note: Participants will be followed with weekly ALT assessment until they return to ≤ Grade 1

Grade 2

CMC will determine if study product may continue

- Cases of CK abnormality, presumed to be exercise induced, ≥ Grade 3 accompanied by ALT ≤ Grade 3 should be reported to the CMC for adjudication of further management and administration of study product.
- Grade 4 ALT elevation will always prompt permanent discontinuation of study product.
- Report as an EAE any abnormality of ALT > 3x ULN AND total bilirubin > 2x ULN (both occurring at the same time)

If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.

Grade ≥ 3

STOP study product. Repeat testing as soon as possible. Participant will transition to Step 3, off study product.
Specified Toxicities

ALT

Open-label Phase (Step 3)

- Participant discontinued product during Step 2 due to ALT elevation
- Participants will be followed per the Schedule of Procedures and Evaluations for Step 3 except for provision of study product.

- Participant will be followed annually until three years from the date of Enrollment.
- The timepoint during Step 2 that a participant transitions to Step 3 will determine whether they will be asked to attend annual visits following the completion of Step 3.
- If the completion of open label TDF/FTC for Step 3 post-dates three years from the date of Enrollment, no further annual follow-up is required. All such cases must be reported to the CMC.
Specified Toxicities

ALT

Considerations

• Grade 1 elevations – study product will continue
• Pre-existing HBV infection is not likely to be a cause of AST/ALT elevations.
  • Participants will be HBsAg negative at enrollment and those without evidence of immunity to HBV will be referred for HBV vaccination.
  • Incident HBV infection acquired while on-study will mandate permanent discontinuation of blinded study products; please ensure non-immune participants are vaccinated to the best of the site’s ability
• Careful assessments should be done to rule out the use of alcohol, lactic acidosis syndrome, non-study medication-related product toxicity, herbal medications/supplements, or viral hepatitis as the cause of elevation in AST or ALT of any grade.
• The participant must be assessed for any symptoms or signs of hepatotoxicity, including fatigue, malaise, anorexia and nausea, jaundice, acholic stools, right upper quadrant pain, or hepatomegaly.
• If the AST/ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, if possible, should be undertaken.
• If symptoms or signs of clinical hepatitis are present, study product must be held or discontinued
• All participants with elevated values should be considered for testing for Hepatitis A, B, and C infection.
• In areas where Hepatitis A outbreaks are ongoing or likely to occur, vaccination of all participants, or non-immune participants, should be considered. Please contact the CMC for any questions.
Specified Toxicities
Creatinine Clearance

Estimated CrCl < 60 mL/min

- Confirm within a week*
- Hold study product AND consult the CMC for adjudication and recommendation for further testing and follow-up

Confirmed CrCl < 60 mL/min?

- YES
  - Permanently discontinue study product. Participant will transition to Step 3
  - Notify the CMC.

- NO
  - Consult the CMC for guidance

Injection phase

Oral phase

STOP study product. Participant will NOT transition to Step2. Follow participant annually until 3 years from Enrollment date

*Participants that fail to have confirmation within 2 weeks, product will be discontinued until CMC adjudication and recommendations

NOTE 1: For gradable changes in creatinine clearance per the DAIDS Toxicity Table, please refer to the "General Guidance" management schema, even if the estimated absolute value of the Cr Cl is >= 60 mL/min.

NOTE 2: Calculated creatinine clearance must be performed at every visit where chemistry testing is being performed, using the Cockcroft-Gault formula.
Specified Toxicities
Creatinine Clearance

• Adverse events related to creatinine clearance should be based on examination of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Enrollment/Visit 2.0).

• When gradable, only the higher grade of these two assessments should be entered on the Adverse Event e-CRF.

• Clinical Management of Grade 3 and Grade 4 changes in creatinine clearance should follow the “Toxicity Management General Guidance” ONLY when the absolute creatinine clearance is < 90 mL/min. That is, changes in creatinine clearance of >30% from baseline that DO NOT result in an absolute creatinine clearance < 90 mL/min DO NOT need to be reported to the CMC or more frequent clinical monitoring.

• Changes in creatinine clearance of > 30% that are accompanied by a serum creatinine that remains within normal limits DO NOT need to be reported to the CMC and DO NOT require more frequent clinical monitoring.
Specified Toxicities
Creatinine Phosphokinase (CK or CPK)

Grade 1 or 2

Continue Study Product
No retesting required
Specified Toxicities
Creatinine Phosphokinase (CK or CPK)

Grade 3

Continue study product until repeat results are available and Retest within 4 weeks*

Grade 3 results after retesting?

YES

Consult CMC for guidance

NO

If other causes for the results can be attained, study product may continue.

*Use of products know to cause increase of CPK and physical activities proceeding CPK evaluation should be obtained
Specified Toxicities
Creatinine Phosphokinase (CK or CPK)

**Grade 4**
- *Continue study product until repeat results are available. Retest within 2 weeks at least 24 hours after participant has abstained from exercise.*

**Persistent asymptomatic° Grade 4 elevation?**
- Consult the CMC for guidance

**Persistent symptomatic° Grade 4 elevation?**
- **Injection phase**
  - Yes: Discontinue study product. Participant will transition to Step 3
  - No: Consult the CMC for guidance
- **Oral phase**
  - Yes: STOP product. Participant will NOT transition to Step 2. Follow participant annually until 3 years from Enrollment date

° Myalgias, muscle pain, dark urine, or clinically significant changes in creatinine clearance, defined in consultation with the CMC

*Use of products known to cause increase of CPK and physical activities proceeding CPK evaluation should be obtained*
Specified Toxicities

**QTc***

ECG demonstrates a prolonged QT interval (QTc is >550 ms or >60ms above baseline?

Obtain two more ECGs within one hour. Use the averaged QTc values of the three ECGs

Results

- QTc > 550 msec
- Change from baseline: QTc > 60 msec

Permanently discontinue study product in consultation with CMC. Participant will transition to Step 3

*QTc correction formula used at baseline for a participant should be the same formula throughout the study.
Specified Toxicities
Injection Site Reactions (ISRs)

Grade 3 or 4

Inform the CMC to determine etiology and assess continued study participation

Manage symptomatically if reaction interferes with participant’s daily activities

Follow Section 9.3.5.4 of the SSP for guidance on interventions to mitigate ISRs
Specified Toxicities
Allergic Reactions

- **Grade 1 or 2**
  - Continue study product at the discretion of the IoR
  - Participant to be instructed to immediately contact site if condition worsens or new symptoms develop.
  - Medications for the allergies may be prescribed
Specified Toxicities
Allergic Reactions

*Grade ≥ 3

Related?

NO

Consult the CMC for guidance

YES

Injection phase

Permanently discontinue study product. Participant will transition to Step 3

Oral phase

STOP product. Participant will NOT transition to Step 2. Follow participant annually until 3 years from Enrollment date

*Treat participants as appropriate and followed until resolution of the AE.
**General Toxicity Management Considerations**

- Participants who discontinue study product for any reason (other than HIV infection) during Step 1 will be followed annually until 3 years from Enrollment date (see Protocol Appendix ID and SSP Section 5.3.1 for procedures to be performed in these cases).

- Participants who discontinue study product for any reason (other than HIV infection) during Step 2, will transition to Step 3.
  - Depending on the toxicity (e.g. decreased renal function), Step 3 follow-up may be "off" study product.

- Always consult Appendix III of the Protocol for specific toxicity management guidance and detailed information.

- Contact the CMC for guidance on toxicity and product use management, and general questions related to participant safety.

- For protocol-required consultations, contact the CMC ideally within 72 hours of site awareness of the AE in question.

- **All** AEs will be followed until resolution or stabilization.

- The IoR has the discretion to hold study product at any time to safeguard participant’s safety. When product is held for conditions not described in the protocol, the CMC must be informed.