CLINICAL TRIAL PROTOCOL
NEW ERA STUDY

HIV and Eradication:
A multicenter, open-label, non-randomized trial
to evaluate treatment with multi-drug class (MDC) HAART and its impact on the decay rate of latently infected CD4+ T cells

incl. Amendment 1.0 Additional laboratory measures

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ACCORDING TO §§ 40,41 AMG**:**

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Use SAE Form (see Investigator Site File or
Case Report Form (CRF))

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1 SUMMARY OF IIT (INVESTIGATOR INITIATED TRIAL)

1.1 TITLE

NEW ERA Study

SUBTITLE: HIV and Eradication: Treatment with multi-drug class HAART and its impact on the decay rate of latently infected CD4+ T cells

1.2 SUMMARY OF RATIONALE

Two cooperating HIV-specialized centres represented by Dr. med. Hans Jaeger and Prof. Dr. Johannes Bogner are planning to perform an IIT (investigator initiated trial) with the goal to eradicate HIV in N=40 HIV-infected patients with either primary infection or chronic infection and successful HAART (Highly Active Antiretroviral Treatment) of several years. All patients will be started on a multi-drug HAART including two Nucleoside-Reverse-Transcriptase-Inhibitors (NRTI´s), one Protease-Inhibitor (PI), a CCR5-inhibitor and an Integrase-Inhibitor (INI). Decay of viral reservoirs like latently HIV-infected CD4+ T-cells will be monitored over time.

1.3 SUMMARY OF STUDY

This is a multi-center, open-label, non-randomized proof-of-concept trial.

Recruitment will be stratified according to stage of HIV-infection and pre-treatment:

- Stratum I (PHI patients):
  Patients presenting with primary HIV infection
- Stratum II (CHR patients):
  Chronically HIV-infected patients with suppressed plasma viral load for >=36 months under continuous HAART

CHR and PHI patients will be treated with an antiretroviral combination of five approved substances. Every regimen will contain Maraviroc and Raltegravir (see 1.4 Treatment regimens and dosing).

The duration of the study is 5-7 years for PHI patients and 2.5 - 7.5 years for CHR patients.

1.4 TREATMENT REGIMENS AND DOSAGES

All patients entering the study will be treated with MDC HAART consisting of

2 NRTI + 1PI + 1 CCR5 antagonist (= Maraviroc; MVC) + 1 INI (= Raltegravir; RAL).

The patients of the PHI-group will be immediately treated with MDC HAART for a duration of >=5-7 years.
The patients of the CHR-group will be treated with MDC HAART after a 6-month observational lead-in phase for measuring laboratory parameters. Then HAART will be intensified with the respective missing drug classes of MDC HAART (MVC+RAL). The respective treatment time will be >2-4 years.

DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN
Dosing of antiretrovirals including study drugs Raltegravir and Maraviroc will be according to standard dosing as outlined in respective product informations (attached).

- Patients will take Raltegravir 400 mg (one 400 mg tablet) PO b.i.d. (without regard to food). Raltegravir which can be taken at any time of day but should be taken at the same time each day.

- Patients will take Maraviroc 150 mg (one 150 mg tablet) PO b.i.d. (without regard to food) if the co-administered PI is RTV-boosted Lopinavir, RTV-boosted Atazanavir, RTV-boosted Saquinavir, RTV-boosted Darunavir.
  Patients will take Maraviroc 300 mg (two 150 mg tablets) PO b.i.d. (without regard to food) if the co-administered PI is Fosamprenavir or Tipranavir

In both treatment groups NRTI´s or PI´s can be replaced by other NRTI´s or PI´s in case of intolerability or other reasons at the discretion of the investigator.

Other treatments which are initiated by the treating physicians and which may have a potential impact on viral reservoirs (like valproic acid) or immunomodulators will not be discouraged during the course of the study.
If new antiretroviral agents will be approved or available through expanded access programs during the course of the study that might be beneficial for a study patient at the discretion of the treating physician, the treatment regimen can be modified based on current knowledge (=addition of new antiretroviral agent or replacement of drugs of the regimen). Patients will not be excluded from the study unless they reach the virological endpoint (see 2.3.).

1.5 SAMPLE SIZE

The design of this proof-of-concept study is based on a fixed sample size of 40 patients.

40 HIV-infected patients will participate in this study:
20 primary infected patients (Stratum I, PHI) and
20 chronically infected patients (Stratum II, CHR)

Patients discontinuing the study prior to month 12 will be replaced.

1.6 STUDY FLOW CHART

Screening, Baseline and Follow-up	Screening [1] CHR	Pre-baseline CHR	Screening/ Baseline [2 3] PHI	Baseline CHR	1	2	3	4	5	6
Timepoints	**Month -6**	**Month -3**	**Week -2**	**Day 0**	**Month 1**	**Month 3**	**Month 6**	**Month 12 (y1)**	**Month 18**	**Month 24 (y2)**
PHI group			x		x	x	x	x	x	x
CHR group	x	x		x	x	x	x	x	x	x
Informed consent	x		x							
Inclusion/exclusion criteria	x		x							
ELISA/Western Blot			x[3]							
Complete physical examination		x	x[7]							
Targeted physical examination			x[7]	x	x	x	x	x	x	x
Vital signs (height, weight,blood pressure, pulse rate)		x	x	x	x	x	x	x	x	x
Standard electrocardiogram (ECG)		x	x							
Medical history	x		x							
Urine/Serum Pregnancy (HCG) test	x	x	x	x	x	x	x	x	x	x
Measurement of coreceptor tropism (genotypic test from proviral DNA)	x									
Measurement of coreceptor tropism genotypic test (phenotypic test for back-up)			x							
Proviral DNA (infectious copies per 10^6 PBMC and CD4)	x	x	x	x	x	x	x	x	x	x
Plasma HIV RNA 1-copy assay	x	x	x	x	x	x	x	x	x	x
Plasma HIV RNA (local) [4]	x	x	x	x	x	x	x	x	x	x
CD4 cell count (local) [4]	x	x	x	x	x	x	x	x	x	x
Safety standard laboratory parameters (local) (complete blood count, clinical chemistry)[4]	x	x	x	x	x	x	x	x	x	x
Further immunological parameters (local) (CD8, CD38, CD45) [4]	x	x	x	x	x	x	x	x	x	x
Genotypic resistance testing (local) (RT and PRO) [4]			x							
Adverse events		x		x	x	x	x	x	x	x
Initiation of multi-drug HAART			x[5]	x						
Compliance					x	x	x	x	x	X
Specific laboratory parameters as depicted in 2.8.4.1*										

STUDY FLOW CHART CONT´D

Follow-up	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**PFU1**	**PFU2**	**PFU3**
Timepoints	**Month 30**	**Month 36 (y3)**	**Month 42**	**Month 48 (y4)**	**Month 54**	**Month 60 (y5)**	**Month 66**	**Month 72 (y6)**	**Month 78**	**Month 84 (y7) Or Pre-mature disc.**	**Month 3 post Tx[6]**	**Month 6 post Tx[6]**	**Month 12 post Tx[6]**
PHI group	x	x	x	x	x	x	x	x	x	x	x	x	x
CHR group	x	x	x	x							x	x	x
Complete physical examination										x			
Targeted physical examination	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs (height, weight,blood pressure, pulse rate)	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine/Serum Pregnancy (HCG) test	x	x	x	x	x	x	x	x	x	x			
Proviral DNA (infectious copies per 10^6 PBMC and CD4)	x	x	x	x	x	x	x	x	x	x	x	x	x
Plasma HIV RNA 1-copy assay	x	x	x	x	x	x	x	x	x	x	x	x	x
Plasma HIV RNA (local) [4]	x	x	x	x	x	x	x	x	x	x	x	x	x
CD4 cell count (local) [4]	x	x	x	x	x	x	x	x	x	x	x	x	x
Safety standard laboratory parameters (local) (complete blood count, clinical chemistry) [4]	x	x	x	x	x	x	x	x	x	x	x	x	x
Further immunological parameters (local) (CD8, CD38, CD45) [4]	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x
Compliance	x	x	x	x	x	x	x	x	x	x			
Specific laboratory parameters as depicted in 2.8.4*		(x)*	(x)*	(x)*	(x)*	(x)*	(x)*	(x)*	(x)*	(x)*	(x)*	(x)*	(x)*

[1] If laboratory parameters of screening visit (including proviral DNA) and pre-baseline visit have been performed within the preceding 3-6 months, chronically infected patients can enter the study starting with the baseline visit after written informed consent.
[2] Baseline and screening visit can be performed on the same day.

[3] If a patient already presents with a positive HIV diagnosis (≤ 2 bands), multi-drug HAART must be initiated within two weeks after blood sampling for HIV test
[4] If laboratory measurements like clinical chemistry, immunological parameters, plasma viral load and resistance testing are not part of routine laboratory measurements at the time point of study visit, sampling for respective parameters and measurements will be performed as study-related interventions.
[5] HAART must be initiated within two weeks after blood sampling for HIV test.
[6] Post-follow-up visits are foreseen for all patients with pre-mature or regular discontinuation including HAART interruption due to eradication (as defined in section 2.2.1.).
[7] At screening complete physical examination, at baseline targeted examination
*For exploratory analyses additional laboratory parameters (see 2.8.4.1) will be measured at a single study visit in all patients having initiated MDH HAART in the New Era Study and giving extra written informed consent.

2. CORE PROTOCOL AND DETAILS

2.1 RATIONALE

Two cooperating HIV-specialized centres represented by Dr. med. Hans Jaeger and Prof. Dr. Johannes Bogner are planning to perform an IIT (investigator initiated trial) with the goal to eradicate HIV in N=40 HIV-infected patients with either primary infection or chronic infection and successful HAART (Highly Active Antiretroviral Treatment) of several years. All patients will be started on a multi-drug HAART including two Nucleoside-Reverse-Transcriptase-Inhibitors (NRTI´s), one Protease-Inhibitor (PI), a CCR5-inhibitor and an Integrase-Inhibitor (INI). Decay of viral reservoirs like latently HIV-infected CD4+ T-cells will be monitored over time.

The persistence of replication competent latently infected memory CD4+ T-cells impedes eradication of HIV-1. Factors influencing the longevity of the latent reservoir may be a continuous replenishment by low-level viral replication even in successfully treated patients as well as the intrinsic stability of the reservoir (Sedaghat 2007). Eradication of established HIV-infection might only be achieved by successfully purging the latent reservoir of an HIV-infected individual (Lehrman 2005). Based on divergent mathematical models, eradication of HIV is discussed controversially (Sedaghat 2008). Half-lifes of up to 44 months even in treated patients with undetectable viral load for as long as 7 years argue for lifetime persistence of HIV (Siliciano 2003). However, reduction of half-lifes of the latent reservoir in treated patients to six or even less than six months have been reported and thus rendering HIV elimination again conceivable (Zhang 1999, Ramratnam 2000, Di Mascio 2003). Encouraging results come from a longitudinal study in seven patients who had started antiretroviral treatment after the onset of primary HIV infection. After a treatment time of 31-54 months, the half life estimates of the resting CD4 cells lay between 1.9 and 8.7 months (mean 4.6 months). Assuming a half life of 4.6 months and 10exp6 latently infected CD4 cells, the projected time of HIV elimination was 7.7 years (range 3.1-14.5 years) (Chun 2007).

2.2 Objectives

2.2.1 Primary Objective

The primary objective of this trial is to reduce proviral DNA in PBMC and thereby achieve HIV eradication* using multi-drug class HAART (MDC HAART*) in patients with primary HIV infection and in successfully treated chronically HIV-infected patients after an overall treatment period of at least 5 years including multi-drug HAART for at least 2 years.

‘Eradication’* is defined as

1. Plasma VL < 50 copies/ml for at least 5 years
and
2. Undetectable plasma viral load (HIV RNA < 1 copy/ml, 1-copy assay) for at least 2 years
and
3. Undetectable proviral DNA in PBMC for at least 2 years

PHI patients can reach the goal at the earliest 5-6 years after initiation of HAART. For a PHI patient reaching a plasma viral load level < 50 copies/ml during the first 6 months of multi-drug HAART, plasma viral load and proviral DNA in PBMC must be below the limit of detection from months 42 to 66 (5.5 years from baseline)

CHR patients, whose plasma viral load is below 50 copies/ml for at least three years at the time of screening, reach the goal at the earliest 2 years after the baseline visit, provided that plasma viral load and proviral DNA in PBMC are below the limit of detection at baseline and the follow-up visits until month 24.

Primary outcome measures:

- Cell-associated proviral DNA (copies per 10exp6 PBMC (= peripheral blood mononuclear cells) and CD4)
- Plasma HIV RNA (detection levels: <40 copies/ml; <1 copy/ml)

**Annotation:*

'Eradication' has been defined in the New Era Study as undetectability of HIV-1 RNA in plasma and proviral DNA in PMBC for several years. In published literature, there is one patient known, which is considered to be cured from HIV after a successful hematopoietic stem cell transplantation (HSCT) transferring donor-derived cells with a natural resistance against HIV infection (homozygous CCR5 32-bp deletion in the CCR5 allele). To date, the patient has not required any ART for more than 4 years after HSCT. In the analysis of peripheral blood cells and different tissue samples, including gut, liver, and brain, no HIV-1 RNA or proviral DNA could be detected (Hütter 2011).

Undetectability while still on antiretroviral therapy has been considered as a predictive marker for virus control in case of treatment interruption (so called post-treatment control) or for sterilizing cure. However, clinical case reports have shown, that undetectability of these viral markers while on ART does not necessarily mean sterilizing cure or post treatment control (Persaud 2013, Persaud 2014, Henrich 2014).

On the other hand post treatment control was reported in patients treated early duing acute HIV infection and despite ongoing detectability of HIV RNA and/or proviral DNA (Saez-Cirion 2013). These patients are characterized by early ART during primary HIV infection, a rapid immune reconstitution after having started ART, a high CD4 cell count often connected to a normal CD4 / CD8 ratio and low but usually detectable titers of cell-associated proviral DNA before ART interruption.

In summary, the information on criteria specific for PTC is still very limited to date. There is a worldwide unmet need for laboratory markers to predict later post-treatment control.

2.2.2 Secondary Objectives

The secondary objectives of this evaluation are

- to provide good estimates of the latently infected reservoir size (copies/10exp6 PBMC (= peripheral blood mononuclear cells) and copies/10exp6 resting CD4+ T cells)

- to evaluate the decay rates of latently infected CD4+ T cells

and

- to quantify specific laboratory parameters (see 2.8.4.1 Additional Laboratory Parameters - Amendment 1.0) in the two groups of the New Era Study and to evaluate differences between groups

- to discriminate and characterize patients with a 'favorable' profile concerning all virologic and immunologic and otherspecific laboratory parameters (see 1.6 and 2.8.4.1)

in patients with primary HIV-infection treated with MDC HAART* and in antiretrovirally treated chronically HIV-infected patients before and after intensification of HAART

**MDC HAART:*
CCR5 antagonist [1)] + 2 NRTI + PI +INI [2)]
([1)] =Maraviroc (MVC); [2)] =Raltegravir (RAL))

2.3 STUDY ENDPOINT DEFINITION

Endpoints:
- Eradication (as defined in section 2.2.1.)
- Virologic failure
  Definition:
  - For CHR:

  Confirmed virologic rebound in plasma viral load to levels >1000 copies/ml (measurements should be at least two weeks apart).
  - For PHI:

  a) Confirmed persisting plasma viral load 6 months (> 50 copies/ml) after HAART initiation (measurements should be at least two weeks apart)
  or
  b) Confirmed virologic rebound in plasma viral load to levels >1000 copies/ml (measurements should be at least two weeks apart)

2.4 PATIENT INCLUSION CRITERIA

FOR Stratum I (PHI) only
N=20 patients with primary HIV infection:
- Detectable plasma viral load
- Elisa positive or negative **and** Western Blot negative or positive with ≤ 2 bands at screening visit;
- no primary resistance to PI´s and NRTI´s

FOR Stratum II (CHR) only
N= 20 patients with chronically HIV infection:

- Chronically HIV-infected patients with a plasma VL < 50 copies/ml for >=36 months under continuous PI-based HAART (≤2 single viral load blips <500 cop./ml allowed) and without preceding virological failure
- Current HAART exists of 2 NRTI plus 1 PI

FOR ALL PATIENTS

- Age ≥18 years.
- For women of reproductive potential negative serum or urine pregnancy test within 48 hours prior to initiating study medications.
- Use of reliable method of contraception while receiving the protocol-specified treatment and for 6 weeks thereafter.
- For males and their female sexual partners use of adequate, acceptable (highly effective) methods for birth control and prevention of HIV transmission during the entire study.
- CCR5-tropic HI-virus
  - CAVE for PHI stratum:

    Patients will have to start treatment within 2 weeks after blood sampling for HIV test; If resistance testing and/or tropism testing are not available at the time of treatment initiation, treatment should be adapted in case of dual mixed (D/M) tropic or CXCR4-tropic virus at the discretion of the treating physician. In this case, the patient will be discontinued from the study.
- Written informed consent

2.5 PATIENT EXCLUSION CRITERIA

- Evidence for drug intolerability or contraindication concerning any drug foreseen for MDC HAART
- Documented HIV-1 resistance to PI and/or NRTI.
- CD4 nadir <200/µl
- Acute AIDS-defining disease or history of AIDS-defining disease
- CHR: preceding virological failure
- History of alcohol or other substance abuse or other condition which in the opinion of the investigator would interfere with the patient compliance or safety.
- Any of the following abnormal laboratory test results in screening:
  a. Hemoglobin < 8 g/dL
  b. Neutrophil count < 750 cells/µL
  c. Platelet count < 50,000 cells/µL
  d. AST or ALT > 5x the upper limit of normal
- Presence of malignancy (requiring active treatment and malignancy within 5 years prior to enrolment (even if in complete remission)
- Significant underlying disease (non-HIV) that might impinge upon disease progression or death
- Prior use of any experimental HIV- Integrase-Inhibitor or CCR5-antagonist.
- Patient is pregnant or breastfeeding, or expecting to conceive (within the duration of the study). Patient is expecting to donate eggs (within the duration of the study). Patient is expecting to donate sperm (within the duration of the study).
- Contraindications for Maraviroc (Celsentri®) or Raltegravir (Isentress®) according to the respective summary of product characteristics (see also product informations attached to the protocol) (Hypersensitivity to the active substances or any of the excipients).

2.5.1 Special warnings and precautions for use of Maraviroc (see also protocol attachment SmPc)

- Maraviroc should only be used when only CCR5-tropic HIV-1 is detectable (i.e. CXCR4 or
- dual/mixed tropic virus not detected) as determined by an adequately validated and sensitive detection method.
- Dose adjustment: physicians should ensure that appropriate dose adjustment of Maraviroc is made when Maraviroc is co-administered with CYP3A4 inhibitors and/or inducers since Maraviroc concentrations and its therapeutic effects may be affected (sections product information in protocol attachment).
- Please also refer to the respective Summary of Product Characteristics of the other antiretroviral medicinal products used in the combination.
- Caution should be used when administering Maraviroc in patients with a history of postural hypotension or on concomitant medicinal products known to lower blood pressure.
- Potential effect on immunity: CCR5 antagonists could potentially impair the immune response to certain infections. This should be taken into consideration when treating infections such as active tuberculosis and invasive fungal infections. The incidence of AIDS-defining infections was similar between Maraviroc and placebo arms in the pivotal studies.
- Hepatic safety: the safety and efficacy of Maraviroc have not been specifically studied in patients with significant underlying liver disorders therefore Maraviroc should be used with caution in this population. Patients with pre-existing liver dysfunction, including chronic active hepatitis, can have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice.
- Discontinuation of Maraviroc should be considered in any patient with signs or symptoms of acute hepatitis, in particular if drug-related hypersensitivity is suspected or with increased liver transaminases combined with rash or other systemic symptoms of potential hypersensitivity (e.g.pruritic rash, eosinophila or elevated IgE).
- Since there are very limited data in patients with hepatitis B/C co-infection, special caution should be exercised when treating these patients with Maraviroc. In case of concomitant antiviral therapy for hepatitis B and/or C, please refer also to the relevant product information for these medicinal products.
- Renal impairment: the safety and efficacy of Maraviroc have not been specifically studied in patients with renal impairment.Therefore, Maraviroc should be used with caution in patients with renal impairment (CLcr <80 ml/min) who are also taking potent CYP3A4 inhibitors. Please consider dose interval adjustment guidelines based on simulations of increasing renal impairment in patients being co-administered potent CYP3A4 inhibitors. The safety and efficacy of these dose interval adjustments have not been clinically evaluated. Therefore, clinical response to treatment should be closely monitored in these patients (see sections 4.2 and 5.2 and product information).
- Soya lecithin: Maraviroc contains soya lecithin. If a patient is hypersensitive to peanut or soya, Maraviroc should not be used.

2.5.2 Special warnings and precautions for use of Raltegravir (see also see protocol attachment,SmPc)

- Overall, considerable inter- and intra-subject variability was observed in the pharmacokinetics of raltegravir (see product information in protocol attachment).
- Please also refer to the respective Summary of Product Characteristics of the other antiretroviral medicinal products used in the combination.
- The safety and efficacy of Raltegravir have not been established in patients with severe underlying liver disorders. Therefore Raltegravir should be used with caution in patients with severe hepatic impairment (see product information in protocol attachment).
- Patients with pre-existing liver dysfunction including chronic hepatitis have an increased frequency of liver function abnormalities during combination anti-retroviral therapy and should

be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment should be considered.

- There are very limited data on the use of raltegravir in patients co-infected with HIV and hepatitis B virus (HBV) or hepatitis C virus (HCV). Patients with chronic hepatitis B or C and treated with combination anti-retroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events.
- Caution should be used when co-administering Raltegravir with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (e.g., rifampicin). Rifampicin reduces plasma levels of raltegravir; the impact on the efficacy of raltegravir is unknown. However, if co-administration with rifampicin is unavoidable, a doubling of the dose of Raltegravir can be considered (see section 4.5 of product information in protocol attachment).
- Myopathy and rhabdomyolysis have been reported; however, the relationship of Raltegravir to these events is not known. Use with caution in patients who have had myopathy or rhabdomyolysis in the past or have any predisposing issues including other medicinal products associated with these conditions (see section 4.8 of product information in protocol attachment).
- During the clinical studies in treatment-experienced HIV-infected patients there was a slightly higher rate of cancer in the raltegravir group compared to the group that received only optimised background therapy. At present there are insufficient data to be able to exclude the possibility that raltegravir might be associated with a risk of cancer (see section 4.8 of product information in protocol attachment).
- Raltegravir contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

2.6 STUDY DESIGN

This is a multi-center, open-label, non-randomized proof-of-concept trial.
Recruitment will be stratified according to stage of HIV-infection and pre-treatment.

2.7 STUDY INTERVENTIONS

Patients of both strata will be treated with an antiretroviral combination of five approved substances. Every regimen will contain Maraviroc and Raltegravir (see attachments).

PHI stratum: Treatment initiation with MDC HAART in patients presenting with primary HIV-infection will be no later than two weeks after positive HIV testing (= ≤2 weeks after blood sampling for HIV test).
CHR stratum: In chronically HIV-infected patients with HI-viral load below the level of detection (<50 cop./ml) for at least 36 months under effective HAART existing of 2 NRTI plus 1 PI, HAART will be intensified with Maraviroc and Raltegravir.

PHI group	N= 20	2 NRTI + PI + MVC + RAL (MDC HAART)
CHR group	N= 20	Existing HAART + MVC + RAL (MDC HAART)

Patients of PHI group will remain on MDC HAART for at least 5 years up to a maximum of 7 years from baseline.

Patients of CHR group will remain on MDC HAART for at least 2 years, up to a maximum of 7 years from baseline.

Patients fulfilling the criteria for eradication (as defined in section 2.2.1.) and willing to stop HAART will be monitored for proviral DNA for a follow-up period of 12 months. Visits are corresponding to the post-follow-up visits 3, 6 and 12 months after discontinuation of HAART (Flow chart 1.6). All plasma viral load measurements up to 12 months post treatment will be recorded.

2.8 STUDY PROCEDURES

The study procedures outlined in table 1.6 flow chart are discussed in detail in this section. The study procedures should be performed as close to the scheduled time as possible.

Any patient who becomes pregnant during the course of the study must immediately be discontinued from all study medication. All pregnancies must be reported immediately to the Sponsor and must be followed to the completion/termination of the pregnancy. The outcome of all pregnancies must be reported to the Sponsor. Patients who become pregnant will be asked to join a pregnancy registry which collects information about the outcome of the pregnancy.

2.8.1 Informed Consent

The investigator must obtain documented consent from each potential patient in biomedical research or when an investigational drug is administered to patients in a clinical study.

Consent must be documented by the patient´s dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward both the patient (if capable) and the impartial witness should sign and date the informed consent.

If the patient is legally incompetent, the written consent of a parent, legal guardian or legal representative must be obtained. Depending on local law, such consent may also need to be signed by an impartial witness.

When the study includes non-English speaking people, the information in the consent form should be translated and communicated to the subject in language understandable to the subject. Either the investigator or Sponsor may take the responsibility for the translation. An accurately translated consent form should be provided.
A copy of the signed and dated consent form should be given to the patient before participation in the trial.
The initial informed consent form and any subsequent revised written informed consent form, and any written information provided to the patient must receive the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) approval/favorable opinion in advance to use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient´s willingness to continue participation in the trial.

2.8.2 Assignment of Allocation Number

Each patient will be assigned to a unique allocation number at the first screening visit.
A single patient cannot be assigned to more than one allocation number. Allocation number will be provided by the coordinating study centre.

2.8.3 Screening visits

Procedures to be performed at Screening visit and Pre-baseline for CHR (see also 1.6 Flow Chart)

Screening visit

- In order to minimize the number of screening failures, eligibility criteria (inclusion and exclusion criteria) concerning patient history must be checked prior to any study procedure.
- Written informed consent must be obtained prior to performing any study-specific procedures.
- Documentation of complete medical history is required.

- Laboratory screening, including hematology, chemistry and virology, measurement of coreceptor tropism from proviral DNA (as defined in Appendix 5.1), virological and immunological parameters must be performed at the first screening.
- Female patients of childbearing potential will have a pregnancy test performed prior to the study start date. Women who are found to be pregnant will be excluded from the study.

Pre-baseline visit

- Virological and immunological parameters and complete physical examination including vital signs and ECG must be performed at the Pre-baseline visit.
- Recording of adverse events
- Female patients of childbearing potential will have a pregnancy test performed prior to the study start date. Women who are found to be pregnant will be excluded from the study.

Procedures to be performed at Screening/Baseline visit for PHI

- In order to minimize the number of screening failures, eligibility criteria (inclusion and exclusion criteria) concerning patient history must be checked prior to any study procedure.
- Written informed consent must be obtained prior to performing any study-specific procedures.
- Documentation of complete medical history (including the assumed time point of HIV infection) is required.
- HIV Elisa/Westernblot, laboratory screening including hematology, chemistry and virology, genotypic measurement of coreceptor tropism (as defined in Appendix 5.1) virological and immunological parameters and complete physical examination including vital signs and ECG must be performed at the first screening.
- Female patients of childbearing potential will have a pregnancy test performed prior to the study start date. Women who are found to be pregnant will be excluded from the study.

2.8.4 Baseline, Follow-up, and Post Tx Visits

Patients who meet the eligibility requirements will start their medication at baseline.
Monitoring of patient safety as outlined in the flow chart (1.6) will be performed at all study visits; Specific laboratory measures are performed at a single visit after month 6 in all patients For management of adverse events see section 2.10 SAFETY.

Pregnancy test in female patients and blood collection (Flow chart 1.6) will be performed at every visit. The blood collection is used for laboratory safety and efficacy assessment. Targeted physical examination and recording of adverse events will be performed at baseline and all follow-up visits.

Visit time schedule

PHI-group:
Screening/Baseline, Month 1, Month 3, Month 6 and following half-yearly
CHI-group:
Month -6 (Screening), Month -3 (Pre-baseline), Baseline, Month 1, Month 6 and following half-yearly

Post Tx visits after pre-mature and regular discontinuation (including HAART interruption due to eradication, as defined in section 2.2.1):
Follow-up visits post Tx (PFU1, PFU2, PFU3) are foreseen at months 3, 6 and 12.
For respective study assessments see Flow chart 1.6

2.8.4.1 Specific laboratory parameters

2.8.4.1.1 Background

According to the New Era study protocol, treatment can be interrupted in case of reaching undetectability of HIV-1 RNA in plasma and proviral DNA in PMBC (criteria see 2.2.1). As shown by the Visconti post-treatment controllers additional virologic, immunologic or genetic markers are needed to better predict virus control after treatment interruption (Saez-Cirion 2013). For further

explorative analyses the measurement of specific laboratory parameters (one additional blood sampling per patient) is foreseen in the New Era Study– with the aim to better characterize and discriminate the New Era patients in terms of immunologic, virologic and other laboratory parameters.

2.8.4.1.2 Specific laboratory parameters

- HIV-specific CD8 + T cell response (Elispot, HIV-peptides: HIV-1 env, gag, pol, nef), markers of depletion/mobilization, suppressive immune cells (for example Myeloid-derived Suppressor Cells (MDSC)), HIV-specific CD4+T-cell responses and Treg, investigation of innate immunity (NK cells), cytokine-release assays for determination of Th1/Th2 immune responses
- Sampling and sample storage for later analyses of mRNA expression of genes involved in antiviral immune response, viral sequence alterations/changes, specific HLA- and KIR-allele, neutralizing and not-neutralizing antibodies.
- HIV-antibody test incl. Westernblot from stored blood samples at study baseline and defined time points
- CRP, Neopterin

2.8.4.1.3 Statistical Methods

Evaluation of the additional laboratory parameters will be performed as described in 2.12.3. Statistical Methods.

2.8.4.1.4 Informed consent

All patients having initiated MDC HAART in the New Era Study can participate. This includes patients with premature discontinuation. Patients have to give written informed consent for additional blood sampling and the corresponding laboratory analyses. Measurement of laboratory parameters will be performed in specific specialized laboratories.
Handling of the patient information and the informed consent are as described in 2.8.1.

2.8.4.1.5 Collaborating Laboratories

University Munich, University Hospital, Dept. of Infectious Diseases,
Med. Poliklinik, Pettenkoferstr. 8a 1, 80336 Munich, Germany
Contact person: Prof. J. Bogner, Tel.: +49 (0)89 5160 -3550 (or -3598)

University Medical Center Hamburg-Eppendorf,
Martinistraße 52, 20246 Hamburg, Germany
Contact person: Dr. J. Schulze zur Wiesch, Tel.: +49 (0)40 7410- 50071

Heinrich Pette Institute, Leibniz Institute for Experimental Virology,
Martinistraße 52, 20251 Hamburg, Germany
Contact person: Prof. M. Altfeld, Tel.: +49 (0)40 48051-221

Immumed GmbH,
Karlsstrasse 46, 80333 Munich, Germany
Contact person: W. Mayer, Tel.: +49 (0)89-543217789

2.8.5 Management of virologic failure or in case of 'eradication'

Definition of virologic failure see section 2.3.

- If a study participant experiences virological failure within the first 12 months of MDC HAART, patients will be excluded from the study and replaced by new study participants fulfilling the inclusion criteria.
- In case of virological failure after 12 months of MDC HAART, patients will be pre-maturely discontinued from the study and will be followed for a period of 12 months patients. Visits are corresponding to the post-follow-up visits 3, 6 and 12 months after discontinuation of HAART (Flow chart 1.6). Patients should receive ongoing counselling, i.e. regarding the importance of adherence. All potential causes for virologic failure will be analyzed and corrected if possible. Treatment can be changed according to the discretion of the treating physician. Measurements of genotypic resistance and tropism testing are recommended.

Definition of for 'eradication' see section 2.2.1.

- Patients fulfilling the criteria for eradication and willing to stop HAART will be monitored for proviral DNA for a follow-up period of 12 months. Visits are corresponding to the post-follow-up visits 3, 6 and 12 months after discontinuation of HAART (Flow chart 1.6). All plasma viral load measurements up to 12 months post treatment will be recorded. Patients can be re-started on HAART at the discretion of the treating physician. All post-follow-up visits will be performed irrespective of HARRT re-initiation.

2.8.6 Discontinuation/Withdrawal from Study

Discontinuation/Withdrawal from Study for Individual Patients:

- Any patient who becomes pregnant during the course of the study must immediately be discontinued from all study medication and from the study. All pregnancies must be reported immediately to the Sponsor and must be followed to the completion/termination of the pregnancy. The outcome of all pregnancies must be reported to the Sponsor. Patients who become pregnant will be asked to join a pregnancy registry which collects information about the outcome of the pregnancy.
- Any patient reaching the endpoint of *virologic failure* (definition see 2.3) within the first 12 months of MDC HAART (definition see 2.3) will be excluded from the study. If an investigator wants to withdraw a patient due to virological criteria other than *virological failure* as defined in 2.3., withdrawal from the study should be discussed with the DSMB and the Oversight Committee.
- Patient may be dropped from the study at the discretion of the investigator should any untoward effects occur.
- In addition, a patient may be withdrawn by the investigator or the Sponsor if he/she violates the study plan or for safety and/or compliance reasons.
- Patients may withdraw from the study at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.
- In case of screening failures (e.g. due to CXCR4-tropism) patients will be discontinued from the study.

Discontinuation of the Study

- For reasonable cause, the sponsor/coordinating investigator may terminate the study at any time in agreement with the DSMB (Data safety monitoring board, see 2.10.).
- If there is a non-significant decline in proviral DNA after 36 months, the Oversight Committee can terminate the study in agreement with the DSMB (Data safety monitoring board, see 2.10.).

Procedures

The investigator or study coordinator must notify the Sponsor immediately when a patient has been discontinued/withdrawn due to an adverse experience. When a patient discontinues/withdraws prior to study completion all applicable activities scheduled for the discontinuation study visit should be

performed at the time of discontinuation. Patients will then be treated at the discretion of the treating physician. Post follow-up visits (PFU1, PFU2, PFU3) are foreseen at months 3, 6 and 12 (see 1.6. Flow Chart). Any adverse experiences which are present at the time of discontinuation/withdraw should be followed in accordance with the safety requirements outlined in section 2.10 SAFETY.

Annotation: If new antiretroviral agents will be approved or available through expanded access programs during the course of the study that might be beneficial for a study patient at the discretion of the treating physician, the treatment regimen can be modified based on current knowledge (=addition of new antiretroviral agent or replacement of drugs of the regimen). Patients will not be excluded from the study unless they reach the virological endpoint (see 2.3.).

2.8.7 Plans for Treatment and Care after Study Discontinuation
Patients will be treated at the discretion of the treating physician after the regular end of the trial or after pre-mature discontinuation. The treatment is not expected to differ from normal management of HIV infection. For patients with pre-mature discontinuation, post follow-up visits 3, 6 and 12 months after discontinuation are foreseen (see 1.6 Flow Chart).

2.9 EFFICACY
Primary efficacy parameters:
Proviral DNA (infectious copies per 10^6 PBMC and CD4) will be measured at the screening visit, at baseline and then 6-monthly at each follow-up visit (see 1.6 Flow Chart)
Plasma HIV-RNA will be obtained at the screening visit, at baseline, at months 1 and 3 and then 6-monthly at each follow-up visit (see 1.6 Flow Chart)
Secondary efficacy parameters:
CD4-T cell count and other immunological parameters (CD8, CD38, CD45) will be obtained at the screening visit, at baseline, at months 1 and 3 and then 6-monthly at each follow-up visit (see 1.6 Flow Chart)

2.10 SAFETY
2.10.1 Safety Monitoring
At all visits, safety measurements of clinical chemistry, hematology and virology and physical examination will be conducted. All adverse events will be recorded.
Treatment naïve (PHI) female patients of childbearing potential will have pregnancy test performed at Screening, Baseline, Month 1, Month 3, Month 6 and following half-yearly until Month 90.
Pretreated (CHI) female patients of childbearing potential will have pregnancy test performed at Screen, 6 Month prior to Baseline, 3 Month prior to Baseline, at Baseline, Month 1, Month 3, Month 6 and following half-yearly until Month 54.

2.10.2 Toxicity Management
Patients will be asked about any adverse experiences during their clinic visits and the information will be recorded in the *Case Report Forms*.
Guidelines for grading the severity of adverse experiences are based on Division of Acquired Immunodeficiency Syndrome (DAIDS) criteria for grading severity of adverse events (Attachment 7.3). Decisions to temporarily withhold therapy because of an adverse experience will be reviewed on a case-by-case basis by the investigator.
The investigator should consider temporarily withholding therapy if the severity of the adverse experience is Grade 3 or above and/or if clinically indicated. The decision to interrupt therapy should take into account the patient´s baseline laboratory values and any concomitant medication that could be contributory.
At the discretion of the investigator, therapy may generally be reinitiated when laboratory abnormalities or clinical adverse events return to near normal or baseline values.

2.10.3 Adverse Experiences: Definition and Recording
An adverse experience (adverse event, AE) is defined as any unfavourable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study

drugs, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the study products, is also an adverse experience. Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. Examples of this may include, but are not limited to onset of menses or menopause occurring at a physiologically appropriate time.
Adverse experiences may occur in the course of the use of a study product in clinical studies, or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse, and from withdrawal.
Adverse experiences may also occur in screened patients during any pre-allocation baseline period.
All adverse experiences will be recorded at the respective study visits in the *Case Report Form.*

2.10.4 Serious Adverse Experiences: Definition, Recording and Reporting

Definition of Serious Adverse Experiences (SAEs)

An SAE is defined as any untoward medical occurrence at any dose that:

- results in **death**
- is **life-threatening**[*]
- requires inpatient **hospitalization** or prolongation of existing hospitalization
- results in a persistent or significant **disability/incapacity**[**]
- results in **congenital anomaly/birth defect**
- **is a cancer;** or
- **is an adverse experience(s) associated with an overdose of study drug** (whether accidental or intentional (see 2.10.6). Any overdose whether or not associated with an adverse experience must be reported within 24 hours to one of the individuals on the Contact Information Page (page 4, see also Site File).
- is an **important medical event**
- ie, may jeopardize the patient/subject and/or may require intervention to prevent any of the above outcomes

[*]Life-threatening = Places the patient/subject/consumer at risk of death at the time of the event.
NOTE: This does NOT refer to an event that might, hypothetically, have caused death if it were more severe.

[**]Disability = A substantial disruption of a person's ability to conduct normal life functions.

Recording and Immediate Reporting of Adverse Experiences to the Sponsor

Any serious adverse experience, whether or not there is a suspected causal relationship to the investigational product (including death due to any cause), which occurs to any subject/patient entered into this study or within 14 days following cessation of treatment or within the established off therapy follow-up period for safety described in the protocol, whether or not related to the investigational product, must be reported within 24 hours to one of the individual(s) listed on the sponsor *Contact Information Page* (see page 4).
For all serious adverse experiences the *Serious Adverse Experience/Pregnancy/Overdose Case Report Form* (*SAE Form*) will be completed. In addition, every single SAE will be recorded at the respective study visit in the *Case Report Form*.
Each SAE will be fully investigated and, if drug related, a decision will be made as to whether the risk/benefit warrants the patient´s continuation in the study.

2.10.5 Reporting of Pregnancy to Sponsor

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a subject/patient (spontaneously reported to them) which occurs during the study or within 14 days of completing the study. All subjects/patients who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be 24 hours to one of the individual(s) listed on the sponsor *Contact Information Page* (see page 4). For all pregnancies the *Serious Adverse Experience/Pregnancy/Overdose Case Report Form* (*SAE Form*) will be completed.

2.10.6 Definition and Reporting of Overdose to the Sponsor

In clinical trials dosages of Raltegravir with 1600 mg per day and dosages of Maraviroc with 1200 mg per day there was no evidence of toxicity, therefore the dosages for Raltegravir ≥ 1600 mg per day and for Maraviroc ≥ 1200 mg per day are defined as overdose. No further specific information is available on the treatment of overdosage with Raltegravir and Maraviroc,

In the event on an overdose, it is reasonable to employ the standard supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

Any overdose, whether or not associated with an adverse experience, must be reported within 24 hours to the Sponsor. If an adverse experience(s) is associated with ("results from") the overdose of test drug, the adverse experience(s) is reported as a serious adverse experience on the *Serious Adverse Experience/Pregnancy/Overdose Case Report Form (SAE Form)*, even if no other criteria for serious are met. If a dose of test drug meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse experience must be reported within 24 hours to one of the individuals listed on the sponsor contact information page found in the Administrative Binder.

2.10.7 Data Safety Monitoring Board (DSMB)

The study will be monitored by an independent external Data Safety Monitoring Board (DSMB)/ Data Monitoring Committee (DMB). The DSMB will provide recommendations to the Oversight Committee. The Oversight Committee (consisting of the sponsor and coordinating investigator Dr. med. Hans Jaeger and principal investigator Prof. Johannes Bogner) will provide the overall scientific direction for the trial, and will receive and decide on any recommendations made by the DSMB. The Oversight Committee must approve all scientific reports concerning the main findings of the trial. The membership, procedures, functions and responsibilities of the Oversight Committee and DSMB will be identified in the *New Era DSMB Charter*.

- Membership

The DSMB consists of independent experts in infectious diseases (including HIV infection) and in biostatistics and has expertise in conducting clinical trials. The members of the committee are independent of the Sponsor and the clinical investigators participating in this trial, and will not have any other involvement in the study.

- Role of the DSMB

The DSMB evaluates the overall safety of the study and assesses the effects of the study intervention during the trial and may give advice to the Oversight Committee. The DSMB may recommend any steps needed to ensure the safety of study participants and the integrity of the trial. Furthermore, it may recommend that the trial be terminated or that specific high-risk patient groups be withdrawn from the study, if any subgroup manifests serious or widespread side effects. To guarantee the unrestricted performance of its task, the DSMB will receive the study data from a designated statistician.

Procedures

Prior to any schedule meeting, the DSMB will be provided with the following reports. Reports will be cumulative, generated from an up-to-data file.

- Patient enrollment status: counts of patients enrolled by study site.
- Counts tables of: all adverse experiences (AEs) including laboratory abnormalities of grade 3 or 4, drug-related AEs, serious AEs (incl. SUSARs), drug-related serious AEs, and AEs leading to discontinuations.
- Counts tables of patients with adverse experiences by body systems.
- Counts tables of clinical significant laboratory AEs (grades 3 and 4)
- Annual Safety Reports (ASR) (see chapter *Annual Safety Report (ASR)*

In addition to independently evaluating and ensuring patient safety, the DSMB will oversee the interim analyses (see protocol 2.12.4) and recommend if the study should continue. The need for additional reports will be assessed once the board has been appointed and the Study is underway.
Based upon review of the reports, the DSMB will recommend to the Oversight Committee whether the study should be continued, modified, or stopped for safety reasons. Guidelines for making such a decision will be developed by the Sponsor, in consultation with the DSMB in advance of any analysis. Further details regarding the DSMB will be described in the *New Era DSMB Charter*. The specific data that will be provided by the Sponsor for DSMB review will be identified in the *DSMB Charter*.

2.10.8 Suspected Unexpected Serious Adverse Reactions (SUSARs), Annual Safety Report (ASR)
European regulatory authorities require a database in order to provide each of them with an overview of the suspected unexpected serious adverse reactions (SUSARs) linked to investigational medicinal products used in clinical trials being conducted in the community, and in the respective Member States (legal basis Clinical Trial Directive 2001/20/EC).
The Sponsor will report all SUSARs according to the standards for reporting SUSARs which are defined in 'Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use - April 2006' and in accordance with all applicable global laws and regulations. SUSAR reports will include all informations required according to the *Council for International Organizations of Medical Sciences* CIOMS I reporting form.
The Sponsor who is non-commercial and not Marketing Authorization Holder (MAH) for any of the Investigational Medicinal Products (IMPs) will report all relevant information about a suspected unexpected serious adverse reaction (SUSAR) which occurs during the course of a clinical trial and is fatal or life-threatening as soon as possible to competent authority (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM), the relevant Ethics Committees, the investigators and the manufacturers of the study drugs. This needs to be done not later than 7 days after the Sponsor was first aware of the reaction. Any additional relevant information should be sent within 8 days of the report.
A Sponsor will report unexpected serious adverse reaction (SUSAR) which is not fatal or life-threatening as soon as possible, and in any event not later that 15 days after the Sponsor is first aware of the reaction.
The sponsor will inform all investigators concerned of findings that could adversely affect the safety of study subjects. If appropriate, the information can be aggregated in a line listing of SUSARs in periods and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the investigational medicinal product.
If a significant safety issue is identified, either upon receipt of an individual case report or upon review of aggregate data, the sponsor will issue as soon as possible a communication to all investigators.
A safety issue that impacts upon the course of the clinical study or development project, including suspension of the study program or safety-related amendments to study protocols should also be reported to the investigators.

Annual Safety Report (ASR):
In addition to the expedited reporting required for SUSAR, Sponsor will submit once a year throughout the clinical trial (or on request) a safety report to the competent authority (BfArM), and the relevant Ethics Committees of the concerned Member States according ENTR/CT3 (*Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use - April 2006*) and GCP-Verordnung §13 (6) and to the investigators and the manufacturers of the study drugs. The annual safety report should take into account all new available safety information received during the reporting period. The annual safety report should be the same for the competent authorities concerned and the
Ethics Committee concerned.
The aim of the Annual Safety Report is to describe concisely all new safety information relevant for one or several clinical trial(s) and to assess the safety of subjects included in these studies.
The Annual Safety Report of a clinical trial should have three parts:

Part 1:
Analysis of the subjects' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk:benefit.
Part 2:
A line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the concerned trial(s), including all serious adverse reactions from third countries.
Part 3:
An aggregate summary tabulation of suspected serious adverse reactions that occurred in the concerned trial(s).
Full details of what to include in an Annual Safety Report can be found in *"Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use - April 2006"* of the European Commission.

2.11 CONCOMITANT MEDICATION

It is the responsibility of the investigator to check potential drug-drug interactions between Maraviroc, Raltegravir and background antiretroviral therapy and other concomitant medications.
Medication that is contraindicated according to the product informations (see also protocol attachments SmpC) of the respective antiretrovirals will be disallowed in the course of the study.

2.12 DATA ANALYSIS

2.12.1 Sample Size

This proof-of-concept study using a small, targeted number of subjects is carried out to determine if eradication of HIV is possible. A design with a placebo was discouraged in the light of possible eradication. The chronically infected patients serve as their own controls. Prior to baseline, these patients are monitored while on persistently suppressive HAART lasting already for at least 36 months and then switched to multi-drug class HAART.
Chun et al. (J Infect Dis. 2007; 195(12): 1762-4.) showed in a small group of patients starting HAART during the first 0-4 months after the onset of symptoms of primary HIV infection (PHI), that proviral DNA in PBMC can be reduced significantly (mean reduction –0.94 log/year, standard deviation 0.48). The mean time until eradication of HIV was estimated at 7.7 years.
In a larger study in patients with PHI, a similar effect was observed. The median cell-associated DNA level decreased from 2.8 log cop./million PBMCs (IQR, 2.4–3.0 log cop./million PBMCs) to 1.6 log copies/million PBMCs (IQR, 1.2–1.9 log cop./million PBMCs) (Hoehn et al, Clinical Infectious Diseases 2007; 45:381–90).
Based on the assumption, that MDC (multi-drug class) HAART with Raltegravir and Maraviroc leads to a mean reduction of at least one 1 log in patients with PHI and assuming a standard deviation of 1 and a 95% confidence interval (0.5-1.5 log) with a width of 1, the sample size is calculated at >=16 (assumption of normal distribution).
Intensification of HAART with Raltegravir and Maraviroc in chronically infected HIV-patients may have similar effects (Ramratnam B, J Acquir Immune Defic Syndr 2004; 35:33-37). Sample size calculation can be used also for chronically infected HIV-patients.
A sample size of **40 patients** (**20 primary infected patients (Stratum I, PHI**) and **20 chronically infected patients (Stratum II, CHR)** was chosen. Drop-outs in the first 12 months will be replaced.
In the course of this study no gender specific differences are expected. The application of Maraviroc and Raltegravir does not differ in male and female patients. The proportion of male and female patients will probably be in accordance with the epidemiologic data in Germany.

2.12.2 Hypotheses

The hypotheses of this study is, that with MDC HAART, a mean reduction in proviral DNA of 1 log can be achieved by 36 months.

Null hypotheses H_0:	Mean reduction of proviral DNA < 1 log.
Alternative hypotheses H_1:	Mean reduction of proviral DNA >= 1 log
Level of significance :	0.05
Statistical test:	One-tailed paired t-test

The null hypotheses will be rejected if the p-value of the test is less than the significance level (0.05). The null hypotheses will be accepted if the p-value of the test greater than 0.05.

2.12.3 Statistical Methods

- For accepting or rejecting the primary hypothesis (see protocol 2.12.3.) of the trial, one-tailed paired t-test will be used.
- Further analysis will be descriptive and explorative.
    - Data will be analysed on an intention-to-treat and on a per-protocol basis. Analysis will be stratified according to treatment strata (PHI and CHR)
    - Kaplan-Meier statistics will be applied concerning
        1) time to eradication (discontinuations other than due to virological failure or side effects will be censored)
        2) time to virological failure (as defined in section 2.3); (discontinuations other than due to virological failure will be censored)
    - For estimating the decay rates of proviral DNA regression lines will be generated.
    - Specific laboratory parameters (see 2.8.4.1) and all quantitative/continuous variables will be described with N, mean, SD, and 95% confidence intervals or median values and selected percentiles (lower quartile (25%), upper quartile (75%)), minimum and maximum.
    - The categorization of socalled 'favorable' outcomes will be data based (e.g. by median values or by cut-offs)
    - Changes from baseline in efficacy and safety laboratory parameters as well as in other continuous variables will be described using the following information: N, mean, SD, 95% confidence interval, and range (minimum and maximum) or median value, selected percentiles (lower quartile (25%), upper quartile (75%)), and range.
    - The Wilcoxon sign rank test and the Mann-Whitney U test will be used to compare continuous variables within groups and between groups, respectively. The p-level for significance is $P<0.05$.

2.12.4 Interim Analyses

- An interim analyses will be performed as soon as 10 PHI patients and 10 CHR patients have completed month 12-study visit and then on a yearly basis. Further analyses will be after 20 PHI patients and 20 CHR patients have completed month 36-study visit and at study completion.
- The analyses will include:

    - Patient enrollment status: counts of patients enrolled by study site.
    - Counts tables of: all adverse experiences (AEs) including laboratory abnormalities of grade 3 or 4, drug-related AEs, serious AEs, drug-related serious AEs, and AEs leading to discontinuations.
    - Counts tables of patients with adverse experiences by body systems
    - Counts tables of clinical significant laboratory AEs (grades 3 and 4)
    - Changes from baseline in renal, hepatic and haematological parameters
    - Changes from baseline in proviral DNA, plasma viral load, CD4 cell count

3 REGULATORY ISSUES, COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT, AND FINANCING

3.1 SPONSOR OF THE STUDY/APPLICANT TO IRB/COORDINATING INVESTIGATOR

MUC Research GmbH, Dr. med. Hans Jaeger, Karlsplatz 8, 80335 Munich
Tel. # +49 89 558 70 30, Fax # +49 89 550 39 41

Email: info@mucresearch.de3.1.1 Curriculum vitae of coordinating investigator

Full Name:	**Jaeger**	**Hans**	**Date:**	26/FEB/2008
	Last Name	***First Name***		

Role in this study: Coordinating and principal investigator and Sponsor

x Principal Investigator ☐**Sub Investigator** ☐**Coordinator**

Professional Mailing Address: (Include institution name.)	**Study Site Address:** (Include institution name.)
Dr.med. Hans Jaeger Karlsplatz 8 80335 Munich info@mucresearch.de	MUC Research Karlsplatz 8 80335 Munich
Telephone No.: +49 89 558 70 30	**Telephone No.: +49 89 558 70 30**

Academic Qualifications (most current date first)

Degree/Certification	**Date (mmm/yyyy)**	**Institution, Country**
MD Internal Medicine	1974 1984	Technical University Munich, Germany Academic Teaching Hospital München-Schwabing, Germany

Current and Previous Four Relevant Positions Including Academic Appointments (most current date first):

Dates In Years	**Title**	**Institution/Company, Country**
1981 – 1982	Fellow	Oncology Department, University of Rochester, New York
1982 - 1983	Fellow and Instructor	Memorial Sloan Kettering Cancer Center, New York
1983 - 1989	Clinical Director	Out-Patient Department for Immunedeficiency, Academic Teaching Hospital München-Schwabing
1990	Chairman	Board of Directors of KIS - Curatorium for Immunedeficiency (Non Profit AIDS Research Institute)
1992	Head of institution	HIV Research and Clinical Care Centre Munich
1999	Chairman	MUC Research organizes clinical research, participation in national and international phase II-IV clinical trials, planning, data collection and statistical analyses of research projects

Brief Summary of Relevant Clinical Research Experience:

- Head investigator for several clinical studies especially on HIV / AIDS
- Advisor for national and international boards, e.g. WHO
- Author of scientific papers and text books on HIV/AIDS
- Chairman of numerous scientific conferences on HIV/AIDS
- List of publications: see www.jajaprax.de.

License/ID Number:	**Licensed in State/Province/Country:**
63/19924	Germany

3.2 PARTNERS/PRINCIPAL INVESTIGATORS IN COOPERATIVE GROUP

- Dr. med Hans Jaeger, HIV Research and Clinical Care Centre Munich/MUC Research, Karlsplatz 8, 80335 Munich, Germany; Tel. +49 (0)89 558 70 30, Fax +49 (0)89 550 39 41, Email: info@jajaprax.de
- Prof. Dr. Johannes Bogner, University Munich University Hospital, Dept. of Infectious Diseases, Med. Poliklinik, Munich, Germany; +49 (0)89 5160 -3550 (or -3598),Fax +49 (0)89 5160 3593, Email: johannes.bogner@med.uni-muenchen.de

3.3 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (GCP) (*http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)* and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study. The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review, and regulatory agency inspection of trial related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects/patients, their insurance providers, or from government programs for procedures reimbursed to the investigator by the Sponsor. The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject/patient participating in the study, provide all data, and upon completion or termination of the clinical study submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

International Conference of Harmonization Good Clinical Practice (ICH-GCP) guidelines (http://www.fda.gov/oc/gcp/guidance.html#ich) recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

According to European legislation, a Sponsor must designate a principal or coordinating investigator to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study. The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study. Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies.

The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred, or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened. In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that site's IRB/IEC.

3.4 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the investigator agrees to provide to the Sponsor accurate financial information and disclosure statements. The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by the Sponsor. This requirement also extends to subinvestigators.

3.5 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study. The Sponsor or a designated person (see 0. *Contact Information Page*) reviews data for accuracy, completeness and consistency: data are verified versus source documentation according to standard operating procedures.

3.6 FINANCING

The study will be funded by:

- Pfizer Inc. 235 East 42nd Street, NY 10017 USA; formerly Pfizer Pharma GmbH;
- MSD Sharp & Dohme, Lindenplatz 1, 85540 Haar, Germany;
- Abbvie Deutschland GmbH & Co KG, Mainzerstr. 81, 65189 Wiesbaden, Germany; formerly Abbott GmbH & Co. KG
- TTU HIV, Thematische Translations-Einheit HIV des DZIF e.V., Deutsches Zentrum für Infektionsforschung e.V., Germany

Funding will cover the following expenses:

1. Drug supply and/or drug supply expenses; comprises supply for 20 PHI patients for 5-7 years of treatment and supply for 20 CHI patients for 2-7,5 years of treatment
2. Study-related personnel costs
3. Diagnostic fees and services
4. Data management expenses
5. IRB
6. Start-up/administrative expenses

3.7 PUBLICATION

- First publications of results of interim analyses after every patient has reached week 24 or 48 of treatment
- Target conferences: Conference on Retroviruses and Opportunistic Infections, International AIDS Conference and IAS Towards an HIV Cure Symposium
- Target Journal: Peer-reviewed journal, e.g. AIDS or J Infect Dis;

4 LIST OF REFERENCES

- Chun TW, Justement JS, Moir S, Hallahan CW, Maenza J, Mullins JI, Collier AC, Corey L, Fauci AS. Decay of the HIV reservoir in patients receiving antiretroviral therapy for extended periods: implications for eradication of virus. J Infect Dis. 2007 Jun 15;195(12):1762-4.
- Di Mascio M, Dornadula G, Zhang H, et al. In a subset of subjects on highly active antiretroviral therapy, human immunodeficiency virus type 1 RNA in plasma decays from 50 to <5 copies per milliliter, with a half-life of 6 months. J Virol 2003; 77: 2271–75.
- Ginger Lehrman, Ian B Hogue, Sarah Palmer, Cheryl Jennings, Celsa A Spina, Ann Wiegand, Alan L Landay, Robert W Coombs, Douglas D Richman, John W Mellors, John M Coffin, Ronald J Bosch, David M Margolis. Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. The Lancet: 366 August 13, 2005.
- Henrich TJ, Hanhauser E, Marty FM, et al. Antiretroviral-free HIV-1 remission and viral rebound after allogeneic stem cell transplantation: report of 2 cases. Ann Intern Med. 2014 Sep 2;161(5):319-27. doi: 10.7326/M14-1027.
- Hütter G1, Ganepola S. Eradication of HIV by transplantation of CCR5-deficient hematopoietic stem cells. ScientificWorldJournal. 2011 May 5;11:1068-76. doi: 10.1100/tsw.2011.102.
- Leung A et al. Innovative Proof -of -Concept Designs. ScianNews 2006: 9 (1): 1-7.
- Ramratnam B, Mittler JE, Zhang L, Boden D, Hurley A, et al. (2000) The decay of the latent reservoir of replication-competent HIV-1 is inversely correlated with the extent of residual viral replication during prolonged anti-retroviral therapy. Nat Med 6: 82–85.
- Persaud D, Gay H, Ziemmak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. N Engl J Med. 2013;369(19):1828-35.
- Persaud D. The path towards HIV cure: Lessons from the MISSISSIPPI CHILD. Oral presentation, MOSY0501, Internat. AIDS Conference, 20-25 July 2014, Melbourne, Australia.
- Saez-Cirion A, Bacchus C, Hocqueloux L, Avettand-Fenoel V, Girault I, Lecuroux C, et al. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. PLoS Pathog 2013; 9(3):e1003211. (Update ANRS Meeting, 7th IAS 7th IAS Conference 2013)
- Sedaghat AR, Siliciano JD, Brennan TP, Wilke CO, Siliciano RF. Limits on Replenishment of the Resting $CD4^+$ T Cell Reservoir for HIV in Patients on HAART. PLoS Pathogens 3 (8): e12
- Sedaghat AR, Siliciano RF, Wilke CO. Low-level HIV-1 replication and the dynamics of the resting CD4+ T cell reservoir for HIV-1 in the setting of HAART. BMC Infect Dis 2008;8:2.
- Siliciano JD, Kajdas J, Finzi D, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4_ T cells. *Nat Med* 2003; **9:** 727–28.
- Zhang L, Ramratnam B, Tenner-Racz K, He Y, Vesanen M, et al. (1999) Quantifying residual HIV-1 replication in patients receiving combination antiretroviral therapy. N Engl J Med 340: 1605–1613.

5 APPENDICES

5.1 LABORATORY ANALYSES FOR ADMISSION TO STUDY AND FOR SAFETY ASSESSMENT

Hematology Laboratory Test
To be done at every visit

Blood haemoglobin
Whole blood hematocrit
Red blood cell count
White blood cell count
White blood cell differential:
Blood neutrophil count
Blood monocyte count
Blood eosinophilic leukocyte count
Blood basophilic leukocyte
Blood lymphocyte count
Normocytic erythrocyte observation

Blood platelet count
Blood helper/inducer cell lymphocyte count (absolute and %) (blood CD4 count)
Blood suppressor/cytotoxic cell lymphocyte count blood helper/inducer cell lymphocyte count (absolute and %) (blood CD8 count)
Blood helper cell/suppressor cell lymphocytic ratio (blood CD4/CD8 ratio)
Further immunological parameters are CD38 and CD45.

Blood chemistry Test (Serum)
To be done at every visit

Aspartate aminotransferase (AST or (SGOT)
Alanine aminotransferase (ALT or SGPT)
Alkaline phosphatase
Total bilirubin
Creatinine
Gucose
Total cholesterol
Low-density lipoprotein cholesterol (LDL-C)
High-density lipoprotein cholesterol (HDL-C
Triglycerides

Pregnancy Test
To be done at every visit

Urine/Serum Pregnancy (HCG) test
Virological Tests
To be done at every visit
Plasma HIV-1 measurement
HIV- RNA level well be measured using the respective local viral load assays (e.g. CAP/CTM HIV-1 Test) and 1-copy assay.

To be done at every visit except from Month 1 and 3
Proviral DNA in PBMC (= peripheral blood mononuclear cells)

Measurement of coreceptor tropism

To be done at screening

PHI-group: Genotypic test (standard phenotypic tropism measurement for back-up)
CHI-group: Genotypic tropism measurement: material: proviral DNA

5.2 INVOLVED LABORATORIES

- Viral load in plasma:

Labor Gemeinschaftspraxis Dr. H. Jäger, Herzog-Wilhelm-Str. 1, 80331 Munich, Tel: +49 (0)89 555 404, Fax: +49 (0)89 555400
Or Local laboratories of the Principal investigators

- Viral load in plasma (1-copy assay):

Swedish Institute for Infectious Disease Control, Karolinska Institute, Nobels väg 18, 171 82 Solna, Sweden. Tel: +46 8 457 2508, Fax. +46 8 337 272

- Proviral DNA in PBMC, CD4-T cells:

Laboratoire de Virologie, Hôpital Necker - Enfants malades, 149 rue de Sèvres, 75015 Paris, France, Tel: (33) 1 44 49 49 61 direct: 01 42 19 28 93, Fax: (33) 1 44 49 49 60

- Phenotypic co-receptor tropism:

Monogram biosiences, Patrick Joseph, MD, 345 Oyster Point Blvd, South San Francisco, CA 94080, Tel: +1-650-866-7400

- Genotypic co-receptor tropism

Labor Dr. Berg, Dr. Thomas Berg, Seestr. 13, 10439 Berlin, Tel: +49(0)30 4465 3595, Fax: +49(0)30 4473 8145

- Blood count, CD4 cell count, clinical safety parameters:

Local laboratories of the Principal investigators

5.3 ABBREVIATIONS

ASR	Annual Safety Report
b.i.d.	Twice daily
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
cART	Combination Antiretroviral Therapy
CHI patients	Chronically HIV-infected patients
CCR5	Chemokine (C-C motif) coreceptor 5
CRF	Case Reoprt Form
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
ECG	Electrocardiogram
ERB	Ethical Review Board
HAART	Highly active antiretroviral treatment
HBV	Hepatitis B virus
HCG	human chorionic gonadotropin
HCV	Hepatitis C virus
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medical Product
INI	Integrase-Inhibitor
IRB	Institutional Review Board (IRB)
MAH	Marketing Authorization Holder
MDC HAART	Multi-drug class HAART
MVC	Maraviroc
NRTI	Nucleoside-Reverse-Transcriptase-Inhibitor
PBMC	Peripheral blood mononuclear cells
PFU	Post-follow-up
PHI patients	Patients with primary HIV-infection
PI	Protease-Inhibitor
PO	Per os
PRO	Protease
PTC	Post treatment controller
RAL	Raltegravir
RNA	Ribonucleic acid
RT	Reverse Transcriptase
RTV	Ritonavir
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UGT	Uridine diphosphate glucuronosyltransferase
VL	HI-Viral load

6 SIGNATURES

6.1 SPONSOR OR SPONSOR´S REPRESENTATIVE

TYPED NAME	SIGNATURE	DATE

6.2 INVESTIGATOR´S AGREEMENT

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in the safety measurements section (see 2.10. Safety Parameters) of this protocol. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol.

COORDINATING INVESTIGATOR'S NAME	SIGNATURE	DATE

PRINCIPAL INVESTIGATOR'S NAME	SIGNATURE	DATE

7 THE SPONSOR'S CODE OF CONDUCT FOR CLINICAL TRIALS

Introduction

The study will be consistent with standards established by the *Declaration of Helsinki* (http://www.wma.net/e/policy/pdf/17c.pdf, Homepage of World Medical Association) and in compliance with all local and/or national regulations and directives.

Site Selection

The Sponsor selects investigative sites based on medical expertise, access to appropriate patients, adequacy of facilities and staff, previous performance of, as well as budgetary considerations. Prior to study initiation, sites are evaluated by the Sponsor to assess the ability to successfully conduct the trial.

Data management

Case Report Forms will be provided by the SPONSOR. After completion of a single study visit, case reports will be faxed to the Sponsor or a designated person (monitor). An electronic data base (including archive data-backup) will be established by the Sponsor or a designated person. The Sponsor and the sites have to comply with the record retention periods for clinical trials.

Site Monitoring/Scientific Integrity

Study sites are monitored to assess compliance with the study protocol and general principles of Good Clinical Practice. The Sponsor or a designated person (monitor) reviews data for accuracy, completeness and consistency: data are verified versus source documentation according to standard operating procedures. If misconduct are suspected, the issue is investigated: when necessary, the clinical site will be closed and, if appropriate, the responsible regulatory authorities and ethics review committees notified.

Publication and Authorship

The Sponsor's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines (*www.emea.europa.eu/pdfs/human/ich/013595en.pdf)*. In summary, authorship should reflect significant contribution to the design and conduct of the study, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the study results and conclusions. Funding of a study will be acknowledged in publications.

IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB (institutional review board)/ERC (ethical review board) before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect patient safety and well-being may be enacted in anticipation of IRB/ERC approval. The IRB/ERC will approve the patient informed consent form.

Patient Safety

The guiding principle in decision-making in clinical trials is that patient welfare is of primary importance. Potential patients will be informed of the risks and benefits of, as well as alternatives to, study participation. At a minimum, study designs will take into account the local standard of care.

Patients are never denied access to appropriate medical care based on participation in the study. All participation is voluntary. Patients are enrolled only after providing informed consent for participation.

Patients may withdraw from the study at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

Confidentiality

The Sponsor is committed to safeguarding patient confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

Financial Considerations

- **Clinical Research Funding**

The investigator or sponsoring institution is being paid or provided a grant for performing the study. Funding of travel by investigators and support staff (e.g. to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

Investigator Commitment

Investigators will be expected to review the Sponsor's Code of Conduct as an attachment to the study protocol, and in signing the protocol, agree to support these ethical and scientific standards.

8 ATTACHMENTS

Product information of maraviroc
Product information of Raltegravir
Guidelines for grading clinical and laboratory abnormalities
Serious Adverse Experience/Pregnancy/Overdose Case Report Form (SAE Form)