Statistical Methods

Given the small number of participants, descriptive statistics and Wilcoxon Signed Rank tests were performed. Daily MPI scores were examined in two ways: (1) fourth week MPI scores and (2) four-week change in MPI scores. Secondary analyses examined the nighttime MPI scores, which were analyzed in a similar fashion. The analyses were as-treated and the missing outcomes were not imputed. Type I error was not adjusted for multiple testing.

Efficacy

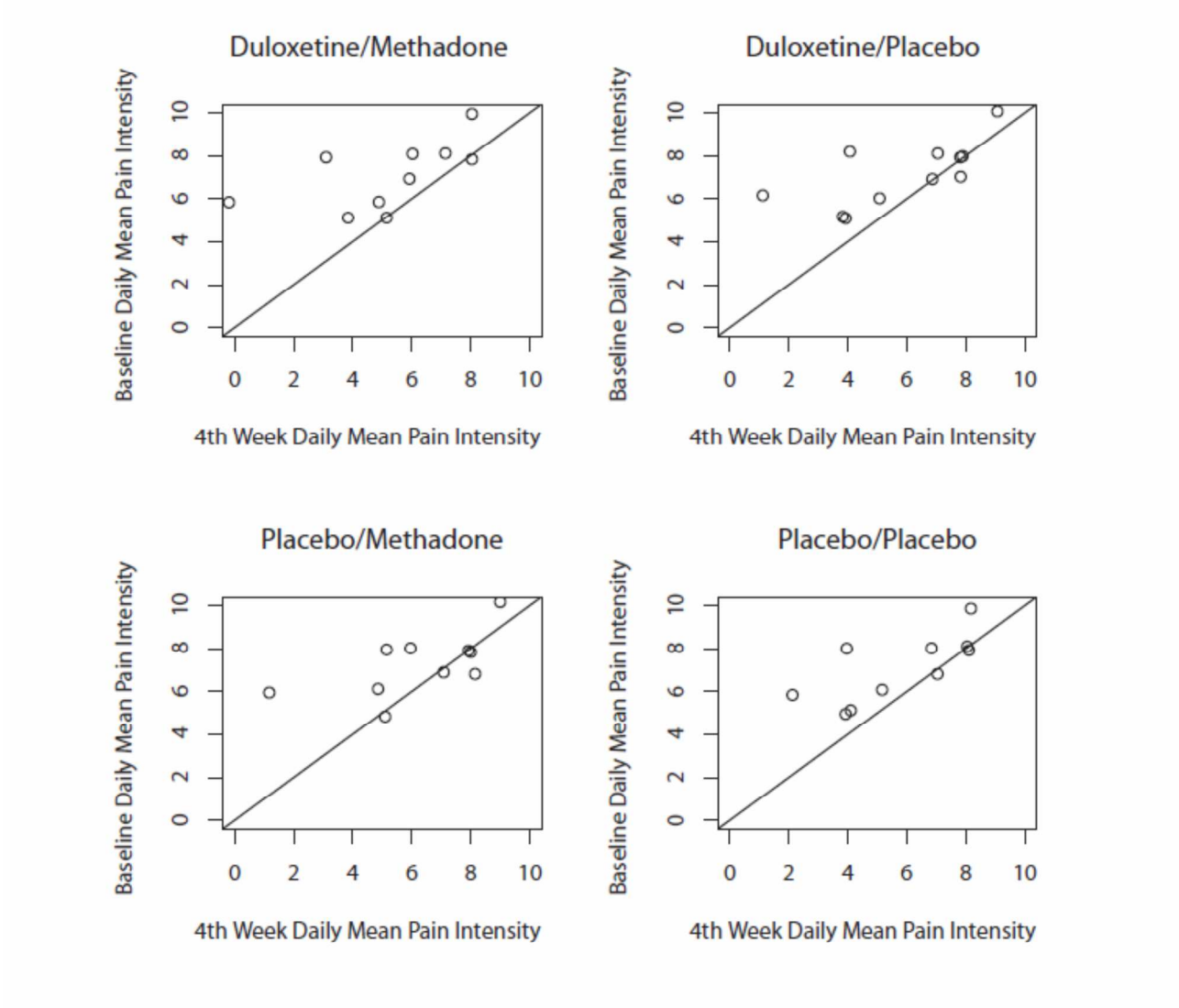
No differences in the daily MPI scores were detected between any of the active treatments and placebo, or between combination duloxetine-methadone and duloxetine or methadone monotherapy (Supplemental Table1). Scatterplots for first and fourth week MPI scores are presented in Supplemental Figure 1. When evaluating pain improvement from baseline, MPI scores during combination duloxetine-methadone showed significant improvement from baseline (median change -1.0; Q1 and Q3 -2.0, 1.0; p=0.008); MPI score during placebo, however, also resulted in significant improvement (median change -1.0; Q1 and Q3 2.0, 0.0; p=0.016) and the observed effect of combination therapy was not statistically different from that observed with the other study treatments or placebo (data not shown).

Significant pair-wise differences were not detected in nighttime MPI scores between treatments. Nighttime MPI scores in the combination and monotherapy treatments resulted in significant improvement from baseline (p=0.004 for DM, p=0.016 for both duloxetine and methadone).

All patients on duloxetine took 60 mg as the MTD. The mean MTD for methadone was 24.6 mg. Pill counts corresponded with study regimen 79% (58/74) with duloxetine and 72% (53/74) with methadone.

According to blinding questionnaire responses, correct guesses by patients with respect to treatment arm was observed with 4 (40%) patients on duloxetine, 4 (40%) patients on methadone, and 5 (50%) patients on duloxetine-methadone. Correct guesses by investigators with respect to treatment arm was noted in 6 (60%) on duloxetine, 3 (30%) on methadone, and 5 (50%) on duloxetine-methadone. Given the small sample size, these data do not make it possible to determine whether unblinding from the side effects or other factors may have occurred in the trial.

Supplemental Figure 1: Scatter plots of baseline and 4th week MPI scores by treatment



Supplemental Table 1: Fourth week daily mean pain intensity scores between treatment groups

Comparison Groups		Median (Q1, Q3)		Median (Q1, Q3) Treatment Difference*	n	p-value**
Treatment 1	Treatment 2	Treatment 1	Treatment 2			
Duloxetine/Placebo	Placebo/Placebo	7 (4, 8)	6 (4, 8)	0.0 (0.0, 1.0)	9	1.00
Placebo/Methadone	Placebo/Placebo	6.5 (5, 8)	6 (4, 8)	0.0 (0.0, 1.0)	9	1.00
Duloxetine/Methadone	Placebo/Placebo	5.5 (4, 7)	6 (4, 8)	-1.0 (-1.0, 0.0)	9	0.25
Duloxetine/Methadone	Duloxetine/Placebo	5.5 (4, 7)	7 (4, 8)	-1.0 (-1.0, 0.0)	10	0.11
Duloxetine/Methadone	Placebo/Methadone	5.5 (4, 7)	6.5 (5, 8)	-1.0 (-1.0, 0.0)	9	0.06

* Treatment Difference = Treatment 1 – Treatment 2.

** Based on the one-sample Wilcoxon Signed Rank test

APPENDIX I (Cont'd)

APPENDIX I

DIVISION OF AIDS
SAMPLE INFORMED CONSENT

For Protocol

A5252, FINAL Version 1.0, 02/04/09: A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of Duloxetine and Methadone for the Treatment of HIV-Associated Painful Peripheral Neuropathy

SHORT TITLE FOR THE STUDY: A5252, FINAL Version 1.0, 02/04/09: Combination Pain Therapy in HIV Neuropathy

INTRODUCTION:

You are being asked to take part in this research study because you are infected with the human immunodeficiency virus (HIV, the virus that causes AIDS) and have pain in your feet and/or legs because of neuropathy. Neuropathy results from damage to the nerves in your feet and legs. It is usually felt as pain, tingling, or numbness. In HIV, neuropathy can result from the infection itself or may be related to drugs used to treat the infection.

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.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

The main purpose of this study is to find out if two different drugs, methadone and duloxetine, reduce neuropathy pain in persons infected with HIV. This study will also look at whether two drugs are better than one for treating neuropathy pain.

Methadone is approved by the Food and Drug Administration (FDA) for treating moderate to severe pain. Duloxetine is approved by the FDA for treating neuropathy pain in diabetics, depression, and anxiety. Neither drug is approved by the FDA for treating neuropathy pain in HIV infection. No studies have looked at whether these drugs are helpful for treating neuropathy pain in HIV infection.

APPENDIX I (Cont'd)

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

During this study, you will take a methadone study drug and a duloxetine study drug, but you will not know whether you are taking active drug or placebo. A placebo is like a "sugar pill." Placebos in this study look like the methadone and duloxetine pills, but do not contain active medicine. The study treatments are: (1) methadone with duloxetine placebo, (2) duloxetine with methadone placebo, (3) methadone and duloxetine, and (4) methadone placebo with duloxetine placebo. For more details on the study treatments, see the section titled "Study Treatment." During this study, you may also receive acetaminophen as a "rescue medication," which can be used as needed to treat neuropathy pain.

You will be assigned by chance (like flipping a coin) to the order of study treatments. Your chance of being assigned to any particular treatment is equal and you will not be able to choose the group. You, your doctor, and the study staff will not know which group you are in, a situation called "double blind." This is a crossover study, meaning that you will get all of the possible study treatments. There will be a total of four treatments lasting four weeks apiece (Treatment Periods), each followed by one week when the study drugs are gradually decreased and stopped (Crossover Periods).

<u>Screening</u>

- After you read and sign the consent form, you will have a screening visit to make sure you qualify to join the study. This visit will last about 3 hours.
- Your HIV infection will be confirmed. If there is no record of an earlier test, an HIV test will be done. You may have to sign another consent form to have this test.
- You will have a physical exam and will be asked about your health and medicines you have taken or are taking now.
- You will have a neurologic exam to look at the feeling or pain in your legs and feet.
- About 2 tablespoons of blood will be drawn for routine lab tests.
- You will have an EKG (electrocardiogram) if you have not had one in the last 3 months. An EKG measures the electrical signals that control the rhythm of your heartbeat.
- If you are a woman who is able to become pregnant, you will have a pregnancy test. You will have an extra teaspoon of blood drawn or you will give a urine sample for this test. You cannot enter the study if you are pregnant.
- You will be asked about your mood.
- You will be told the results of the blood tests and pregnancy test (if done).

If you qualify to be in the study, you may need to gradually stop some of your medicines before your next study visit. These include certain pain medicines for your neuropathy pain and some antidepressant medications. Whether or not you are asked to do this depends on what you are taking at your screening visit. You will not be asked to make any changes in your HIV drugs.

The decision to stop some of these medicines will be made by you and your primary care provider and/or your mental health provider, as needed. You will be asked to stop the medicines gradually over a 1-2 week period. The study staff will carefully instruct you how to do this.

APPENDIX I (Cont'd)

We know that alternative therapies are used by some people to treat neuropathy pain. If you use alternative therapy on a regular basis, it is very important that you do not make changes while you are on this study. Changes while on this study may make it hard to tell how the study drugs affect neuropathy pain.

Pre-Entry Visit

- If you qualify for the study, you will return to the clinic. This visit will last about 2 hours.
- You will have a limited physical exam and be asked about changes in your health or medicines since the last visit.
- You will be given a pain diary. You will be writing down how severe your neuropathy pain is in your diary. The study staff will instruct you to record your neuropathy pain once a day in the morning, every day for each of the seven days before you start the study.

It is important to note that this study is specifically looking at the effect of the study drugs on neuropathy pain. The only pain that you will record in your pain diary is your neuropathy pain, not pain from headache, backache, joint pain, stomach pain, or the like. Pain from neuropathy can be shooting pains, burning, pins and needles sensations, or pain from contact with ordinarily non-painful items, like sheets.

Entry Visit

- After filling in your pain diary over one week, you will return to the clinic. This visit will last about 3-4 hours.
- You will have a limited physical exam and will be asked about changes in your health and medicines since the last visit.
- You will have a neurologic exam to look at the feeling or pain in your legs and feet.
- Your pain diary will be collected and reviewed. Another diary will be given to you to be filled out for the seven days before your next visit.
- The use of rescue medication (acetaminophen) will be reviewed.
- You will have about 2 tablespoons of blood drawn for a CD4 count (the number of infection-fighting cells in your blood) and an HIV viral load (the amount of HIV in your blood).
- If you are a woman who is able to become pregnant, you will have a pregnancy test before you take any study drugs.
- You will answer some questionnaires about your emotions and feelings, and your neuropathy pain and its impact on how you function. These questionnaires may take about 20 minutes to complete.
- You will be told the results of the CD4 count, HIV viral load, and pregnancy test (if done).

If you do not enroll in the study

If you decide not to take part in this study or if you do not qualify for this study, we will still use some of your information. As part of the screening visit, some demographic (e.g., age, gender, race), clinical (e.g., diagnosis and disease condition), and lab information is being collected from

APPENDIX I (Cont'd)

you so that ACTG researchers may help determine whether there are common reasons why people do not join a study. No information that could identify you personally will be shared with these researchers.

During the Study

You will return to the clinic for another 8 visits after you join the study. These visits are at the end of each 4-week treatment period and at the end of each 1-week crossover period. At each visit, you will have a limited physical exam and will be asked about changes in your health and medicines since the last visit. For most visits, you will be at the clinic for about 2 hours. For most visits, you will be at the clinic for about 2 hours. You will be told the results of the routine lab tests and pregnancy tests (if done) performed during the study.

Treatment Period Visits

These visits will occur at the end of the fourth and final week of each of the four treatment periods. It is extremely important that you remember to fill out your pain diary accurately each morning during the final week of the treatment. Each morning, you will record the intensity of your neuropathy pain over the past 24 hours. You will also record the intensity of your nighttime neuropathy pain from the previous night (pain after you have gone to bed).

- Your pain diary will be collected and reviewed.
- Your use of rescue medication (acetaminophen) will be reviewed.
- You will be asked how much study drug you have taken and will return any remaining study drug to the site staff. You will be given your study drugs for the crossover period.
- You will have about 2 tablespoons of blood drawn for routine lab tests. Some of this blood will be stored and tested after the study for the level of study drugs in your blood. This blood will only be stored at the end of the first 2 treatment periods.
- You will answer some questionnaires about your emotions, your neuropathy pain, the impact of neuropathy pain on your ability to function, and your impression regarding the effects of the study treatment you received over the past 4 weeks.
- You will be asked to guess which study treatment you received over the past 4 weeks.

After each of these visits, you will slowly decrease the doses of study drugs over one week. The study staff will carefully instruct you how to do this.

Crossover Period Visits

These visits occur at the end of each crossover period.

- You will be given a pain diary to be filled out for the seven days before your next clinic visit.
- You will be asked how much study drug you have taken and will return any remaining study drug to the study staff.
- You will be given your study drugs for the next treatment period.
- Your use of rescue medication (acetaminophen) will be reviewed.
- If you are a woman who is able to become pregnant, you will have a pregnancy test.

APPENDIX I (Cont'd)

STUDY TREATMENT

You may take the study drugs with or without food. During each treatment period, you will take both a methadone study drug (white tablet) and a duloxetine study drug (blue capsule), but will not know whether either one is active or placebo because in this study the active drugs and placebo look alike.

It is extremely important that you keep your study drugs in a secure location that is not easily accessible to friends or family members. This will protect others, like children or the elderly, from mistakenly taking these drugs and will prevent people from taking your study drugs without your knowledge.

During the first two weeks of each treatment period, you will slowly increase the doses of study drugs. This is called a titration period.

- For the first 5 days of the study, you will take one white tablet two times a day and one blue capsule daily. The clinic will call you 2-3 days after you have started taking the study drugs to see how you are doing. If you are having any serious problems with the medications, you will be told what to do.

- After 5 days, you will increase the doses of study medications to one white tablet three times daily and two blue capsules daily. The clinic will call you 2-3 days after you have started this schedule to see how you are doing. If you had previously reduced your dose during the initial titration period, or you are having any serious problems with the medications, you will be told what to do.

- After another 5 days, you will increase the dose to two white tablets three times daily and continue two blue capsules a day. The clinic will call you 2-3 days after you have increased the study drugs to see how you are doing. If you had previously reduced your dose during the titration period, or you are having any serious problems with the medications, you will be told what to do.

You will continue taking study drugs without changes in dose until your next clinic visit.

After your clinic visit at the end of the treatment period, you will reduce the number of pills that you take over one week. This is called a crossover period.

- Assuming you are on the maximum dose of study drugs, for the first 3 days you will take one white tablet three times daily and one blue capsule daily. If you are on a different dose of study drugs, you will be told what to do at your Treatment Period Visit.
- For the next 3 days you will decrease your medication to one white tablet twice daily and stop the blue capsule.
- For the final day of the crossover week, you will take no study drugs.

APPENDIX I (Cont'd)

Sample treatment schedule for crossover periods

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1 white tablet three times a day 1 blue capsule a day	1 white tablet three times a day 1 blue capsule a day	1 white tablet three times a day 1 blue capsule a day	1 white tablet twice a day	1 white tablet twice a day	1 white tablet twice a day	

IS THERE OTHER INFORMATION THAT I SHOULD KNOW?

If you agree, some of your blood that is left over after all required study testing is done may be stored indefinitely and used for future ACTG-approved HIV testing. No information that could identify you personally will be shared with these researchers.

Storage of leftover blood is not a requirement to be in this study. You may withdraw your approval for the storage of your leftover blood at any time. Please indicate with your initials below whether you agree to have your leftover blood samples stored for future use.

_____ YES _____ NO

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 120 people will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study between 21 and 23 weeks.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- The study is stopped or cancelled.
- The study doctor thinks that you are at major risk of failing to comply with the study.

The study doctor may need to take you off the study drugs without your permission if:

- Continuing the study drugs may be harmful to you.
- You need a treatment that you may not take while on the study.

APPENDIX I (Cont'd)

- You become pregnant.

If you stop the study drugs before the study is over, you will be asked to come for an extra visit and have evaluations identical to the treatment period visits plus a pregnancy test. You will be asked to continue to be part of the study and return for scheduled study visits and tests.

IF I HAVE TO PERMANENTLY STOP TAKING STUDY-PROVIDED DRUGS OR ONCE I LEAVE THE STUDY, HOW WOULD THESE DRUGS BE PROVIDED?

During the study:

If you must permanently stop taking study-provided drugs before your study participation is over, the study staff will discuss other options that may be of benefit to you.

After the study:

After you finish the study, the study will not continue to provide you with methadone and duloxetine. If continuing to take these or similar drugs would be of benefit to you, the study staff will discuss how you may be able to get them.

WHAT ARE THE RISKS OF THE STUDY?

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship to the study drugs. If you have questions concerning additional study drug side effects, please ask the study staff at your clinic.

Risks with Duloxetine:

The following side effects have been associated with the use of duloxetine:

- Nausea
- Somnolence (sleepiness)
- Constipation
- Increased sweating
- Dizziness or lightheadedness
- Restlessness
- Fatigue
- Sleeping difficulties
- Headache
- Dry mouth
- Loss of appetite
- Suicidal thoughts

APPENDIX I (Cont'd)

Risks with Methadone:

The following side effects have been associated with the use of methadone:

- Constipation
- Sedation that may progress to extreme drowsiness
- Nausea or vomiting
- Increased sweating
- Dry mouth
- Dizziness or lightheadedness
- Fast or slowed heartbeat, heart palpitations
- Sleeping difficulties
- Itching without rash
- Breathing problems in people with lung conditions
- Addiction or dependence

You may be asked to discontinue certain medicines that you have been taking to treat your neuropathy pain. Stopping these medicines may result in more severe pain. Discontinuation of antidepressants may increase the risk of depression if you are taking these medicines to treat depression symptoms.

Use of methadone may raise concern about your risk of drug addiction and drug dependence while on this study. Methadone is a type of drug called an opioid. You should know that, when drugs like methadone are used for medical problems such as chronic pain, the risk for opioid addiction is low even in people who have been addicted to drugs before. Even active drug or alcohol abusers have a right to have their pain treated and, even when there is current or ongoing substance abuse, the risks and benefits of study participation must be considered for each person. If addiction to methadone occurs, treatment to get over the addiction may not be simple. If you have concerns about possible addiction and its treatment, talk to the health care team at your site to learn how they monitor and manage possible addiction.

Drug dependence is altogether different from addiction and may be seen with other medicines, like some blood pressure and antidepressant medicines. Dependence is characterized by a withdrawal syndrome noted when drug use is stopped or reduced. This is generally seen after a few days and, while uncomfortable, is typically self-limited and not life-threatening. Opioid dependence is usually seen with abrupt changes in medication dose after chronic or long-term treatment, and risk of withdrawal is minimized with gradual decreases in drug doses like those in this study.

In people under 25 years old, treatment of major depression and other psychiatric illness with antidepressants may be associated with suicidal thinking and behaviors that may occur within the first 1-2 months of treatment. As suicidal thinking and behaviors are very rare, there is no definitive evidence that antidepressants like duloxetine actually cause suicidal thinking and behavior. This study will enroll people with a primary complaint of painful neuropathy, so we feel this risk is extremely low. Should suicidal thinking occur, however, it may arise suddenly, and

APPENDIX I (Cont'd)

agitation or restlessness may be early signs. Tell your study staff right away if you have any such suicidal thoughts or behaviors at any time.

There may be a risk of serious or life-threatening side effects when non-study drugs are taken with the study drugs or with HIV drugs. For your safety, you must tell the study staff at your clinic about all the medicines you are taking before you start the study and also before starting any new medicines while on the study. Also, you must tell the study staff before joining any other clinical trials while on this study.

Risks of Blood Draws

- May cause some discomfort, bleeding, or bruising where the needle enters the vein.
- In rare cases, fainting or infections may occur.

ARE THERE RISKS RELATED TO PREGNANCY?

The drugs in this study may cause harm to unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant.

Some of the drugs that you must take to be in this study may make some birth control drugs less effective. This type of birth control is given by pills, shots, or placed under the skin. This means that you cannot depend on this method of birth control alone.

You and your partner must use a reliable birth control that you discuss with the study staff. You must continue to use birth control until 6 weeks after stopping study drug.

If you can become pregnant, you will have a pregnancy test at every Crossover Period Visit. Tell your study staff right away if you think you may be pregnant. If your pregnancy test is positive, your study drugs will be stopped, and your doctor or the study staff will talk to you about your choices.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. You may benefit by reducing the symptoms of nerve damage and experiencing less pain in your feet or legs. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV and have painful feet or legs.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study, you have the choice of:

- Treatment with other pain medication available to you

APPENDIX I (Cont'd)

- Not participating in this study
- Participating in another study, if you qualify

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

Everything possible will be done to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

People who may review your records include: the FDA, (insert name of site), the Institutional Review Board (IRB), NIH, ACTG, Neurologic AIDS Research Consortium (NARC), Office for Human Research Protections, study staff, study monitors, and the drug company supporting this study and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or risk of harm to yourself or others, we will be required to tell the proper authorities.

WHAT ARE THE COSTS TO ME?

Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. You will be treated the same no matter what you decide.

APPENDIX I (Cont'd)

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research subject, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

APPENDIX I (Cont'd)

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (print)	Participant's Signature and Date
Participant's Legal Guardian (print) (As appropriate)	Legal Guardian's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
Witness' Name (print) (As appropriate)	Witness' Signature and Date

A5252 Patient Information Sheet: Use of Placebo

What is a placebo?

A placebo, sometimes referred to as a "sugar pill", is an inactive pill, liquid, or powder that has no physical or chemical effect. Clinical trials frequently compare an investigational treatment with an inactive placebo for the purpose of measuring an investigational treatment's effectiveness. Such trials are called "placebo-controlled" and are widely considered essential for evaluating an investigational treatment when uncertainty exists about its benefits and harms. A study design where a placebo is compared to an investigational treatment allows the study to answer the important scientific question: "If the people we gave this treatment to respond in this way, how does that compare with people we did not give this treatment to?"

How will placebo be used in this study?

The overall purpose of this study is to evaluate the effectiveness of duloxetine and methadone both a single treatments and in combination for the symptomatic therapy of neuropathy pain. In this study each participant will receive, in random order, each of the investigational treatments: duloxetine, methadone, the combination of duloxetine and methadone, as well as placebo. Neither study participants nor the study staff will know whether active treatment or placebo is being given during any particular treatment period. This trial design will allow for the comparison of the investigational treatments and placebo, focusing on each treatment's impact on neuropathy pain.

Is the use of placebo ethical for a trial of painful polyneuropathy?

The use of an inactive or inert placebo is not always appropriate for a clinical trial, particularly in the setting where a particular therapy has been shown to improve survival or to prevent a serious or permanent medical complication. In this study, the use of a placebo is considered ethical given that neuropathy is not a fatal condition and available neuropathy treatments are not curative. Importantly, uncertainty exists about the relative benefits and harms for each of the investigational study treatments (duloxetine and methadone) as well as for the use of single-drug versus combination therapies.

What are the risks associated with placebo use?

Risks associated with receiving placebo include increased neuropathy pain as well as common medication side effects (such as nausea). Risk of increased neuropathy pain may also be associated with the discontinuation of particular medical treatments required for study entry. While many standard medications typically used to treat neuropathy pain may be continued during the study, antidepressants and opioids must be discontinued as ongoing use would make study results difficult to interpret and would pose unacceptable risks for toxic side effects from multiple antidepressants. Such medication discontinuation will be a voluntary decision made on an individual basis based upon such factors as severity of baseline neuropathy pain, the presence or absence of depression, as well as the perceived benefits and risks to study participation. Specific study design features to minimize placebo risks include the following: the duration of placebo treatment is relatively short compared to the duration investigational treatments (four weeks versus twelve weeks), rescue medication (acetaminophen) is allowed to treat breakthrough pain throughout study participation, and only inactive (inert) placebo is to be used. Study participants reserve the right to withdraw from the study at any time.