P1108: A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Pharmacy Considerations

Presented by: Thucuma Sise, PharmD, BCPS
Overview

- Review the Study product
- Review Administration of smaller doses
- Review Dispensing guidance
- Next Steps
Bedaquiline--Pharmacology

• Diarylquinoline antimycobacterial
• > 99.9% plasma protein bound
• Central compartment VD is approximately 164 Liters.

• The elimination half life of the active and the metabolite is 5.5 months
• Excreted mostly in the feces
• The urinary excretion of unchanged bedaquiline was less than or equal to 0.001% of the dose.
Bedaquiline-Pharmacology

• Inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, by binding to subunit c of the enzyme that is essential for the generation of energy in *M. tuberculosis*.
Bedaquiline-Pharmacology

- CYP3A4 was the major CYP isoenzyme involved in vitro in the metabolism of bedaquiline and the formation of the N-monodesmethyl metabolite (M2), which is 4 to 6-times less active in terms of antimycobacterial potency.
Bedaquiline- Drug Interactions

Drugs that decrease Bedaquiline concentrations
• Rifampin
• Efavirenz *decreased the AUC but did not affect the Cmax

Drugs that increase Bedaquiline concentrations
• Ketoconazole
• Lopinavir/ritonavir
Bedaquiline in P1108

• Study drug is Bedaquiline
  • TB regimen and Rifampin will not be provided through the study

• Participants will be dosed according to Table in section 5

• Study product accountability records should be maintained as per DAIDS guidelines for study product.

• Study product accountability for ARV’s and TB medications should be maintained as per site guidelines.

• Order study drug as per the protocol
  • Protocol Register
  • Receive the DSS from the CRPMC/ICRPMC
  • Order study product
  • Study product will be shipped from the ICRPMC in Johannesburg

• Study treatment will continue for 24 weeks
Study Products: Management

Participants should return unused study product to the Pharmacy upon discontinuation of Bedaquiline.
## Bedaquiline dosing table

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Weeks 1-2</th>
<th>Weeks 3-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 6 to &lt; 18 years</td>
<td>≥30 kg*</td>
<td><strong>BDQ 400 mg once daily, every day</strong></td>
<td><strong>BDQ 200 mg once a day only on Monday, Wednesday and Friday with at least 48 hours between doses</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Given as four of the 100 mg tablets to equal 400 mg per dose</td>
<td>Given as two of the 100 mg tablets to equal 200 mg per dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Total weekly dose of 2800 mg</strong></td>
<td><strong>Total weekly dose of 600 mg</strong></td>
</tr>
<tr>
<td>≥15 kg to &lt; 30 kg</td>
<td></td>
<td><strong>BDQ 200 mg once daily, every day</strong></td>
<td><strong>BDQ 100 mg once a day only on Monday, Wednesday and Friday with at least 48 hours between doses</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Given as two of the 100 mg tablets to equal 200 mg per dose</td>
<td>Given as one of the 100 mg tablets to equal 100 mg per dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Total weekly dose of 1400 mg</strong></td>
<td><strong>Total weekly dose of 300 mg</strong></td>
</tr>
</tbody>
</table>
Bedaquiline Administration

- **Bedaquiline tablets**
  - Should be swallowed whole*
  - 10-20 mL of water
  - Take with food

- **Timing of doses**
  - At least 48 hours between doses when taken 3 times per week on Monday, Wednesday and Friday.

- **Missed doses**
  - **Within the first two (2) weeks**
    - **DO NOT** make up a missed dose if within the first two weeks
  - **From week 3 onwards**
    - **TAKE AS SOON AS POSSIBLE** within 48 hours, then resume TIW schedule maintaining the 48 hours between doses
Bedaquiline Administration

• Bedaquiline
  • It is recommended that Bedaquiline tablets be swallowed whole and intact.
  • Document the method of administration.

• Please see the Manual of Operations for instructions on participants who are unable to swallow the tablets whole and intact.
Bedaquiline Administration

- The study participant or caregiver should be instructed on how to split the BDQ tablet if needed.
- Insert the 100 mg tablet into the tablet cutter. The tablet cutter will be provided by the study team.
- Place the tablet facing up on the “V” shaped holder of the tablet cutter.
- Position the tablet such that the tablet is in line with the blade and the tablet can be cut along the scored line on the tablet.
Dissolving tablets

- For $\frac{1}{2}$ to 1 BDQ tablet, use a 20-25 mL syringe and 10 mL clean water.
- For 1 BDQ tablets, use a 20-25 mL syringe and 10 mL clean water.
- For 1$\frac{1}{2}$ to 2 BDQ tablets, use a 20-25 mL syringe with 20 mL clean water.
- For 3 to 4 BDQ tablets, use a 40-50 mL syringe with 40 mL clean water. In general, 10 mL clean water should be used to dissolve every 1 tablet of 100 mg BDQ.
Dissolving tablets

• Remove the syringe cap
• Remove the syringe plunger
• Put the required tablets into the syringe
• Replace the syringe plunger
• The volume of clean tap water required is as follows:
  • For ½ to 1 tablets, draw up 10 ml of clean tap water
  • For 1 ½ to 2 tablets, draw up 20 ml of clean tap water
  • For 3-4 tablets, draw up 40 ml of clean tap water
• Place the syringe cap back on the syringe
• Shake gently for 4 minutes to dissolve the BDQ tablet(s)
• Remove the syringe cap and administer the entire volume to the child
• Draw up an extra 10 mL clean tap water and place the syringe cap back on the syringe
• Gently shake the syringe to dissolve any remaining medication left in the syringe
• Administer this rinse to the child
• Clean and dry the syringe
Dispensing

- Bedaquiline is supplied as 100 mg tablets
- Each bottle contains 188 tablets
- Store and dispense in the original container per the package insert
- Dispense full quantity of the bottle*
- If tablets are to be split or crushed, the remainder of the tablet should be discarded accordingly.*

  - A new prescription will be required for dose changes.

- *Per the package insert, tablets dispensed outside of the original container must be in a tight light-resistant container with an expiration date not to exceed 3 months.
- Any site opting to dispense outside of the original container should develop a Standard Operating Procedure and share it with PAB to ensure all elements are covered.
Administration

• **PK Sampling day**
  - Bedaquiline, all routine TB drugs and ARV’s will be administered by the study team on the day of and evening prior to PK sampling and this will be documented
  - Participants must be reminded to bring study drug and study supplied drugs to intensive PK clinic in-patient admissions for administration in the clinic.
Questions/ Concerns

Contact Thucuma Sise

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