

Clinical Study Protocol
HMR3647A/3003

31 Dec 1997

INFORMED CONSENT

Evaluation of the efficacy and safety of oral HMR 3647 800 mg once daily for 5 days vs amoxicillin/clavulanic acid 500/125 mg three times daily for 10 days in the treatment of acute exacerbation of chronic bronchitis in adults.
A double-blind, multinational, multicenter, comparative study.

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Subject number: _____

1. I have read the informed consent document for this trial. I have received an explanation of the nature, purpose, duration, and foreseeable effects and risks of the trial and what I will be expected to do. My questions have been answered satisfactorily.
2. I agree to take part in this trial. I agree to cooperate fully with the investigator and will contact *him/her* immediately if I suffer any unexpected or unusual symptoms during the trial. For the duration of the study, I will notify the investigator of any other medical treatments that may be necessary for me to undergo.
3. I have informed the investigator of all my previous or present illnesses and medication and of any consultation that I have had with my doctor in the last months.
4. I have further informed the investigator of any participation by me in other clinical studies in the past year.
5. I am aware that if I do not cooperate fully with the investigator's requests and directions, I may harm myself by participating in the study.
6. I understand that my participation in the trial is voluntary and that I may refuse to participate or may withdraw from the trial at any time, without penalty or loss of benefits to which I am otherwise entitled. I further understand that any information that becomes available during the course of the study that may affect my willingness to take part will be disclosed to me as soon as practicable.
7. I agree that results of the study may be passed on to the appropriate authorities, to the sponsor, and to the manufacturer of the drug under study. My name and address will be kept confidential.
8. Representatives of the sponsor, independent ethics committee/Institutional Review Board, or local or foreign regulatory authorities may wish to examine my medical records to verify the information collected. By signing this document, I give permission for this review of my records.

Last name: _____	First name: _____
(block letters)	(block letters)
Signature: _____	Date: _____
	(to be completed by subject at time of consent)

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Investigator/Subinvestigator

I confirm that I have personally explained the nature, purpose, duration, and foreseeable effects and risks of the trial to the subject named above.

Last name: _____ **First name:** _____
(block letters) (block letters)

Signature: _____ **Date:** _____

(If required)

Witness

Last name: _____ **First name:** _____
(block letters) (block letters)

Signature: _____ **Date:** _____

Cons3003

Rare cases of ECG abnormalities were reported with some of the orally administered macrolides, which are one of the commonly prescribed treatment for respiratory tract infections. Since HMR 3647 is a derivative of the same group of antibacterials, an ECG will be taken before, during and after the administration of the study drug, as a safety investigation, as described above.

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SUBJECT INFORMATION SHEET

Evaluation of the efficacy and safety of oral HMR 3647 800 mg once daily for 5 days vs amoxicillin/clavulanic acid 500/125 mg three times daily for 10 days in the treatment of acute exacerbation of chronic bronchitis in adults.

A double-blind, multinational, multicenter, comparative study.

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You have been diagnosed as suffering from an acute exacerbation of chronic bronchitis (AECB). This disease is due to microorganisms and has to be treated with an antibiotic. We propose you to take part in a study to evaluate the efficacy and safety of a new antibiotic (a ketolide HMR 3647) for the treatment of AECB. This new drug is under development (clinical research) and will be submitted for approval after the end of the studies conducted worldwide. Around one hundred subjects have already received this drug. Bacteriological studies have shown that this product is efficient against the pathogens usually responsible for AECB. This drug is expected to be at least as effective as the common drugs prescribed to treat AECB, such as amoxicillin/clavulanic acid which will be the comparative antibiotic in this study.

Two different treatment regimens will be studied. A total of 340 subjects will take part in this study and receive one of the following treatments :

- HMR 3647 : 800 mg once a day during 5 days followed by a 5-day placebo treatment,
- amoxicillin/clavulanic acid : 500 mg three times a day during 10 days.

These treatments will be randomly assigned using a previous list, and neither you nor your doctor will know which treatment you are receiving until the end of the study (double-blind study).

You will have equal chance of receiving one or the other treatment. Whatever the treatment group you will be assigned to, you will be prescribed 6 capsules per day by oral route during 10 days.

If you are selected for inclusion and if you decide to participate, you will be requested to come to five medical visits :

- Before starting the treatment, you will have your first medical consultation, with a chest x-ray. A blood and urine sample will also be taken including a blood and urine pregnancy test for women. A lung function test will be performed if not done in the previous 12 months. Respiratory samples (and blood if deemed necessary by your doctor) will be taken for bacteriological cultures. Arterial blood gases will also be taken, and peak expiratory flow rate will be measured.
- A second visit will be required during treatment, 2 to 3 days after the beginning of treatment. Laboratory tests (blood and urine) and peak expiratory flow rate will be repeated and respiratory/blood samples for culture will be repeated if necessary.

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- A third visit will be required at the end of treatment, 11 to 13 days after beginning. You will have a medical consultation. Laboratory tests (blood and urine) and peak expiratory flow rate will be repeated and respiratory/blood samples for culture will be repeated if necessary.
- A fourth visit is compulsory 7 to 14 days after the end of treatment (17 to 24 after beginning). A physical examination will be done, peak expiratory flow rate, blood gases, and samples for cultures will be performed. A chest-x-ray will be performed and blood/urine samples will be taken only if necessary. If you are a woman, a urine pregnancy test will be done at this visit, if it is doubtful or positive, a blood pregnancy test will be done as well.
- A fifth visit will be required 21 to 28 days after the end of treatment (31 to 38 days after beginning). A physical examination will be done, a blood sample will be taken, lung function test and peak expiratory flow rate will be performed. Chest-x-ray, blood gases, urine sample and respiratory/blood samples for culture will be done if necessary.

During the course of the study, you will have a blood sampling at each visit for routine assessments, two to three times for blood gases analysis and three times for measurement of the drug concentration in blood.

Your participation in the study will be approximately 1 month.

The possible adverse reactions to HMR 3647 are : nausea, vomiting, diarrhea, abdominal pain and allergic reactions.

The side effects which may occur with amoxicillin/clavulanic acid are mainly digestive (nausea, vomiting, diarrhea, abdominal pain), allergic and skin reactions (rashes).

If you are a woman, a pregnancy test will be done before entry into the study. If the result is positive, you will not be included in the study. This pregnancy test will be repeated at the end of treatment. It is requested that you avoid becoming pregnant during your participation in the study. An effective method of contraception must be used. If you take an oral contraceptive, you must also use a barrier method (for example, condoms) during your participation in this study. If you suspect that you are pregnant or if you are not using an effective contraceptive method, you must immediately inform your doctor. In the event of pregnancy, you will be, for your own security, withdrawn from the study medication. If you became pregnant, there will be a clinical follow-up until the end of the pregnancy to assess the effects of the drug.

HMR 3647 is not yet on the market, and your doctor will not be able to prescribe it after the completion of the treatment. However, your doctor will prescribe the appropriate available antibiotic proved to be efficient for the disease you will be suffering from.

Participation in this study is entirely voluntary; you are not obliged to take part. **Your treatment and the attitude of your doctor towards you will not be affected if you decide not to take part in this study.** Refusal to participate will not affect any benefits to which you are otherwise entitled. If you decide to take part, you will need to sign a document to say that you have given your consent to participate. If you agree to participate, you may nevertheless withdraw from the study at any time, although for your own safety it is advisable to tell the investigator if you intend to do this.

For the duration of the study, you must notify the investigator of any other medical treatments that may be necessary for you to undergo.

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In the event that you experience any adverse reaction to the investigational drug during the course of this study, you should immediately contact the investigator (for name and telephone number see below).

All personal information obtained about you during the course of this study will remain confidential; in recording the results of the study, you will be referred to only by a code number and initials.

The data related to your participation in the study will be stored in a computer in compliance with applicable data protection laws.

Sponsor representatives or mandated by the sponsor, regulatory authorities, independent ethics committee/institutional review board will be granted direct access to your original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality. Your identity will remain confidential, even if the results of the trial are published.

You or your legally authorized representative will be informed in a timely manner if information becomes available that may be relevant to your willingness to continue your participation in the trial.

You are free to ask for further information at any time and an explanation of whom to contact for answers to pertinent questions about the study and your rights, and whom to contact in the event of a trial-related injury.

This study has been subjected to review by an independent ethics committee/institutional review board.

The sponsor has taken out insurance coverage in accordance with the requirements in your country.

Additional text for Centers in France:

A contract with Gerling-Konzern Allgemeine Versicherungs AG, Von-Werth-Str. 4-14, 50597 Cologne, No 01 80 87047 (adhesion No. 97/00028) has been subscribed to. This insurance covers the liability of the sponsor as a sponsor of biomedical research, as well as the liability of any intervening party, in accordance with article L. 209.7 of the Code of Public Health.

Additional text for centers in Germany:

A subject insurance policy pursuant to paragraph 40, Section 1, Clause 8, and Section 3 of the Medecines Act has been taken out with the Gerling-Konzern Allgemeine Versicherungs AG, Von-Werth-Str. 4-14, 50597 Cologne. The policy No. is 1/016/02/13/8160186/1 (Phases I-III).

Additional text for Centers in Belgium:

The information which will be collected during the study, including your race and gender, will be transcribed on a computer system. This procedure will be done under the supervision and responsibility of M. Puttemans, B. Pharm., Ph.D, Hoechst Marion Roussel. As foreseen in art. 10 of the law dd. 08/12/1992 about the protection of private life, you will have the possibility to check those data. In case of mistakes, you will be able to ask your treating doctor to make the adequate corrections.

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You will be given a copy of this informed consent document and may ask for additional information.
at any time during the study, from

_____ (*insert name and telephone number of investigator*).

You may also contact _____ (*insert name and telephone number*) **if you**
have questions about your rights as a research subject.