Impact of Naloxegol (Movantik) on Prevention of Lower Gastrointestinal Tract Paralysis in Critically Ill Adults Initiated on Scheduled IV Opioid Therapy: A Randomized, Double-Blind, Placebo-Controlled, Phase II, Single-Center, Proof of Concept Study

NCT02977286

Version Date: September 22, 2018

Approved on: October 25, 2018

TUFTS MEDICAL CENTER

DEPARTMENT OF MEDICINE, DIVISIONS OF PULMONARY, CRITICAL CARE AND SLEEP DIVISION AND GASTROENTEROLOGY

Impact of Naloxegol (Movantik) on Prevention of Lower Gastrointestinal Tract Paralysis in Critically Ill Adults Initiated on Scheduled IV Opioid Therapy: A Randomized, Double-Blind, Placebo-Controlled, Phase II, Single-Center, Proof of Concept Study

INFORMED CONSENT TO PARTICIPATE IN RESEARCH

Principal Investigator: Erik Garpestad, MD
Co-Investigators: John W. Devlin, PharmD, Harmony Allison, MD, Ioana Preston, MD, Matthew Duprey, PharmD, Eric Anketell, RN, Haregwoin Woldetensay, BS
Study team telephone number: 617-636-6142

AS USED IN THIS CONSENT FORM "YOU" REFERS TO THE SUBJECT WHO WILL TAKE PART IN THE RESEARCH STUDY.

INTRODUCTION

You are being invited to participate in a clinical research study because you have been started on a pain medication (i.e. opioid) through the vein [intravenous (IV)] and are at risk for having a hard time passing bowel movements [i.e. paralysis of the lower gastrointestinal (GI) tract].

If you are not the subject, you are being asked to consent the subject to participate in this clinical research study because you have the authority to do so. You are being asked to review and sign this form because your relative or friend cannot decide for themselves whether to take part or not, and you are designated as their decision maker in these matters.

Before deciding to participate in this research study, it is important that you read and understand the following explanation of the research procedures. This document describes the purpose, procedures, benefits, risks, discomforts and precautions of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at any time for any reason.

No guarantees or assurances can be made as to the results of the study. Your participation in this research study is entirely voluntary.

Taking part in this research study is totally your choice. You can decide to refuse to participate in this study. If you decide to participate in this study, you can then choose to stop taking part in the study at any time for any reason. If you refuse to participate in the study or stop being in this study, it will not affect your care or treatment outside this study, payment for your healthcare, or your healthcare benefits.

Tufts Medical Center/TUHS IRB # 12043
Approved on 10/25/2018

Please read all of the following information carefully. Ask Dr. Garpestad or his representative, to explain any words, terms, or sections that are unclear to you. Ask any questions that you have about this study. Do not sign this consent form unless you understand the information in it and have had your questions answered to your satisfaction.

If you decide to take part in this research study, you will be asked to sign this form. You will be given a copy of the signed form. You should keep your copy for your records. It has information, including important names and telephone numbers, to which you may wish to refer to in the future.

New things might be learned during this study that you should know about. The investigators will tell you about new information that may affect your willingness to stay in this study.

If you are eligible to participate and decide to be in the study, the Principal Investigator may still choose to stop your participation in this study if he thinks it is in your medical best interest. You may also be withdrawn from the study if the study ends because of issues related to the safety of the subjects who have participated in it.

If you withdraw or are withdrawn from the study, any data collected from you before your withdrawal will be used for the study.

As a participant in this study, your identity, medical records, and data relating to this study will be kept confidential, except as required by law. The U.S. Food and Drug Administration (FDA), which regulates investigational drug and device studies, and the study sponsor, AstraZeneca Pharmaceuticals may also look at records that identify you if applicable to the study.

If you have question about the rights as a research study subject, call the Tufts Medical Center and Tufts University Health Sciences Institutional Review Board (IRB) at (617) 636-7512. The IRB is a group of doctors, nurses, and non-medical people who review human research studies for safety and protection of people who take part in the studies. Federal law requires the IRB to review and approve any research study involving humans. This must be done before the study can begin. The study is also reviewed on a regular basis while it is in progress.

This research study has been reviewed and approved by the IRB of Tufts Medical Center and Tufts University Health Sciences.

PURPOSE OF STUDY

The present standard of care for preventing paralysis of the lower GI tract in critically ill patients like you includes using drugs like stool softeners (e.g. docusate) and sometimes laxatives [e.g. senekot (senna), dulcolax (bisacodyl), miralax (polyethylene glycol)]. Even when these drugs are used early in the ICU stay, many people who require IV opioid therapy do not adequately move their bowels. Therefore, there is a need to find a safe and efficacious drug to prevent lower GI tract paralysis.

The reason for this study is to evaluate the efficacy and safety of a drug called naloxegol (Movantik) as a way to prevent lower GI tract paralysis. Naloxegol is approved by the Food and

Drug Administration (FDA) for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain. The use of naloxegol in this study is considered investigational because the use of naloxegol to prevent paralysis of the lower GI tract in ICU patients is not approved by the FDA.

You are being asked to take part in this study because you:

- Are critically ill in the ICU
- Need IV opioid medicine for your pain

You may not participate in any other clinical research study that involves the testing of another drug, device or behavior while participating in this research study.

This study will be conducted at Tufts Medical Center.

Up to 44 subjects will take part in this study, all from Tufts Medical Center.

This study is funded by AstraZeneca, the company that manufactures naloxegol (Movantik).

Naloxegol is not available at Tufts Medical Center outside of the study but it may be available to patients at other hospitals.

PROCEDURES TO BE FOLLOWED

For this research study, you will be randomized to receive either naloxegol or placebo. You will have an equal chance (i.e., 50% chance) to receive either naloxegol or placebo. This study is blinded which means that neither you nor your doctor will know or be able to choose which drug you receive. You will receive naloxegol or placebo once daily for a maximum of 10 days. The study medication may be stopped before 10 days if you are started on a new medication that may increase the amount of naloxegol in your blood or if you develop kidney problems (dysfunction) that may also increase the amount of naloxegol in your blood. You will also be started on a stool softener (docusate) twice daily that is a standard of care for ICU patients at Tufts Medical Center. You will also be managed with a study laxative guideline that has been created for use in this study. . This laxative guideline will be used by your ICU doctor to treat you if you fail to have a bowel movement, despite being on the study medication. The protocol follows a standard approach that is used to prevent lower GI paralysis in patients in the ICU at Tufts Medical Center.

Naloxegol is not available at Tufts Medical Center for non-research purposes. The standard of care for preventing lower GI tract paralysis in ICU patients like you includes using medications such as stool softeners and laxatives. Participating in this study is different from the standard of care because you will be receiving either naloxegol or placebo in addition to any other medications that might be used to prevent lower GI tract paralysis as needed for you.

You will be eligible for this study if you are admitted to the medical intensive care unit (MICU) service, require the use of an IV opioid medication, and meet the other study requirements.

On the day you are enrolled in the study, the following will happen:

- We will collect information about your age, gender, race and your past and present medical history. You do not have to answer any questions that you feel uncomfortable about.
- Female subjects of childbearing age will receive a blood test for pregnancy, for research only, if you have not already had one completed for routine care. The amount of blood taken for this test is about ½ teaspoon. If the pregnancy test is positive, you will be excluded from the study.
- The study activities on this day will take about 20-30 minutes.

During the 10-day study drug period, the following will happen:

- Your relative or friend will then be placed randomly (as if by flipping a coin) into one of two groups:

  Group #1: Naloxegol either taken by mouth or crushed and administered into a feeding tube.

  OR

  Group #2: Placebo either taken by mouth or crushed and administered into a feeding tube.

  You, your family and the study staff will not know which drug has been assigned to you. Only the pharmacy will know whether you are have been assigned to receive naloxegol or placebo.

- For research only, you will receive study drug by mouth for up to 10 days. You will not be continued on study drug past 10 days even if you have not yet been discharged from the ICU.
- You will be monitored closely for any side effects from the drug including diarrhea and opioid withdrawal, which has symptoms such as sweating, increased heart rate, restlessness, and anxiety. This monitoring will take about 10 minutes each day.

Both groups will continue to receive their standard intensive care treatment in addition to either naloxegol or placebo. You will continue to receive all other necessary medical treatment for the medical conditions you were admitted to Tufts Medical Center for as determined by your regular doctor. After you are enrolled into the study, your care will not be altered in any way.

Your regular nurse, doctor, and the study investigators will carefully monitor you throughout the entire study period for side effects associated with the study drug. If you are found to have a side effect that is associated with naloxegol, both a study team member and your doctor will be promptly informed and will determine together if you should be discontinued from the study. You have the right to discontinue your participation in the study at any time for any reason.

RISKS

Naloxegol is FDA approved and used as a drug to treat opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain but it is not approved by the FDA as it is being used in this study. The dosage of the drug that you will receive is the same dose that is used to treat OIC, but side effects can occur.

Although all information regarding your participation in this research study will be held confidential to the extent permitted by the law and you will be identified by a code number (rather than by your name), it is still possible that a loss of confidentiality could occur.

a. Naloxegol

Common (> 10%): Abdominal (stomach) pain, diarrhea

Uncommon (2-10%): Flatulence, nausea, vomiting, muscle pain (arthralgia), headache, dizziness, feeling hot and blood pressure changes (both low and high).

Rare (<2%): Chills, yawning, withdrawal symptoms (e.g., increased heart rate, sweating, nausea, vomiting, agitation, restlessness), tears in your gastrointestinal tract (perforation)

b. Placebo

None

c. Measurement of Bladder Pressure

Bladder pressure may be measured if you have a foley catheter in place for a reason other than being a part of this study. If it is done, this measurement will be done by your regular nurse every 8 hours. The measurement of your bladder pressure does not pose any additional risk to you. This procedure will not be done unless you already have a foley catheter in place for a non-study reason.

d. Risks that are not known

Because the use of naloxegol to prevent paralysis of the lower GI tract is not an FDA approved indication, this intervention is considered investigational and there may be risks that we do not know about at this time.

If you become pregnant or are breastfeeding, naloxegol may involve risks to the embryo or fetus, which are currently unknown. If you are female and of child-bearing potential, you will be admitted to this study only if you are not pregnant as determined by a blood pregnancy test. If you are pregnant, become pregnant, or are currently breastfeeding, you may not participate in this study.

Tell the study doctor if you think you might have a history of allergy or intolerance to naloxegol.

Your doctor and the study doctors will carefully monitor you for side effects associated with the

study drug. If you have an adverse side effect associated with the study drug, the dose of the study drug will be decreased. If the side effect persists, the study drug will be stopped and you will no longer be in the study. Should any adverse side effects or other reactions occur while on this study, you should notify your regular nurse and the principal investigator, Dr. Erik Garpestad at 617-636-5388.

BENEFITS

This study is not designed to benefit you.

If you receive a placebo you will receive no benefit from participating in this study.

The benefits you might get from being in this study include preventing lower GI tract paralysis, which may reduce nausea, vomiting, inhaling your stomach contents into your lung(s) (aspiration), abdominal pain, and prevent delirium. However, this cannot be guaranteed.

You may or may not receive any benefit from taking part in this study; however knowledge gained from this study may help us to treat other subjects in the future.

ALTERNATIVES

You do not have to participate in this study you might be able to receive naloxegol at another hospital but this is not guaranteed. You can receive standard treatment to prevent paralysis of the lower GI tract if needed, including stool softeners and laxatives. Your doctors have experience in using stool softeners and laxatives to prevent lower GI tract paralysis in patients like you and they are often eventually effective. Everything about the care you receive at Tufts Medical Center would remain the same if you decide not to participate in this study or withdraw early from the study. You can decide to stop being in this research study at any time for any reason. If you decide to withdraw permission to participate in the study, tell your doctor or a member of the research staff as soon as you make the decision. If you stop being in this research study, it will not affect how you are treated at Tufts Medical Center. The alternative is not to participate.

STUDY TERMINATION AND WITHDRAWAL

If you are eligible to participate and decide to be in the study, the Principal Investigator may still choose to stop your participation in this study if he thinks it is in your medical best interest. You may also be withdrawn from the study if the study ends because of issues related to the safety of the subjects who have participated in it.

If you withdraw or are withdrawn from the study, any data collected from you before your withdrawal will be used for the study.

RESEARCH RELATED INJURY

If you feel you have become hurt or sick as a result of being in this research study you should

contact a member of the study team whose contact information is listed at the end of this form. Emergency medical treatment will be given to you if you are hurt or get sick as a direct result of being in this research study. You or your insurance carrier are to pay for any such medical care. Any needed medical care is available at the usual cost. All needed facilities, emergency treatment, and professional services are available to you just as they are to the general public. There are no plans to pay for your treatment if you get hurt or sick as part of this study. The institution has not set aside any money to pay for a research-related injury or illness.

COSTS

Neither you nor your insurance plan will be charged for the naloxegol you receive as part of the study nor the tests done as part of this study that are not required for the care and management of your illness. All costs for the routine treatment received in the ICU at Tufts Medical Center for your medical condition(s) will be charged to your health insurer. If your insurer refuses to pay these costs because you are in this study then it will be you responsibility to pay them. If you are referred for specialized care should a side effect from participating in the study occur, your insurance company, and not the study, will be responsible for the costs associated with treating any side effect(s).

PAYMENT

If you are enrolled and randomized into the study, you will not be paid for your time.

PRIVACY AND CONFIDENTIALITY

All information regarding your participation in this research study will be held confidential to the extent permitted by the law and will not be released without your written permission. Your medical records, study records and results will not be identified in any publication resulting from these from these studies. You will be issued a code number which will be used to identify you. Only the Principal Investigator and research staff will know your identity. All information about you will be identified only by this code number, and not by your name. Information about the code will be kept in a locked, secure location and access will be limited to only study personnel and any other regulatory bodies, whether in the United States or other countries. Any information about participants will not be shared with anyone else (including your relatives, friends or health providers), without your written permission.

We will make every effort to keep your information private, but it cannot be completely guaranteed. Certain government agencies such as the FDA, the Institutional Review Board at Tufts Medical Center and the study sponsor, AstraZeneca, may request to review your medical records and this signed consent form. The records of this study might also be reviewed to make sure all rules and guidelines were followed.

Data from this study may be included in publications or presented at scientific meetings. You will not be identified.

A description of this clinical trial will be available at http:www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, this web site

will include a summary of results. You can search this web site at any time.

AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION

If you sign this document, you give permission to the Principal Investigator named above and research staff at Tufts Medical Center as well as other individuals at Tufts Medical Center who may need to access your information to do their jobs [such as for treatment, payment (billing) or health care operations) to use or disclose (release) your information that identifies you for the research study described above.

The parties listed in the preceding paragraph may disclose the health information described below to the following persons and organizations for their use in connection with the research study:

- Individuals or organizations working under the direction of the Principle Investigator(s) for the study,
- Outside individuals or entities that have a need to access this information to perform activities relating to the conduct of this research, such as analysis by outside laboratories on behalf of Tufts Medical Center,
- Other researchers that are conducting or participating in this study,
- The study sponsor, AstraZeneca and any companies they use to oversee, manage, or conduct the research,
- The Office for Human Research Protections in the U.S. Department of Health and Human Services, the United States FDA and other federal and state agencies that have the right to use the information as required by law,
- The members and staff of any Institutional Review Board (IRB), and Data and Safety Monitoring Board that oversee the study.

The health information that we may use or disclose (release) for this research study includes all information in your medical record related to the diagnosis and management of your ICU sedation, including the record of your care, as well as any information collected or created during the course of this study.

Tufts Medical Center is required by law to protect your health information. By signing this document, you authorize Tufts Medical Center to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them. You may not be allowed to see or copy the information described on this form as long as the research is in progress, but you have a right to see and copy the information upon completion of the research in accordance with hospital policies.

You can decide to sign or not to sign this form. However, if you choose not to sign this form, you will not be able to take part in the research study and you may not receive any research-related clinical care.

This authorization does not have an expiration date. You may change your mind and revoke (take back) this authorization at any time. Even if you revoke this authorization, this site's clinical, administrative and research staff may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this authorization, you must write to HIPAA Privacy Officer for Research, 800 Washington St, Box 5100, Boston, MA 02111. If you revoke this authorization, you may no longer be allowed to participate in the research described in this form.

WHOM TO CONTACT

Ask any questions about this study anything that you do not understand before you sign this form. The study doctor or study staff will answer questions before, during, and after this study.

You can call the study team at:

Principal Investigator:	Erik Garpestad, MD Phone 617-636-5388 (daytime) Pager: 617-604-8100 (anytime)
OR	Sub-Investigator: John W. Devlin, PharmD Phone: 617-636-6124 (daytime) Pager: 617-647-3057 (anytime)
OR	Sub-Investigator: Ioana Preston, MD Phone: 617-636-7609 Pager: 617-747- 2558
OR	Sub-Investigator: Harmony Allison, MD Phone: 617-636-7754 Pager: 617-647-3364
OR	Sub-Investigator: Matthew Duprey, PharmD Phone: 617-636-4576 Pager: 617-647-3061

DOCUMENTATION OF CONSENT

I have been given a copy of this form. I had read it or it has been read to me. I understand the information and have had my questions answered to my satisfaction. I agree to take part in this study.

I understand that I will be informed of any new findings developed during the course of this research study that may affect my willingness to stay in this research study.

_____
Date Subject's Signature

I have fully explained to _____ the nature and purpose of this
Subject
above-described study and the risks that are involved in its performance. I have answered all questions to the best of my ability.

Printed Name of Principal Investigator or Person Conducting the Informed Consent Discussion

_____
Position

_____
Date Principal Investigator or Representative's Signature

Witness Signature (for Non-English Speaking Persons)

_____ _____
Date Witness' Signature Witness Name

Use below only when enrolling persons with impaired decisin-making capacity
I have been given a copy of this form. I had read it or it has been read to me. I understand the inform ation and have had my questions answered to my satisfaction. I agree to take part in this study.
I understand that I will be informed of any new findings developed during the course of this research study that may affect my willingness to stay in this research study.

Legally Authorized Representative signature

Check the relationship of the legally authorized representative to the subject (list in order of recognized hierarchy):

- [ ] 1. The health care agent, upon proper invocation of the health care proxy
- [ ] 2. Spouse
- [ ] 3. Adult children
- [ ] 4. The subject's parent
- [ ] 5. Adult siblings
- [ ] 6. Legally appointed guardian or conservator.

I have fully explained to _____ the nature and purpose of the
Legally Authorized Representative

above-described study and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____ _____
Printed Name of Principal Investigator or Person Conducting the Informed Consent Discussion — Position

_____ _____
Date — Signature of Principal Investigator or Person Conducting the Informed Consent Discussion

Witness Signature (for Non-English Speaking Persons or Phone Consent)

_____ _____ _____
Date — Witness' Signature — Witness Name

Subject Re-Consent

My legally authorized representative gave his/her consent for me to be in this research study. This is because I was not able to make decisions on my own due to my illnesses. My condition has now improved and I am now able to make decisions on my own. I am now being asked to decide whether to continue to be in this study. My decision is voluntary. This means the decision is up to me. I have read this consent form, and the research study has been explained to me verbally. All my questions have been answered. My decision is checked below:

☐ I agree to continue in the study.

☐ I do NOT agree to continue in the study.

_____ _____
Subject's Signature Date

_____ _____
Printed Name of Investigator or Person Conducting the Informed Consent Discussion Position

_____ _____
Date Signature of Principal Investigator or Person Conducting Informed Consent Discussion