NOVARTIS

Clinical Development

RAD001 (Everolimus)

CRAD001HDE13 / NCT01551212

A 12 month, multi-center, open-label, randomized, controlled study to evaluate efficacy/safety and evolution of renal function of everolimus in co-exposure with tacrolimus in de novo liver transplant recipients

The Hephaistos Study

Author(s): [redacted]

Document type:	Clinical Study Protocol
EUDRACT number :	2011-003118-17
Meets criteria for posting on clinicaltrials.gov	Yes
Development phase:	III
Version No.	5.0 (including amendment 5)
Release date:	19.08.2015

Signature Pages

Everolimus

CRAD001HDE13

Approved by the following

Signatures of Novartis Personnel:

[redacted] (Clinical Trial Leader)	signature	Date
[redacted] (Trial Statistician)	signature	Date
[redacted]	signature	Date
[redacted]	signature	Date

Signature of Principal Investigator:

[redacted] _____ _____
(Principal Investigator) signature Date

Signature Page for Investigator

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I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the principles outlined in the Declaration of Helsinki.

_____ _____
(Investigator) signature Date

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List of post-text supplements

None

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None

List of abbreviations

AE	Adverse Event
ALAT (SGPT)	Alanine Aminotransferase (Serum Glutamate Pyruvate Transaminase)
AP	Alkaline Phosphatase
ASAT (SGOT)	Aspartate Aminotransferase (Serum Glutamatoxalacetate Transaminase)
ATC	Anatomical Therapeutic Chemical dictionary
ATG	Antithymocyte Globulin
BPAR	Biopsy-Proven Acute Rejection
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology collaboration
Cmax	Maximum Plasma Concentration
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
CPK	Creatinine Phosphokinase
CR	Clinical Research
CRF	Case Report/Record Form
CRO	Clinical Research Organization
CRP	C-Reactive Protein
CS	Corticosteroids
DSMB	Data Safety Monitoring Board
EBV	Epstein Barr Virus
EDV	End diastolic velocity
EVR	Everolimus, Certican®
eGFR	Estimated GFR
ENR	Enrolled Patient Population
EOS	End Of Study
ESRD	End Stage Renal Disease
GFR	Glomerular Filtration Rate
GCP	Good Clinical Practice
GST	Glutathione-S-Transferase
HA	Hepatic Artery
HBsAg	Hepatitis B Surface Antigen
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HDL	High-Density Lipoproteine Cholesterine

HIV	Human Immunodeficiency Virus
HK	Hematokrit
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IS	Immunosuppression
ITT	Intention-to-Treat
LCMS	Liquid Chromatography - Mass Spectometry
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoproteine Cholesterine
LTx	Liver Transplantation
MDRD	Modification of Diet in Renal Disease Study Group
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model of End Stage Liver Disease
MMF	Mycophenolate mofetil
mmHg	Millimeters of Mercury
MPA	Mycophenolic Acid
NODM	New Onset Diabetes Mellitus
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCP	Pneumocystis Carinii Pneumonia
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-Protocol
PSV	Peak Systolic Velocity
PV	Portal vein
RAD	Everolimus, Certican®
RI	Resistant Index
RNA	Ribonucleid acid
RND	Randomization
SAE	Serious Adverse Event
SAF	Safety Population
Scr	Serum creatinine
SMPC	Summary of Product Characteristics
SNOMED	Systematized Nomenclature of Medicine
SOP	Standard Operating Procedures
TAC	Tacrolimus
tmax	Time until Maximum Plasma Concentration
Tx	Transplantation

ULN	Upper Limit of Normal
WHO	World Health Organization
WOCBP	Women Of Child Bearing Potential

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study
Patient number	A number assigned to each patient who enrolls in the study; when combined with the center number, a unique identifier for each patient in the study is created.
Phase	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Amendment 2

Amendment rationale

To allow more patients to be randomized into this study the following parameters of the in- and exclusion criteria were adapted (see next section). According to these adaptations the patient management was changed.

In addition some editorial changes and changes regarding the statistical analysis were performed.

At the time of the amendment 15 patients have been randomized to the study.

Changes to the protocol

The major changes that are made to the protocol are as follows:

- Measurement of the Tacrolimus C-0h levels can now be performed as per local practice (section 4 and 6.3)
- Inclusion criteria – randomization 2 was rephrased for a clearer understanding (section 5.1).
- Inclusion criteria – randomization 3: AST and ALT levels were raised to ≤5 times ULN, evaluation of gamma GT was deleted due to the fact that it does not reflect a prognostically important marker (section 5.1).
- For a better understanding, exclusion criteria – randomization 2 was separated in 4 independent criteria. Platelet, neutrophil and white blood cell count was reduced to 50,000/mm^3, 1,000/mm^3 and 2,000/mm^3 respectively (section 5.1).
- Former inclusion criteria – randomization 2 (now 6): Calculation mistake of concentration of hypertriglyceridemia was corrected (section 5.1).
- Graft loss was added as reason for premature patient withdrawal (section 5.2).
- Dispensing of study drug and instruction for use of study drug are described in more detail to avoid misuse (section 6.6.1, 6.6.2).
- According to the adaptation of in- and exclusion criteria, the permission of study drug adjustment and interruption in case of inability of tolerance of the protocol-specific dosing scheme is described in more detail (section 6.6.3 and appendix 5)
- PCP prophylaxis and treatment of oral candida will be performed according to local practice (section 6.6.5)
- It was added, that pregnancy outcomes must be collected for the female partners of any males who took study drug in this study (section 8.2)

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font~~ for deletions and red underlined for insertions.

A copy of this CRAD001HDE13 Protocol Amendment will be sent to the EC for review. The changes described in this amendment require IRB/EC approval prior to implementation.

In addition, a revised informed consent that takes into account the changes to the protocol described herein will be submitted to the IRB/EC for approval.

Amendment 3

Amendment rationale and changes

Details of five sub-studies which will be conducted in selected centers were added to the protocol in chapter 3.3 and in the assessment schedule in section 7.

In addition some editorial changes were performed.

A copy of this CRAD001HDE13 Protocol Amendment will be sent to the EC and HA for review. The changes described in this amendment require EC and HA approval prior to implementation.

Amendment 4

Amendment rationale and changes

The protocol has been refined to clarify the mandatory usage of corticosteroids in this study. Additionally, Inclusion Criterion 3/Exclusion Criterion 11 has been adjusted to include total abstinence as acceptable contraception method.

In addition some editorial changes were performed.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font~~ for deletions and red underlined for insertions.

A copy of this CRAD001HDE13 Protocol Amendment will be sent to the EC for review. The changes described in this amendment require IRB/EC approval prior to implementation.

In addition, a revised informed consent that takes into account the changes to the protocol described herein will be submitted to the IRB/EC for approval.

Amendment 5

Amendment rationale and changes

The purpose of this amendment is to adapt one exclusion criteria (Excl.Crit.N°5) to better align with given clinical praxis and patients' condition post liver transplantation.

Therefore Exclusion Criterion 5 (at randomization) has been adjusted to allow inclusion of patients with hemoglobin < 6.0 g/dL (transfusion of erythrocytes concentrate during or after transplantation are allowed according to investigator discretion.) (see Section 5).

In addition some smaller editorial changes were performed (correction of spelling errors).

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font~~ for deletions and red underlined for insertions.

A copy of this CRAD001HDE13 Protocol Amendment will be sent to the EC and HA for review. The changes described in this amendment require IRB/EC and HA approval prior to implementation.

1 Background

The success rate of liver transplantation has drastically increased over the last 25 years. Data from the European Liver Transplant Registry have recently indicated that the current 5-year patient survival rate in Europe is 72% (Adam et al. 2003). Calcineurin inhibitors (CNI) have contributed largely to the improvement in patient and graft survival after liver transplantation. However long-term use of CNI, cyclosporine or tacrolimus, is associated with side-effects which are source of morbidity. Among long-term survivors population chronic renal dysfunction is a well-recognized cause of morbidity.

In addition to CNI therapy pretransplantation renal impairment, post-operative acute renal failure, age of recipient, hepatitis C (HCV) infection, hypertension, diabetes mellitus, hyperlipidemia can contribute to development of chronic renal dysfunction after liver transplantation (Gonwa et al. 2001, Cohen et al., 2002, Velidedeoglu et al. 2002, Pawarode et al. 2003, Moreno et al. 2003, Ojo et al. 2003).

Recently a population-based cohort analysis estimated the 5-year cumulative incidence of chronic renal failure defined as a glomerular filtration rate of 29 ml/min/1.73 m^2 of body-surface area or less or the development of end-stage renal disease among 36 849 liver transplant patients to be 18% (Ojo et al. 2003). The prevalence of moderate chronic renal impairment would be several times higher (Pawarode et al. 2003, Moreno et al. 2003). Importantly, chronic renal failure as well as moderate chronic renal dysfunction has been associated with adverse outcome, namely increased mortality (Pawarode et al. 2003, Moreno et al. 2003, Ojo et al. 2003). Ultimately, a safe and effective therapeutic intervention which would reduce the incidence of chronic renal dysfunction is strongly recommended.

As stated before, the major contributor to the level of renal function in a recipient of a liver allograft is the use and level of CNIs. Reducing or eliminating the exposure to tacrolimus early within the first several months post-transplant should result in improved renal function. Although MMF has been evaluated as a strategy to eliminate CNIs, the incidence of acute rejection after elimination of the CNIs of 19-40% is unacceptable to many clinicians and this approach has not been widely adopted. In contrast to MMF, data from the RAD001H2401 study in 144 maintenance liver transplant recipients provides evidence to support that concentration controlled everolimus allows elimination of CNIs without increasing the risk for acute rejection compared to patients who remain on CNI-based therapy.

The previous RAD001B158 study enrolled and randomized 119 de novo liver transplant patients to one of three fixed doses of everolimus (1, 2, or 4 mg/day) or to placebo in combination with standard Neoral trough drug blood levels. Overall, data from this Phase 2 study supported that everolimus can be safely introduced into de novo recipients of liver allografts. Further, the results of pharmacokinetic modeling from this trial are consistent with the results from renal and cardiac transplant trials indicating that the trough level of everolimus in blood of less than 3 ng/mL is associated with the risk for acute rejection with loss of efficacy. Other recent trials substantiate that concentration controlled everolimus provides for the minimization of cyclosporine or for tacrolimus in de novo renal transplantation, as well as significant reduction of cyclosporine in cardiac transplantation without increasing the risk for acute rejection and preserving renal function.

Fibrosis of an allograft among recipients who are HCV positive is another important factor that contributes to the loss of the liver allograft. This group of recipients that may require antiviral therapy comprises at least 50% of the liver transplant population in many countries. However, there is at present no available therapeutic agent or regimen that has reliably demonstrated an effect on the development of fibrosis, or is well tolerated by HCV positive patients. Preclinical data suggest that there is an effect of proliferation signal inhibitors such as everolimus on processes that contribute to the development of liver fibrosis. Everolimus may directly or indirectly, by reducing or eliminating exposure to tacrolimus, reduce development or the rate of development of fibrosis in liver allografts (Verrill et al., 2002, Zhu et al., 1999, Frizell et al., 1994).

Based on the experience that has accumulated in other solid transplant studies as well as in smaller liver transplant studies, introduction of everolimus may provide the opportunity to address the medical need of providing superior renal function by allowing for the reduction or for the elimination of tacrolimus early post-transplant, and possibly may impact the development or the rate of progression of fibrosis in HCV positive recipients.

2 Study purpose

This study is designed to provide data on efficacy and safety of a post-transplantation regimen in liver allograft patients consisting of reduced tacrolimus in the presence of everolimus.

3 Objectives

3.1 Primary objective(s)

To demonstrate that an immunosuppressive regimen based on everolimus (EVR) in co-exposure with tacrolimus (TAC) has superior efficacy compared to tacrolimus alone on estimated glomerular filtration rate (MDRD-4 formula) at Month 12 in *de novo* liver transplant recipients.

3.2 Secondary objective(s)

Key secondary objective:

To evaluate the incidence of a composite of treated biopsy proven acute rejection (BPAR), graft loss or death at Month 12.

Efficacy related objectives

- To evaluate the incidence of a composite of treated BPAR, graft loss, death or loss to follow-up at months 6 and 12.
- To evaluate the incidence of each component of the composite efficacy endpoint at month at months 6 and 12.
- To evaluate the incidence of a composite of death or graft loss at months 6 and 12.
- To evaluate treated BPAR by: (1) incidence, (2) time to event, (3) severity, (4) diagnosis leading to transplantation.

- To evaluate any acute rejection by: (1) incidence, (2) time to event, (3) severity.
- To evaluate the incidence of:
  - Treated acute rejection.
  - BPAR.
  - Treated BPAR.

Renal function-related objectives

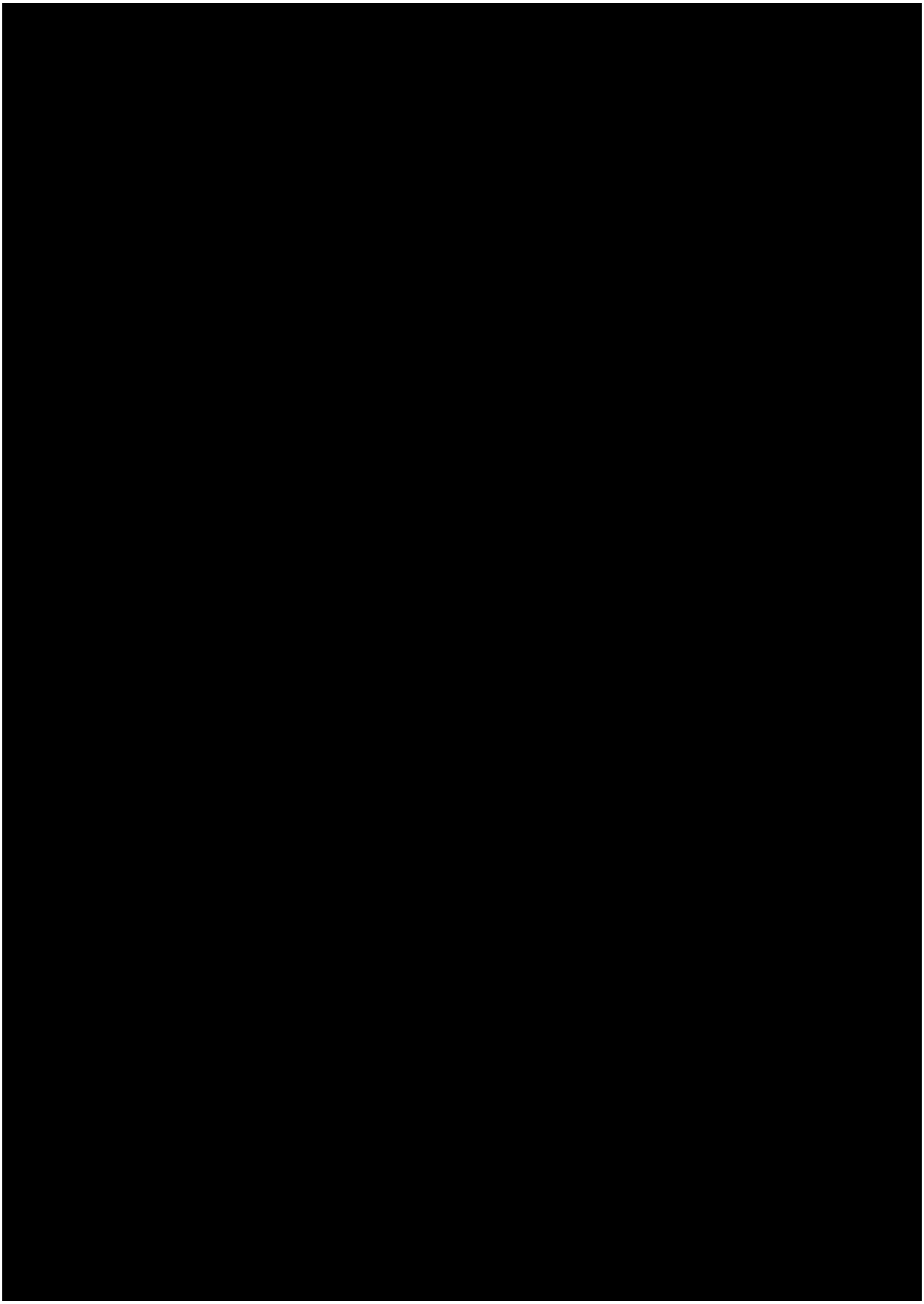
- To evaluate the evolution of post-randomization renal function over time assessed by the change in estimated GFR (MDRD-4), including to Months 6, and 12.
- To evaluate renal function by eGFR using various methods (MDRD-4, Nankivell, Cockcroft-Gault, CKD-EPI and Hoek formulae).
- To evaluate the incidence of patients experiencing a decline in eGFR (MDRD-4) of < 10, 10<15, 15<20, 20<25, and ≥ 25 mL/min/1.73m^2 from Screening, Week 2 post transplantation and randomization to Months 6, and 12.
- To evaluate serum creatinine at various time points.
- To evaluate renal function and change in eGFR from screening, randomization, and Week 2 post transplantation to Months 6 and 12 eGFR in following subgroups: age (< 60 and ≥ 60 years), gender, race, renal function strata (< 30, 30<45, 45<60, ≥ 60 mL/min/1.73m^2, below/above 45 mL/min/1.73m^2, below/above 60 mL/min/1.73m^2), HCV status, lab MELD score categories (≤14, 15-19, 20-24, 25-29, ≥ 30), and diagnosis leading to transplantation.
- To evaluate urinary protein/creatinine ratio at various time points.
- To evaluate the incidence of proteinuria of 0.5<1.0 g/day, 1.0<3.0 g/day and ≥ 3.0 g/day at various time points.
- To evaluate the incidence of and time to renal replacement therapy.

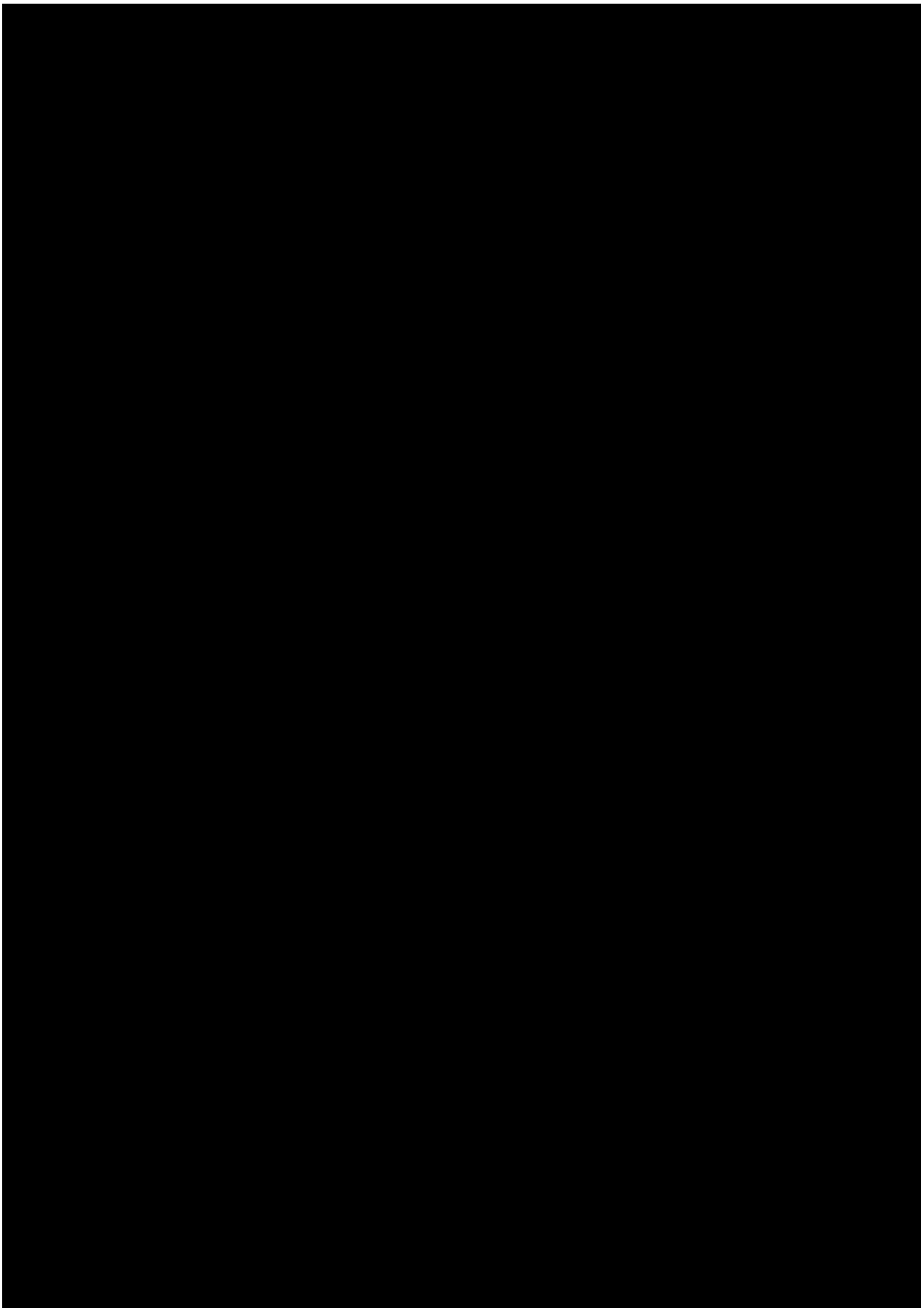
Safety related objectives

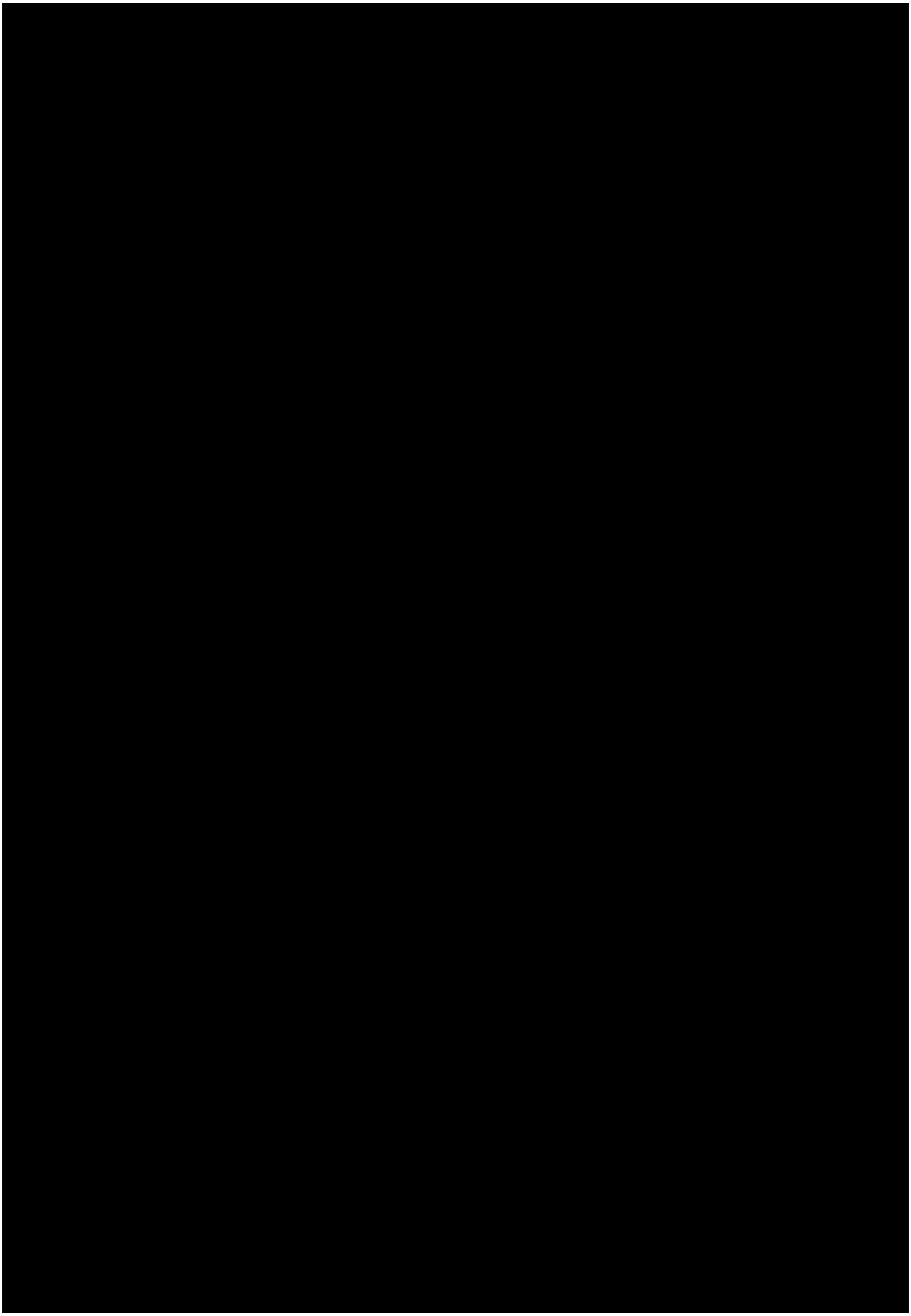
- To evaluate the incidence of Adverse Events (AEs)/Infections/Serious Adverse Events (SAEs).
- To evaluate the incidence of treatment-related side effects, including incidence of new onset diabetes mellitus (NODM), evolution of metabolic parameters as subdivisions of serum/plasma lipid panel, neurotoxicity and hypertension.
- To evaluate the incidence and reason (e.g. AE) of premature discontinuation of study medication and premature discontinuation from the study.
- To evaluate the incidence and reason (e.g. AE) of interruption and dose adjustment of study medication.

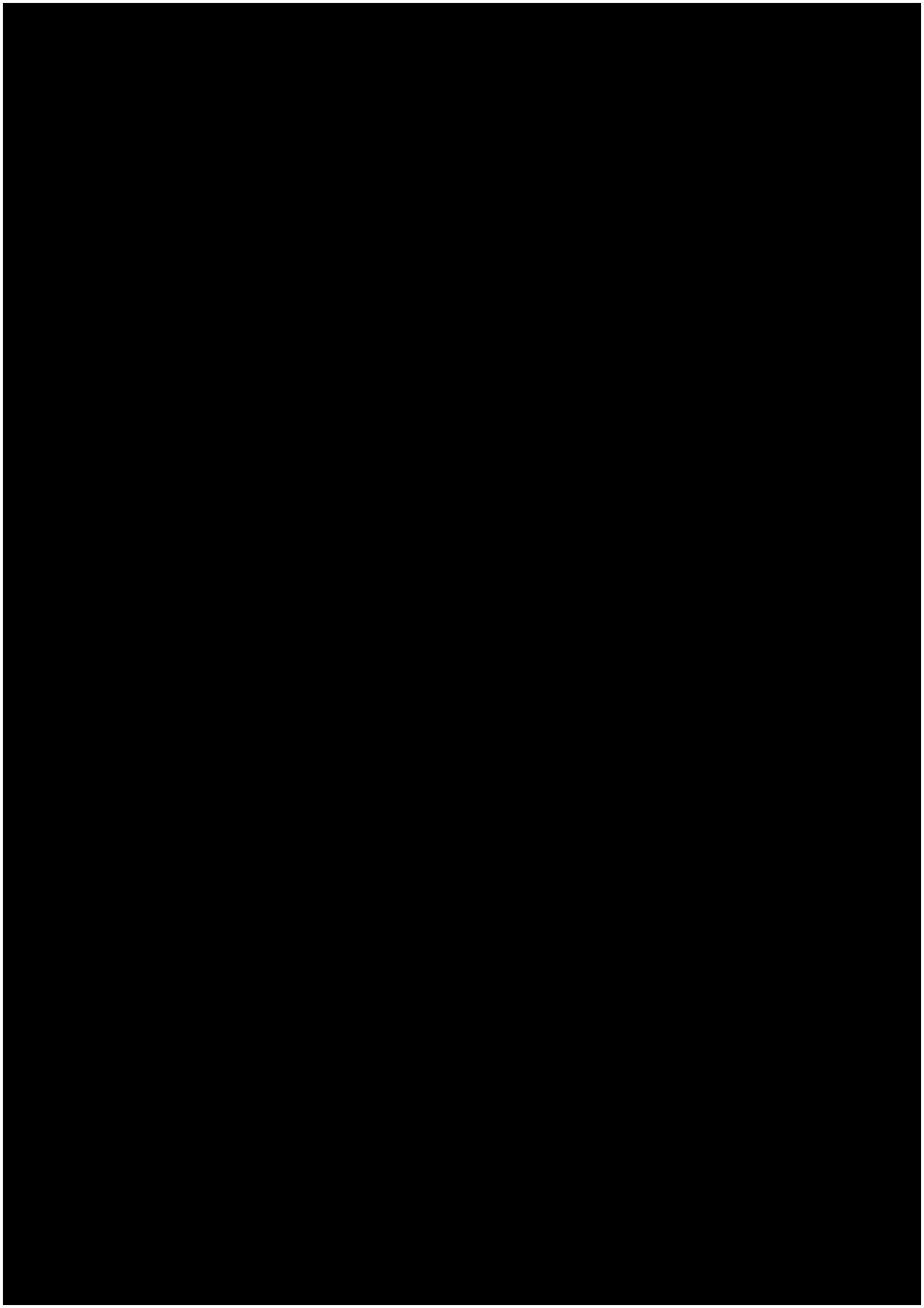
Virus (HCV, CMV) and Hepatocellular Carcinoma (HCC) related objectives

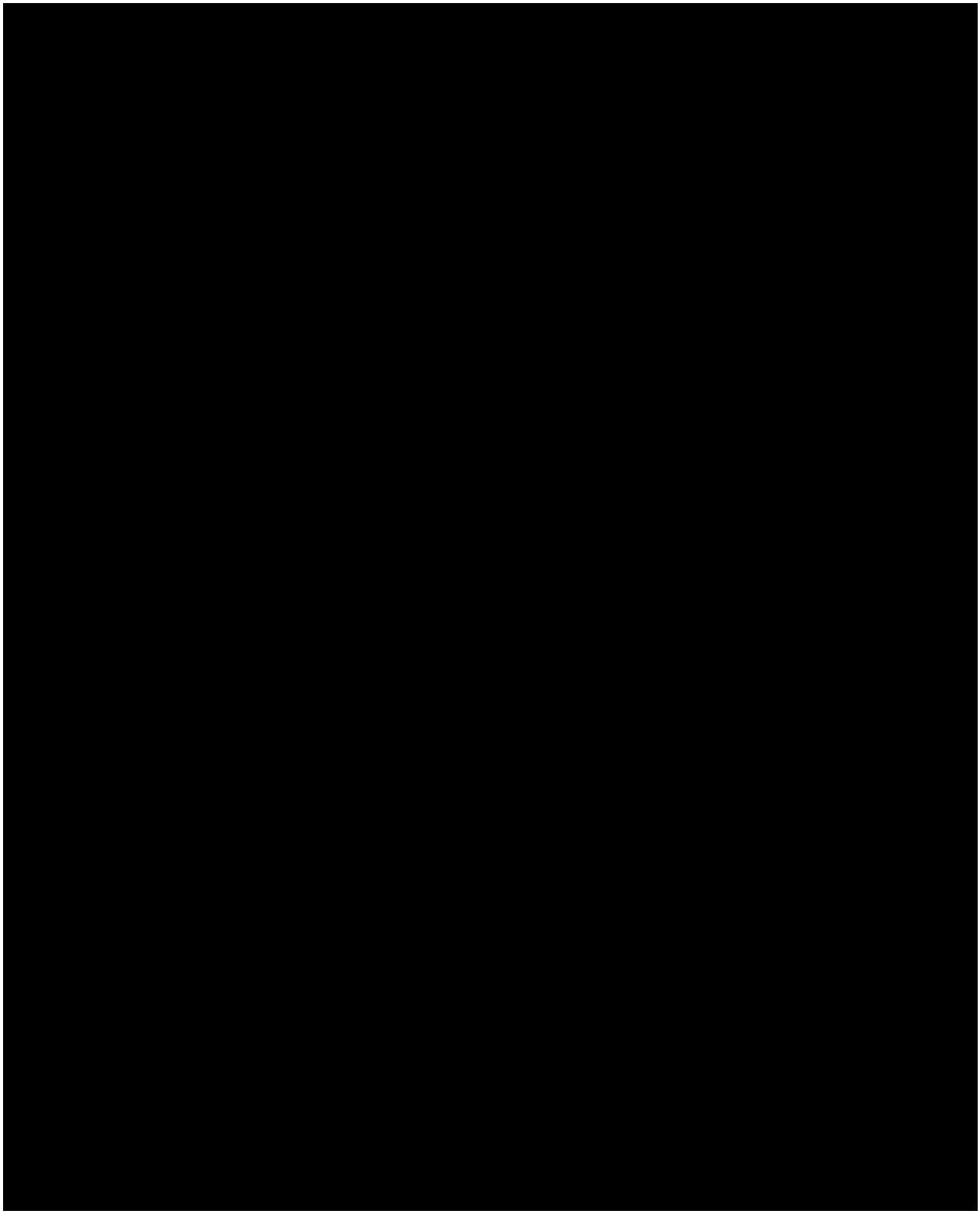
- To evaluate the incidence of HCV and HCV related fibrosis.
- To evaluate rates of progression of HCV related allograft fibrosis.
- To evaluate HCV viral load (HCV- messenger ribonucleic acid (mRNA) levels overall and by genotype).
- To evaluate incidence of and response to HCV antiviral treatment.
- To evaluate the rate of recurrence of HCC at 12 post-transplantation in patients with a diagnosis of HCC at the time of liver transplantation adjusting for various risk factors, such as number of tumor nodules, total tumor diameter, alpha fetoprotein level, etc.
- To evaluate the incidence of de novo HCC malignancies.
- Incidence and severity of CMV viral infections.

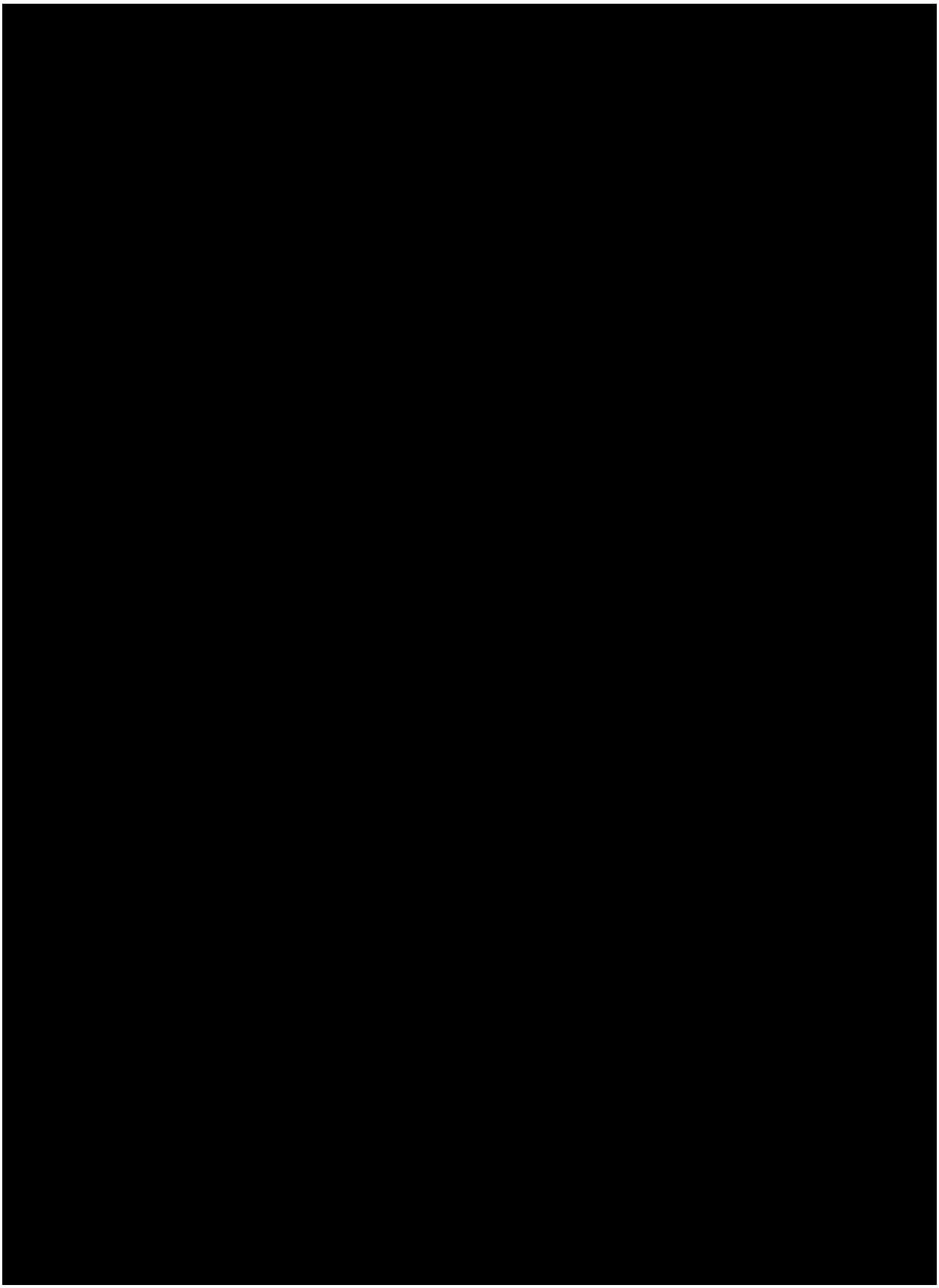


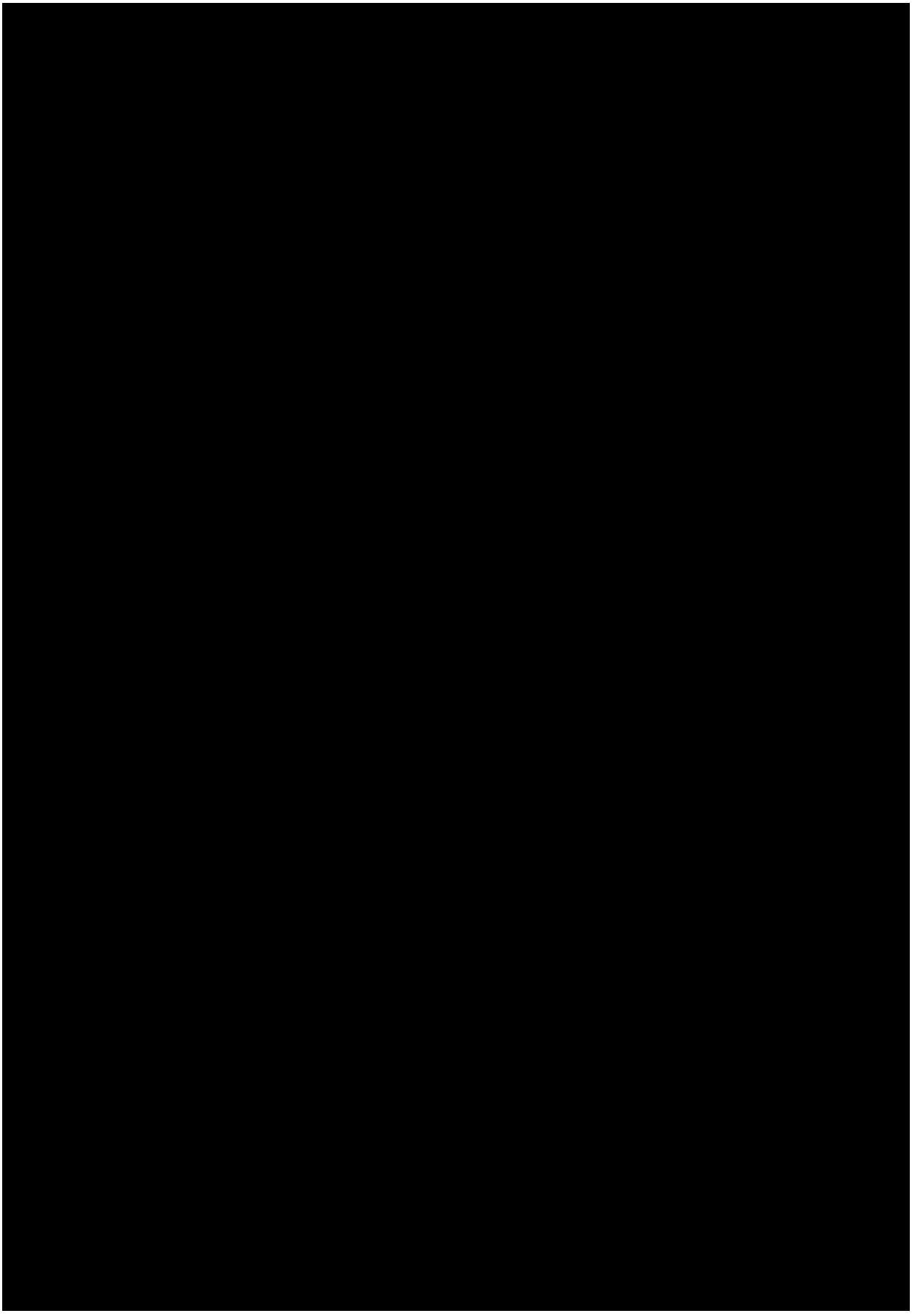


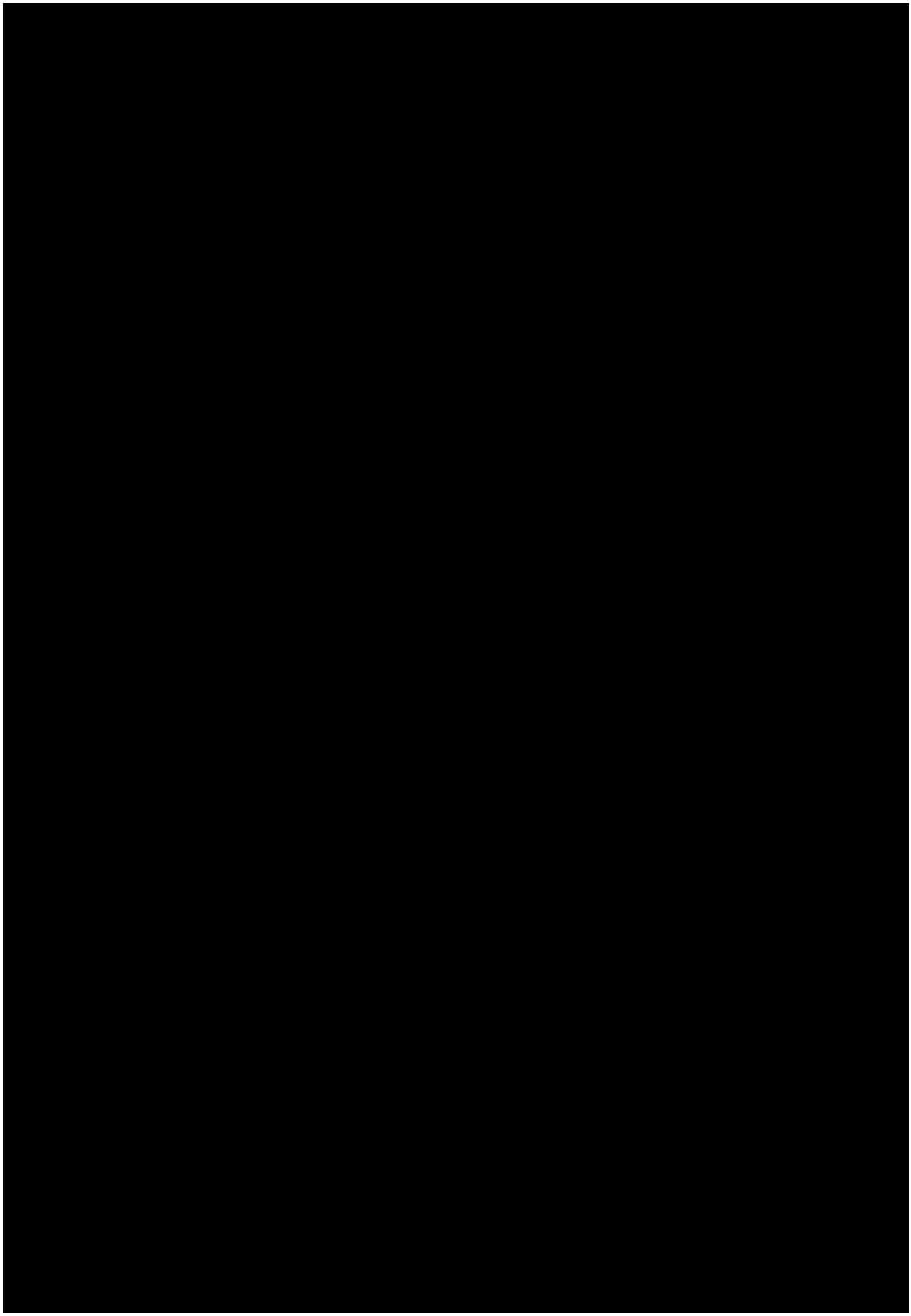












4 Study design

This is a 12-month, multi-center, open-label, randomized, controlled study to evaluate efficacy and safety and evolution of renal function of everolimus (EVR) in co-exposure with tacrolimus (TAC) in *de novo* liver transplant recipients.

Patients will be consented and screened for eligibility prior to liver transplantation (LTx). The study treatment will start with a run-in period that ends on the day of randomization (RND), scheduled at 7-21 post- LTx. Patients after consent who have undergone successful LTx (with optional induction therapy) will be entered in this run in period (between 3 and 5 days post-LTx) and may be initiated on an optional induction therapy, MMF, TAC at investigators' discretion until at least day 7 or maximally until day 21 post LTx with mandatory CS therapy until at least Month 6 post Tx.
Patients on MMF according to local practice must have the MMF administration discontinued by the time of RND. MMF is discontinued according to local practice.
At day 7-21 post-transplantation the following information at minimum has to be obtained from a patient to be randomized into the study:

- Abbreviated MDRD eGFR > 30 mL/min/1.73m^2. Creatinine results obtained in local laboratory within 5 days prior to RND are acceptable.

All eligible patients (according to in-/exclusion criteria at RND) will be randomized in between 7 and 21 days post LTx to one of the two treatment groups in a 1:1 ratio:

Arm 1: EVR/TAC group (Tacrolimus minimization arm)

Everolimus should be initiated at the day of randomization. Therapeutic drug monitoring will be mandatory throughout the duration of the study. Whole blood trough levels should be obtained 5 ± 2 days after either everolimus or tacrolimus doses are changed.

Everolimus dosing: Everolimus study drug will be started at the day of randomization at a dose of 1.0 mg b.i.d (2.0 mg daily dose). The everolimus whole blood trough (C-0h) levels should be targeted to be maintained between 3-8 ng/mL. The twice daily dose can be changed in order to maintain the 3-8 ng/mL C-0h levels through the remainder of the study.

Tacrolimus dosing: After everolimus whole blood trough levels have been confirmed to be in the target range (3-8 ng/mL), tacrolimus tapering should begin, achieving a target tacrolimus C-0h levels of <5 ng/mL plus corticosteroids by three weeks after randomization and continuing through the remainder of the study.

Arm 2: TAC group

Tacrolimus dosing: Tacrolimus C-0h levels should be targeted to be maintained at 6-10 ng/mL plus corticostroids.

Control assessments will be performed at day 8 and 15 and at month 1, 3, 6, 9, and 12 after randomization. The final examination will be performed at Month 12 after randomization and at timepoint of early discontinuation from study treatment, if applicable. Drug dosage will be modified regarding to C-0h level measured as per local practice at standard visits (target C-0h levels: Certican® 3-8 ng/mL; TAC <5 ng/mL in Arm I and TAC 6-10 ng/mL in Arm II). The established treatment will be continued until Month 12 post RND (final assessment). Renal function (eGFR) as well as efficacy (treated BPAR, graft loss, and/or death) will be assessed at every study visit.

Management of corticosteroids for all study arms

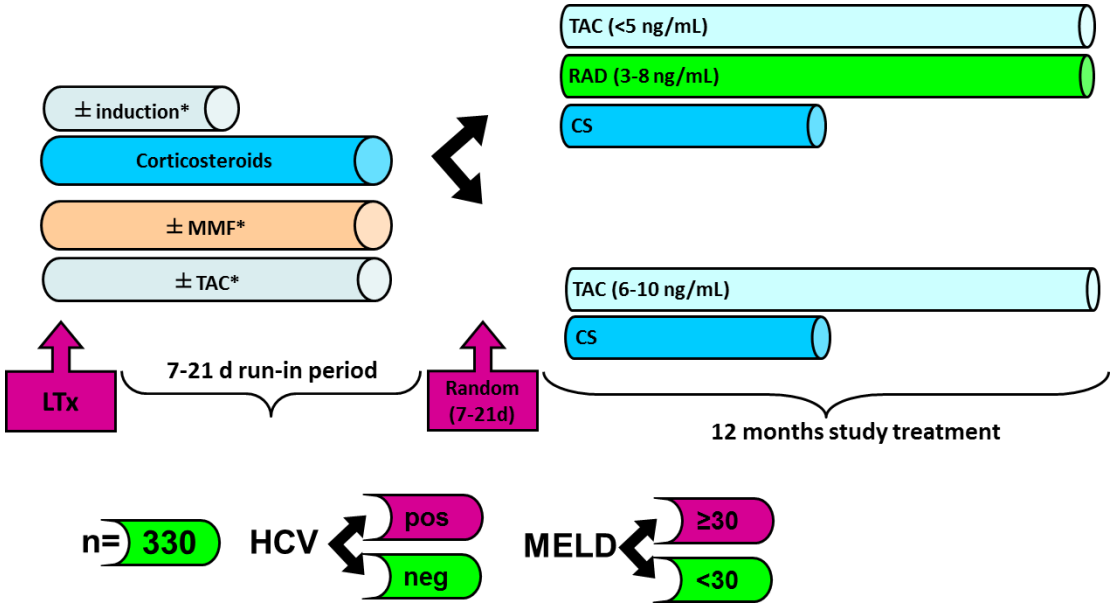
For patients in all groups, corticosteroids will be initiated at or prior to the time of transplantation according to local practice. Corticosteroids may be used for the duration of the study according to the investigator`s discretion, but may not be eliminated sooner than 6 months post-transplantation.

Peri-operative i.v. steroids may be used per local practice. Oral corticosteroids will be administered according to local practice during the trial. However, after randomization, the minimum dosage of corticosteroids must be equivalent to 5 mg prednisone/day. Corticosteroids may not be discontinued earlier than Month 6 post-transplantation.

Table 4-1 Study outline

Period	Screening*	Run in Period#	Baseline RND	Treatment						EOS
Visit	1		2	3	4	5	6	7	8	9
Days after Tx	Before Tx	7-21	7-21							
Days of treatment			1	8	15	30	90	180	270	360
Month of treatment						1	3	6	9	12

*day 21-day 1 (= day of transplantation)
day 1-day 7/21 after transplantation, end with randomization



*optionally center-specific

EVR / TAC group (ARM I)	
EVR	C0-h: 3-8 ng/mL
TAC	C0-h: <5 ng/mL
CS	prednisone equivalent at least until Month 6
TAC group (ARM II)	
TAC	6-10 ng/mL
CS	prednisone equivalent at least until Month 6

5 Population

The study population will consist of *de novo* liver transplant recipients who will be enrolled prior to LTx and randomized 7 to 21 days post LTx in a 1:1 ratio to either everolimus (EVR)

in co-exposure with tacrolimus (TAC) at a reduced dose (< 5ng/ml) or TAC (6-10 ng/ml). 330 evaluable patients (165 in each treatment group) will be recruited.

The study will be conducted in 15 transplant centers in Germany.

5.1 Inclusion/exclusion criteria

The investigator must ensure that all patients who meet the following inclusion and do not fulfill any of the exclusion criteria are offered enrollment in the study. No additional inclusion/exclusion parameters can be applied by the investigator, in order that the study population will be representative of all eligible patients.

Inclusion Criteria

1. Patients who are willing and able to participate in the study and from whom written informed consent has been obtained.
2. Male or female recipients of a full-size liver allograft, aged 18 to 65 years.
3. Females capable of becoming pregnant must have a negative pregnancy test prior to start of study and before randomization and are required to practice a medically approved method of birth control or live in total abstinence for the duration of the study.

Exclusion Criteria

1. HIV positive patients.
2. Patients who are recipients of multiple solid organ or islet cell tissue transplants, or have previously received an organ or tissue transplant.
3. Patients with renal failure or CKD/ESRD who require renal replacement therapy for more than 2 weeks prior to transplantation.
4. History of malignancy of any organ system within the past 5 years whether or not there is evidence of local recurrence or metastases, other than non-metastatic basal or squamous cell carcinoma of the skin or HCC (see next criteria).
5. HCC that does not fulfill Milan criteria (1 nodule ≤ 5 cm, 2-3 nodules all ≤ 3 cm) at the time of transplantation.
6. Patients with a known hypersensitivity to the drugs used on study or their class, or to any of the excipients.
7. Patients receiving drugs known to significantly interact with any immunosuppressant used in the trial.
8. Patients who are recipients of AB0 incompatible transplant grafts.
9. Patients with a current systemic infection or sepsis requiring active use of IV antibiotics.
10. Patients with symptoms of significant mental illness and with inability to cooperate or communicate with the investigator. Patients who are unlikely to comply with the study requirements, or who are unable to give informed consent.
11. Women
    - who are pregnant or breast feeding (pregnancy defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/ml)).

- who are menstruating and capable of becoming pregnant* and not practicing a medically approved method of contraception (Pearl Index <1**) during and up to at least 4-8 weeks after the end of treatment. A negative pregnancy test (serum) for all women entering menarche is required with sufficient lead time before inclusion.
  *definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/m or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy
  **examples of particularly reliable methods with Pearl Index (PI) <1, according to guidelines of Deutsche Gesellschaft für Gynäkologie und Geburtshilfe:
  - Combination pill with estrogen and gestagen (no mini-pill, PI=0.1-0.9)
  - Vaginal ring (NuvaRing®, PI=0.65 uncorr.; 0.4 corr.)
  - Contraceptive patch (EVRA®, PI= 0.72 uncorr.; 0.9 corr.)
  - Estrogen-free ovulation inhibitors (Cerazette®, PI=0.14)
  - Progestin-containing contraceptives (Implanon®, PI=0-0.08)
  - Injectable 3-month depot progestins (PI=0.3-1.4; 0.88 corr.)
  - Intra-uterine progestine device (Mirena®, PI=0.16)
- Highly effective contraception methods include total abstincence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

12. Patients, who have already been randomized into this study earlier must not be included a second time.
13. Participation in another clinical trial.

Inclusion Criteria - Randomization

1. eGFR (MDRD4 formula) > 30 mL/min/1.73m^2 at time of randomization.
2. Absence of thrombosis via Doppler ultrasound of the major hepatic arteries, major hepatic veins, portal vein and inferior vena cava at time of randomization and prior to any initiation of treatment with everolimus.
3. Allograft is functioning at an acceptable level by the time of randomization as defined by total bilirubin levels ≤3 times ULN and AlkP, AST, ALT levels ≤ 5 times ULN.

Exclusion Criteria - Randomization

1. Patients who are not able to take oral medication at time of randomization.
2. Patients with platelet count <50,000/mm³)
3. Patients with an absolute neutrophil count of <1,000/mm³
4. Patients with a white blood cell count of <2,000/mm³)
5. Patients with hemoglobin < 6.0 g/dL.(transfusion of erythrocytes concentrate during or after transplantation are allowed according to investigator discretion.)
6. Patients with uncontrolled hypercholesterolemia (>350mg/dL; >9mmol/L) or hypertriglyceridemia (>750 mg/dL, >8.5 mmol/L).
7. Patients with a protein/creatinine ratio indicating daily urinary protein excretion >1 g/24h at time of randomization.
8. Patients with clinically significant or uncontrolled systemic infection requiring active use of IV antibiotics at the time of randomization.

9. Patients who have received an investigational drug within 30 days prior to randomization.

5.2 Premature patient withdrawal

Patients must be withdrawn from the study drug for any of the following reasons:

- Withdrawal of informed consent (which leads also to study withdrawal)
- Occurrence or detection of severe medical disorder jeopardizing the life of the patient in the immediate future
- Occurrence of an episode of acute rejection that requires T-cell depleting therapy or occurrence of more than three steroid sensitive episodes of acute rejection.
- Pregnancy
- Graft loss

Patients who discontinue study drug should NOT be considered withdrawn from the study. See Section 7 for the required assessments of these patients after study drug discontinuation.

Patients also should be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason. Protocol violations may lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

If premature withdrawal of study drug occurs for any reason, the investigator must determine the primary reason for a patient's premature withdrawal from the study medication and record this information on the Study Drug Completion CRF.

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study drug will not be replaced by newly enrolled patients.

6 Treatment

6.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 2, the third patient is assigned patient number 3). Once assigned to a patient, a patient number will not be reused. If the patient fails to be randomized for any reason, the reason for not being randomized will be entered on the Screening Failure Log.

6.2 Investigational and control drugs

Investigational drug

Certican®

Active ingredient:	everolimus (RAD001)
Galenic form:	tablets
Dose:	one tablet containing 0.25mg, 0.5mg, 0.75mg or 1.0mg
Dosing schedule:	twice daily, dose according to blood levels
Packaging:	blisters of 10 tablets

Other immunosuppressive drugs

- **Tacrolimus**

  Tacrolimus Hexal®

Active ingredient:	tacrolimus
Galenic form:	capsules
Dose:	one capsule containing 0.5, 1.0, or 5.0mg
Dosing schedule:	twice daily, dose according to blood levels
Packaging:	blisters of 10 capsules

- **Corticosteroids**
  are mandatory within the first six months after TX.

Further immunosuppressive agents are excluded. Everolimus and Tacrolimus Hexal® will be supplied by Novartis.

6.3 Treatment arms

At Baseline (Visit 2) between 7 and 21 days post LTx patients will be assigned to one of the following two treatment groups in a ratio of 1:1.

- **EVR/TAC group (ARM I):**

  Everolimus (C0-h: 3-8 ng/mL*) + tacrolimus (C0-h: < 5 ng/mL*)

- **TAC group (ARM II):**

  Tacrolimus (C0-h: 6-10 ng/ml*)

  *Trough levels as per local practice, e.g. liquid chromatography coupled with mass spectrometry (LCMS). Values derived from enzyme based assays will be corrected (as described in the manufacturer's instructions).

6.4 Treatment assignment

At Baseline (Visit 2), which has to take place prior to randomization, all patients who meet the inclusion and do not fulfill any of the exclusion criteria will be given the lowest available number on the randomization list of the respective stratum. This number assigns them to one of the treatment arms. The investigator will enter the randomization number on the CRF.

The randomization numbers will be generated using the following procedure to insure that treatment assignment is unbiased and concealed from patients and investigator staff. A

randomization list will be produced under the responsibility of the Novartis Nürnberg GCP Officer using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. Randomization will be stratified by HCV status (positive/negative) and lab MELD (Model of End Stage Liver Disease) score below/equal or above 30 at transplantation.

Randomization of individual patients will be performed centrally by a CRO. Allocation of a patient to one of the two treatment groups will be performed in the following steps.

1. Information about patient enrolment (Screening Visit):
   Study sites will inform the CRO about each patient inclusion via fax
2. Randomization (Baseline Visit):
   At day of randomization, the site will provide the information of eligible patient to the CRO by fax.
   The CRO will allocate the patient the next free consecutive randomization number allocated to the site. Randomization number and allocated treatment (according to the randomization list) will be provided to the site by fax.

The randomization number will be entered on the CRF of an individual patient.

6.5 Treatment blinding

Not applicable, since this is an open-label study.

6.6 Treating the patient

6.6.1 Dispensing the study drug

Each study site will be supplied by Novartis with Certican®and Tacrolimus Hexal®. Certican® will be provided as tablets in 0.25 mg, 0.5 mg, 0.75 mg and 1.0 mg strength, packaged in packages, and labeled according to the German legal requirements. Tacrolimus Hexal® will be provided as capsules in 0.5 mg, 1.0 mg and 5 mg strength.

Immediately before dispensing study drug (Certican®) to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Accounting Form) containing that patient's unique patient number. Tacrolimus Hexal® dispensing will be also recorded on the Drug Accounting Form.

6.6.2 Instructions for use of study drug

The starting dose will be 1 tablet of 1.0 mg everolimus in the morning, and 1 tablet of 1.0 mg in the evening for all patients. First dose of study drug has to be applied within 24h after randomization.

Additional medication for dose adjustments will be provided in 0.25 mg, 0.5 mg and 0.75 mg tablet strengths. The dose will be adjusted to maintain the everolimus trough blood levels between 3-8 ng/mL. Five (5) days after randomization or any later, everolimus dose should be doubled if the trough level is below 3 ng/mL. The trough level should not exceed 8 ng/mL during the whole study duration.

Target level of Certican® should be achieved within 14 days post randomization. Close monitoring of trough levels is required at least once monthly.

Patients in Arm 1 will take everolimus (C0-h: 3-8 ng/mL) twice daily in 12 hours intervals simultaneously with tacrolimus (C0-h: < 5 ng/mL), on a consistent schedule with regards to time of day and relation to meals. No grapefruit or grapefruit juice should be taken at all throughout the study.

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

At each patient's study visit, site personnel should count remaining study medication (everolimus, tacrolimus) to check compliance.

All dosages dispensed to and returned by the patient during the study must be recorded on the Drug Accounting Form in the Investigator Folder. Patients randomized to a specific immunosuppressive regimen in Arm I or Arm II have to remain on this medication up to the end of the study – otherwise the patient will be discontinued form the study drug regimen.

Patients may be seen by local general practitioner in between protocol defined visits. The main PI is responsible to give guidance to the local general practitioners for patient's management. The PI is responsible to obtain all information about measured levels of immunosuppressive medications and changes of dosages throughout the study.

6.6.3 Permitted study drug dose adjustments and interruptions

For patients who are unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions are permitted in order to keep the patient on study drug. All changes must be recorded on the Dosage Administration Record CRF.

The following guidelines should be followed as far as clinically feasible:

Everolimus

Because everolimus is the mainstay of the protocol in the investigational arm (Arm 1), everolimus dose should be continued on a stable level according to trough levels. Treatment interruptions and dose reduction will be allowed for those patients who do not tolerate the prescribed dose of everolimus indicated by the occurrence of adverse events.

In both renal and heart transplantation, everolimus trough concentrations ≤ 3 ng/mL were associated with a significantly lower protection from acute rejection compared with trough levels > 3 ng/mL. Although hyperlipidemia was common over the full exposure range, it responded to corticosteroid dose reduction, dietary management, and lipid-lowering therapies, and were, therefore, not dose-limiting. The incidence of leukocytopenia did not show any exposure-response relationship to everolimus trough concentrations. The incidence of notable thrombocytopenia (< $100x10^9$/L) increased with everolimus exposure; however, the incidence of clinically meaningful platelet reductions (< $75x10^9$/L) was generally low.

In severe hematologic adverse events (CTCAE 4.0) including leukocytopenia and thrombocytopenia everolimus should be interrupted until the condition has resolved. If a hemolytic uremic syndrome (hemolytic anemia, acute renal failure, uremia) occurs, everolimus has also to be permanently discontinued.

In case of a decrease of renal function all potential nephrotoxic medication other than the immunosuppressive agents should be discontinued first. If stadium 1 of acute kidney injury is met (an increase in SCr >or=0.3 mg/dl or 25µmol/l (Chertow, 2005) or an increase in SCr of 50-100% from the initial value (Mehta, 2007)), everolimus and tacrolimus has to be reduced to the lowest trough levels according to the protocol (see above). If the acute kidney injury is not responsive to these measures, everolimus has to be discontinued.

Target therapeutic ranges for everolimus whole blood trough levels should be 3-8 ng/mL.

Dose should be adjusted if everolimus whole blood trough levels outside the target range are measured. Dose adjustments of everolimus should be monitored 5 ± 2 days later by a measurement of the everolimus blood trough level.

For patients who are unable to tolerate the protocol-specified dosing scheme due to a decrease in the platelet count, a decrease in hemoglobin level, a decrease in white blood cell count, an increase in cholesterol level, an increase in triglyceride level, or other adverse events, dose adjustments are permitted in order to keep the patient on investigational drug. The respective guidelines are appended to the clinical trial protocol (see Appendix 5).

The everolimus dose should be decreased by one dosing step (0.25mg b.i.d.) if a dose reduction is necessary. If a temporary reduction in everolimus level is needed the everolimus trough blood level should still be maintained no lower than 3 ng/mL. Everolimus should be discontinued if a trough level ≥ 3 ng/mL cannot be maintained due to toxicity. Severe and unremitting changes may also lead to investigational drug discontinuation.

If everolimus is interrupted for longer than 4 consecutive weeks, or more than 8 cumulative weeks, discontinuation of study medication should be discussed with the sponsor. Study drug may be interrupted during antibody treatment of rejection episodes. During the course of the trial the study drugs will be administered on a b.i.d. regimen. Study medication will not be provided to patients after they have discontinued the study.
If reduction of everolimus is necessary for the patient to remain in target trough range, everolimus dosing may be reduced by 0.25 mg intervals.

Appropriate information needs to be recorded on the Dosage Administration CRF.

The End of Treatment Visit will be performed and documented for all patients who are withdrawn prematurely from the treatment at time point of discontinuation. The Month 12 assessments will be performed for all patients randomized in the study.

Tacrolimus

Dose should be adjusted if tacrolimus whole blood levels are outside the target range. Target therapeutic ranges for tacrolimus whole blood trough levels should be < 5 ng/mL in the investigational arm (Arm I) and 6-10 ng/ml in the control arm (Arm II). In case of severe tacrolimus toxicity, dose reductions below the target levels may be performed on the investigators' discretion.

If tacrolimus medication is interrupted for more than 4 consecutive weeks, or more than 8 cumulative weeks, discontinuation of the tacrolimus should be considered.

Prednisone/Prednisolone

Oral corticosteroids (prednisolone or equivalent) will be administered according to local practice during the trial. However, after randomization, the minimum dosage of corticosteroids must be equivalent to 5 mg prednisone/day. Corticosteroids may not be discontinued earlier than Month 6 post-transplantation.

6.6.4 Rescue medication

Treatment for acute rejection episodes
Treatment for biopsy proven acute rejection will commence at the clinician's discretion or according to the center-specific protocol. An acute rejection episode will be considered to have been treated if a patient has received at least 3 days' treatment with a daily dose of 15mg/kg (max.1000 mg) or more of i.v. methylprednisolone (or equivalent) and/or at least 3 days of antilymphocyte therapy.
Treatment of acute rejection or presumed acute rejection will be recorded on the appropriate CRF page.

The biopsies will be read locally and the severity of acute rejection will be classified using the Rejection Activity Index (RAI) as defined by the World Gastroenterology Consensus Document (Banff, Hepatology 1997). In the event that a rejection episode is not confirmed by biopsy or a biopsy is not done, the clinician will score the severity of that rejection episode on the basis of clinical and functional criteria into severe (hospitalization, death) and non severe (all others).

6.6.5 Other concomitant treatment

Cytomegalovirus prophylaxis
Cytomegalovirus (CMV) prophylaxis or preemptive monitoring for CMV should be according to local practice and applied uniformly for all enrolled patients at the center. Treatment with valganciclovir, ganciclovir, cytomegalovirus hyperimmune globulin, acyclovir or valacyclovir is permitted and will be administered according to local practice. CMV prophylaxis is also recommended for CMV Donor positive, Recipient negative (D+/R-) patients and following any antibody treatment of acute rejection episodes.

***Pneumocystis carinii* pneumonia prophylaxis**
Prophylactic treatment for pneumocystis carinii pneumonia (PCP) consisting Bactrim® or equivalent (trimethoprim / sulfamethoxazole), starting when oral medication can be tolerated will be used as per local practice. Aerolized pentamidine (300 mg/month) or dapsone (100 mg/day) should be administered to patients unable to tolerate trimethoprim / sulfamethoxazole as per local practice.
Treatment of oral Candida
All patients will be treated according to local standard of care. The same prophylaxis strategy should be applied for all patients at a given site. Nystatin suspension in a swish and swallow regimen is recommended for the prophylaxis or treatment of oral thrush (Candida). Alternative clotrimazole lozenges/troches may be used. Routine use of systemic antifungal "azole" agents (i.e. ketoconazole, itraconazole, voriconazole and fluconazole) for oral candidiasis will not be allowed unless patients are systemically infected. Administration of

"azoles" may increase blood concentrations of both tacrolimus and everolimus; therefore their use should be minimized. Particular attention to side effects is required (see Appendix 3).

Hepatitis B prophylaxis
Prophylaxis for recurrent hepatitis B during the course of this study will be left to the investigator's discretion.

Treatment of HCV disease
Treatment for HCV disease can be done but not preemptively. Investigators will be allowed to treat HCV only when recurrent HCV disease has been documented, based on histological evidence as determined by the local pathologist. Therapies used for post-transplantation HCV disease will be documented on the appropriate CRF section. HCV patients should not receive HCV therapy during the time of tacrolimus elimination.

Recommended follow-up for HCC patients
It is highly recommended to monitor and follow-up the HCC patients as per the best local practices. Patients may be evaluated every three months during the 12 months study duration. In addition to the routine laboratory monitoring/tests, tumor markers (AFP-alphaprotein) and hepatic ultrasound may be performed on a quarterly basis and computed tomography scans (CAT, CT) or MRI (especially Fe-MRI) twice a year.

Other medication
The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the investigational drug. All medications (other than investigational drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after patients screening visit must be listed on the Prior-/Concomitant Medications/Significant Non-Drug Therapies pages in the CRF. If administered for an AE, it should be appropriately cross-referenced on the AE CRF.

6.6.6 Study drug discontinuation

In case of elevated cholesterol and/or triglyceride levels, lipid lowering medications should be optimized. HMG Co-A reductase inhibitors (e.g., fluvastatin) are to be administered according to local practice for the management of hyperlipidemia. The use of lovastatin is prohibited in this study. The starting dose of HMG Co-A reductase inhibitors will be equivalent to 20 mg pravastatin, 5 mg simvastatin or 20 mg fluvastatin, and may be increased to target and maintain a LDL level of < 130 mg/dL. Lipid lowering therapy should be optimized before dosage reduction of study medication is considered. If the elevation persists, the dosing of everolimus should be adjusted following the recommendations given in Appendix 5.

Dose may be reduced for those patients with other moderate/severe AEs according to the investigators' judgment. Also in these cases, the medication doses can be reduced by half or interrupted until event resolves.

If the everolimus medication is interrupted for more than 4 consecutive weeks, or more than 8 cumulative weeks within the 12 months study treatment, discontinuation of the respective medication should be considered and the patient withdrawn from study treatment.

Patients who discontinue study drug before completing the 12-months period should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit (EoT, Visit 9a) will be performed. The End of Study Assessment (Visit 9, Month 12) should be repeated at the originally planned time point, i.e. on Month 12 post randomization.

At a minimum, all patients who discontinue study drug, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days the last dose of study drug.

Patients who discontinue study drug should be considered withdrawn from the study when it is clear that the patient will not return for the Month 12 assessments.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Suspicion of thrombotic microangiopathy is raised when creatinine levels increase more than 50% from previous level in combination with thrombocytopenia and signs of hemolysis. In these cases everolimus should be discontinued and clinical workout is required (e.g. blood smear, kidney biopsy, etc).

6.6.7 Emergency unblinding of treatment assignment

Not applicable, since this is an open-label study.

6.6.8 Study completion and post-study treatment

For all patients who were included into this study (i.e., who signed informed consent and are randomized), whether discontinued the study treatment prematurely or completed the study, the final examination 12 months after randomization (Visit 9) will be performed.

The investigator also must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate routine care according to center practice.

7 Visit schedule and assessments

Table 2 lists all of the assessments and indicates with an “X” the visits when they are performed.

Patients should be seen for all visits on the designated day or as close to it as possible. During first month of treatment (until Visit 5) a time interval of ± 3 days and ±14 days thereafter may be acceptable. For the final visit (Visit 9) a time interval of 30 days is acceptable.

Patients who discontinue study drug before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which all of the assessments listed for the EoT visit (visit 9a) will be performed.

At a minimum, they will be contacted for safety evaluations during the 30 days following the last dose of study drug, including final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the patient record.

All data obtained from the assessments listed in Table 2 and described in detail in the subsections below must be supported by the patient's source documentation.

Table -2 Assessment schedule

Phase	Screening[1]	Baseline[2]	Treatment Phase						EOT[3]	EOS
Visit	1	2	3	4	5	6	7	8	9a	9
Days		1	8	15	30	90	180	270		360
Month					1	3	6	9		12
Informed consent	X									
Inclusion/ exclusion	X	X								
Randomization		X								
Demography	X									
General medical history	X									
Transplantation information	X									
Physical examination	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
Laboratory test:										
- Hemat. / Biochemistry		X	X	X	X	X	X	X	X	X
GFR		X	X	X	X	X	X	X	X	X
Urinalysis		X			X	X	X	X	X	X
Viral Serology	X									
CMV Monitoring	X	X			X	X	X	X	X	X
HCV Monitoring										
Viral load (RNA-level)	X	X[4]			X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Genotype	X									
Pregnancy test[5] (β-HCG)	X	X								X
Liver Doppler Ultrasound[6]		X								
Tacrolimus C0 level		X	X	X	X	X	X	X	X	X
Everolimus C0 level			X	X	X	X	X	X	X	X
[redacted]										
Rejection episodes		← as necessary →								
Biopsies[8]	X[7]	← as necessary →								X
Infections		← as necessary →								X
AEs		← as necessary →								X
SAEs		← as necessary →								X
Comments		← as necessary →								
Concomitant therapy		← as necessary →								
Immunosuppressive therapy		← as necessary →								
End of treatment / End of study									X	X

1) day 21-day of transplantation
2) Visit 2 (Baseline) has to be performed prior to randomization, 7-21 days after Tx.
3) End of Treatment Visit in case of premature study discontinuation
4) Only in HCV positive Patients
5) Only in women of childbearing potential

6) Liver Doppler Ultrasound of the hepatic artery, hepatic vein, portal vein, and inferior vena cava will be carried out up to 5 days prior to randomization.

7) Intraoperatively

8) For analysis of allograft fibrosis (only HCV positive patients)

[redacted]

Screening Visit - Visit 1 (day -21 to Tx)

1. Patient signs informed consent.
2. Patient's eligibility for the study according to in- and exclusion criteria will be checked.
3. Demographic data will be recorded (sex, age, ethnic origin).
4. Relevant medical history will be obtained and recorded until time point of randomization.
5. Transplantation information will be recorded (donor and recipient information).
6. A complete physical examination will be performed.
7. Vital signs will be measured.
8. Venous blood will be drawn for measurement of viral serology (HBsAg, HCV).
9. Venous blood will be drawn for CMV monitoring (including pp65 Ag).
10. Venous blood will be drawn for HCV monitoring: Viral load (RNA level), HCV genotype (only at screening)
11. Menopausal status will be recorded and in all women of childbearing potential a pregnancy test will be performed (β-HCG) (see also section 7.3).
12. An intraoperative biopsy (preferably after reperfusion) will be performed for analysis of allograft fibrosis (only HCV positive patients).

Baseline Visit - Visit 2 (day 1)

The Baseline assessment has to be performed prior to randomization.

1. Patient's eligibility for the study according to in- and exclusion criteria will be checked.
2. A complete physical examination will be performed.
3. Vital signs will be measured.
4. Urinalysis will be performed.
5. Venous blood will be drawn for measurement of hematology and biochemistry.
6. Glomerular Filtration Rate (GFR) will be calculated.
7. Venous blood will be drawn for HCV monitoring: Viral load (RNA level), in HCV positive patients only.
8. Venous blood will be drawn for measurement of the tacrolimus C0-h blood levels.
9. Prior/Concomitant medications / significant non-drug therapies will be recorded.
10. Patients eligible for the study will be randomized to one of the two treatment groups.
11. Study drug intake will be performed within 24h.
12. Information on rejection episodes biopsies, hospitalization, infections, and other (S)AEs that occurred since the last visit will be recorded.

Treatment phase – Visits 3, 4, 5, 6, 7, and 8 (Day 8, 15, Month 1, 3, 6, 9)

1. A complete physical examination will be performed at each study visit.
2. Vital signs will be measured at each study visit.
3. Returned study medication (everolimus) and returned tacrolimus will be counted. Patient will be provided with new study medication (if necessary) and dosing instructions for drug intake until following visit.
4. Venous blood will be drawn for measurement of hematology and biochemistry at each study visit.
5. Venous blood will be drawn at Month 1, 3, 6, and 9 for CMV monitoring (including pp65 Ag).
6. Venous blood will be drawn at Month 1, 3, 6, and 9 for HCV monitoring in HCV positive patients only: Viral load (RNA level).
7. Venous blood will be drawn for measurement of the tacrolimus and everolimus C0-h blood levels.
8. Urinalysis will be performed at Month 1, 3, 6 and 9.
9. Glomerular Filtration Rate (GFR) will be calculated at each study visit.
10. Changes in Concomitant medications / significant non-drug therapies will be recorded at each study visit.
11. (Changes in) Immunosuppressive medication will be recorded at each study visit.
12. Information on rejection episodes, biopsies, hospitalization, infections, and other (S)AEs that occurred since the last visit will be recorded.

End of Treatment/End of Study – Visit 9a and Visit 9 (Month 12)

In case of early discontinuation of study drug treatment, Month 12 assessments need to be performed

- as soon as possible after study drug discontinuation (Visit 9a).
- additionally at the originally planned time point, i.e. 12 months post randomization (Visit 9). At Month 12 for patients who discontinued study drug prematurely, only the following numbers 1, 2, 4, 5, 6, 8, 9, and 13 are mandatory.

1. A complete physical examination will be performed.
2. Vital signs will be measured.
3. Returned study medication (everolimus) and returned tacrolimus will be counted.
4. Venous blood will be drawn for measurement of hematology and biochemistry.
5. Venous blood will be drawn for CMV monitoring (including pp65 Ag).
6. Venous blood will be drawn for HCV monitoring: Viral load (RNA level), in HCV positive patients only.
7. Venous blood will be drawn for measurement of the tacrolimus and everolimus C0-h blood levels.
8. Urinalysis will be performed.
9. GFR will be calculated.
10. A control biopsy will be performed for analysis of allograft fibrosis (only HCV positive patients).

11. End of Study / End of Treatment information will be obtained.
12. Menopausal status will be recorded and in all women of childbearing potential a pregnancy test will be performed (β-HCG) (see also section 7.3).

For patients who prematurely discontinued study drug, information about rejection episodes, biopsies, opportunistic infections, malignancies and the current immunosuppression will be collected. SAEs will be collected until 30 days after the patient has stopped study participation (or longer in case of suspected relationship).

7.1 Information to be collected on screening failures

Only demography data and the reason for failing (screening failure log) are collected for those patients who fail to enter the treatment phase.

7.2 Patient demographics/other baseline characteristics

The following demographic data and other baseline characteristics will be recorded:

- **Demography:** age, sex, and ethnic origin
- **Relevant medical history / current medical conditions:**
  Relevant prior diseases and surgeries as well as concomitant diseases will be recorded with date of diagnosis / surgery and information on whether it is an active problem.
  For women, the menopausal status will be recorded. The pregnancy test (e.g. β-HCG) will be performed locally within 7 days prior to visit 1, 2 and 9. Results must be available and negative prior to administration of study medication and reported on the CRF.

7.3 Transplantation information

Donor information:

Viral serology on CMV, EBV, HCV, HBsAg.

Recipient information:

Viral serology on CMV, EBV, HCV, HBsAg, underlying liver disease prior to transplantation

7.4 Immunosuppressive Drugs/Compliance

Records of all immunosuppressive drugs (induction therapy, CS, MMF, everolimus, tacrolimus) used and dosages administered are to be kept during the study. All changes to the medication dosing regimen should be recorded in the Dosage Administration Record CRF, along with the reason for change and dates.

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient. This information should be captured in the source document at each visit.

7.5 Efficacy

The following efficacy variables will be obtained and recorded:

Renal function

Renal function will be assessed by measuring serum creatinine, serum cystatin C by Hoek's formula, and estimated GFR (eGFR) by CKD EPI, by Cystatin C-based Hoek's formula, MDRD-4, Nankivell and Cockcroft-Gault and proteinuria as determined by a spot urine protein/creatinine ratio. The evolution of renal function by chronic kidney disease strata (CKD) will be evaluated. The incidence of and time to renal replacement therapy will be assessed and the incidence of proteinuria at various timepoints will be evaluated.

- **Serum creatinine and serum cystatin C**
  For the analysis of serum creatinine and serum cystatin C, venous blood will be drawn and analyzed in the center's local laboratory.

- **Glomerular Filtration Rate (GFR)**
  The GFR is the best clinical estimate of renal function in health and disease, and correlates well with the clinical severity of renal function disturbances. Several studies have shown that in patients with progressive renal disease, GFR declines or reciprocal serum creatinine and cystatin C levels respectively elevate linearly over time in a predictable manner.

  With the help of the serum creatinine and cystatin C values respectively, the GFR [ml/min] will be calculated via the following formulas:

  Nankivell formula

  cGFR will be estimated as $6.7/(SCr \times 0.0884) + 0.25 \times weight - 0.5 \times urea - 100/height^2 +$ 35(25 for women).

  Hoek's formula

  cGFR will be estimated as -4.32+80.35/cystatin C [mg/L].

  CKD EPI

  The CKD-EPI equation, expressed as a single equation, is GFR = 141 x $\min(Scr/\kappa, 1)^{\alpha}$ x $\max(Scr/\kappa, 1)^{1.209}$ x 0.993^{Age} x1.018 [if female] x 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 (Levey et al., 2009).

  Cockroft-Gault

  GFR [mL/min] =[(140-A)*weight/(72*C)]*(0,85 if female), where
  C is the serum concentration of creatinine [mg/dL] and A is age (years).

  MDRD-4 formula

  eGFR [mL/min/1.73m2] = eGFR= $186.3 * C^{-1.154} * A^{-0.203} * G * R$, where
  C is the serum concentration of creatinine [mg/dL],
  A is age (years), G=0.742 when gender is female, otherwise G=1,
  R=1.21 when race is black, otherwise R=1.

Graft function:

The incidence of acute rejection episodes, of CMV and HCV infections will be assessed.

- **Acute rejection episodes**

  Acute rejection is defined as a clinically suspected acute rejection, whether biopsy-proven or not, which has been treated and confirmed by the investigator according to the response to therapy. Each acute rejection must be recorded on the relevant CRF page with the clinical diagnosis specified, and, if a biopsy was performed, with the histological diagnosis.

- **Biopsy-proven acute rejection**

  Biopsy-proven acute rejection (BPAR) is defined as a clinically suspected acute rejection confirmed by biopsy. For all clinically suspected rejection episodes a graft biopsy is performed at investigator's discretion before or within a 24-hour period from the initiation of anti-rejection therapy. The local pathologist will grade biopsies. The results of the biopsy read by the local pathologist will be listed in the Allograft Biopsy CRF page.

- **Graft loss**

  The allograft will be presumed to be lost if a patient has a liver retransplant or dies due to liver failure.

  The reason for graft loss will be recorded on the Graft Loss CRF page. If graft loss occurs after the patient has discontinued study medication prematurely, the graft loss will be entered on the Study Completion and Graft Loss CRF page. Graft loss is considered a Serious Adverse Event and must be reported.

- **Death**

  In the event of patient death, a SAE form including the event leading to death must be completed and faxed to Novartis CS&E within 24 hours. The events leading to the death must be entered on the AE CRF page and the death must be indicated on the Premature Discontinuation and on the Study Completion CRF pages.

- **HCV infection**

  The evolution of Hepatitis C (HCV) and the rate of progression of HCV related allograft fibrosis will be evaluated. The HCV viral load, the incidence of and response to HCV antiviral treatment and the incidence of de novo hepatocellular carcinoma (HCC) malignancies and the rate of recurrence of HCC will be assessed. Biopsies will be obtained in all patients who are listed as HCV positive by serology testing, at time of transplantation and at Month 12. The biopsies will be read by the local pathologist (who will remain blinded to patient treatment) according to the Ishak-Knodell scores (Ishak 1995) (see Appendix 9).

7.6 Safety

7.6.1 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after start of study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before obtaining informed consent have to be documented as medical history and are only considered adverse events if they worsen after study start. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, require study drug discontinuation or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study drug (everolimus) and tacrolimus (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
  - treatment of acute rejection; acute rejections are considered to be a protocol exempted event. They should not be reported simply because they result in a hospitalization and thus meet the criteria for an SAE. Acute rejections should be reported as SAEs only if they are unusual in appearance, clinical course and/or are graft threatening
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- is a graft loss

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.1.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged, Other immunosuppressant taken/adjusted, concomitant medication stopped. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the informed consent process and the study as needed.

Unusually severe rejection episodes

Allograft rejection is an expected event in all forms of transplantation and will not be considered an SAE even though it may require prolonged hospitalization and medical therapy. These events will be reported in the Rejection CRF and no SAE form has to be completed. However, if in the opinion of an investigator a rejection episode is unusually severe and warrants specific notification, then an SAE form must be completed and submitted according to SAE reporting procedures outlined in Section 8.1. In this particular case, information needs also to be reported in the Adverse Event CRF.

Infections

All infection episodes must be recorded on the Infection CRF; they should not be collected on the AE CRF. Infections should be listed with severity, relationship, sample site, genus and species of microorganism specified, start and end dates, action taken.

CMV infection: Information will be captured on laboratory-defined CMV (antigenemia-positive, PCR positive), CMV syndrome (fever for the last 2 days, neutropenia, leukopenia, viral syndrome) and CMV-disease (organ involvement), on the CMV-specific CRF. CMV and HCV viral load (HCV positive patients only) will be measured locally at baseline, month 1, 3, 6, 12, for evaluation of incidence and severity. Suspected CMV infections will be recorded on the Infection CRF and on the CMV-specific CRF-field during visits. CMV infections will be also assessed by donor/recipient constellation (D+R+ / D-R- / D+R- / D-R+).

HCV infection: HCV information will be recorded on the Infection CRF. HCV viral load (HCV positive patients only) will be measured locally at baseline, month 1, 3, 6, 12, for evaluation of incidence and severity. HCV genotype will be assessed locally at baseline (HCV positive patients only).

7.6.2 Physical examination

Information about the physical examination must be present in the source documentation at the study site.

Any clinically significant conditions that are present prior to the start of study drug intake must be recorded on the Relevant Medical History/Current Medical Conditions pages of the CRF.

All new conditions found after start of the study drug intake which meet the definition of an Adverse Event must be recorded on the Adverse Event part in the CRF.

7.6.3 Vital signs

Height will be recorded at Screening visit (Visit 1) only. Vital signs will be recorded at every study visit, and include radial pulse rate, systolic and diastolic blood pressure and weight (kg). Blood pressure and pulse rate will be assessed after the patient has rested in the sitting position for at least five minutes; blood pressure should be assessed at the same arm each time of determination.

7.6.4 Laboratory evaluations

The center's local laboratory will be used to analyze the clinical laboratory data during the study.

The following variables will be examined:

Hematology:	hemoglobin, leukocytes (including differential blood count and absolute neutrophil count), platelet count, hematokrit (HK)
Blood chemistry:	creatinine, urea/BUN, sodium, potassium, calcium, ALAT, ASAT, protein, AP, albumin, CRP, phosphate, magnesium, CPK, total bilirubin, glucose (fasting), cystatin C, Hb1c, LDH
Lipid profile:	total cholesterol, HDL, LDL, triglycerides
Viral serology:	Hepatitis B (HBsAg, only at Screening), HCV, CMV (including pp65 Ag)
Urinalysis:	creatinine, protein, albumin

Viral serology

All patients will be tested for Hepatitis B (HBsAg), HCV, CMV at Screening, earlier tests ≤ 6 months are acceptable. Any HIV positive patients will be excluded. If results are not available at Baseline, the patient may be included. However, an assessment has to be performed immediately. If results of a newly initiated assessment will be positive, the patient will subsequently be dropped from the study and administered the standard care provided by the center.

New onset diabetes mellitus (NODM)

The incidence of NODM will be assessed from Day 30 post-transplantation. NODM post-transplantation, in patients without diabetic history, is defined by any of the following:

- Two consecutive fasting plasma glucose levels ≥ 126 mg/dL (7.0 mmol/L) post-transplantation (> 30 days).
- HbA1c ≥ 6.5 % from Day 75 onward.
- Diabetes mellitus (DM) reported as an adverse event that is prevalent after Day 30.
- Any concomitant medication with ATC level 2 code "A10" drugs used in diabetes, if prevalent after Day 30 and used for more than 30 days.

Non-diabetic patients, identified at the time of transplantation by all the following:

- DM or diabetic related terms were not included in medical history.
- Glucose (random) < 11 mmol/L at the time of transplantation.
- HbA1c < 6.5 % at the time of transplantation.

In addition, incidence of patients that are pre-diabetic will be assessed using an HbA1c range of 5.7 to 6.4%.

Pregnancy and assessments of fertility

All women of childbearing potential will have a urine or serum pregnancy test (β-HCG) during pre-study/baseline/EOS evaluations and during the course of the study only, if clinically indicated.

Additional blood samples

Additional blood samples (unscheduled visits) can be scheduled for everolimus and tacrolimus trough levels determination at investigator's discretion.

7.7 Tolerability/acceptability

Tolerability of study medication can be assessed from the rate of patients who withdraw prematurely from study medication or in whom study medication had to be converted to another immunosuppressive regimen due to abnormal laboratory results, adverse events, or toxicity.
All changes to the immunosuppressive medication dosing regimen will be recorded on the Dosage Administration Record CRF, along with the reason for change.

7.8 Resource utilization

Not applicable

7.9 Health-related Quality of Life

None

7.10 Pharmacomonitoring

Everolimus C0-h whole blood levels will be measured only in patients included into ARM I (=investigational arm), tacrolimus C0-h whole blood levels will be measured in all patients included into ARM I (=investigational arm) and Arm II (control arm).

- **Everolimus whole blood tests**

  Analysis of the everolimus whole blood levels will be performed locally at the center during all visits throughout the study, starting on day 1 (Visit 2). Whole blood level for everolimus will be assessed as per local practice on blood taken within 5 minutes prior to everolimus administration (C-0h level).

- **Tacrolimus whole blood tests**

  Analysis of the tacrolimus whole blood levels will be performed locally at the center during all visits throughout the study, starting on day 1 (Visit 2). Whole blood level for tacrolimus will be assessed by liquid chromatography coupled with mass spectrometry (LCMS). Values derived from enzyme based assays will be corrected (as described in the manufacturer's instructions).

7.11 Pharmacogenetics/pharmacogenomics

None.

[redacted]

[redacted]

8 Safety monitoring

8.1 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the German Novartis Drug Safety & Epidemiology Department. The telephone and telefax number of the contact persons in the local department of Drug Safety & Epidemiology, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Drug Safety & Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported.

8.2 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the German Novartis Drug Safety & Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.3 Data Monitoring Board

An external and independent Data Safety Monitoring Board (DSMB) will be instituted before study start. The DSMB will review safety-related issues in a meeting and will be entitled to make recommendations for changes in study conduct. Details on the function of the DSMB and the frequency of the DSMB meetings will be laid out in a separate DSMB Charter.

9 Data review and database management

9.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs, which will be documented as being the source data. The investigator must also keep the original informed consent form signed by the patient (a signed copy or a second original is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 Data collection

Designated investigator staff must enter the information required by the protocol onto the Novartis CRFs that are printed on 3-part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any

required corrections or additions. The CRFs are forwarded to Data Management by field monitors, one copy being retained at the investigational site. Once the CRFs are received by Data Management, their receipt is recorded and they are reviewed prior to data entry.

9.3 Database management and quality control

Data from the CRFs are entered into the study database by Contract Research Organization staff following their own internal standard operating procedures that have been reviewed and approved by Novartis. Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious errors are corrected by Data Management personnel. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are kept with the CRFs at the investigator site, and a copy is sent to Novartis so the resolutions can be entered into the database. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

At the conclusion of the study the occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Trial Statistician and Statistical Reporting and the Clinical Trial Leader.

10 Data analysis

The data will be analyzed by Novartis and/or by the designated CRO. Any data analysis carried out independently by the investigator(s) should be submitted to Novartis before publication or presentation. The final analysis will be done when all patients have completed their Visit 9 (Month 12) assessment or discontinued prematurely. It is planned that the data from all centers that participate in this protocol will be used, so that an adequate number of patients will be available for analysis.

Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and pharmacokinetic measurements. All summary statistics will be presented by treatment group. Categorical variables will be summarized by absolute and relative frequencies. Continuous variables will be summarized by descriptive statistics of the number of valid and missing observations, mean, standard deviation, minimum, median and maximum. Time-to-event data including rates of affected patients will be assessed by Kaplan-Meier statistics. Group comparisons will be performed using appropriate two-sided statistical tests.

10.1 Populations for analysis

The **Full Analysis Set (FAS)** will consist of all patients as randomized that received at least one dose of study drug and have a valid baseline assessment of the primary efficacy variable.

Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

The **Per-protocol Set (PP)** will consist of a subset of patients of the FAS who did not show major deviations from the protocol procedures that may have an impact on the study outcome. Reasons for exclusion of the Per-protocol Set may be (but are not limited to): deviations from entry criteria, errors in treatment assignment, use of excluded/forbidden/un-allowed medication, premature discontinuation of randomized treatment or study, poor compliance, loss to follow-up, missing data in the primary efficacy variable. Criteria that are assumed to have such an impact will be defined in the Protocol Deviations Module of the Validation and Planning (VAP) documentation, and assessed before database lock during the data review meeting.

The **Safety Set** will consist of all patients that received at least one dose of study drug and had at least one post-baseline safety assessment. Patients will be analyzed according to treatment received. Of note, the statement that a patient had no adverse events also constitutes a safety assessment.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline characteristics will be summarized for the full analysis set (FAS) by treatment group. Baseline characteristics include prior medication, past/current medical conditions and transplant history.

Medical history will be coded using MedDRA and will be presented by MedDRA system organ class, preferred term and treatment group. Separate tables will be provided for past medical conditions and current medical conditions. Prior medication will be coded according to the WHO Drug Reference List and summarized by ATC class, preferred term and treatment group.

10.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

10.3.1 Study medication

Duration (days) of drug exposure to each individual component of the immunosuppressive treatment regimen will be summarized using descriptive statistics. Duration of drug exposure will be calculated as the difference between the last and first day of drug application +1. Dosage averages will be calculated including and excluding zero doses for periods of temporary interruption of treatment regardless of whether this was due to safety reasons or patients' non-compliance. Daily dose levels will be summarized descriptively. Frequencies of the number of patients with any dose reduction (including temporary dose interruption) as well as the number of dose reductions by reason will be given. These analyses will be performed by treatment group for the safety set.

Frequency tables displaying cumulative frequencies of 'crude rates' will be presented for the number of patients with trough levels below/within/above the defined therapeutic windows drug and by visit. If appropriate, treatment groups will be compared exploratory using the Pearson's Chi-Square test (where all expected numbers are at least 1), otherwise Fisher's exact test will be used (Campbell 2007). Furthermore, frequency tables for the number of

patients with trough levels below/within/above the defined therapeutic windows drug and by period.

10.3.2 Concomitant therapy

Prior and concomitant medications and non-drug therapies will be coded according to WHO-DRL. Concomitant medications taken through the study will be summarized by preferred term, ATC class and treatment group for the safety set. Dosages of corticosteroids will be converted to prednisolone dose equivalents and summarized as described above.

10.4 Analysis of the primary objective(s)

The primary objective of the trial is to demonstrate that an immunosuppressive regimen based on everolimus (EVR) in co-exposure with tacrolimus (TAC) has superior efficacy compared to tacrolimus alone on estimated glomerular filtration rate (MDRD-4 formula) at 12 months after transplantation in *de novo* liver transplant recipients.

10.4.1 Variable

The primary efficacy variable of this trial is the renal function at Month 12 after baseline assessed by estimated GFR based on recalculated values according to the MDRD-4 formula: eGFR [mL/min/1.73m^2] = eGFR= 186.3 * $C^{-1.154}$ * $A^{-0.203}$ * G * R, where C is the serum concentration of creatinine [mg/dL], A is age (years), G=0.742 when gender is female, therwise G=1, R=1.21 when race is black, otherwise R=1.

10.4.2 Statistical hypothesis, model, and method of analysis

The trial tests the null hypothesis that the treatment difference (investigational minus control) in mean eGFR at Month 12 after baseline is zero versus the alternative hypothesis that the treatment difference is different from zero.

The hypotheses will be tested with an analysis of covariance (ANCOVA) with treatment , center, HCV-Class (positive, negative) and MELD (<=30 vs >30) as factors, and eGFR at Visit 1 (Baseline) as covariate. Raw as well as adjusted means (= LS-means, LS: least square means) will be presented for the treatment contrast together with a two-sided *p* value and the appropriate confidence interval, respectively. The significance level will be 5% (two-sided). There are no multiplicity issues to be addressed since only the hypothesis of superior efficacy of the investigational vs. the control regimen will be tested confirmatority.

The Full Analysis Set will be used for the primary analysis. If patients of the FAS are switched from the reference to the investigational group during the study, they will be analyzed in their randomized group. If appropriate, a subgroup analysis will be performed comparing patients of the reference group with and without switch to the investigational group including a further analysis comparing the subgroups to the randomized investigational group. If treatment will be modified in the investigational group, they will be analyzed as randomized.

10.4.3 Handling of missing values/censoring/discontinuations

Missing values in cGFR will be imputed with the last valid observed value from that patient (LOCF). Under the assumption that the eGFR will remain fairly stable in the control group but will probably improve in the investigational group, this strategy corresponds to a

conservative estimate of the treatment effect. Alternative missing value procedures may be performed additionally as sensitivity analyses (see below).dealt with by multiple imputation (Molenberghs & Kenward 2007; White, Royston & Wood 2010). The multiple imputation procedure will be presented in detail (e.g. seed value, method for imputation) in the statistical analysis plan to be finalized before database lock.

10.4.4 Supportive analyses

For sensitivity, the following analyses will be performed:

> The primary analysis will be repeated with the Per-protocol Set using the same ANCOVA model as described above.

As a further supportive analysis, a Mixed Model for Repeated Measures (MMRM) will be fitted using treatment group, visit (as a categorical time variable) and subject as categorical variables (Molenberghs & Kenward 2007). Assuming that the time profile is not the same in the two treatment groups, a full visit-by-treatment interaction will be used. If a baseline is to be included in the model, the baseline-by-time interaction will be included in the model, otherwise strange and unrealistic restrictions on the implied covariance structure would be made in this case. An unstructured covariance matrix will be used. Since there are sufficient data, using a different covariance matrix in each treatment group might be considered:

```
proc mixed;
class subject visit treatment;
model gfr = baseline treatment visit baseline*visit treatment*visit / s ddfm=kr;
repeated time / subject = subject type = un group=treatment;
run;
```

The estimated adjusted treatment effect as well as the treatment contrast will be presented for the Month 12 visit together with appropriate two-sided 95% confidence intervals. The model will be fitted for both, the FAS as well as the PP set.

Only in case of substantial drop-out (>20%) or if relevant differences in the drop-out-patterns between the two treatment groups are observed, a multiple imputation of missing values (Molenberghs & Kenward 2007; White, Royston & Wood 2010) will be performed as an alternative to account for missing values. The necessity of this procedure will be decided during the data review meeting, computational details (e.g. seed value, method for imputation) will be described in the statistical analysis plan to be finalized before database lock.

The course of eGFR will be summarized descriptively by visit and treatment group for the FAS. Only observed cases will be used (no data imputed by multiple imputation, since multiple imputation implies the creation of more than one imputed value per patient). Absolute and percent changes from baseline to each post-baseline measure will be calculated by treatment group for each study visit as post-baseline minus baseline value. Between-group as well as within-group comparisons will be performed exploratory using suitable parametric (*t*-test/paired *t*-test) and nonparametric (Wilcoxon rank-sum test/Wilcoxon signed-rank test) statistical tests for paired and two-sample data, respectively.

10.5 Analysis of secondary objectives

10.5.1 Efficacy (secondary)

The following secondary efficacy variables will be analyzed in an explorative manner for the full analysis set (FAS):

- efficacy-related endpoints, such as acute rejection, treated biopsy proven acute rejection (BPAR), graft loss, death and loss to follow-up (as composites or individual endpoints)
- endpoints related to renal function: eGFR using various methods (MDRD-4, Nankivell, Cockcroft-Gault, CKD EPI and Hoek formulae

Efficacy-related objectives

The incidence of efficacy-related endpoints will be estimated using the Kaplan-Meier method. The number of events as well as the number of censored observations will be presented. Kaplan-Meier estimates will be presented by visit up to Month 12. Percentiles (25%, median, 75%) of the event time distribution will be presented together with their two-sided 95% confidence interval. The two groups will be compared using the log-rank test. Kaplan-Meier curves will be displayed graphically. For rejections, Kaplan-Meier analyses may be stratified by severity grade.

The following endpoints will be analyzed:

- Incidence of a composite of treated biopsy proven acute rejection (BPAR), graft loss or death at Month 12.
- Incidence of a composite of treated BPAR, graft loss, death or loss to follow-up.
- Incidence of a composite of death or graft loss.
- Incidence of acute rejection, treated acute rejection, BPAR, treated BPAR, graft loss, or death

Renal function-related objectives

Renal function as assessed by cGFR calculated according to the CKD-EPI, Cockcroft-Gault, Nankivell, MDRD-4, and Hoek formulas (see Section 7.5) will be analyzed using the ANCOVA model specified for the primary analysis. Raw as well as adjusted means will be presented for the treatment contrast together with its confidence interval and two-sided exploratory *p* values separately for each time point. Missing values will be dealt with in the ANCOVA analysis by multiple imputation. Additionally to the analysis at Month 12, an analysis at Month 6 will be performed.

Descriptive statistics for observed values and changes from baseline as well as within-group and between-group comparisons using suitable parametric and non-parametric statistical tests will be displayed by visit and treatment group. Additionally, descriptive statistics will be presented for the following subgroups:

- age: <60 vs. ≥60 years
- gender: male vs. female
- renal function at baseline: 30 – <45, 45 – <60, ≥60 mL/min/1.73m²; <45 vs ≥45 mL/min/1.73m², <60 vs. ≥60 mL/min/1.73m²
- HCV status at baseline: positive vs. negative

- lab MELD score at baseline: ≤14, 15 – 19, 20 – 24, 25 – 29, ≥30

Serum creatinine as well as the urinary protein/creatinine ratio will be summarized using descriptive statistics for observed values and changes from baseline. Within-group and between-group comparisons will be performed using suitable parametric and non-parametric statistical tests and will be displayed by visit and treatment group.

The incidence of patients experiencing a decline in eGFR of <10, 10 – <15, 15 – <20, 20 – <25, and ≥25 mL/min/1.73m^2 from baseline will be analyzed using frequency tables by visit and treatment group. Treatment groups will be compared exploratory using the Pearson's Chi-Square test (where all expected numbers are at least 1), otherwise Fisher's exact test will be used.

The incidence of proteinuria of 0.5 – <1.0 g/day, 1.0 – <3.0 g/day and ≥3.0 g/day will be analyzed using frequency tables by visit and treatment group. Treatment groups will be compared exploratory using the Pearson's Chi-Square test (where all expected numbers are at least 1), otherwise Fisher's exact test will be used.

10.5.2 Safety

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. electrocardiogram, vital signs, and special tests) will be considered as appropriate. Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (e.g. severity (CTCAE) or relatedness to study medication) will be listed as appropriate.

Adverse events/infections

Data collected by AE CRFs and by Infection CRFs will be coded using MedDRA. The number of AE/patients with AE will be summarized by MedDRA system organ class and preferred term. Additionally, AE will be summarized by maximum severity, and for AE with suspected drug relation, serious AE (SAE), and AE leading to permanent discontinuation of study drug. In addition to being analyzed together with AE data, the incidence of bacterial, viral and fungal infections will be tabulated separately for all infections, by maximum severity, for infections with suspected drug relation, serious infections and infections leading to premature discontinuation of study drug. These summary tables will include adverse events of special interest, such as New Onset of Diabetes Mellitus (NODM, for definition see Section 7.6.4), *de novo* HCC malignancies, HCV- and HCC-related fibrosis.

All information pertaining to AE noted during the study will be listed by treatment group and patient, detailing the verbatim term given by the investigator, MedDRA preferred term and system organ class, start/end dates, severity, seriousness, relationship to study drug and action taken. The AE onset will also be shown relative (in number of days) to the date of initial dose.

AE starting before, or 28 or more days after the discontinuation of study medication, will not be considered as treatment-emergent and will not be included in AE/infection summary tables but listed only.

Laboratory data

Abnormalities according notable criteria (see Appendix 2) will be identified. The proportions of patients with clinically notable abnormalities according to the notable criteria will be summarized. Shifts from baseline value to worst post-baseline value based on the normal ranges will be presented graphically (Amit et al., 2008). The worst observation is defined as the highest or lowest measure during the different observations periods whereby high or low are chosen according to the direction of abnormality. Descriptive statistics of absolute values as well as change from baseline of all laboratory variables will be presented by visit and treatment group. A by-patient listing of all clinically notable abnormal laboratory data will be generated. Only assessments obtained up to 28 days after the discontinuation of study medication will be considered "on-treatment" and analyzed with relationship to immunosuppressive therapy.

10.5.3 Tolerability

Tolerability of the study drug will be assessed from the rate of patients who withdraw prematurely from study drug or in whom study drug had to be converted to another immunosuppressive regimen due to abnormal laboratory results or adverse events. The frequency distribution of these reasons will be presented and compared between the treatments.

10.5.4 Resource utilization

Not applicable. No resource utilization data will be generated.

10.5.5 Health-related Quality of Life

Not applicable. No health-related quality of life data will be generated.

10.5.6 Pharmacokinetics

Everolimus C0-h whole blood levels will be summarized by visit using descriptive statistics. Tacrolimus C0-h whole blood levels will be summarized by visit and treatment group using descriptive statistics.

10.5.7 Pharmacogenetics/pharmacogenomics

Not applicable. No pharmacogenetic/pharmacogenomic data will be generated.

10.5.8 Biomarkers

HCV viral load (HCV-ribonucleic acid (RNA) levels overall and by genotype) will be summarized descriptively by visit and treatment group.

[redacted]

The number of patients with deviations from the therapeutic window will be counted and tabulated separately by visit and in total.

10.5.9 PK/PD

Not applicable. No PK/PD data will be generated.

10.6 Interim analysis

Not applicable. No interim analysis is planned for this trial.

10.7 Sample size calculation

The trial tests the null hypothesis that there is no difference in renal function, estimated by cGFR according to the MDRD-4 formula, at 12 months after randomization between the everolimus-based tacrolimus-minimization regimen and the tacrolimus-based control regimen versus the alternative hypothesis that the difference is 7.0 ml/min/1.73m^2. A sample size of 105 in each group will have 80% power to detect a difference in means of 7.0 ml/min/1.73m^2 assuming that the common standard deviation is 18.0 ml/min/1.73m^2 with a 5% two-sided significance level. (One will decide in favor of H_1 when the difference in means would be 5.1 ml/min/1.73m^2 or greater in favor of the everolimus-based group.) To adjust the sample size for a common drop-out rate (DOR) of 20% (using the fomula $N_{adj}=N/(1\text{-}DOR)^2$), 165 patients need to be randomized per group. Sample sizes were estimated using NQuery (Version 6.1) procedure "Two-group *t*-test for equal means (equal n's)".

10.8 Power for analysis of critical secondary variables

Not applicable. Power for the analysis of critical secondary variables was not investigated.

11 Discussion and rationale for study design features

The evaluation of the efficacy and safety of an immunosuppressive regimen in liver transplant recipients is best investigated using a randomized control trial, as opposed to observational studies where confounding by indication cannot be fully accounted for by adjusting by multivariate procedures for differences in confounders that are imbalanced at the time of transplantation. This protocol will not utilize procedures to blind investigators or subjects to treatment assignment. The duration of experience of liver transplant physicians with tacrolimus indicates that optimizing the safety of this medication requires the physician to be aware of the use of tacrolimus and to the trough levels. This open label study, however, does include prospective collection of assessments that relate to potential issues that may be impacted by an open label design, e.g. management of tacrolimus levels above or below target ranges. Importantly, the occurrence of the primary endpoints of this study are objectively measured – renal function by laboratory data, and death or graft survival.

The choice of the control arm for this study is based upon the predominance of tacrolimus use in liver transplantation worldwide in combination with corticosteroids, which are eliminated sometime after the first several months post-transplantation. As opposed to renal transplantation where triple or quadruple therapy is standard, adjunctive therapy with MMF is not pervasive and tends to be used short-term to allow a slow increase in the tacrolimus level while renal function recovers. The present study requires the discontinuation of MMF prior to randomization so that the control group is reflective of a regimen that has an approved liver transplant indication.

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13 Appendicies

13.1 Appendix 1: Administrative procedures

Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Approval letters concerning protocol and informed consent will be filed by Novartis. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

Informed consent

Eligible patients may only be included in the study after providing written, IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the

protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

Study drug supply and resupply, storage, and tracking

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in and comply with the legal requirements of Germany. They will include storage conditions for the drug, but no information about the patient except for the randomization number.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study and as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

13.2 Appendix 2: Clinically notable laboratory values and vital signs

Laboratory variable	Standard units	SI units
Liver function and related variables		
SGOT (AST)	≥3 × ULN	≥3 × ULN
SGPT (ALT)	≥3 × ULN	≥3 × ULN
Bilirubin	≥3 × ULN	≥3 × ULN
Renal function, metabolic and electrolyte variables		
Urea	None	None
Creatinine	Day 8 or after: >30% above value from preceding visit **or** Day 8 to Wk 4: ≥ 4 mg/dL, After Wk 4: ≥ 3 mg/dL	Day 8 or after: >30% above value from preceding visit **or** Day 8 to Wk 4: ≥ 354 µmol/L, After Wk 4: ≥ 265 µmol/L
Uric acid	M ≥12 mg/dL F ≥9 mg/dL	M ≥714 µmol/L F ≥535 µmol/L
Glucose	<45 mg/dL >250 mg/dL	<2.5 mmol/L >13.9 mmol/L
Cholesterol	≥350 mg/dL	≥9.1 mmol/L
Triglycerides	≥750mg/dL	≥8.5 mmol/L
CPK (MB)	None	None
Potassium	≤3.0 mEq/L ≥6.0 mEq/L	≤3 mmol/L ≥6 mmol/L
Calcium	≤6mg/dL ≥13mg/dL	≤1.5mmol/L ≥3.2mmol/L
Hematology variables		
Hemoglobin	<7 g/dL	<4.39 mmol/L
Platelets (thrombocytes)	<50 k/mm^3 ≥700 k/mm^3	<50 × 10^9/L ≥700 ×10^9/L
Leukocytes (WBCs)	≤2.0 k/mm^3 ≥16 k/mm^3	≤2.0 × 10^9/L ≥16 × 10^9/L
Hematology variables: differential		
Granulocytes (poly, neutrophils)	≤1,000/mm^3	≤1 x 10^9/L
Eosinophils	≥12%	≥12%
Lymphocytes	≤1,000/mm^3	≤1× 10^9/L

Harmonized notable vital signs (and weight)	
Vital sign variables	**Notable criteria**
Pulse (beats/min.)	None
Systolic BP (mm/Hg)	Either an increase of ≥30 that results in ≥180 or >200(mm/Hg) or Either a decrease of ≥30 that results in ≤90 or <75 (mm/Hg)
Diastolic BP (mm/Hg)	Either an increase of ≥20 that results in ≥105 or >115 (mm/Hg) or Either a decrease of ≥20 that results in ≤50 or <40 (mm/Hg)
Weight (Kg)	None

13.3 Appendix 3: Possible drug interactions

During treatment with immunosuppressive agents such as everolimus and tacrolimus vaccination may be less effective. The use of live vaccines should be avoided.

Possible Everolimus Drug Interactions

Everolimus is mainly metabolized by CYP3A4 in the liver and to some extent in the intestinal wall and is a substrate for the multi-drug efflux pump, P-glycoprotein. Therefore, absorption and subsequent elimination of systemically absorbed everolimus may be influenced by medicinal products that affect CYP3A4 and/or P-glycoprotein. Concurrent treatment with strong 3A4-inhibitors and inducers is not recommended. See also drugs known to interact with tacrolimus (see Appendix 4). Grapefruit and grapefruit juice have the potential to affect the metabolism of drugs metabolized by CYP450 enzymes. Caution should be used in patients being administered everolimus.

Drugs not allowed	Sirolimus	Patients to be discontinued from everolimus if these immunosuppressive drugs are given
	Terfenadine Astemizole Cisapride	Inhibitors of P-450 (CYP), in particular CYP3A (as everolimus) have the potential to increase the exposure to these drugs, resulting in prolongation of QT intervals on ECGs
	Rifampicin Rifabutin	Strong inducers of P-450 (CYP) have the potential to decrease the exposure of everolimus
	Clarithromycin Telithromycin Ritonavir	Strong inhibitors of P-450 (CYP) have the potential to increase the exposure of everolimus
	Itraconazole** Voriconazole** Fluconazole** Ketoconazole**	Strong inhibitors of P-450 (CYP) have the potential to increase the exposure of everolimus
	Cerivastatin Rosuvastatin	Insufficient data available to make recommendations regarding concomitant use of the newer statins and everolimus
	Lovastatin* Simvastatin*	Confirmed interaction between these drugs and drugs which are CYP3A substrates and/or inhibitors
Drugs strongly discouraged	Quinidine Fluoxetine Paroxetine	Potential interaction of everolimus with CYP 2D6 substrates
Drugs necessitating close monitoring	Digoxin	Potential interaction with everolimus has not been evaluated, patients on digoxin should have periodic measurements of digoxin levels

*Patients requiring treatment with this class of medication should be monitored closely for signs of rhabdomyolysis, such as, dark-colored urine, fever, muscle cramps, pain, spasm, or stiffness, unusual tiredness or weakness.

**Concomitant administration of everolimus and these drugs necessitates close monitoring of everolimus levels. Fluconazole may pose the smallest risk for drug drug-interaction.

13.4 Appendix 4: Tacrolimus drug interactions

Drug interactions

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering Tacrolimus with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, amphotericin B, and cisplatin.

Drugs that may alter tacrolimus concentrations

Since Tacrolimus is metabolized mainly by the CYP3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism or increase bioavailability of Tacrolimus as indicated by increased whole blood or plasma concentrations. Drugs known to induce these enzyme systems may result in an increased metabolism of Tacrolimus or decreased bioavailability as indicated by decreased whole blood or plasma concentrations. Monitoring of blood concentrations and appropriate dosage adjustments are essential when such drugs are used concomitantly.

*Drugs that may increase Tacrolimus blood concentrations

Calcium Channel Blockers	**Antifungal Agents**	**Macrolide Antibiotics**
Diltiazem	clotrimazole	clarithromycin
nicardipine	fluconazole	erythromycin
nifedipine	itraconazole	troleandomycin
verapamil	ketoconazole**	
	voriconazole	
Gastrointestinal Prokinetic Agents	Other Drugs	
Cisapride	bromocriptine	
metoclopramide	chloramphenicol	
	cimetidine	
	Cyclosporin A	
	danazol	
	ethinyl estradiol	
	methylprednisolone	
	lansoprazole***	
	omeprazole	
	protease inhibitors	
	nefazodone	
	magnesium-aluminum hydroxide	

**In a study of 6 normal volunteers, a significant increase in Tacrolimus oral bioavailability (14±5% vs. 30±8%) was observed with concomitant ketoconazole administration (200 mg).

The apparent oral clearance of Tacrolimus during ketoconazole administration was significantly decreased compared to Tacrolimus alone (0.430±0.129 L/hr/kg vs. 0.148±0.043 L/hr/kg). Overall, IV clearance of Tacrolimus was not significantly changed by ketoconazole co-administration, although it was highly variable between patients.

*** Lansoprazole (CYP2C19, CYP3A4 substrate) may potentially inhibit CYP3A4-mediated metabolism of Tacrolimus and thereby substantially increase Tacrolimus whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers, as compared to those patients who are efficient CYP2C19 metabolizers.

***Drugs that may decrease Tacrolimus blood concentrations**

Anticonvulsants	**Antimicrobials**
carbamazepine phenobarbital phenytoin	rifabutin caspofungin rifampin
Herbal Preparations	**Other Drugs**
St. John's Wort	sirolimus

*This table is not all inclusive.

St. John's Wort (*Hypericum perforatum)* induces CYP3A4 and P-glycoprotein. Since Tacrolimus is a substrate for CYP3A4, there is the potential that the use of St. John's Wort in patients receiving Tacrolimus could result in reduced Tacrolimus levels.

In a single-dose crossover study in healthy volunteers, co-administration of Tacrolimus and magnesium-aluminum-hydroxide resulted in a 21% increase in the mean Tacrolimus AUC and a 10% decrease in the mean Tacrolimus Cmax relative to Tacrolimus administration alone.

In a study of 6 normal volunteers, a significant decrease in Tacrolimus oral bioavailability (14±6% vs. 7±3%) was observed with concomitant rifampin administration (600 mg). In addition, there was a significant increase in Tacrolimus clearance (0.036±0.008 L/hr/kg vs. 0.053±0.010 L/hr/kg) with concomitant rifampin administration.

Interaction studies with drugs used in HIV therapy have not been conducted. However, care should be exercised when drugs that are nephrotoxic (e.g., ganciclovir) or that are metabolized by CYP3A (e.g., nelfinavir, ritonavir) are administered concomitantly with Tacrolimus. Based on a clinical study of 5 liver transplant recipients, co-administration of Tacrolimus with nelfinavir increased blood concentrations of Tacrolimus significantly and, as a result, a reduction in the Tacrolimus dose by an average of 16-fold was needed to maintain mean trough Tacrolimus blood concentrations of 9.7 ng/mL. Thus, frequent monitoring of Tacrolimus blood concentrations and appropriate dosage adjustments are essential when

nelfinavir is used concomitantly. Tacrolimus may affect the pharmacokinetics of other drugs (e.g., phenytoin) and increase their concentration. Grapefruit juice affects CYP3A-mediated metabolism and should be avoided (see Dosage Administration).

Following co-administration of Tacrolimus and sirolimus (2 or 5 mg/day) in stable renal transplant patients, mean Tacrolimus AUC0-12 and Cmin decreased approximately by 30% relative to Tacrolimus alone. Mean Tacrolimus AUC0-12 and Cmin following co-administration of 1 mg/day of sirolimus decreased approximately 3% and 11%, respectively. The safety and efficacy of Tacrolimus used in combination with sirolimus for the prevention of graft rejection has not been established and is not recommended.

13.5 Appendix 5: Guidelines for everolimus dose reduction

An investigator may interrupt temporarily or reduce the dosage of everolimus, if in his/her opinion this is clinically warranted, in response to any causally associated AE (e.g., neutropenia, thrombocytopenia, leukocytopenia, hyperlipidemia, hypertriglyceridemia). The following guidelines should be followed:

1- PLATELETS

Platelet count < 75,000/mm^3

Step 1: dose reduction should be considered and the first dose reduction may be instituted at the discretion of the Investigator.

Step 2: if the platelet count remains below 75,000/mm^3 despite the initial dose reduction, a further dose reduction may be implemented per the table below.

Platelet count < 50,000/mm^3 Dose interruption should be considered.
Platelet count < 30,000/mm^3 Dose interruption will be mandatory.

If the platelet count returns to 50,000/mm^3 for 3 days, everolimus may be restarted at lowest reduced dose. If the platelet count is stable at the reduced dose for 3 days, everolimus may be increased to the next higher dose. If the platelet count remains stable at greater than 75,000/mm^3 for 7 days, the full dose of everolimus may be restarted.

2- HEMOGLOBIN

Hemoglobin < 8 g/dL

Step 1: dose reduction should be considered and the first dose reduction may be instituted at the discretion of the Investigator.

Step 2: if the hemoglobin remains below 8 g/dL despite the initial dose reduction, a further dose reduction may be implemented per the table below.

Hemoglobin < 6 mg/dL: dose interruption will be mandatory.
Once hemoglobin returns to > 6 mg/dL for 3 days, everolimus may be restarted at the lowest (one
tablet b.i.d) level. If the hemoglobin is stable at the reduced dose for 3 days, everolimus may be increased to the next higher dose. Once hemoglobin returns to levels > 8 mg/dL for 7 days, everolimus may be increased to the full dose.

3- WHITE BLOOD CELLS

WBC < 3,000/mm^3

Step 1: dose reduction should be considered and the first dose reduction may be instituted at the discretion of the Investigator.

Step 2: if the white count remains below 3,000/mm^3 despite the initial dose reduction, a further dose reduction may be implemented per the table below.

WBC < 1,500/mm^3: dose interruption will be mandatory.
Once WBC returns to 1,500/mm^3 for 3 days, everolimus may be restarted at the lowest (one tablet b.i.d) level. If the WBC is stable at the reduced dose for 3 days, everolimus may be increased to the next higher dose. Once WBC returns to levels > 3,000/mm^3 for 7 days, everolimus may be increased to the full dose.

4- CHOLESTEROL

Cholesterol > 300 mg/dL or > 8 mmol/L:
Dietary instruction is strongly recommended and statin therapy, e.g. fluvastatin, should be considered.

If the abnormality persists, the dosing of everolimus will be adjusted as follows:

Cholesterol > 300 mg/dL or > 8 mmol/L: Dose reduction should be considered.
Cholesterol > 350 mg/dL or > 9 mmol/L: Everolimus should be interrupted.

5- TRIGLYCERIDES
Triglycerides > 575 mg/dL or > 6.5 mmol/L: Dietary instruction is strongly recommended and statin therapy should be considered.

If the abnormality persists, the dosing of everolimus will be adjusted as follows:

Triglycerides > 575 mg/dL or > 6.5 mmol/L: Dose reduction should be considered.
Triglycerides > 750 mg/dL or > 8.5 mmol/L: everolimus should be interrupted.

Everolimus dose reduction

	Platelet count (/mm^3)	Hemoglobin (g/dL)	WBC count (/mm^3)	Cholesterol (mmol/L)	Triglycerides (mmol/L)
Dose reduction	<75,000	<8	<3000	> 8	>6.5
Interruption	<30,000	<6	<1500	>9	>8.5

An investigator may interrupt temporarily or reduce, the dosage of the investigational drug (everolimus), if in his/her opinion this is clinically warranted.

Dose reduction steps
It is recommended to reduce the dosing from by one dosing step e.g. from 0.75 mg bid to 0.5 mg bid . The dosing should, however, always follow a bid schedule.

13.6 Appendix 6: Grading of acute liver allograft rejection

Rejection Activity Index (RAI)		
Criteria which can be used to score liver allograft biopsies with acute rejection, as defined by the World Gastroenterology Consensus Document.		
Category	**Criteria**	**Score**
Portal inflammation	Mostly lymphocytic inflammation involving, but not noticeably expanding, a minority of the triads	1
	Expansion of most or all of the triads, by a mixed infiltrate containing lymphocytes with occasional blasts, neutrophils and eosinophils	2
	Marked expansion of most or all of the triads by a mixed infiltrate containing numerous blast and eosinophils with inflammatory spillover into the periportal parenchyma	3
Bile duct inflammation / damage	A minority of the ducts are cuffed and infiltrated by inflammatory cells and show only mild reactive changes such as increased nuclear: cytoplasmic ratio of the epithelial cells	1
	Most or all of the ducts infiltrated by inflammatory cells. More than an occasional duct shows degenerative changes such as nuclear pleomorphism, disordered polarity and cytoplasmic vacuolization of the epithelium	2
	As above for 2, with most or all of the duct showing degenerative changes or focal lumenal disruption	3
Venous endothelial inflammation	Subendothelial lymphocytic infiltration involving some, but not a majority of the portal and/or hepatic venules	1
	Subendothelial infiltration involving most or all of the portal and/or hepatic venules	2
	As above for 2, with moderate or severe perivenular inflammation that extends into the perivenular parenchyma and is associated with perivenular hepatocyte necrosis	3

Total RAI Score = /9

Reference: Banff Schema for Grading Liver Allograft Rejection: An International Consensus Document. Hepatology 1997;25(3):658-63.

Grading of acute liver allograft rejection	
Global assessment of rejection grade made on a review of the biopsy and after the diagnosis of rejection has been established	
Global assessment*	**Criteria**
Indeterminate	Portal inflammatory infiltrate that fails to meet the criteria for the diagnosis of acute rejection (see reference below)
Mild	Rejection infiltrate in a minority of the triads that is generally mild and confined within the portal spaces
Moderate	Rejection infiltrate expanding most or all of the triads
Severe	As above for moderate with spillover into periportal areas and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis

*Verbal description of mild, moderate or severe acute rejection could also be labeled as Grade 1, 11, and 111, respectively.

Reference: Banff Schema for Grading Liver Allograft Rejection: An International Consensus Document. Hepatology 1997;25(3):658-63.

13.7 Appendix 7: Definitions of CMV disease in solid organ transplant recipients

Disease type	Probable	Definite
CMV syndrome	One or more of the following: 1. Fever >38°C for at least 2 days 2. New or increased malaise 3. Leukopenia 4. ≥5% atypical lymphocytes 5. Thrombocytopenia 6. Elevation of hepatic transaminases (ALT or AST) to 2 × upper limit of normal (applicable to nonliver transplant recipients) plus evidence of CMV in blood by viral culture, antigenemia or a DNA/RNA-based assay	Clinical and laboratory findings as in 'probable' case and no other cause of symptoms/signs identified
Pneumonia[1]	Signs and/or symptoms of pulmonary disease in the absence of other documented cause plus evidence of CMV in blood and/or[3] bronchoalveolar lavage (BAL) fluid by viral culture, antigenemia or a DNA/RNA-based assay	Signs and/or symptoms of pulmonary disease plus detection of CMV in lung tissue by culture, immunohistochemical analysis or *in situ* hybridization[4] with or without evidence of CMV in blood or BAL fluid by viral culture, antigenemia (BAL) or a DNA/RNA-based assay
Gastrointestinal disease	Symptoms of upper or lower gastrointestinal disease plus macroscopic mucosal lesions on endoscopy plus evidence of CMV in blood or biopsy tissue by viral culture, antigenemia or an RNA/DNA-based assay	Symptoms or signs of upper or lower gastrointestinal disease plus detection of CMV in gastrointestinal tissue by culture, immunohistochemical analysis or *in situ* hybridization[4]
Hepatitis	Elevation of bilirubin and/or hepatic enzymes in the absence of other documented cause of hepatitis[2] plus evidence of CMV in blood by anti-genemia or a DNR/RNA-based assay	Elevation of bilirubin and/or hepatic enzymes plus detection of CMV in liver tissue by culture, immunohistochemical analysis or *in situ* hybridization[4]
CNS disease	CNS symptoms in the absence of other documented cause plus evidence for CMV in CSF samples by viral culture or DNA-based assay	CNS symptoms plus detection of CMV in CNS tissue by culture, immuno-histochemical analysis or *in situ* hybridization[4]
Retinitis	Not applicable	Lesions typical of CMV retinitis must be confirmed by an ophthalmologist
Other tissue invasive disease (nephritis, cystitis, myocarditis, pancreatitis, etc.)	Evidence of organ dysfunction in the absence of other documented cause[2] plus evidence of CMV in blood by viral culture, antigenemia or DNA/RNA-based assay	Symptoms/signs of organ dysfunction plus detection of CMV in affected tissue by culture, immunohistochemical analysis or *in situ* hybridization[4]

[1] Superinfection or coinfection with other pathogens may occur and should be noted when present.
[2] If affected organ is the allograft, acute rejection must be excluded as a cause for the clinical symptoms.
[3] The detection of CMV in both BAL and peripheral blood strengthens the evidence for probable CMV pneumonitis.
[4] Although, immunohistochemistry and *in situ* hybridization techniques are more sensitive for the detection of CMV-infected cells than morphologic examination, the presence of typical cytomegalovirus inclusions should be considered evidence of definite disease.

Humar et al.,2006

13.8 Appendix 8: Milan Criteria

The United Network of Organ Sharing (UNOS) decided to prioritize allocation of organs to those HCC patients who met the tumor criteria recognized in the Milan experience to have the best outcomes (TNM = T2N0). The Milan criteria are based on tumor burden and limit prioritization for OLT to those who have either a single tumor under 5 cm or those with 3 or less tumors each under 3 cm, without evidence of metastatic disease or vascular invasion. The Milan criteria provide a simple means of selecting patients with HCC for transplantation who are at low risk (˜10%) for recurrence.

Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med;334:693–699.

Shetty K, Timmins K, Brensinger C, Furth EE, Rattan S, Sun W, Rosen M, Soulen M, Shaked A, Reddy KR, Olthoff KM. (2004) Liver transplantation for hepatocellular carcinoma validation of present selection criteria in predicting outcome. Liver Transpl;10(7):919-21.

Modified Tumor Node Metastaces (pTNM) Classification of HCC

pT0	Tumor not found
pT1	1 nodule ≤ 1.9 cm
pT2	1 nodule 2.0 – 5.0 cm; 2 or 3 nodules, all ≤ 3.0 cm
pT3	1 nodule > 5.0 cm; 2or 3 nodules, at least one > 3.0 cm
pT4a	4 or more nodules, any size
pT4b	pT2, pT3 or pT4 plus gross intraphepatic portal or hepatic vein involvement as indicated by CT, MRI, or US
N1	Regional (portal hepatitis) nodes, involved
M1	Metastatic disease, including extrahepatic portal or hepatic vein involvement
Stage I	T1
Stage II	T2
Stage III	T3
Stage IVA1	T4a
Stage IVA2	T4b
Stage IVB	Any N1, any M1

13.9 Appendix 9: Histological grading and staging of chronic hepatitis – Ishak-Knodell

Modified HAI grading: necroinflammatory scores

	Score
A. Periportal or periseptal interface hepatitis (piecemeal necrosis)	
Absent	0
Mild (focal, few portal areas)	1
Mild/moderate (focal, most portal areas)	2
Moderate (continuous around < 50% of tracts or septa)	3
Severe (continuous around > 50% of tracts or septa)	4
B. Confluent necrosis	
Absent	0
Focal confluent necrosis	1
Zone 3 necrosis in some areas	2
Zone 3 necrosis in most areas	3
Zone 3 necrosis + occasional portal-central (P-C) bridging	4
Panacinar or multiacinar necrosis	6
C. Focal (spotty) lytic necrosis, apoptosis and focal inflammation*	
Absent	0
One focus or less per 10 x objective	1
Two to four foci per 10 x objective	2
Five to ten foci per 10 x objective	3
More than ten foci per 10 x objective	4
D. Portal inflammation	
None	0
Mild, some or all portal areas	1
Moderate, some or all portal areas	2
Moderate/marked, all portal areas	3
Marked, all portal areas	4

* Does not include diffuse sinusoidal infiltration by inflammatory cells

Maximum possible score for grading 18

Additional features which should be noted but not scored:

Bile-duct inflammation and damage
Lymphoid follicles
Steatosis, mild, moderate or marked
Hepatocellular dysplasia, large-or small cell
Adenomatous hyperplasia
Iron or copper overload
Intracellular inclusions (e.g. PAS-positive globules, Mallory bodies)

Immunohistochemical findings

Information on viral antigens, lymphocyte subsets or other features, when available, should be recorded and may be semi-quantitatively expressed.

Histological staging of chronic hepatitis – Ishak-Knodell

Modified staging: architectural changes, fibrosis and cirrhosis

Change	Score
No fibrosis	0
Fibrous expansion of some portal areas, with or without short fibrous septa	1
Fibrous expansion of most portal areas, with or without short fibrous septa	2
Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging	3
Fibrous expansion of portal areas with marked bridging (portal to portal (P-P) as well as portal to central (P-C)	4
Marked bridging (P-P and/o P-C) with occasional nodules (incomplete cirrhosis)	5
Cirrhosis, probable or definite	6
Maximum possible score	6

Additional features which should be noted but not scored:

Intra-acinar fibrosis, perivenular ("chicken wire" fibrosis). Phlebosclerosis of terminal hepatic venules.