

**CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY**

**PROTOCOL NO. 072-01, "A Phase III Study of the Effect of MK-0966 in the Treatment of Post Orthopedic Surgical Pain."**

**SPONSOR:** Merck & Co., Inc.  
Rahway, NJ

**PRINCIPAL INVESTIGATOR:** Scott T. Jackson, M.D.

**SITE OF INVESTIGATION:** Utah Valley Regional Medical Center  
1034 North 500 West  
Provo, Utah 84604

I am being asked to participate in a drug research study. However, before I give my consent to be a volunteer, you want me to read the following and ask as many questions as necessary to be sure that I understand what my participation will involve.

I understand that I cannot be participating in another research study or be taking another investigational drug while participating in this study.

**Nature and Purpose of the Study**

MK-0966 is an investigational drug being developed by Merck & Co., Inc. as an analgesic (pain relieving) medication. The purpose of this study is to evaluate the effectiveness of MK-0966 when used to treat post orthopedic surgical pain in comparison to placebo (an inactive substance) and naproxen sodium. Approximately 200 male and female volunteers will participate in this study. My participation in this study will last up to 36 days, including the time from my screening visit until the end of the study. I will be randomly assigned (like the toss of a coin) to one of the following treatments:

- ▶ One 50 mg tablet of MK-0966 on Day 1 followed by one 50 mg tablet of MK-0966 daily for the next four days
- ▶ One 50 mg tablet of MK-0966 on Day 1 followed by one 25 mg tablet of MK-0966 daily for the next four days
- ▶ 550 mg of naproxen sodium on Day 1 followed by placebo for the next four days
- ▶ Placebo medication for five days

Due to the differing appearance of the study medications, I will be asked to take a combination of an active medication and a placebo (inactive medication) if I am assigned to the group that receives active medication. If I am assigned to the placebo group, all of my medication will be inactive.

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The purpose of this is so that I and the staff at the clinic cannot tell which medication I am on during the course of the study, thereby potentially influencing the results. However, the information is available if needed. I will be able to take LORTAB® 7.5, a standard pain medication, should the study medication not provide adequate relief. The study staff will provide me with detailed instructions on how and when to take my study medication.

During the course of the study, I will be informed of any significant new findings which may relate to my willingness to participate or to continue my participation in this study.

### Entry Requirements

I must satisfy the following entry criteria to enter this study:

- ▶ I must be 18 years of age or older. Female patients must have a negative serum pregnancy test at the prestudy visit and within 48 hours of surgery (if the prestudy visit does not fall within this time) and agree to abstain from sex or use oral contraceptives, or double-barrier contraception (partner using condom and patient using diaphragm, contraceptive sponge, IUD, or spermicidal foam/jelly) from study start until your participation in the study ends. Women who are postmenopausal or status post hysterectomy or tubal ligation are exempt from this requirement.
- ▶ I will have been scheduled to have major orthopedic surgery defined as a total hip replacement, or a total knee replacement, or a fracture repair with open reduction internal fixation.
- ▶ I must be experiencing moderate-to-severe pain following orthopedic surgery and discontinuation of all post-operative medication.
- ▶ I must have completed surgery within 72 hours of study drug administration.
- ▶ I must be able to tolerate food and oral medication.
- ▶ I am judged to be in otherwise good health based on a medical history, physical examination, and routine laboratory tests.
- ▶ I understand the study procedures and agree to participate in the study by giving written consent.

There may be other reasons why I cannot participate which will be discussed with me by the investigator or his staff.

All pain medications must be discontinued prior to first dose of study drug.

Any hypnotic, sedative, tranquilizer, or muscle relaxant must be discontinued within 4 hours of the first dose of study drug.

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I may not enter this study if I meet any of the following criteria:

- ▶ I am under the age of legal consent, I am mentally or legally incapacitated, have significant emotional problems at the time of the study, or have a history of psychiatric disorders.
- ▶ I have had prior therapy which could interfere with the evaluation or efficacy, safety, or tolerability.
- ▶ I am allergic to naproxen sodium, aspirin, ibuprofen, indomethacin, or other NSAIDS, or have a history of asthma in association with nasal polyps. I am intolerant to naproxen sodium. I am allergic or intolerant to VICODIN®, hydrocodone, bitartrate, or acetaminophen. Any exceptions to this will be discussed with you by your investigator.
- ▶ I am obese or have health problems stemming from obesity.
- ▶ I have uncontrolled hypertension, uncontrolled diabetes mellitus, renal disease, stroke or neurological disorder, cardiovascular, hepatic or neoplastic disease, or history of any illness that, in the opinion of the investigator, might interfere with the study or pose additional risk to you.
- ▶ I have a history of gastric, biliary, or small intestinal surgery that results in clinical malabsorption.
- ▶ I have a personal or family history of inherited bleeding disorder.
- ▶ I have clinically significant abnormalities of prestudy clinical examination or laboratory safety tests.
- ▶ I have a history of significant clinical or laboratory adverse event that in the opinion of the investigator contraindicates multiple-dose therapy with an NSAID such as naproxen sodium.
- ▶ I have a recent history (within 5 years) of chronic analgesic or tranquilizer abuse or dependence.
- ▶ I am currently a user (including "recreational use") of any illicit drugs, or have a history of drug or alcohol abuse within the last 5 years.
- ▶ I have donated a unit of blood or plasma or participated in another investigational drug study within the last four weeks. (If I have donated my own blood prior to having surgery, I may still participate in this study.)
- ▶ I have been in a previous study with MK-0966.

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### Procedures to be followed during the Study

Patients may be selected for the study pre-operatively. Each patient selected will be scheduled for a major orthopedic surgical procedure. The risks of the orthopedic surgical procedure as well as any post-operative procedures and/or pain relief medications not associated with this study will be discussed with me by the study doctor or his/her staff. I will be required to sign a separate consent form for the orthopedic surgical procedure. I will be assigned a screening (baseline) number and receive a physical examination, have vital signs measured, and be interviewed by one of the research personnel who will take my medical history. In addition, blood will be drawn by venipuncture and urine will be collected for laboratory tests.

Venipuncture is a routine procedure that will be used for obtaining blood samples from me by inserting a needle into a vein in my arm and withdrawing a small sample of blood. Sterile, single-use needles will be used for each blood sample. I may experience bruising and/or discomfort from this blood draw.

For the initial screening, the amount of blood drawn will be approximately 3 teaspoonfuls (15 ml). (Please note that this is in addition to any blood draws that would be routinely required for your surgical procedure). Women, of childbearing potential, will have an additional 7 ml drawn for a serum pregnancy test. If this test is done more than 48 hours prior to surgery, it will be repeated prior to surgery.

The blood and urine samples collected pre-study will be used to determine if I meet all the study eligibility criteria. If all criteria are met, the next set of study procedures will occur post-operatively.

My medical chart will be reviewed to ensure that I still meet the inclusion/exclusion criteria of the study. Additional blood and urine samples will be obtained as previously described.

Ice packs may be used for the management of post-operative swelling but must be removed 15 minutes before any evaluation of pain can be conducted. At this point, I will be given a patient diary and will be instructed on its completion by the study nurse.

I will be encouraged to stay awake during the 8-hour period after receiving my first dose of study medication.

Vital signs will be conducted two times after which I will be assigned a patient number and administered the first dose of randomly assigned study medication with 4 to 8 ounces of liquid. I will then be asked to record the severity of my starting pain in my diary. Patients who do not develop moderate-to-severe pain will not continue in the study.

Additionally, vital signs will be obtained 1 and 6 hours after receiving study medication.

My weight will be recorded on a daily basis on Days 2 to 5 while I am hospitalized.

Patient diaries will be completed at 30 minutes, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, and 12 hours post-

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administration of the first dose of study medication. I will be asked to record my pain intensity and relief of pain. At the end of the 8 and 12 hours, I will be asked to provide my evaluation of the study medication. The study medication may not provide adequate relief particularly if I receive placebo. If the study medication does not provide adequate relief, I will receive LORTAB® 7.5, a standard pain medication. I will be encouraged to refrain from taking the LORTAB® 7.5 during the first 90 minutes after receiving the first dose of study drug but I may request it at any time. If LORTAB® 7.5 is taken during the first 60 minutes after receiving study drug I will be discontinued from the study. LORTAB® 7.5 taken after the first 60 minutes will not require discontinuation from the study. The date, time, type, and number of LORTAB® 7.5 analgesic medication must be recorded by me or the study coordinator in the patient diary.

I will be instructed to take the remaining study medication every morning for a total of 5 days. If I am discharged from the hospital prior to 5 days, I will be sent home with study medication, a diary, and enough LORTAB® 7.5 to complete the study. On Days 2 to 5, I will be asked to record my pain intensity just prior to my morning dose, 4 hours after my morning dose and at bedtime. Additionally, I will be asked to provide my evaluation of the study medication just prior to bedtime. I will be discharged based on the medical judgement of my physician.

As part of my routine post-operative care I will receive physical therapy sessions. I must record all these sessions in my diary along with the date and start and stop times of the sessions.

I will be given an appointment to return to my physician no later than 14 days after my last dose of study medication. Additional blood and urine samples will be obtained at this time. Women of childbearing potential will be required to take a serum pregnancy test. A physical examination including vital signs will again be conducted.

I will be contacted by telephone to see how I am feeling if my follow-up office visit is less than 2 weeks after my last dose of study medication.

#### **Prior Experience with Drug/Risks and Benefits**

Single and multiple dose safety studies with the MK-0966 have been conducted in approximately 2000 individuals and it has been generally well tolerated.

Side effects considered possibly associated with the use of MK-0966 may include, but are not limited to headache, mouth sores, heartburn, loose stools, abdominal discomfort, nausea, vomiting, drowsiness, dizziness, blood in stools, dry mouth, shortness of breath, abnormal liver function, blood clots, transient ischemic attack (temporary mini strokes) and fluid retention with swelling.

Other unknown side effects could possibly occur, including life-threatening reactions.

The most common side effects experienced by being treated with naproxen sodium are heartburn, nausea, abdominal pain or discomfort, constipation, diarrhea, skin rash, itching, headache, dizziness, drowsiness, fluid retention, and hearing disturbances. Allergic reactions are also possible. Rarely these may be life threatening. Other less common side effects have been reported. The investigator or his/her staff will discuss these with me.

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The most common side effects experienced by being treated with LORTAB® 7.5 include lightheadedness, dizziness, sedation, nausea, and vomiting. Other less common side effects have been reported. The investigator or his/her staff will discuss these with me.

My pain may not be relieved and it may worsen while participating in this study. There may be more pain experienced with the placebo group. Relief of pain cannot be guaranteed.

During the collection of blood samples, I may experience pain and/or bruising at the site on my arm where blood is taken. Blood clots may form and infections may occur, but this is rare. Fainting may occur during or shortly after having blood drawn. If I experience faintness, I should lie down immediately to avoid possible injury caused by falling, and notify study personnel.

Due to the unknown effects which may be caused by combination of drugs, I should be aware that the use of alcohol or any drug (over-the-counter, prescription, or illegal) other than the study medication anytime during the study without approval of the investigator could result in serious and even life-threatening reactions.

In addition to the risks listed above, there may be others that are unforeseeable at this time.

#### **Pregnancy Risks**

It is imperative that I not become pregnant during this study. I am aware that abstinence from sexual activity is the only certain method to prevent pregnancy. If I am a female of childbearing potential and choose to be sexually active during the course of this study, I agree to use oral contraceptives, or double-barrier contraception (partner using condom and patient using diaphragm, contraceptive sponge, IUD, or spermicidal foam/jelly) throughout the study period, and to accept the risk that pregnancy could still result.

There is a slight risk that a pregnancy test could be wrong, thus exposing me to potential loss of pregnancy as well as other unknown effects on a developing fetus. The effects of the study drug on a fetus are unknown. There may be other side effects and discomforts to me (and to the embryo or fetus, if I am to become pregnant), which are not yet known.

#### **Potential Benefits**

I may receive therapeutic benefit from participation in this study such as the reduction of my post-surgical pain. Society may also benefit from the information obtained based on my response to study medication. It is possible that no therapeutic or other direct health benefit may result during or following my completion of the study.

#### **Alternative Treatments**

I understand that if my pain is not sufficiently relieved with the study medication, my doctor will provide me with an alternative pain medication LORTAB® 7.5. Other medications used to treat post-surgical pain may include TORADOL®, ULTRAM®, or PERCOCET®, however, use of these medications while I am taking study medication will require that I discontinue from the study. The

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study doctor or study coordinator will discuss with me the risks associated with any alternative medication I may take. In no way will my decision not to participate affect my current or future treatment. The investigator will provide me with information regarding the side effects of alternative treatments.

#### **Compensation for Medical Treatment**

I will receive \$75 for my time and travel associated with participation in this protocol.

If I suffer any adverse drug experience resulting directly from the Merck study drug, Merck & Co., Inc., will provide reimbursement for the reasonable costs of medical treatment to the extent such costs are not covered by my medical or hospital insurance or by third-party or governmental programs providing such coverage. No other form of compensation is available.

#### **Confidentiality**

Unless required by law, only the investigator, Merck & Co., Inc. (the sponsor), Jean Brown Associates, Inc. (an agent for the sponsor), and governmental regulatory agencies will have access to confidential data which identifies me by name. I will not be identified in any reports or publications resulting from the study.

#### **Parties to Contact**

The investigator or his designate has answered all of my questions. If I have additional questions during the course of this study about the research or my rights as a research subject, I may address them to T. J. Blair, Utah Valley Regional Medical Center IRB Chairman at (801) 371-7200. In the event of a research-related injury or if any other problems arise, please contact Dr. Jackson at (801) 371-7350.

#### **Voluntary Participation**

My participation in this study is voluntary. I may refuse to participate or may discontinue participation at any time during the entire duration of the study without penalty or loss of benefits to which I am otherwise entitled. If I terminate my participation, I may receive a standard medication and no prejudice will be shown toward me for medical care or participation in future studies. In addition, my participation may be terminated by the investigator or sponsor without regard to my consent if I need additional medication, violate the study plan, experience a study-related injury or for administrative reasons. Any time my participation is terminated I shall go through the termination procedures--physical, blood, and urine tests for my own safety.

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I have read the above and understand this consent form. My questions have been answered. I voluntarily consent to participate. I will receive a signed copy of this consent form.

\_\_\_\_\_  
(Signature of Volunteer)

\_\_\_\_\_  
(Date)

\_\_\_\_\_  
(Signature of Parent or Legal Guardian)

\_\_\_\_\_  
(Date)

\_\_\_\_\_  
(Signature of Person Obtaining Consent)

\_\_\_\_\_  
(Date)

\_\_\_\_\_  
(Signature of Investigator)

\_\_\_\_\_  
(Date)

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