EudraCT-number: 2007-002433-37
Trial name: LENAMAINT
Trial Code: TUD-LENAMA-022

1) Name of Sponsor/Company

Technische Universität Dresden

2) Name of Finished Product

Revlimid

3) Name of Active Substance

Lenalidomide

4) Individual Study Table: Referring to Part of the Dossier

Not applicable

5) Title of Study

sponsor-protocol-version-date: 2009-12-04

Lenalidomide maintenance therapy in patients with MDS or AML with cytogenetic abnormalities involving monosomy 5 or del(5q) after allogeneic hematopoietic stem cell transplantation (HSCT)

This sponsor-protocol-version includes:
sponsor-protocol-version-date :2007-08-10
sponsor-protocol-version-date :2008-03-13

6) Investigators

PD Dr. med. Uwe Platzbecker (coordinating investigator)

Prof. Dr. med. Bunjes (investigator)

Prof. Dr. med. Einsele (investigator)

Prof. Dr. med Kröger (investigator)

Prof. Dr. med. Ganser (investigator)

PD Dr. med. Kobbe (investigator)

Prof. Dr. med. Beelen (investigator)

Prof. Dr. med .Finke (investigator)

Prof. Dr. med. Dr. h. c Niederwieser (investigator)

7) Study centre(s)

Universitätsklinikum C. G. Carus
Medizinische Klinik und Poliklinik I
Fetscherstr. 74
01307 Dresden

Universitätsklinikum Ulm
Klinik für Innere Medizin II
Albert-Einstein-Allee 23
89081 Ulm

Universitätsklinikum Würzburg
Medizinische Klinik und Poliklinik II
Oberdürrbacher Str. 6
97080 Würzburg

Universitätsklinikum Hamburg-Eppendorf
Interdisziplinäre Klinik und Poliklinik für Stammzelltransplantation
Martinistraße 52
20246 Hamburg

Medizinische Hochschule Hannover
Hämatologie, Hämostaseologie und Onkologie
Carl-Neuberg-Str. 1
30625 Hannover

Universitätsklinikum Düsseldorf
Klinik für Hämatologie, Onkologie und klinische Immunologie
Moorenstr. 5
40225 Düsseldorf

Universitätsklinikum Essen
Klinik für Knochenmarktransplantation
Hufelandstr. 55
45122 Essen

Medizinische Universitätsklinik
Hämatologie/Onkologie
Hugstetter Str. 55
79106 Freiburg

Universitätsklinikum Leipzig AöR
Medizinische Klinik und Poliklinik II
Abt. Hämatologie/Onkologie
Johannisallee 32A
04103 Leipzig

8) Publication (reference)

SOCKEL K, BORNHAEUSER M, MISCHAK-WEISSINGER E, TRENSCHEL R, WERMKE M, UNZICKER C, KOBBE G, FINKE J, GERMING U, MOHR B, GREINER J, BEELEN D, THIEDE C, EHNINGER G AND PLATZBECKER U. Early lenalidomide maintenance to prevent relapse of high-risk MDS or AML patients with del(5q) undergoing allogeneic HSCT after reduced-intensity conditioning - results of the “LENAMAINT” Trial. Haematologica in press

9) Studied period (years): date of first enrolment, date of last completed

Date of first enrollment: 2008-08-11
Date of last completed: 2011-02-17
Date of early termination: 2011-01-07

The justification for the early termination of the trial was mainly of suspected induction of severe GvHD by Lenalidomide.
Also a low recruitment and that the scientific rationale was not applicable anymore to all patients justified the early termination of the study (see annex 1).

10) Phase of development

Phase II study

11) Objectives

Main objective of trial:

To determine whether Lenalidomide maintenance therapy in MDS or AML patients with monosomy 5 or del(5q) abnormalities after allogeneic HSCT can result in a relapse rate ≤ 50%.

Secondary objectives of trial:

Determination of the safety of Lenalidomide when given after allogeneic HSCT

12) Methodology

Open label, multicenter, non-randomized

13) Number of patients (planned and analysed)

Patient planned:	50
Patient analysed/ recruited:	10

14) Diagnosis and main criteria for inclusion

Diagnosis:

Patients with MDS or AML with cytogenetic abnormalities involving monosomy 5 or del(5q) after allogeneic hematopoietic stem cell transplantation

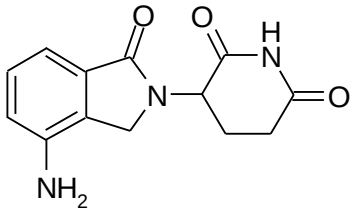
Main inclusion criteria:

1. Understand and voluntarily sign an informed consent form
2. Age ≥ 18 years at the time of signing the informed consent form
3. Able to adhere to the study visit schedule and other protocol requirements
4. AML (≥20% blasts) including secondary (s)AML (after radio-chemotherapy) with karyotype abnormalities involving monosomy 5 or del(5q) or - MDS and sMDS RAEB-1 and RAEB-2 with karyotype abnormalities involving monosomy 5 or del(5q) or - MDS and sMDS type RA(+/-RS) or RCMD(+/-RS) only with complex karyotype abnormalities involving monosomy 5 or del(5q)
5. in complete hematological remission documented by bone marrow aspiration within 8-16 weeks after allogeneic HSCT
6. All previous cancer therapy, including radiation, hormonal therapy and surgery, must have been discontinued at least 4 weeks prior to treatment in this study.
7. ECOG performance status of ≤ 2 at study entry (see Appendix II).
8. Laboratory test results within these ranges: - Absolute neutrophil count ≥ 1.0 x 10^9/L - Platelet count ≥ 100 x 10^9/L - Serum creatinine ≤ 2.0 mg/dL - Total bilirubin ≤ 1.5 mg/dL - AST (SGOT) and ALT (SGPT) ≤ 5 x ULN
9. Females of childbearing potential (FCBP) must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.
10. Disease free of prior malignancies for ≥ 5 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast
11. Able to take aspirin (ASA) 100mg daily as prophylactic anticoagulation in case of concomitant steroid treatment (patients intolerant to ASA may use low molecular weight heparin)

15) Test product, dose and mode of administration, batch number

Test product: REVLIMID® (lenalidomide)

REVLIMID®, a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2H-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:



Chemical Structure of Lenalidomide

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3. Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

REVLIMID® (lenalidomide) is available in 5 mg and 10 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg capsule shell contains gelatin, titanium dioxide and black ink. The 10 mg capsule shell contains gelatin, FD&C blue #2 (indigo carmine), yellow iron oxide, titanium dioxide and black ink.

Mechanism of Action:

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5 additional to other cytogenetic changes) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5 additional to other cytogenetic changes) and other cell lines without chromosome 5 deletions 14. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic sampling in MDS patients has not been performed so far. In multiple myeloma patients maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and Cmax values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Distribution:

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion:

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

Mode of administration:

Lenalidomide was supplied as 5 mg and 10 mg capsules for oral administration.
Maximum dose allowed per day was 10mg oral.

batch number:

09F0338, WK90234 001, 08B0056

08F0096, WK80102 001, 07B0032

07F0143, WK70194 001, 06B0025

16) Duration of treatment

Maximum duration of treatment of a subject according to the protocol was 1 year.

17) Reference therapy, dose and mode of administration, batch number

Not applicable

18) Criteria for evaluation: Efficacy, Safety

Efficacy evaluation:

Patients underwent regular bone marrow evaluation after HSCT in order to determine hematological relapse, which was considered as treatment failure.

Safety evaluation:

Data from all subjects who received any study drug were included in the safety analyses. Subjects who entered the study and did not take any of the study drug and had this confirmed, were not be evaluated for safety. The severity of the toxicities was graded according to the NCI CTCAE v3.0 whenever possible.

Fifty patients will be treated, which will yield a 95% confidence interval for grade 4 non-hematological toxicity of +/- 15%. Data will be evaluated after groups of 15 and 30 patients. If results at those times suggest with greater than 80% confidence that the true rate of grade 4 non-hematological toxicity at 3 months exceeds 15%, then the trial will be stopped. Operationally, this will occur if 5 out of 15 or 8 out of 30 patients have experienced grade 4 non-hematological toxicity in the first 3 months of the trial. Should the requisite number of grade 4 toxicities be reached before the 15 or 30 patient benchmarks, the trial will be stopped at that time.

Safety analyses will be performed after 15 and 30 patients.

19) Statistical methods

Datasets to be analyzed:

All efficacy and safety analysis will be based on the intent-to-treat (ITT) population. The ITT population will include all patients that have received lenalidomide within the trial regardless of duration of therapy. For safety analyses after 15 and 30 patients the last patient will have to have a minimum follow-up of 100 days. The data-set will be closed after the last patient included is alive and has a minimal follow-up of 12 months. Data listings for each variable will include all enrolled subjects.

Sample size, power considerations and statistics:

Historical data in patients with del(5q) or monosomy 5 associated aberrations not receiving lenalidomide maintenance therapy suggest that the incidence of relapse at one year after transplantation is 67%. Therefore, for design purposes the one-year RR difference of 17% is set at 50% vs. 67%. A simulation used an accrual period of two years, one additional year of follow-up, and a two-sided 0.05 significance level. Based on this, a sample size of 49 patients is sufficient to meet the 80% power requirement.

Categorical variables such as demographics and baseline characteristics will be summarized using frequencies and percentages. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum).

Cumulative incidences will be used to assess the primary end-point with relapse and treatment-related death as competing variables. Overall survival will be estimated using Kaplan Meier Statistics. Cumulative incidence of acute and chronic GvHD will be calculated with relapse and death as competing variables.

20) Summary – Conclusions: Efficacy Results, Safety Results, Conclusion

Recently, Kneppers et al. reported that early Lenalidomide (LEN) maintenance in patients (pts) with multiple myeloma undergoing allogeneic hematopoietic stem cell transplantation (HSCT) is associated with an increased incidence of acute graft-versus-host disease (GvHD).This is in accordance with our recently terminated prospective phase II trial evaluating LEN maintenance in high-risk MDS or AML pts with del(5q) cytogenetic abnormalities undergoing allogeneic HSCT. The aim of this trial was to improve the progression-free survival of these pts post-transplantation.

Ten pts with either high-risk MDS (n=1) or AML (n=9) and a median age of 65 years (range 40-72) being in documented complete remission (CR) were enrolled (Table 1). LEN maintenance started at a median of 2.5 months (range 2-4 months) after allogeneic HSCT from matched sibling or unrelated donors at a dose of 10mg/day for 21 days of a 28 days cycle. Thus, the scheduling of LEN was comparable to the study of Kneppers et al.

The trial was terminated prematurely mainly because of suspected induction of severe GvHD by LEN. In fact, 6 of 10 pts (60%) developed severe acute GvHD grade 3-4 within the first 2 cycles of LEN maintenance. Notably, all patients were still under systemic immunosuppression at that time. LEN treatment was discontinued and aGvHD resolved in 2 patients after the initiation of steroids. Nevertheless, 4 pts had to stop treatment completely due to persistent severe aGvHD after re-initiation of LEN. Additionally, another 4 pts had to stop treatment prematurely due to relapse (n=4) resulting in a premature study termination rate of 80%.

The immunomodulatory effect of LEN, including T- and NK-cell activation is well known and has been demonstrated in previous studies. In order to exclude pts at risk to develop GvHD prior to start of LEN, proteomics of urine samples of 5 pts developing GvHD were analyzed, as described in recent studies. However, we could not find a GvHD-specific signature in any pt, pointing at the de-novo induction of GvHD by LEN. Previous studies reporting a lower rate of acute GvHD during LEN treatment post-transplantation differ in various study objects from our trial and that of Kneppers et al. In fact, none of these studies involved early maintenance, but used LEN in myeloma pts with overt relapse in combination with steroids, which might have further abrogated the potential effects of LEN.

Myelotoxic side effects were manageable with reversible neutropenia grade 3/4 being documented in 3 of 10 pts (30%), while thrombocytopenia grade 3/4 occurred in 4 of 10 pts (40%). Currently, 5 of 10 pts (50%) are alive and 4 of them in continuous CR after a median follow-up time of 331 days (range 122-751 days) after HSCT.

In conclusion we confirm the data published by Kneppers et al. in an independent cohort of patients with myeloid malignancies. Early LEN maintenance to prevent relapse following allogeneic HSCT is not feasible, mainly due to the induction of severe GvHD. Whether lower doses or a delayed initiation of LEN maintenance therapy (6-12 months following HSCT) have

the potential to improve these results has to be evaluated in further trials. These studies will have to be planned carefully, with an intensive monitoring of GvHD, especially in the target group of MDS and myeloma pts, who are at higher risk for GvHD in general.

21) Dresden, 2012, July 13

Annex 1

Patient	Disease	Cyto-genetic	Donor (sibling/unrelated)	Start LEN (days after HSCT)	Cycles of LEN	relapse	aGvHD grade	Cause of treatment discontinuation
1011	AML	complex	matched, sibling	90	1	No	bowel 3°	aGvhD 3°
1012	AML	del (5q), trisomy (8q22)	single allele mismatch, unrelated	76	5	Yes	skin 3°, bowel 2°	relapse
1013	AML	complex	matched, unrelated	67	4	Yes	bowel 3°	relapse
1014	AML	complex	matched, unrelated	74	2	Yes	skin 3°, mucositis	aGvhD 3°
1015	AML	del (5q), del (7q)	matched, unrelated	68	3	Yes	0	relapse
1021	RAEB 1	del (5q)	matched, unrelated	114	12	No	skin 1°	regularly
1041	AML	del (5q)	matched, sibling	63	12	No	0	regularly
1042	AML	del (5q)	matched, sibling	69	1	No	skin 2°	aGvhD 2°
1061	AML	complex	single antigen mismatch, unrelated	108	5	Yes	0	relapse
1081	AML	complex	single antigen mismatch, unrelated	111	5	No	bowel 3°	aGvhD 3°

Table 1: Patient characteristics within the LENAMAINT trial, all patients underwent dose reduced-Conditioning

AML= acute myeloid leukemia
MDS= Myelodysplastic syndrome
HSCT= allogeneic hematopoietic stem cell transplantation
LEN= Lenalidomide
aGvHD= acute graft-versus-host disease