PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM

Study title: **A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED MULTI-CENTER AND PARALLEL GROUP STUDY OF THE SAFETY, TOLERABILITY AND EFFICACY OF YM150 IN COMBINATION WITH STANDARD TREATMENT IN SECONDARYPREVENTION OF ISCHEMIC VASCULAR EVENTS IN SUBJECTS WITH ACUTE CORONARY SYNDROMES.**

(THE RUBY-1 STUDY)

Protocol No: **150-CL-201**

Sponsor: **Astellas Pharma Europe B.V.**

Sponsor's Address **PO Box 108, 2350 AC Leiderdorp, The Netherlands**

Principal Investigator: **<<<INSERT NAME, ADDRESS, TEL NUMBER>>>**

1. Introduction

You have been asked to take part in this research study, which has been organized and funded by Astellas Pharma Europe B.V., because you have experienced a heart condition called Acute Coronary Syndrome or ACS (heart problems such as a heart attack or chest pains due to insufficient blood supply to the heart muscle [ischemia]). This study is considered as a biomedical research subjected in France to the Code of the public health (Title II of the first book relating to biomedical research). The information contained within this Information Sheet is very important; it tells you about what the study involves. Before you decide if you want to take part, please make sure that you read it carefully and understand why the research is being done and what it will involve, and discuss it with your family and friends if you wish. Your study doctor will spend time explaining the study to you. Please ask your study doctor or a member of the study team if there is anything that is not clear, or if you would like more information.

2. What is the purpose of this study?

The purpose of the study is to investigate a new drug under development, YM150, which has been designed to prevent further ischemic events from occurring in the future when given in combination with the current standard therapy for ACS. Currently, it is recommended that after the occurrence of an ACS, standard therapy of aspirin and clopidogrel is given for up to a period

of 1 year. Despite the current standard therapy, the recurrence of ischemic events after ACS still remains high.

The study compares 6 different dosage groups of YM150 and placebo. Placebo is a dummy medication which looks like the real medication but it contains no active ingredient. YM150 is taken as a tablet. The information collected in this study will be analyzed to find out at what strengths and doses of YM150 are safe and effective in addition to the standard treatment with aspirin, with or without clopidogrel. It may be used for seeking approval from the medicines regulatory authorities to market the medicine for prevention of ischemic cardiac events.

The total study duration is approximately 30 weeks. After being discharged at the start of the study you will be asked to return to the hospital for follow-up visits.

3. How many people will take part in the study?

A total of approximately 1264 patients, including 30 patients in France will be recruited to take part in this study from about 200 sites in Europe, Latin America, South East Asia, etc.

4. Do I have to take part?

No. Your participation in this study is entirely voluntary. It is up to you to decide whether to take part or not. You should not feel pressured. You are free to go away and think about it or discuss it with your own doctor or family/relatives if you so wish. If you decide to take part, you will be asked to sign a consent form and you will be given a signed and dated copy of the consent form and this information sheet to keep. With your permission your GP will be informed of your participation in this study

You may stop taking part at any time during the study without penalty or loss of benefits. You do not have to give a reason why. This will not affect your regular medical treatment from your doctor. If you discontinue your participation in the study, you will be asked to return to your study doctor for a final visit and final procedures. It is important for your health and safety to have this last visit. Your study doctor will talk to you about any potential medical issues that may arise and arrange for you to receive alternative treatment for your condition.

If you decide to withdraw from the study, the company sponsoring the study or it's partners will still have access to your data obtained up to the date when you withdrew from the study, but no new data will be added to the sponsor's database.

5. What will happen to me if I take part?

If you decide to participate in the study, you will be allocated to one of seven treatment groups. The groups are selected by a computer, which has no information about the individual – i.e. by chance. Patients in each group then get a different treatment and these are compared. You will have a three in four chance of actually getting the drug. The treatment in this study is double-blind. This means neither you nor your study doctor will know which treatment you get. Your study doctor will have access to a code list, which will be stored in a secure location, confirming the treatment group you have been allocated to, therefore if a medical emergency that requires

knowledge of your treatment occurs during the study, the doctor will be able to get this information.

Study medication

Patients in each group receive a different treatment, and the groups are compared at the end of the study. Your treatment will be either:

- YM150 5mg twice a day,
- YM150 10mg once a day,
- YM150 15mg twice a day,
- YM150 30mg once a day,
- YM150 30mg twice a day,
- YM150 60mg once a day,
- Placebo.

Each patient will receive a morning dose of two tablets and an evening dose of one tablet. The daily dose is a combination of the study drug, YM150 and placebo tablets. Only the placebo group will receive no YM150 at all, but all YM150 groups will receive in addition to the study drug also placebo tablets to mask the YM150 dose and to mask for once a day against twice a day treatment, e.g. patients on once a day treatment will receive YM150 in the morning and only placebo in the evening.

You will receive study medication in addition to many other medications, which you may receive to treat your condition. For participation you are required to receive at least a standard treatment as shown below:

- Aspirin daily (oral treatment to thin the blood and avoid the agglutination of the platelets), or
- Clopidogrel daily (oral treatment to thin the blood and avoid the agglutination of the platelets - e.g. if allergic to aspirin or when aspirin is not allowed for other reasons), or
- Both aspirin and clopidogrel.

After being discharged from the hospital at the start of the study you will continue the same double-blind treatment and return to the hospital at the following times: week 2, 6, 12, 18, 26. At the end of the study (4 weeks after stopping study medication) you will be asked to attend a follow-up visit.

Blood samples

Blood samples will be taken for routine safety analysis as would be taken in the course of your routine treatment (e.g. sodium, potassium, glucose, cholesterol, platelet count). Some blood samples will be taken to measure the level of the study drug and study drug action or effect in your blood and will need to be taken at specific time points in relation to your intake of study drug. The total amount of blood to be taken during your participation in this study according to the scheduled assessments will be approximately 162 ml.

Some tests on your blood will be carried out in the laboratory local to the hospital where you are treated, while other blood samples will be shipped to a central laboratory for testing. The central laboratories being used in this study (*BARC Laboratories, Ghent, Belgium* for pharmacodynamic assessments and *SGS Cephac, Saint Benoît Cedex, France* for analysis of FXa) are experienced in handling and testing samples from research studies. All samples will be destroyed once all tests are complete.

Each sample will have labeling, which will not include your personal details, and will be made anonymous. Samples will be collected, processed and reported as necessary for the purposes of this study only. No other analyses other than study related analyses will be performed without approval from both you and the ethics committee. Access to the samples will be limited to the research staff on site who will take the samples from you, and staff designated by both the local and central laboratories to process the samples.

Pharmacogenetic testing

You are now being asked whether you want to participate in a pharmacogenetic testing procedure as an optional part of the main study, in which a blood sample will be taken from you for testing your genes. The pharmacogenetic testing will be performed for research purposes.

Please read the Pharmacogenetic Consent Form for further details. If you wish to participate to this pharmacogenetic testing, you will be asked to sign this Informed Consent Form.

Study assessments

Visit 1 – Screening (within 7 days of Baseline/randomization)

If you wish to participate in the study and you have given your written informed consent, screening assessments will be performed by the study doctor mostly from your medical records. They are done to see if you are suitable for the study and to check in more detail if it is safe for you to participate. Assessments are: your demography (date of birth, race and sex), your medical history and previous and ongoing medication use, and a blood sample can be taken for routine analysis if needed, i.e. if not available from your recent medical records. This visit takes approximately 1 hour.

Visit 2 – Baseline/randomization (Day 1)

Before being allocated to a treatment, the doctor will ask about your medical history, previous/current medication and your general health. A routine physical examination, including measurement of blood pressure, pulse rate, height and weight, ECG (electrocardiogram – measures the activity of your heart), and blood and urine sampling will be performed. Tests to monitor the action or effects of the drugs will also be performed on blood samples at this visit. For women who could become pregnant, a urine sample will be taken for pregnancy testing, and the use of adequate contraception (such as condom and spermicide, diaphragm and spermicide, oral birth control pills or hormonal implant) will be discussed and is essential during the study. A pregnancy test will not be required if you are a woman who is two years or longer

postmenopausal. And male patients will be advised to use male condom in addition to having their female partner use another acceptable method. You will also be asked to complete questionnaires about your health status. You will also be asked questions about how you are feeling and any signs and symptoms you are currently having. If your study doctor finds you eligible to take part in the study, you will be assigned to one of the 7 treatment groups, and you will receive and take your first dose of study medication (YM150 or placebo). This visit takes approximately 1.5 hours.

Visit 3 – (Day 3)

If you leave the hospital between Day 3 to 5 your vital signs (blood pressure and pulse) will be taken and an ECG will also be done. You will be asked about your health and any other medication you are taking. You will also be asked questions about how you are feeling and any signs and symptoms you are currently having. This visit takes approximately 1 hour. If you are not in the hospital on Day 3, you will be contacted (e.g. by telephone) and asked about your health and any other medication you are taking. You will also be asked questions about how you are feeling and any signs and symptoms you are currently having. You should return any unused medications to your study site and you will be dispensed additional study drug.

Visit 4 (Day 14)

At this visit vital signs (blood pressure and pulse) will be taken, a routine physical examination and an ECG will be performed. Blood and urine samples will be taken for routine analysis as well as for tests to measure the level of the study drug and to measure the study drug action or effect. You will be asked about your health and any other medication you are taking. You will also be asked questions about how you are feeling and any signs and symptoms you are currently having. You should return any unused medications to your study site and you will be dispensed additional study drug. This visit takes approximately 1 hour.

Visit 5 (Week 6)

For this visit you will be asked not to take your morning dose of study medication at home. You will need to attend the hospital before 1 p.m. for a blood sample to be taken before you take the study medication. Another blood sample will be taken about 1 to 2 hours after taking the first dose of the study medication at this visit. These samples will be used for tests to measure the level of the study drug and study drug action or effect. In addition, blood and urine samples will be taken for routine analysis. Your vital signs (blood pressure and pulse), ECG will be measured. A physical examination will be performed. You will be asked about your health and any other medication you are taking. You will also be asked questions about how you are feeling and any signs and symptoms you are currently having. A urine sample will also be taken for analysis. You should return any unused medications to your study site and you will be dispensed additional study drug. This visit is expected to last approximately 4 hours.

Visit 6 (Week 12)

During this visit vital signs (blood pressure and pulse) will be taken, a routine physical examination and an ECG will be performed. Blood and urine samples will be taken for routine analysis and a pregnancy test will be done for women who could become pregnant. You will be asked about your health and any other medication you are taking. You will also be asked questions about how you are feeling and any signs and symptoms you are currently having. You should return any unused medications to your study site and you will be dispensed additional study drug. This visit will last approximately 1 hour.

Visit 7 (Week 18)

During this visit your vital signs (blood pressure and pulse), an ECG and a physical examination will be carried out. Blood and urine samples will be taken for routine analysis. A blood sample will be taken in the afternoon after 1 p.m., but before 5 p.m. and a second sample will be taken 30 minutes later. These samples will be used for tests to measure the level of the study drug and study drug action or effect. You will be asked about your health and any other medication you are taking. You will also be asked questions about how you are feeling and any signs and symptoms you are currently having. You should return any unused medications to your study site and you will be dispensed additional study drug. This visit will last approximately 1 hour.

Visit 8/End of treatment (Week 26)

You will be asked about your general health and any other medication you are taking. A routine physical examination, including measurement of blood pressure and pulse rate, ECG, weight, and blood and urine sampling will be performed. You will also be asked to complete questionnaires about your health status. You will also be asked questions about how you are feeling and any signs and symptoms you are currently having. You should return any unused medications to your study site This visit will last approximately 3 hours.

Visit 9 – Follow-up Visit (4 weeks after end of treatment)

During this visit your vital signs (blood pressure and pulse), an ECG and a physical examination will be carried out as well as a pregnancy test in women who could become pregnant. Blood and urine samples will be analyzed. Tests to monitor the action or effects of the drugs will also be performed on blood samples at this visit. You will be asked about your health and any other medication you are taking. You will also be asked questions about how you are feeling and any signs and symptoms you are currently having. This visit will last approximately 1 hour.

6. What do I have to do?

Please inform your study doctor about any medication that you are taking either bought by yourself (over the counter) or on prescription from your own doctor. You may not be allowed to participate in the study if you use certain medications. Your study doctor will discuss this with you in more detail if you are eligible to participate. You will have to take the study medication as

advised by your study doctor with water. Please avoid major changes in your diet and drinking habits during the study.

At each visit, you should return all unused study medication (incl. packaging) to your study doctor. Throughout the study, you should notify your study doctor of any illnesses, ill effects or abnormalities you may suffer, whether or not you think they are related to the study.

You will be given a card with details of the study. You will be asked to carry it at all times while participating in the study and show it to any doctor or dentist that you visit during the study.

Only for male patients: you will be asked to inform your study doctor, if your partner becomes pregnant during the study. Your study doctor will ask you to voluntarily provide information about the pregnancy of your partner

7. What is the drug that is being tested?

The study medication YM150 is a so called anticoagulant, which means it prevents your bloods from forming clots.

8. What are the alternatives for diagnosis or treatment?

The standard treatment for Acute Coronary Syndromes is clopidogrel and aspirin for up to a year. The use of these drugs differs from country to country and even within countries. These drugs are well known; however, please ask your study doctor for information about the different treatment options available to you and their risks and benefits.

9. Are there any side effects of the study treatment?

As with any treatment, side effects cannot be totally predicted and unforeseen complications may occur. It is very important that you report any side effect you may experience to your study doctor.

YM150:

In previous studies the most frequently reported side effects of YM150 included bleeding-related events like gastro-intestinal bleedings, wound bleedings, blood in urine, bleeding from gums, nose bleeds, hematoma, bruises, and changes in platelet (blood cell) count. Other side effects included headache, constipation, nausea, vomiting, joint pain, dizziness, insomnia (trouble sleeping), low blood pressure, neutropenia (a decrease in white blood cells that can make you more prone to infections, abnormal ECG (heart tracing) findings, anemia (a decrease in red blood cells that can cause tiredness), pyrexia (a rise in temperature of the body, usually a symptom of infection) and changes in liver enzyme values. All these events were temporary and of mild or moderate intensity.

In addition to the risks listed above, there may be risks or side effects that are unexpected or unknown at this time.

10. What are the possible risks of taking part?

Patients participating in this study might experience side effects such as bleeding (as known for all anticoagulant drugs). Such bleeding may occur from unknown stomach ulcers, or weak and damaged sites in blood vessels. If serious bleeding occurs after you have received study drug, the doctor may need to give you an additional drug to stop the bleeding or possibly a blood transfusion.

Slight and reversible changes in the kidney and liver function were found in laboratory studies with YM150. However, this has not been confirmed in clinical studies in healthy volunteers and patients given YM150. Blood tests will be used to monitor for any changes in kidney function in this study.

You might experience some discomfort like pain, swelling, bruising or bleeding in connection with blood samples and injections. In connection with ECG measurement a few electrodes (sticky patches) will be fixed to your chest. To ensure correct fixing to your skin a small area may have to be shaved, and you may experience slight itching or irritation from the patches.

It is not know if YM150 causes any damage to unborn children or nursing infant. Breastfeeding women and women, who are pregnant or plan to become pregnant during the study, must not take part. A pregnancy test will be required to exclude pregnancy. Women who could become pregnant must use an adequate contraceptive during the study. Any woman, who finds she has become pregnant while taking part in the study, should immediately inform the doctor, and then she will be withdrawn from the study. In addition, the doctor will monitor the health of the woman and baby by following the course of the pregnancy and delivery as well as the condition of the newborn. It is not known if the study medication will affect sperm or semen and therefore you must not father a child during this study. To prevent your partner from becoming pregnant you must use an adequate contraceptive during the trial.

If during the study previously unknown conditions are found for which medical treatment is necessary, you will be informed. In such a case, you will be referred to your family doctor or specialist for further treatment.

11. What are the possible benefits of taking part?

You may or may not receive a direct benefit from taking part in this study. However, you and future patients may still benefit from this research. The treatment you receive may reduce the risk of new ischemic events to occur. However, this cannot be guaranteed. The information we get from this study may help us to treat future patients with ACS.

12. What if new information becomes available?

Sometimes during the course of a research study new information becomes available about the drug that is being studied. If this happens, your study doctor will tell you about it in a timely manner and discuss with you whether or not you wish to continue in the study. If you decide to withdraw, the study doctor will make arrangements for your regular treatment to continue. If you

decide to continue in the study after reading the new information or if a new test is to be performed, you will be asked to sign an updated consent form.

Also, on receiving new information, the doctor might consider it to be in your best interest to withdraw you from the study. He/she will explain the reasons and arrange for your regular treatment to continue.

Your study doctor may remove you from the study at any time if he/she does not consider it to be in your best interest to continue.

If study drug is discontinued for any reason, except withdrawal of consent, you will remain in the study and end of treatment and follow-up visit procedures will be performed. It is important for your health and safety to have this last visit. Your study doctor will talk to you about any potential medical issues that may arise and arrange for you to receive alternative treatment.

The company developing the drug or regulatory authorities can also request termination of the study before your participation is complete and without your prior consent. If this happens, the reason will be explained to you.

13. What if something goes wrong?

In the event that you become ill or suffer any injury as a direct result of the study drug or procedures you should inform your doctor, who will arrange for the correct treatment.

In accordance with the French legal and regulatory provisions on biomedical research, in particular with the provisions of the article L.1121-10 of the Code of public health, the sponsor of the research has subscribed an insurance guaranteeing its civil liability, like that of the study doctors taking part in this research. The contract n°390-1009613-14003 was issued with the company HDI-Gerling Industries Versicherungs-AG.

14. Will my taking part in the study be kept confidential?

Your personal details and information from the study are processed in accordance with European data protection law, which is designed to protect your privacy.

Your identity and other information obtained during this study will be kept confidential. However, information that does contain your identity maybe disclosed in certain circumstances. For example, at any time during or after the study, representatives of medicines regulatory authorities, members of ethics committees that approved the study or representatives of companies working on Astellas' behalf may inspect the study files and your medical records to ensure that the results of the study have been properly recorded.

Information may be used for seeking approval from the medicines regulatory authorities to market the medicine for treatment of ACS patients. It may also be used in reports of the study or for scientific presentations. Your personal details will be made anonymous. Astellas may also wish to use the information from this study as anonymous data for future medical research into anti-coagulation.

You agree that Astellas may transfer personal information about you to its associated companies and regulatory authorities based in countries outside the European Economic Area, including for example Japan and the United States. Astellas will hold all such information securely and in confidence. However these countries may not have the same legal levels of protection for personal data as apply within the European Economic Area.

The study information will be recorded in your medical notes. In accordance with applicable data protection law ("Processing and Liberties" of January 6, 1978 modified by the laws n°94-548 of July 1, 1994, n°2002-303 of March 4, 2002 and n°2004-801 of August 6, 2004) personal data, which may be sensitive (e.g. ethnic origin, health, date of birth), will be collected and processed electronically, but only for research purposes in connection with this study.

Some information will also be recorded on electronic data forms that will be sent to a data processing office.

Direct access to your medical records will be required by authorized representatives of Astellas Pharma Europe B.V. to check health related information collected for the study is correct and complete.

All data collected will be identified by a code number and your identity will remain unknown. All information, which is collected about you that leaves the clinic/ hospital or <*name of institution*>, will have your name and address removed so that you cannot be recognized by it. All your study data will be protected in accordance with the European Data Protection legislation

At the end of the study, Astellas Pharma Europe B.V. will have access to the code list which makes it possible to link your assigned number to the treatment you were randomized to. The code list will be kept until the last marketing application has been received for the study drug.

In accordance with article 39 and 40 of the law "Processing and Liberties", you have the right to access and correct the information collected about you during the study. You can also access directly or through a doctor of your choice your medical data pursuant to the provisions of the article L 1111 7 of the Code of the Public health.

In accordance with Article L 1122-1 you have the right to be informed about your health information held by your study Doctor

If you decide to stop taking part in the study no new data will be added to the database, and you may ask for your previously retained identifiable samples to be destroyed, to prevent further analysis.

In accordance with the law dated 4 March 2004, your study doctor will inform you about the global results of the study.

The results will be published, though you will not be identified in any report or publication. Your study doctor will be given a copy of the report or publication at the end of the study.

15. Has anyone approved this study?

International guidelines exist to ensure that clinical studies are performed safely. These are called "Good Clinical Practice" and the "Declaration of Helsinki". All Astellas studies are performed in accordance with these standards. This study has also been approved by the

Committee for the Protection of People Ile de France II on (*insert date*) and approved by the AFSSAPS (French Health Products Safety Agency) on (*insert date*)

16. What happens when the study ends?

YM150 is given on top of existing therapy with aspirin and / or clopidogrel. When the study ends only the study treatment with YM150 or placebo will no longer be available to you. Standard treatment with aspirin and/or clopidogrel may continue at the discretion of the investigator and depending on local guidelines. When the study ends and if positive results are shown for YM150, further investigations will be performed to get more insight into the benefits and risks of YM150.

On the other hand, Astellas Pharma Europe B.V. may stop the research. If this is the case the reasons will be explained to you.

Patients can obtain information on which treatment arm they were in after analysis and reporting of the study results

17. Funding and Contact Information

The pharmaceutical company "Astellas Pharma Europe B.V." has designed and is funding this clinical study.

You will not incur any additional medication related costs if you participate in this study, and you will receive the study drug free of charge. You will not be charged for any study related procedures, and you will not receive any payment for taking part in the study. However, you will be reimbursed for any traveling costs incurred for visits that are not considered standard of care.

If you have any questions or concerns about the research or your rights as a patient, or any injury or you are unwell, please contact your study doctor, Dr _____ on _____ or the study coordinator on _____.,

Study Title:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED MULTI-CENTER AND PARALLEL GROUP STUDY OF THE SAFETY, TOLERABILITY AND EFFICACY OF YM150 IN COMBINATION WITH STANDARD TREATMENT IN SECONDARY PREVENTION OF ISCHEMIC VASCULAR EVENTS IN SUBJECTS WITH ACUTE CORONARY SYNDROMES (THE RUBY-1 STUDY)**		
Study Number:	**150-CL-201**	**Center Number:**	
EudraCT Number:	**2008-005972-29**	**Patient Number:**	
Patient's Name:			
Date of Birth:			

1. I confirm I am affiliated with a social security system.
2. I have been informed of the nature and purpose of the study in which I have been asked to participate, including the details of the various procedures necessary to perform the study.
3. I have received a copy of the Patient Information Sheet dated 21-Jul-2009 (version no. 1) about this clinical study and I have read and understood the text, the oral instructions and the oral explanation. The explanation I have been given has mentioned both the possible risks and benefits of the study.
4. Dr. ..... has told me about the contents of the study. I have had time to consider whether I wish to take part in the study and I have had the opportunity to ask questions about the study and the drug and my questions have been answered to my satisfaction.
5. I am aware and agree that personal information from my medical records will be reviewed by competent authorities and authorized representatives from Astellas Pharma Europe. Any information collected about me will be kept confidential.
6. I understand that I am not obliged to participate and may withdraw from the study at any time without any prejudice to my further treatment.
7. I freely consent to take part in the study and to the collection and processing of my personal information including information about my health, which will not be restricted, even if I withdraw from the study.
8. I also agree that Astellas Pharma Europe uses personal information about my health (including sensitive data such as ethnic origin, sex life and health related data), collected in this study for future medical research on anticoagulants. I consent to personal information being passed to other Astellas Pharma group companies or to companies working with Astellas Pharma Europe and/or an authority for registration and/or publication purposes. I understand that this may mean that my personal information is sent to other countries located in- and outside the European Union, like Japan and the United States. My clinical data ascertained in the study may be processed together with my initials, date of birth, gender and/or, if applicable, a unique code number. Only anonymous study data will be used for publication.
9. I agree that my personal coded data can be archived
10. I understand that some of the blood and urine samples taken from me are for the purpose of checking the levels of compound YM150 and metabolites, in my blood and urine. By

signing this form, I also give permission for any such samples remaining at the end of study to be used, when necessary, for any further analyses that may help to adequately characterize the levels of compound in my blood and urine.

11. My consent does not discharge the sponsor and the study doctor for their responsibilities.

A copy of the information sheet and signed consent form will be given to you to keep.
"Read and understood"

Name of Patient:	**Signature:**	**Date:**

I have fully informed the patient of all aspects of the trial.

Name of Investigator Taking Informed Consent:	**Signature:**	**Date:**

Name of Legally Authorized Representative for patients unable to consent themselves (if applicable):	Signature:	Date:
Relationship to patient:		