IMPAACT P1108
CLINICAL MANAGEMENT

Study-Specific Training
7-9 February 2017
Cape Town, South Africa
TOXICITY MANAGEMENT

- Refer to Protocol Section 8 and Appendices V-IX

- Email questions to IMPAACT.PI108CORE@fstrf.org

Management of AEs will be according to the best clinical practice and the judgment of the site investigator. Alternate explanations for clinical and laboratory abnormalities must be sought and lab values repeated as clinically indicated. Abnormal clinical and laboratory findings should be followed until resolution to < Grade 2.
Refer to Section 8 for general guidance on participant management

- **8.2** Background MDR therapy
  - **Appendix III** → Overview of routine anti-TB drugs for pediatric MDR-TB management
- **8.3** Management of TB disease
  - Use for classification of TB disease spectrum and severity during Screening, Week 2, 8, 24, 120, and Early Study Discontinuation Visit
TOXICITY MANAGEMENT GUIDELINES

Refer to Section 8 for general guidance participant management

- 8.4 Mycobacterial culture, smear and DST
- 8.5 TB Treatment Outcome
- 8.6 ECG Monitoring and Reading
- 8.7 Monitoring for Potential Mitochondrial Toxicities
- 8.8 Management of Contraception and Pregnancy
- 8.9 Management of HIV-exposed Participants
Appendix VIII provides general guidance for management of BDQ in response to toxicities.

Appendices V, VI, VII and IX provide guidance on BDQ management for the following specific toxicities:

- ECG-determined or clinical cardiac toxicity
- Bilirubin
- AST or ALT
- Lactate
- Myalgia, nausea or vomiting
Issues requiring consultation with the P1108 Core Team:

**General adverse events**
- Any Grade 3 or 4 toxicity

**ECG-determined or clinical cardiac toxicity**
- Grade 3 or 4 ECG reading
- Grade 3 or 4 clinical criteria

**Bilirubin, AST, ALT**
- Meets Hy’s law
- Confirmed $\geq$ Grade 3 elevations regardless of relatedness

**Lactate**
- Repeat lactate is $\geq$3mmol/L

**Myalgia, Nausea, or Vomiting**
- Grade 3 or 4

Note: when submitting a query, include “P1108” and brief reason for query in the subject line of the message. If the query pertains to an ECG-determined or clinical cardiac toxicity, also include “Cardiac safety” in the subject line.
Questions for IMPAACT P1108 Core Team

Please copy and paste the listing (on next slide) into the body of your email message to IMPAACT.P1108CORE@fstrf.org (or IMPAACT.P1108CORECARDIO@fstrf.org for questions specific to cardiology) to help ensure that all required information is included.

Include the protocol number and PID in the subject line of your email.
1. Site name and number:
2. Name of person submitting query:
3. PID(s):
4. Query is for consultation on (choose one):
   a. Eligibility or enrollment (describe in case description)
   b. AE or toxicity management (specify severity grade in case description)
   c. Optimized background TB treatment regimen (OBR) management (describe in case description)
   d. ARV regimen management (describe in case description)
   e. Other (specify in case description)
5. Cohort: 1, 2, or 3
6. Age of participant:
7. Current week on study:
8. Current optimized background TB treatment regimen (OBR):
9. HIV status of participant
   a. Current ARV regimen (drug names and current dose of each), if applicable:
10. Case description and question or notification for Core Team:
TOXICITY MANAGEMENT: SCENARIO 1

Consider a fourteen year-old girl who enters P1108 weighing 42 kg. The girl starts taking BDQ upon enrollment in the study and continues on her existing OBR MDR-TB and ART regimens. At her Week 4 sparse PK visit she reports no symptoms or health concerns. At Week 4, her hemoglobin is assessed as Grade 2.

Where would you look to find management directions related to this type of event?

A. Section 8 of the P1108 protocol
B. Appendix VIII of the P1108 protocol
C. Email Kate and Tricia
D. Ask the protocol team
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## TOXICITY MANAGEMENT: SCENARIO 1

### APPENDIX VIII: TOXICITY MANAGEMENT OF GENERAL TOXICITIES

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<tr>
<th>Severity</th>
<th>Study Drug Use</th>
<th>Follow-Up and Management</th>
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<td>Grade 1</td>
<td>Continue BDQ</td>
<td>Routine monitoring</td>
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<td>Grade 2</td>
<td>Continue BDQ</td>
<td>Monitor closely with more frequent visits; as per site clinician, work-up to exclude other causes.</td>
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<td>Grade 3 – confirmation pending</td>
<td>Hold BDQ while awaiting confirmation of Grade 3 toxicity unless clinician believes that resuming BDQ will be unsafe and so elects to permanently discontinue.</td>
<td>Contact the study team upon determination of any Grade 3 or 4 toxicity. Indicate in the participant line P1108, grade and type of toxicity.</td>
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<td>Grade 3 – confirmed and presumed, possibly, probably, or definitely related to BDQ</td>
<td>Permanently discontinue BDQ</td>
<td>The participant should be monitored closely until resolution to &lt; Grade 2. As per site clinician, work-up to exclude other causes. Contact the study team upon confirmation of Grade 3 toxicity. Indicate in the participant line: P1108 Grade 3 and specify the toxicity.</td>
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What are your next steps?

A. Continue BDQ
B. Hold BDQ, repeat the assessment, and contact the study team
C. Repeat CBC within 72 hours and hold BDQ until resolved to a Grade 1 or Grade 0
D. Monitor closely with more frequent visits; as per site clinician, work-up to exclude other causes
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Consider a two year-old boy, who attends his Week 20 visit. Following the visit, his bilirubin is assessed as Grade 3. You confirm that the child received BDQ during his Week 16 visit, and there have been no reported adherence issues in the interim.

Where would you look to find management directions related to this type of event?

A. Section 8 of the P1108 protocol
B. Appendix IX of the P1108 protocol
C. Email Kate and Tricia
D. Ask the protocol team
Consider a two year-old boy, who attends his Week 20 visit. Following the visit, his bilirubin is assessed as Grade 3. You confirm that the child received BDQ during his Week 16 visit, and there have been no reported adherence issues in the interim.

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## TOXICITY MANAGEMENT: SCENARIO 2

### APPENDIX IX: TOXICITY MANAGEMENT OF SPECIFIC TOXICITIES

**Toxicity Management of Specific Toxicities: Bilirubin**

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<td>Meets Hy’s law</td>
<td>If ALT/AST elevations are 3-fold accompanied by 2-fold elevation in total bilirubin, BDQ should be permanently discontinued.</td>
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<td>Grade 3 – confirmed, presumed unrelated</td>
<td>Hold BDQ</td>
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- What are your next steps?
  - A. Repeat the assessment
  - B. Hold BDQ and repeat the assessment
  - C. Permanently discontinue BDQ
Consider a two year-old boy, who attends his Week 20 visit. Following the visit, his bilirubin is assessed as Grade 3. You confirm that the child received BDQ during his Week 16 visit, and there have been no reported adherence issues in the interim.

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TOXICITY MANAGEMENT: SCENARIO 2

Consider a two year-old boy, who attends his Week 20 visit. Following the visit, his bilirubin is assessed as Grade 3. You confirm that the child received BDQ during his Week 16 visit, and there have been no reported adherence issues in the interim.

- The repeat assessment confirms the Grade 3 bilirubin. Let’s assume you assess the event as not related to BDQ. What are your next steps?
  A. Monitor closely until resolution to $<\text{Grade 2}$
  B. Restart BDQ
  C. Contact the protocol team
Consider a two year-old boy, who attends his Week 20 visit. Following the visit, his bilirubin is assessed as Grade 3. You confirm that the child received BDQ during his Week 16 visit, and there have been no reported adherence issues in the interim.

- The repeat assessment confirms the Grade 3 bilirubin. Let’s assume you assess the event as not related to BDQ. What are your next steps?

A. Monitor closely until resolution to <Grade 2
B. Restart BDQ
C. Contact the protocol team
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How would your management change if you assessed the confirmed Grade 3 bilirubin as related to BDQ?
IMPAACT PI 108
CLINICAL MANAGEMENT

What are your questions?
Consider a five year-old boy who is enrolled in P1108 and is coming in to the clinic today for his Week 8 visit. At this visit, an ECG is obtained on the study-specific ECG machine. Upon interpretation by the on-site clinician, the child’s QTc = 488 msec.

What is the severity grade of this ECG reading?

A. Grade 1  
B. Grade 2  
C. Grade 3  
D. Grade 4
TOXICITY MANAGEMENT: SCENARIO 3

Refer to Protocol Section 8.6 & Appendix V

What is the severity grade of this ECG reading?

A. Grade 1
B. Grade 2
C. Grade 3
D. Grade 4
As a Grade 2 condition, what action would you take?

A. Continue BDQ; repeat ECG and clinical evaluation of symptoms within 72 hours

B. Hold Fluoroquinolone (FQ) and BDQ; contact the study team

C. Continue BDQ; repeat ECG and clinical evaluation of symptoms within 48 hours

D. Hold FQ and permanently discontinue BDQ if not other explanation; contact study team
Refer to Appendix VI

As a Grade 2 condition, what action would you take?

A. Continue BDQ; repeat ECG and clinical evaluation of symptoms within 72 hours

B. Hold Fluoroquinolone (FQ) and BDQ; contact the study team

C. Continue BDQ; repeat ECG and clinical evaluation of symptoms within 48 hours

D. Hold FQ and permanently discontinue BDQ if not other explanation; contact study team
True or False?

1. A centralized review of all ECFs will occur within 3-7 days and will capture any abnormalities that may not have been identified and/or reported by the site.

2. At the Week 4 and Week 6 study visits, two separate ECG readings will be conducted: one pre-dose and a second 4-6 hours after BDQ administration.

3. Mean QTc interval will be calculated based on triplicate ECG readings at each time point.

4. ECGs are required at all study visits.
BONUS ROUND!

True or False? Refer to Protocol Section 8.6 and Appendix 1

1. A centralized review of all ECGs will occur within 3-7 days and will capture any abnormalities that may not have been identified and/or reported by the site. True

2. At the Week 2 and Week 6 study visits, two separate ECG readings will be conducted: one pre-dose and a second 4-6 hours after BDQ administration. False

3. Mean QTc interval will be calculated based on triplicate ECG readings at each time point. True

4. ECGs are required at: Screening, Entry, Weeks 2, 4, 8, 12, 16, 20, 24 and 40 (off tmt) and at Early BDQ D/C or Study D/C, all study visits. False
TOXICITY MANAGEMENT: SCENARIO 4

Consider a nine year-old boy who attends his Week 4 visit. You send a sample to your local lab for lactate testing and the results indicate that his lactate level increased to 2.0mmol/L to 2.5mmol/L since his Entry/Day 0 visit.

- What toxicity management action would you take:
  A. Send sample for lactate/pyruvate ratio and contact the study team
  B. Consider the test negative
  C. Draw an additional blood sample for repeat lactate
  D. Document and report as a protocol deviation; sample for lactate should not have been collected on a nine-year participant
TOXICITY MANAGEMENT: SCENARIO 4

Refer to Protocol Section 8.7 & Appendix IX

What toxicity management action would you take:

A. Send sample for lactate/pyruvate ratio and contact the study team
B. Consider the test negative
C. Draw an additional blood sample for repeat lactate
D. Document preventative and corrective actions and report as a protocol deviation; sample for lactate should not have been collected on a nine-year participant

Remember! Cohort I only (≥6 to <18 years) will be monitored for lactate and lactate/pyruvate ratios.