DRUG USE INVESTIGATION FOR HIV INFECTION PATIENTS OF MYCOBUTIN

- HRD Joint Survey -

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

(For reexamination)

HRD Joint Survey: Protocol

Drugs for the treatment of HIV infection (anti-HIV drugs and drugs for the treatment of HIV-related diseases), which are currently subject to reexamination, have been approved based on the limited results of Japanese and overseas clinical trials due to the urgency of treatment for the target patients. Therefore, in order to collect further information on the proper use of the said drugs and information particularly on safety after marketing, the Ministry of Health, Labour and Welfare (MHLW) has instructed to investigate and report the clinical course of patients treated with the said drugs, and thus the HRD joint survey has been undertaken jointly by companies having drugs for the treatment of HIV infection which are subject to reexamination.

In this survey, patient registration, input of data on survey items, and data verification have been carried out since April 2009 using an Electronic Data Capture (EDC) system which is an electronic data collection system on the Internet. Please collaborate in this survey.

1. Objectives

This survey is a drug use investigation to investigate the clinical course of patients who received drugs for the treatment of HIV infection, which are the reexamination products, understand the occurrence of adverse events under actual use conditions and figure out factors affecting safety, in addition to evaluate the therapeutic effectiveness and identify factors affecting the effectiveness of the drugs for the treatment of HIV-related diseases.

Survey results will be used as source documents for the reexamination of each drug, and tabulation and analysis results will be provided each year to healthcare professionals as feedback for the promotion of the proper use of the drugs for the treatment of HIV infection.

2. Target Patients and Target Drugs

The patients of this survey are all patients who are prescribed with drugs for the treatment of HIV infection (see P. 6) which are subject to reexamination at limited sites.

3. Survey Period

1) In principle, the drugs for the treatment of HIV infection are designated as orphan drugs, and the reexamination period for each drug is 10 years as a rule (see P. 6).
2) The end date of patient registration for the drug use investigation is as mentioned in page 6.
3) This survey will enroll patients, who are the continuing patients from clinical trials or clinical trials conducted from a humanitarian point of view (expanded access program in Japan), separately after the concerned drugs are approved. Also, the survey will enroll patients, who are the continuing patients from post-marketing clinical trials, separately after the trials of the concerned drugs are completed.

4. Procedures

This survey is a joint survey by companies having drugs for the treatment of HIV infection which are subject to

reexamination (hereinafter referred to as "joint survey participating companies") and will be outsourced to a contracted company [CMIC-PMS Co., Ltd. (hereinafter referred to as "CRO")].

1) Request for the survey and a contract

(1) A request and contract for the survey will be, in principle, made between the CRO and a site.

(2) For sites with which contracts have been concluded, the CRO will inform the joint survey participating companies that the contracts with the sites have been completed.

2) Method for data collection

In this survey, patient registration, input of data on survey items, and data verification will be carried out using the EDC system. The system to be utilized will be ARCS + PMS (hereinafter referred to as "the System"). Security for data transmission will be ensured by authentication of the user's ID and password assigned to each investigator and in accordance with the latest SSL encrypted communication protocol.

3) Patient registration

(1) After the user's ID and password are issued for each investigator upon the conclusion of the contract, the investigator should enter and send required items (medical record or identification number, patient's initials [as necessary], gender, birth date [age such as age group as necessary], pregnancy status, inpatient/outpatient status, name of the target drug and start date of treatment), for patients who have newly started receiving drug treatment in or after April of each year or patients who are on drug treatment but have not yet been registered in the survey on the patient registration screen of the System. It is unnecessary to additionally register patients because of drug changes.

(2) The registration numbers of registered patients will be issued by the System.

(3) The continuing patients will be automatically kept registered based on data of the previous-year case report forms (CRFs).

4) Points to consider for data entry, revision, and review

(1) For registered patients, the administration status of each drug by the end of March of each year based on medical records and medical charts such as test results and survey results on the clinical course such as abnormal changes in laboratory test values and adverse events noted during the survey period should be entered and send using the System during period between April and July by the investigator.

(2) When inquiries on data entered were made by the CRO (data clarification request through the System or e-mail), the investigator should, as necessary, revise and send the entered data.

(3) When drug treatment is discontinued due to reasons such as a patient's death or transfer to another hospital, the investigator should enter and send the administration status of each drug until discontinuation, the clinical course such as abnormal changes in laboratory test values and adverse events, and autopsy status (if the outcome is death) using the System.

(4) After completing entry and revision of all investigation items, the investigator should verify the contents of a CRF (original) printed out (provided) in (by) the CRO and then sign or affix a seal to the CRF.

5) Retention of the original CRF

The CRO will collectively retain all CRFs and registration forms.

6) Affixing a signature or seal to the Statement of Confirmation

(1) At the time of signing or affixing a seal to the CRFs, the CRO will prepare and bring the "Statement of Confirmation" to the investigator for confirming the survey patients. The Statement of Confirmation is intended "to ensure that survey patients are all patients at the site during the survey period". The investigator should verify the Statement of Confirmation and then sign or affix his/her seal to it.

(2) The CRO will retain the original of the signed or sealed "Statement of Confirmation", prepare the "Statement of Confirmation" for each drug based on those from all investigators, and send it to the applicable company.

7) Notifying adverse drug reactions (ADRs), etc.

(1) When ADRs, etc. (including those for which the causal relationship is unknown) suspected to be associated with drugs occurred, the investigator should immediately notify them to the CRO or enter required items in the "HRD Joint Survey - Spontaneous Report of ADRs, etc." form, which is provided beforehand, and fax it to the CRO.

When there are two or more companies of which drugs are related to ADRs, etc., the CRO will inform the relevant companies.

(2) When the onset of ADRs, etc. is notified, the investigator should collaborate with the CRO that it will, as necessary, visit the investigator to collect a detailed report form for ADRs, etc. in the concerned patient, or the investigator will enter and send information using the System.

5. Survey Items

1) Common items (CRF for the drug use investigation)

(1) Background

(2) Prescribed anti-HIV drug

(3) Prescribed concomitant medications (including drugs for the treatment of HIV-related diseases)

(4) Concomitant therapies

(5) Patient's outcome (at the discontinuation of the survey)

(6) HIV-RNA, CD4, Centers for Disease Control and Prevention (CDC) classification, changes over time in body weight, and HIV tropism

(7) Abnormal changes in laboratory test values

(8) Adverse events (including ADRs, abnormal changes in laboratory test values, and newly developed opportunistic infection)

(9) Relationship with the disease or drug (mandatory for the target drugs administered at the time of onset of the adverse event)

(10) Autopsy status (if the outcome is death)

2) Survey items by product (Separated CRF for Mycobutin Capsules)

(1) MAC infection, etc. (when Mycobutin Capsules is used for tuberculosis, non-tuberculous Mycobacterium infection including Mycobacterium avium complex (MAC) infection, and prevention of the development of disseminated MAC infection in patients with HIV infection)

(2) Samtirel (atovaquone) (when Samtirel Oral Suspension 15% is utilized for treatment or prevention of development of Pneumocystis pneumonia)

(3) Edurant Tablets (rilpivirine hydrochloride) (when Edurant Tablets are used)

Complera Combination Tablets (rilpivirine hydrochloride/tenofovir disoproxil fumarate/emtricitabine) (when Complera Combination Tablets are utilized)

Record measurement results and other relevant data if blood drug concentrations are measured.

(4) Tivicay Tablets (dolutegravir sodium) and Triumeq Combination Tablets (dolutegravir sodium/abacavir sulfate/lamivudine) (when Tivicay Tablets or Triumeq Combination Tablets are used)

(i) Record measurement results and other relevant data if blood drug concentrations are measured.

(ii)When pilsicainide is concomitantly used, separately provide electrocardiographic data.

(iii) Record measurement results if a liver function test (e.g., alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [AL-P], and total bilirubin [T-Bil]) is performed.

(iv) Record measurement results if a renal function test (e.g., serum creatinine, urine protein, urinary albumin, and tubular damage markers) is carried out.

(v)Record anti-HIV therapy during 6 months prior to the start of treatment (for patients switching from another drug).

(vi) Separately provide test results if gene testing for drug resistance is implemented.

6. Others

1) Prior to utilizing drugs for the treatment of HIV infection, the investigator should fully explain the details of ADRs and other relevant matters to patients, confirm their consent for the treatment and record in their medical records that consent has been obtained. When giving the explanation to the patients, the "Information to be explained to patients," which is separately prepared by each of the joint survey participating companies, should be used as reference.

2) Of information on ADRs reported to the MHLW, the patient's gender, age (age group), primary disease, suspected drug, route of administration, ADR term, outcome, suspected concomitant medication(s) and other relevant matters will be presented in lists on the "Drug and Medical Device Information Provision," the website of the Pharmaceuticals and Medical Devices Agency (PMDA) via the Internet. Provided information, which concerns the patients' privacy or reporters, will not be reported to the MHLW.

3) As part of information provision to healthcare professionals, of ADR information notified through the CRF or "Spontaneous Report of ADRs, etc." form, the patient's gender, age (age group), primary disease, complications, ADR term, and outcome will be presented on the HRD website (http://www.hrd.gr.jp). Also the results of effectiveness and safety tabulations and analyses in the survey will be disclosed through an annual report and other means for the "proper use," "ensuring safety" and "ensuring transparency." In any event, no provided information, which concerns the patients' privacy or reporters, will be disclosed.

7. Where to contact (Inquiries on the contents of the contract, protocol and CRF, registration, collection of the CRF, and data clarification)

CRO	Contact information
CMIC-PMS Co., Ltd.	1-1-1 Shibaura, Minato-ku, Tokyo Tel: 0120-204393 Fax: 0120-204292

8. List of Contracted Joint Survey Companies (including distributing companies)

Joint survey participating companies (random order)	Contact information
Safety Management Department ViiV Healthcare K.K.	GSK Building, 4-6-15 Sendagaya, Shibuya-ku, Tokyo Tel: 03-5786-5202 Fax: 0120-668-322
Safety Measure Promotion Department MSD K.K.	Urban Ace Kitahama Building 2-3-7 Hiranomachi, Chuo-ku, Osaka Tel: 06-6201-1740 Fax: 06-6201-1980
PMS Department GlaxoSmithKline K.K.	GSK Building, 4-6-15 Sendagaya, Shibuya-ku, Tokyo Tel: 03-5786-5170 Fax: 03-5786-5219
Drug Information Department Japan Tobacco Inc.	JT Building 2-2-1 Toranomon, Minato-ku, Tokyo Tel: 03-5572-4544 Fax: 03-5572-1450
Safety Information Management Department Torii Pharmaceutical Co., Ltd.	3-4-1 Nihonbashi-Honcho, Chuo-ku, Tokyo Tel: 0120-40-6839 Fax: 03-5203-7356
Post marketing Study Strategy and Management ,Development Japan Pfizer Japan Inc.	Shinjuku Bunka Quint Building 3-22-7, Yoyogi, Shibuya-ku, Tokyo Tel: 03-5309-6820 Fax: 03-5309-9186
PMS Department, Research and Development Division Janssen Pharmaceutical K.K.	3-5-2 Nishikanda, Chiyoda-ku, Tokyo Tel: 03-4411-5017 Fax: 03-4411-5530

EOD

Drugs for the treatment of HIV infection participating in the HRD joint survey

(Marketed drugs which are subject to reexamination as of November 2015)

Anti-HIV drugs

Brand name	Name of drug (abbreviation)	Reexamination period	End date of registration
Prezista Tablets 300 mg	Darunavir (DRV)	November 2007 to November 2017	March 31, 2016
Prezista Tablets 600 mg	Darunavir (DRV)	December 2014 to November 2017	March 31, 2016
Prezista Naïve Tablets 400 mg	Darunavir (DRV)	August 2009 to November 2017	March 31, 2016
Prezista Naïve 800 mg	Darunavir (DRV)	Jul 2013 to November 2017	March 31, 2016
Isentress Tablets 400 mg	Raltegravir (RAL)	June 2008 to June 2018	March 31, 2017
Intelence Tablets 100 mg	Etravirine (ETR)	December 2008 to December 2018	March 31, 2017
Celsentri Tablets 150 mg	Maraviroc (MVC)	December 2008 to December 2018	March 31, 2017
Edurant Tablets 25 mg	Rilpivirine (RPV)	May 2012 to May 2022	March 31, 2021
Complera Combination Tablets	Rilpivirine/tenofovir disoproxil fumarate/emtricitabine (RPV/TDF/FTC)	November 2014 to May 2022	March 31, 2021
Stribild Combination Tablets	Elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF)	March 2013 to March 2023	March 31, 2021
Tivicay Tablets 50 mg	Dolutegravir sodium (DTG)	March 2014 to March 2024	March 31, 2022
Triumeq Combination Tablets	Dolutegravir sodium/abacavir sulfate/lamivudine (DTG/ABC/3TC)	March 2015 to March 2024	March 31, 2022

Drugs for the treatment of HIV-related diseases

Brand name	Name of drug	Reexamination period	End date of registration
Mycobutin Capsules 150 mg	Rifabutin		
(Prevention of disseminated MAC infection)		July 2008 to July 2018	March 31, 2017
(Tuberculosis, non-tuberculous mycobacterium infection)		July 2008 to July 2016	March 31, 2015
Samtirel Oral Suspension 15%	Atovaquone	January 2012 to January 2020	March 31, 2018

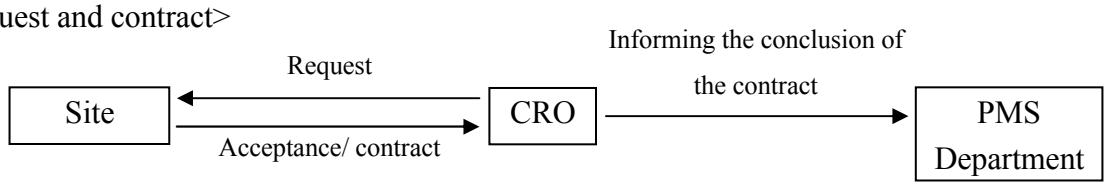
If companies other than those having the above drugs wish to take part in this joint drug use investigation, they may participate in it while the investigation is ongoing as long as new participating companies comply with verification items among the current participating companies.

Procedures for Implementation of the HRD Joint Survey

Medical institutions (Sites) **CRO** **Participating companies**

[CMIC-PMS Co., Ltd.]
Fax: 0120-204292
Tel: 0120-204393

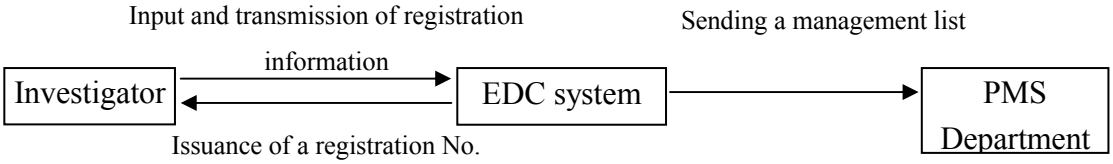
<Request and contract>



[Preparation of the contract status chart per site]

• Issuance of the initial password after concluding the contract

<Patient registration >



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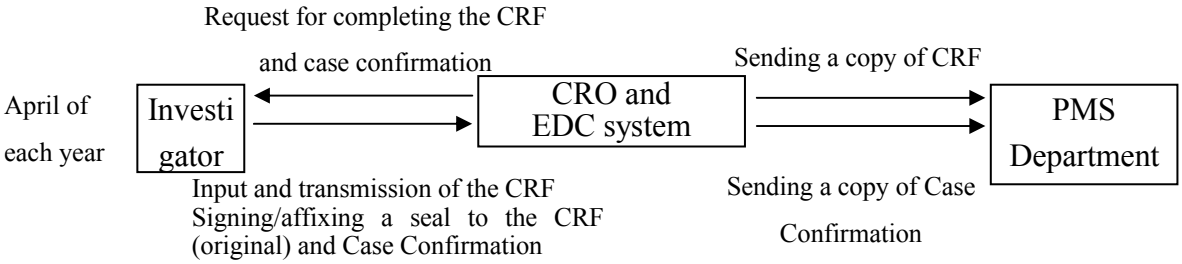
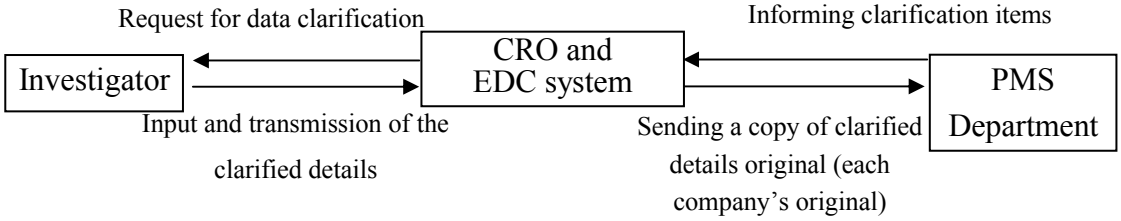


[Retention of the Case Confirmation (original)]

<Data clarification>

[Summary of reinvestigation items]



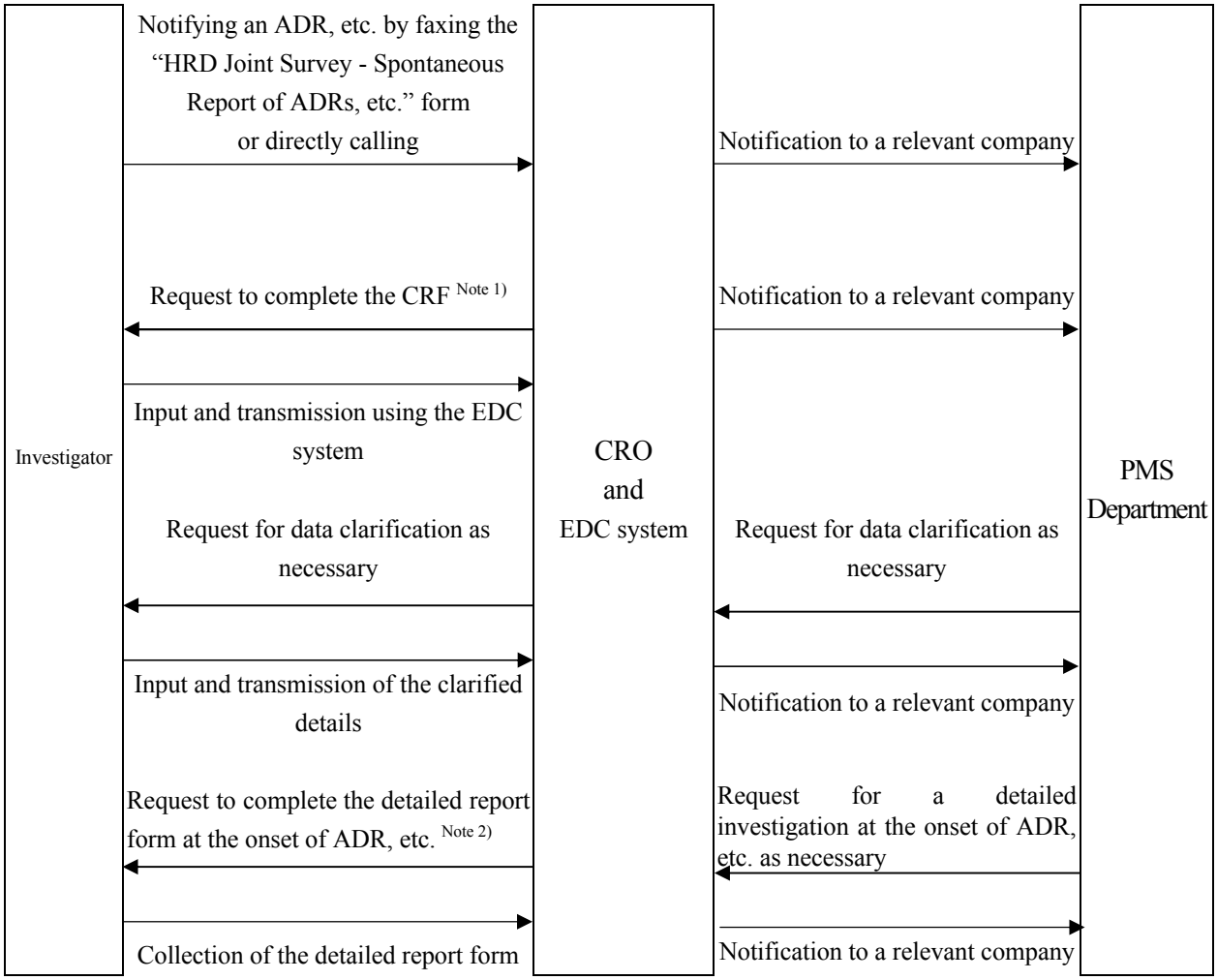
[Retention of the CRF (original)]

Procedures for Notifying ADRs, etc.

Medical institutions (Sites)

CRO
[CMIC-PMS Co., Ltd.]
Fax: 0120-204292
Tel: 0120-204393

Relevant companies having suspected drugs



Note 1) EDC system for the CRF for the HRD joint survey
Note 2) Detailed report form for ADRs, etc. in the HRD joint survey