Summary of Changes Included in the Full Protocol Amendment of:

IMPAACT 2005
A Phase I/II Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-Infected and HIV-Uninfected Children with MDR-TB

The Amended Protocol is Identified as:

Version 2.0, 26 September 2019
DAIDS Study ID #20721
IND #134,732

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Information/Instructions to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the IMPAACT 2005 study, including the study informed consent forms (ICFs), and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, each site should immediately begin implementing this amendment and using the site-specific Version 2.0 ICFs for all new participants enrolled under protocol Version 2.0. Participants enrolled under Version 1.0, at the next study visit, must be re-consented using the site-specific ICFs for protocol Version 2.0. Unless otherwise determined by site IRBs/ECS or other regulatory entities, re-consent for specimen storage and future research use is not required.

Upon receiving IRB/EC approvals and any other applicable regulatory entity approvals, all sites are required to submit an amendment registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will then receive a registration notification for the amendment after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this amendment.

Please file this Summary of Changes, Version 2.0 of the protocol, corresponding site-specific ICFs, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT 2005.
Summary and Rationale

The main purposes of this amendment are to update the delamanid (DLM) dosing regimen for all cohorts, as a result of recent trial results and to update the safety and pharmacokinetic (PK) monitoring procedures for participants <6 months of age.

Modifications incorporated into the protocol include the following:

- The study drug dosing regimen has been modified in response to the Otsuka 232 and 233 trial results, which studied the PK, safety and tolerability of DLM among HIV-uninfected children 0-17 years with MDR-TB. In these trials, pharmacokinetic data analysis showed that DLM \( \text{AUC}_{0-24h} \) exposures were more variable than those seen in similar adult trials, and there were substantial differences in exposures across all cohorts. DLM was well-tolerated and there were no serious safety concerns attributable to DLM. These data, in conjunction with additional PK modeling of the trial data performed by the IMPAACT 2005 pharmacometrician, have led to a revised dosing regimen for all four study age cohorts. In addition, contingency dosing tables referenced in protocol Sections 10.4.3 and 10.4.4 have been added as a new appendix to the protocol (Appendix XI). The tables are being added as an appendix to the protocol at the request of DAIDS.

- Enhanced safety and PK monitoring for participants less than six months of age has been included. For the first three enrolled participants < 6 months of age, all PK assays leading up to Day 56 will be performed in real-time and individual dose adjustments may be implemented, at the discretion of the Clinical Management Committee (CMC), should their Day 56 DLM and DM-6705 \( \text{AUC}_{0-24} \) exposures fall outside of the target range. For any participants who require an individual dose adjustment, an additional study visit two weeks after a dose adjustment occurs will be performed to assess the safety and tolerability of the adjusted dose. An interim analysis of DLM and DM-6705 AUC exposures will also be performed when the first three participants <12 kg or <6 months of age have completed their Day 56 PK sampling.

- The introduction section has been updated to reflect the current safety and PK of DLM from the Otsuka trials and adult trials, to provide a rationale for the modified dosing regimen, to allow use of the WHO shortened MDR-TB treatment regimen, and to add new information on the use of Bedaquiline (BDQ) and DLM for treatment of MDR-TB in children. BDQ has been removed as a disallowed medication. The section has also been updated for consistency with the current version of the DLM Investigator’s Brochure (IB), edition 15, dated 11 April 2019, from Otsuka. Related updates were incorporated into protocol Section 13.5.

- The study eligibility criteria have been modified:
  - To clarify the definition of confirmed or probable MDR-TB and the exclusionary types of TB;
  - To remove the stated weight requirement for Cohorts 1 and 2 and specify minimum weight requirement for all cohorts;
  - To expand the definition of abnormal ECG for consistency with other protocol modifications; and
  - To permit limited DLM-exposure prior to enrollment, consistent with evolving MDR-TB treatment guidelines, which, in some settings, may include initiating patients on DLM as part of standard of care.

- Section 6 and Appendices I (Schedule of Evaluation) and IIA (Sample Informed Consent Form) have been updated to include an additional study visit for participants who require an individual dose adjustment.
• Section 7.3.3 has been updated to specify use of the Corrected Version 2.1, dated July 2017, of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events in IMPAACT 2005.

• Section 8.5 has been updated to further define TB treatment outcomes for children with bacteriologically confirmed MDR-TB and probable and clinically diagnosed MDR-TB.

• Section 8.7 is updated to clarify expectations for ECG review at sites and determination of mean QT interval. Appendix IX is also modified to clarify management following repeat ECGs for confirmed Grade 1 and Grade 2 ECG-determined and clinical cardiac toxicities to ensure appropriate safety monitoring for participants.

• In accordance with ICH GCP E6 4.8.10(n) and DAIDS requirements, Section 11.2 and the sample informed consent form in Appendix IIA have been updated to state that other U.S., local and international regulatory entities may review study records.

• The sample informed consent and assent forms are updated where applicable to reflect the information provided in the current version of the DLM IB as well as current requirements of the Common Rule (per United States Code of Federal Regulations 45 CFR 46).

• Appendix IVA was updated to reflect the current WHO guidance for drug groups routinely used for the treatment of drug-resistant tuberculosis in children.

• The protocol team and study site rosters have been updated to reflect current membership. References have been updated and other administrative updates and corrections have been incorporated throughout the protocol for accuracy, consistency, and clarity. The table of contents has been updated to reflect current protocol sections and page numbers and to include lists of tables and figures.

• Modifications specified in protocol V1.0 Letter of Amendment (LoA) #2 (dated 30 April 2018), LoA #1, (dated 2 November 2017) and Clarification Memorandum (CM) #1 (dated 4 August 2017) have been included.

• Other modifications, clarifications and administrative edits to improve consistency across protocol sections have been incorporated.

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**Implementation**

Modifications of protocol text are described in the section below, generally listed in order of appearance in the protocol.

1. Throughout the protocol, the version number was updated to FINAL Version 2.0, 26 September 2019. The table of contents, abbreviation and acronym list, reference list have been updated. A protocol signature page corresponding to Version 2.0 has been added. External web links have been confirmed and corrected, as applicable, throughout the protocol. Additionally, the cover page was updated to include the IND number (#134,732).
2. The Schema, Figure 1 and Section 5.1, Table 5 (now Table 6) have been revised with the new dosing regimen, as follows:

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Age in Years</th>
<th>DLM Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12 to &lt;18</td>
<td>≥40 kg: 100 mg twice daily (adult formulation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 to &lt;40 kg: 50 mg twice daily (adult formulation)</td>
</tr>
<tr>
<td>2</td>
<td>6 to &lt;12</td>
<td>15 to &lt;30 kg: 25 mg twice daily (pediatric formulation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;15 kg: 15 mg twice daily (pediatric formulation)</td>
</tr>
<tr>
<td>3</td>
<td>3 to &lt;6</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0 to &lt;3</td>
<td></td>
</tr>
</tbody>
</table>

3. The protocol team and study site rosters have been updated to reflect current membership.

4. Section 1.1 was modified to clarify that the World Health Organization (WHO) shortened MDR-TB treatment regimen may be used in accordance with protocol Section 5.6; this section was also updated to incorporate new information regarding the use of Bedaquiline (BDQ) and DLM for treatment of MDR-TB among children.

5. Section 1.2 was modified to incorporate updated cardiac safety information from studies of BDQ/DLM co-treatment in adults; this section was also modified to incorporate updated PK and safety information from Otsuka trials 232 and 233 and the current version of the IB.

6. Section 1.3 was updated to add rationale for the revised dosing strategy to be implemented resulting from the Otsuka 232 and 233 trial results.

7. Sections 3.1 and 10.4.4 have been updated to include information on the interim analysis that will be conducted when the first three participants <12 kg or <6 months of age have completed their Day 56 PK sampling; reference to this additional interim analysis has also been added to the footnote in Figure 1.

8. Inclusion criterion 4.1.5 was modified to clarify the definition of confirmed or probable MDR-TB.

9. Inclusion criterion 4.1.9 has been modified to specify a minimum weight requirement of ≥3 kg at screening for all participants.

10. Exclusion criterion 4.2.3 has been modified to include clarification that participants may have limited previous DLM exposure (up to 17 days) prior to enrollment.

11. Exclusion criterion 4.2.4 has been updated to clarify the definition of abnormal ECG.

12. Exclusion criterion 4.2.8 has been clarified for consistency with inclusion criterion 4.1.5.

13. Sections 5.1 and 5.1.1 have been reorganized for consistency with Sections 1.3, 10.4.3, and Appendix III and the study treatment regimen for all cohorts has been clarified.

14. In Section 5.2.2, additional details regarding preparation for the pediatric dispersible tablet formulation of DLM have been added.

15. Section 5.2.3 was updated to clarify the study product storage instructions.
16. Section 5.6.1 has been revised to include reference to a list of drugs with the potential for mild to moderate QT prolonging effects when administered with DLM, which will be available on the study-specific webpage.

17. Section 5.6.2 has been revised to remove BDQ from the list of medication prohibited during administration of DLM (this change was implemented in LoA #2).

18. Section 6.1 has been updated to clarify expectations for obtaining medical and medications history for participants with previous DLM exposure prior to enrollment; additionally, a second footnote has been added to clarify TB testing requirements for respiratory specimens collected as part of screening.

19. The visit procedural tables in Sections 6.2, 6.9 and 6.16, have been updated to clarify the type of biomarker specimen (i.e. serum or urine) to be collected at each visit.

20. Reference to Section 10.3 concerning additional considerations for PK collections is added to applicable visit procedural tables throughout Section 6.

21. Section 6.9 has been revised to indicate that study drug may not be dispensed after Week 24, for consistency with the overall study drug duration. Similarly, Section 6.10 was corrected to remove reference to DLM administration.

22. Section 6.20 has been added to include a Dose Adjustment visit for children less than six months of age who require an individual dose adjustment, based on their PK results from samples through Week 8. Appendix I has been updated with a new column titled “Dose Adjustment Visit” And corresponding footnotes (#3and 4) have been added with the requirements for this new visit.

23. Section 6.26.1 (now 6.27.1) has been updated to clarify the prioritization of specimens for testing, in the event that the volume of blood collected is insufficient.

24. Section 7.3.3 has been updated to specify the use of Corrected Version 2.1, dated July 2017 of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

25. Section 8.5 has been revised to expand upon the definition of TB treatment outcomes; Tables 7 and 8 have been added.

26. Section 8.7 has been revised to clarify that ECG assessments are based on the mean QTcF of triplicate ECG readings at each time point.

27. Section 9 was updated throughout to reflect study design and statistical considerations associated with the modified dosing strategy as well as all other protocol modifications.

28. In Sections 9.1, 9.5.1, 9.6.2.2, clarification has been added regarding the role of the CMC in the monitoring of study progress, quality of study conduct and participant safety.

29. Section 10 was updated throughout to reflect study design considerations associated with the modified dosing strategy, provision for individual dose adjustment, and the planned interim analysis for the first three participants enrolled who are < 12 kg or < 6 months.

30. Section 11.2 has been updated to state that other U.S., local and international regulatory entities may review study records.
31. Section 13.4 was revised for consistency with the language in Appendix IIA related to the potential benefit to participants.

32. Appendix I was updated with the blood volume requirements for chemistries and TSH testing and the corresponding total maximum blood volumes.

33. Appendix III was updated to include additional information regarding population PK modeling simulations used to inform the revised DLM dosing strategy; Figures 5 and 6 and Table 16 were added.

34. Appendix IVA was updated to reflect the WHO’s 2018 guidance for the grouping of drugs used routinely for the treatment of drug-resistant tuberculosis.

35. In Appendix IX, the clinical management guidelines for confirmed Grade 1 and Grade 2 ECG-determined or clinical cardiac toxicity have been clarified and expanded upon, specifically to include consultation with the CMC.

36. Appendix XI, Contingency Dosing Tables for Children <6 months of Age and/or <12kg, has been added; cross-references within protocol Sections 10.4.3 and 10.4.4 have also been updated.

37. Appendix IIA, Sample Informed Consent Form, has been modified as specified below. Modified protocol text is shown using strike-through for deletions and bold type for additions. In addition, “about” has been added as a qualifier to blood draw volumes in Appendix IIA, when not previously indicated.

INTRODUCTION

This consent form explains the study that your child is invited to join. Here is a summary of important information about the study:

- The study is testing a new medicine to treat tuberculosis for babies, children and adolescents up to 18 years of age, and for whom the first-line tuberculosis medicines do not work.
- The new medicine is called delamanid.
- The new medicine has been studied in adults and children, but more information is needed to determine the best amount to give to children.
- Children will be in the study for 18 months.
- While in the study, children will have clinic visits with physical examinations and blood draws for laboratory tests. Children (or their caregiver) will answer questions about how it feels to take the study medicine.
- There are some possible risks for children in the study. One possible risk is that the medicine being tested could cause side effects.
- There are possible benefits for children in the study. One possible benefit is that the medicine being tested will work well for children.
- Your decision on your child’s participation in the study will have no effect on the medical care your child receives at this clinic. Your child’s access to services, and the benefits and rights he or she normally has, will not be affected.

More information is given in this form about the study, its risks and benefits. You should feel that you understand the study before deciding whether your child will participate. Please read it
or have someone read it to you. Ask any questions you may have. We will take as much time as you need to fully understand the study. We will ask you questions to make sure we have explained the study clearly.

After you understand the study, If you decide that your child will participate, we will ask you to sign or make your mark on this form. We will offer you a copy to keep.

**FINDING OUT IF YOUR CHILD CAN JOIN THE STUDY, #4, item #11:**

11. Take a little more than $\frac{1}{4}$ 1 teaspoon of blood (about 5.0 mL 3.0 mL) in order to check:
   - How well your child’s thyroid, liver and kidneys are working.
   - If your child is HIV negative or positive. There are certain HIV tests that are required for this study. If the required tests are not in your child’s medical records, we will do the tests that are needed. We would need to take a little more than a teaspoon (6.0mL) of blood for these tests.
   - Whether or not your child is pregnant (if urine test is not done). Girls who can have a baby will also be asked to provide a blood or urine sample to test for pregnancy during this visit. If your child is pregnant, she cannot be in the study. If your child is engaged in sexual activity that could lead to pregnancy, your child will be asked to take birth control precautions (ways to prevent pregnancy) throughout the study period first 28 weeks on study (while receiving DLM and for one month after stopping DLM) to prevent any study drug exposure to the unborn baby.

**ON THE STUDY, #5, third bullet, first and second sentences:**

- Blood: The study staff will draw **approximately one to two teaspoons** a little more than $\frac{1}{4}$ a teaspoon (about 5-10.0 mL 3.0 mL) of blood at most visits. The test will check how well your child’s liver, thyroid, and kidneys are working. These tests are routine, so you will be informed of the results. Some of the blood will be used to check the amount of DLM and other anti-TB medications in your child’s blood (see item #6 below).

**ON THE STUDY, #6, “Semi-Intensive PK,” second bullet:**

- “Semi-Intensive PK”: We want to measure the amount of DLM in your child’s blood very closely. For these visits, your child will need to come to the clinic to have blood drawn a few times over 8 hours. This is called an “Semi-Intensive PK Visit.”
  - When will these Intensive PK visits take place? These visits will only happen three times:
    - During the first visit when your child receives their first DLM dose (Day 0 Visit)
    - Week 2 visit
    - Week 8 visit

  *It is possible that we may change the amount of DLM your child receives. If this happens, your child will come for one extra visit about two weeks after the change is made. At this visit we will collect about a teaspoon of blood (4.5-5.0 mL) to make sure that your child is continuing to do well with their new DLM dose.*

**BENEFITS OF THE STUDY, item #11**

11. There may be no benefits to your child from being in the study.

Your child may or may not experience a decreasing number of TB bacteria growing in his or her body while taking DLM, although this cannot be guaranteed. Even if he or she does not personally
benefit from this study, his or her participation may help to increase the knowledge about the treatment of MDR-TB and may help others in the future. You will not have to pay for study drug or procedures that are required.

**RISKS AND DISCOMFORTS, item #13**

13. There are some risks in taking the study drug, DLM, standard treatment for MDR-TB.

As of 11 April 2019, 1,419 people have been given delamanid in studies. Many of these people have MDR-TB, just like your child.

The negative effects or “adverse events” that were less severe but more common among participants taking DLM are included in the table below.

<table>
<thead>
<tr>
<th>Overall Body Effects</th>
<th>Effects on the Stomach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall weakness</td>
<td>Pain or upset stomach</td>
</tr>
<tr>
<td>Fever</td>
<td>Loose or watery stools</td>
</tr>
<tr>
<td>Getting more colds or more lung infections (pneumonia)</td>
<td>Nausea</td>
</tr>
<tr>
<td>Pain in the chest or rapid heartbeat</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effects on Muscle and Bones</th>
<th>Effects on Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aches and pains</td>
<td>Itching</td>
</tr>
<tr>
<td>Shaking (tremor)</td>
<td>Numbing, tingling, or pain on the skin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effects on Activity</th>
<th>Effects on the Head</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleepiness and tiredness</td>
<td>Headache</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Blurry vision</td>
</tr>
<tr>
<td></td>
<td>Ringing in the ears</td>
</tr>
<tr>
<td></td>
<td>Toothache</td>
</tr>
</tbody>
</table>

All patients who choose to participate in this study will receive multidrug treatment for MDR-TB including a combination of multiple drugs from the list described below (alternative treatments). These drugs have known side effects that include, but are not limited to, the following:

<table>
<thead>
<tr>
<th>Alternative Treatments</th>
<th>Known Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol</td>
<td>Liver problems</td>
</tr>
<tr>
<td></td>
<td>Changes in ability to see clearly</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Too much uric acid in the blood</td>
</tr>
<tr>
<td>Amikacin, Kanamycin</td>
<td>Kidney problems</td>
</tr>
<tr>
<td></td>
<td>Difficulty hearing</td>
</tr>
<tr>
<td>Ethionamide and Prothionamide, P-aminosalicyclic acid</td>
<td>Thyroid problems (including tiredness and weight gain)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Kidney problems</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
</tr>
<tr>
<td>Levofloxacin and Ofloxacin</td>
<td>Nausea and/or diarrhea</td>
</tr>
<tr>
<td>Medication</td>
<td>Side Effects</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Headache and dizziness, Restlessness, Sensitivity to light</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Nausea and/or diarrhea, Headache and dizziness, Low platelets, Weakness/numbness in hands and feet, Changes in ability to see (due to damage to a nerve in the eye), Too much lactic acid in the blood</td>
</tr>
<tr>
<td>Imipenem</td>
<td>Nausea and vomiting, Seizures, Serious allergic reaction</td>
</tr>
</tbody>
</table>

14. **There are some risks in taking the study drug, DLM.**

As of 31 January 2016, 17 previous studies gave DLM to a total of 949 adults who had MDR-TB, just like your child. The most common negative effects or “adverse events” that these adult reported when taking DLM were:

**Most common:**
- Nausea/vomiting
- Difficulty sleeping
- Headache
- Dizziness
- Joint or muscle pain

**Less common:**
- Upper abdominal pain
- Loss of appetite
- Ringing in the ear
- Diarrhea
- Chest pain or rapid heartbeat

Some other side effects that might be related to DLM are numbness and tingling, anxiety and tremor.

Sometimes, these adverse events may be due to taking DLM. But, adverse events can also happen because of another underlying disease or other medications, or the development of other illnesses. Please be sure to discuss this and any bad side effects that your child may have with your child’s doctor.

**RISKS AND DISCOMFORTS**, item #14 (formerly #15)

14. We will tell you about the most severe side effects of DLM.

You should also know about the possible more severe but less common side effects. These effects are rare, but they can cause serious health problems to the following parts of the body.

**RISKS AND DISCOMFORTS**, item #17 (formerly #18), second paragraph added:

17. There could be risks of disclosure of your child’s information.

Information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about children with TB. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about your child may be used, but your child’s name will not be shared.
22. Your child’s study records may be reviewed by study staff and groups that oversee the study. Groups that oversee the study include:

- [insert name of site IRB/EC]
- [insert name of site IBC]
- [insert name of national Drug Regulatory Authority]
- [insert name of other local regulatory authorities]
- The United States National Institutes of Health and its study monitors
- The United States Office for Human Research Protections
- **Other U.S., local, and international regulatory entities**
- The United States Food and Drug Administration (FDA)
- The IMPAACT Network that is coordinating the study

38. Appendix IIB, Sample Informed Assent Form, has been modified as specified below. Modified protocol text is shown using strikethrough for deletions and bold type for additions.

**ABOUT THE STUDY, first paragraph:**

We are asking you to take part in this research study on tuberculosis (TB). The reason for this study is to find out if a new medicine called delamanid (DLM) is safe and at what dose this medicine works to treat the specific type of TB that you have, called MDR-TB. MDR-TB (“multidrug-resistant TB”) means that the TB infection (bug) is not killed by the usual TB medicines. DLM has been tested in adults and in animals, but not yet in children. This study will help find the best amount or dose of DLM for babies, children and adolescents under 18 years of age with or without HIV infection, when it is taken with other normal anti-TB medicines for MDR-TB and with HIV medicines. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

**WHAT WILL I HAVE TO DO IN THIS STUDY? Second paragraph:**

DLM will be provided for you by the study, at no cost. The medicine is available in tablet form that can be swallowed whole or can be crushed. These pills will be in addition to your other medicines that you need. You will be asked to take DLM twice every day, for 24 weeks. You will need to take DLM with the TB medications that you are already taking. If you are HIV positive, you will also need to take it with your antiretroviral treatment (ART).

**WILL TAKING PART IN THE STUDY HURT ME? First paragraph:**

DLM is being developed to treat MDR-TB. All drugs can cause unwanted effects called “side-effects.” Not all potential side effects of DLM in humans are known. In studies of people who have been treated with DLM, there are some negative effects or “adverse events” that were less severe but more common among people when they took DLM. This means that they could make you feel more sick than you feel now. We will ask you to tell your parent/guardian any time that you feel more sick. You and your parent/guardian should also tell us if you do not feel well. We will ask you to come here so we can check on you and try to make you feel better. Based on studies that tested DLM in adults, we learned that DLM is generally safe and no serious side effects were seen. The most common side effects that adults in these studies had were:
Most Common: Nausea/vomiting, difficulty sleeping, headache, dizziness, joint pain.
Less Common: Upper abdominal pain, loss of appetite, ringing in the ear, diarrhea, chest pain or rapid heartbeat.