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| **Name of sponsor/company:**<br>GMIHO Gesellschaft für Medizinische Innovation Hämatologie und Onkologie mbH | **Individual study table referring to part of the dossier:**<br>Volume: N/A<br>Page: N/A | (For National Authority Use only) |
| **Name of finished product:**<br>Revlimid® 5, 10, 25 mg capsules | | |
| **Name of active ingredient:**<br>Lenalidomide | | |

**Title of study:**
A randomised comparison of daily 25 mg versus 5 mg lenalidomide as maintenance therapy after high-dose therapy and autologous stem cell transplantation in patients with multiple myeloma (The LenaMain-Trial)

**Versions of study protocol:**
Version 19, 06.10.2008; approved 16.01.2009: - first submission
Version 20, 06.03.2009; approved 13.04.2009: - Changing of Sponsor`s Address; MRT with contrast material
Version 21, 18.06.2012; approved 12.07.2012: - Changing of Sponsor`s Address; changing of the manufacturing of Lenalidomide →Bottles to blister
Version 22, 03.08.2012; Approval not required: changing of the principal clinical investigator in one side
Version 23, 02.10.2012; approved 07.11.2012: - Different reasons of dosis reduction; recommendation on treatment of Infections; new study site
Version 24, 15.01.2013; approved 05.04.2013: - new study site
Version 25, 03.07.2013; not approved → Notice of faults → Version 26
Version 26, 21.08.2013; approved 12.09.2013: - recommendation on prior therapy new SmPC
Version 27, 02.06.2014; approved 04.08.2014: - new SmPC
Version 28, 09.06.2016; Approval not required → Version 29
Version 29, 06.07.2016; approved 01.08.2016: - new PPP (Pregnancy Prevention Plan)

**Registration numbers:**
BfArM/PEI (Vorlagenummer): 4034885
EudraCT: 2007-003945-33

**Investigators:**
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[redacted] – Marien Hospital Düsseldorf
[redacted] – Universitätsklinikum Heidelberg

**Study centre(s):**
Klinik für Hämatologie, Onkologie und Klinische Immunologie, Universitätsklinikum Düsseldorf
Medizinische Klinik II, St. Johannes Hospital Duisburg
Medizinische Klinik IV und V, Justus-Liebig-Universität Gießen
Klinik für Stammzelltransplantation, Universitätsklinikum Hamburg-Eppendorf
Onkologie, Hämatologie und Palliativmedizin, Marien Hospital Düsseldorf
Medizinische Klinik, Abteilung Innere Medizin V, Universitätsklinikum Heidelberg

**Publication (reference):**
ASCO 2018 Abstract 8016

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| **Studies period** (years):<br>04.06.2009 (date of first enrolment)<br>22.06.2017 (date of last completed) | **Phase of development:**<br>Phase III |

**Objectives:**
**Primary:**
Compare the event-free survival of patients with multiple myeloma who receive two different dose levels (25 vs. 5 mg daily) of lenalidomide as maintenance therapy after first line high-dose therapy and autologous stem cell transplantation.

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**Secondary:**

- Evaluate safety, tolerability, and feasibility during consolidation (25 mg) and maintenance (25mg vs. 5 mg) therapy with lenalidomide.
- Evaluate the improvement of remission rates during consolidation therapy with lenalidomide and compare remissions rates during maintenance therapy with two doses of lenalidomide.
- Evaluate the quality of life of patients during consolidation and maintenance therapy with lenalidomide.

**Methodology:**

This trial is a randomised, parallel-group, multicenter phase III study for maintenance treatment with lenalidomide in patients with multiple myeloma who were treated with high-dose therapy and autologous stem cell transplantation as first line therapy.

Patients will be included after high-dose therapy which will be performed as first line treatment. High-dose conditioning should be melphalan 200mg/m2 for patients younger than 66 years and a second high-dose therapy should be performed in those patients who do not achieve at least a very good partial remission (vgPR). For patients between 66 and 75 years a tandem high-dose therapy with 100mg/m2 is recommended.

After high-dose therapy patients will be randomised in a 1:1 ratio to continuous maintenance therapy with either 25 mg or 5 mg lenalidomide daily for 21 days every 28 days. Randomisation will be stratified by ISS-stage (1-2 vs 3), age (younger than 66 years versus 66 years or older), response after high-dose therapy (CR+vgPR vs. PR vs. MR/SD).

Three months after high-dose therapy all patients will receive consolidation therapy with 6 cycles of lenalidomide 25 mg daily for 21 days every 28 days. Afterwards patients will receive maintenance therapy according to their assigned treatment arm. Patients will be treated until disease progression. During the treatment period patients will be seen every 2 weeks for the first 3 cycles of consolidation therapy and then every 4 weeks until disease progression is documented. All patients who have to discontinue the study drug will be followed until disease progression.

In the follow-up phase all subjects who discontinue the study drug for any reasons will continue to be followed for survival and post treatment phase anti-myeloma treatment.

**Number of patients** (planned and analyzed):

Inclusion of 194 patients was planned, and the analysis of the primary endpoint was planned to be done after at least 96 subjects have developed disease progression. 194 patients were included and 188 are eligible for the analysis of the primary endpoint as there were 6 screening failures. Of these 188 patients the data until the timepoint when the 96th patient experienced relapse is used for the analysis of the primary endpoint.

**Diagnosis and main criteria for inclusion:**

- Understand and voluntarily sign an informed consent form.
- Age 18-75 years at the time of signing the informed consent form.
- Able to adhere to the study visit schedule and other protocol requirements.
- Patients with multiple myeloma who have received high-dose therapy and autologous stem cell transplantation as first-line therapy within the last 90 – 120 days and have not shown progressive disease afterwards. Patients may have received a second high-dose therapy in case of less than a vgPR or due to conditioning with intermediate dose melphalan because of an age of more than 65 years.
- Patients may have received up to 6 cycles of prior induction therapy (e.g. idarubicine, dexamethasone) and up to 2 cycles of prior mobilisation chemotherapy (e.g. cyclophosphamide). A bortezomib or thalidomide containing induction therapy is allowed. Patients may also have received prior radiation therapy. The use of lenalidomide as monotherapy or as part of a combination treatment for induction therapy is not allowed.
- Measurable levels of myeloma paraprotein in serum (>0.5 g/dL) or urine (>0.2 g/24hours) or measurable free light chains (FLC) in serum (>50 mg/l) with an abnormal FLC ratio must be documented at the time of first diagnosis.
- ECOG performance status of □ 2 at study entry (see Appendix 02).
- Laboratory and functional test results within these ranges:

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|---|---|---|
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- ANC ≥ 1,000/µL
- Platelet count ≥ 100,000/µL
- Total bilirubin ≥ 2.5 mg/dL
- AST (SGOT) and ALT (SGPT) ≥ 3 x ULN
- Patients with impaired renal function can be included

- The patient must be able to adhere to the pregnancy precautions:

Female subjects of childbearing potential (FCBP) must:

- Understand that the study medication could have a potential teratogenic risk to the unborn child
- Agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting
- The following are examples of highly effective methods of contraception
  - Implant*Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system * [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner's vasectomy

Additional effective methods (barrier methods) are the following examples:

- Male condom
- Diaphragm
- Cervical cap

- The patient may not receive study medication until the study doctor has verified that these tests are negative.
- Agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following the last dose of lenalidomide if they have regular or no menstrual cycles. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following the last dose of lenalidomide.

These requirements also apply to women of childbearing potential who practice complete and continued abstinence:

- Be informed and have to understand the potential consequences of pregnancy and the need to notify the study doctor immediately if there is a risk of pregnancy
- Understand the need for effective contraception, without interruption, 28 days before starting lenalidomide, throughout the entire duration of lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
- Understand the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- Understand the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol (Section 6.3.1)
- Acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Agree to abstain from breastfeeding during study participation and for at least 28 days after discontinuation from the study
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures

Females Not of Childbearing Potential (FNCBP):

For a FNCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be

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counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

Male subjects must:

- practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.
- Agree not to donate semen or sperm while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- Understand the teratogenic risk if engaged in sexual activity with a pregnant female or a female with childbearing potential.
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female with childbearing potential.
- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking lenalidomide, the Investigator must be notified immediately.

All subjects must:

- Agree to abstain from donating blood while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
- Subjects should be instructed to never give lenalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide must be discontinued during this evaluation.

The Investigator must ensure that for male subjects:

- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.

- 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.

**Test product, dose and mode of administration, batch number:**
Lenalidomide [LEN] (Revlimid® Hartkapseln)
Patients will be included in the study 90-120 days after high-dose therapy.
After randomisation all patients will start with consolidation therapy. Consolidation therapy consists of 6 cycles of lenalidomide 25 mg daily for 21 days every 28 days.
After consolidation therapy patients will be treated according to their treatment arm with either 25 mg or 5 mg lenalidomide daily for 21 days every 28 days. Maintenance therapy will be continued until disease progression occurs or untolerable side effects occur despite of dose reduction or the study ends.

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**Duration of treatment:**
Until disease progression occurs or untolerable side effects occur despite of dose reduction or the study ends.

**Reference therapy, dose and mode of administration, batch number:**
Not applicable

**Criteria for evaluation:**

Efficacy:

Primary: The primary efficacy endpoint was event-free survival (EFS) from the time point of randomization.

Secondary: Safety, tolerability and feasibility
Remission rates (RR)
Overall Survival (OS)
Progression-free Survival 2 (PFS2)
Quality of Life (QoL)

Safety:

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 drugs and had this confirmed, were not evaluated for safety. All toxicities were monitored and the differences in the proportions of patients in each arm who had rash, myelotoxicity of grade 2 or more, thrombo-embolic events of grade 2 or more, neuropathy of grade two or more, bradycardia of grade 3 or more, change in performance status, transfusion requirement, bleeding complications grade 3 or more and infections grade 3 or more were examined.
The severity of the toxicities was graded according to the NCI CTCAE v3.0 whenever possible and all data was summarized.

**Statistical methods:**

For the final analysis data until the time point when the 96th patient experienced relapse was used.
The objective of the statistical analysis was to compare the efficacy and safety of lenalidomide as consolidation and maintenance treatment after high-dose therapy and autologous stem cell transplantation. The primary efficacy endpoint was event-free survival (EFS) from the time point of randomization. The hypotheses to be tested were:

H0: EFS (Maintenance with 25mg) ≤ EFS (Maintenance with 5mg)
H1: EFS (Maintenance with 25mg) > EFS (Maintenance with 5mg).

A one-sided log-rank test with a significance level of 0.05 (formally: p = 0.049, because of adjustment for interim analysis) was used to compare the Kaplan-Meier curves of EFS and OS. The event rates at specific time-points (with 95% confidence intervals) were computed for each time-to-event variable. If a patient had not progressed or died, event-free survival was censored at the time of last documented visit.
An interim analysis for efficacy was performed by the responsible biostatistician when 50 % (48 progresses) of the EFS events required for the final analysis had occurred. At the time of the interim analysis 54 events (48 progresses) had occurred. As a consequence of the alpha error spending due to the interim analysis, the alpha error level for the final analysis had to be adjusted formally to 0.049.

To adjust the treatment effects by potential prognostic factors, a regression analysis (Cox proportional hazards model) was performed. In order to choose the best model, several variable selection procedures were applied. The BIC (Bayesian Information Criterion) gives the model with the lowest number of prognostic factors explaining

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EFS.

Subgroup analysis was performed for all evaluable subjects.

The incidence of Secondary Primary Malignancies (SPMs) in the two groups was analyzed using competing risk models (taking into account death as competing risk).

The baseline data for qualitative variables was summarized by frequency and relative frequency.
The quantitative variables were described based on mean, standard deviation, number of patients, number of missing data, minimum, maximum, 25 %, 50 % and 75 % quartiles,
Appropriate tests (t-test for continuous variables and fisher test for discrete variables) were done in an explorative way.

A safety data analysis was performed including the time period from the 96th progress until the end of study.

The statistical software used in the statistical analysis is R version 3.4.0

**Summary – Conclusions:**

Efficacy results:
Patients characteristics were equally distributed in both arms. Response rates improved during CT with an increase of sCR from 8 % to 21 % (p = 0.0001). During MT, 36 % and 23 % of pts. in arm A and B achieved sCR as best response (p = 0.08). After a median follow-up of 46.7 months the primary endpoint event-free survival (EFS) from randomization was significantly different with a median EFS of 44.8 and 33.0 months for arm A and B (HR 0.65, range: 0.44-0.97; p = 0.032). This was confirmed by Landmark analysis including only patients who entered MT (HR 0.63; p = 0.042). Overall survival (OS) was not different with a median 4-year-OS of 79 % and 67 % for arm A and B (p = 0.16).

Safety results:
Len CT could be completed in 86 % pts and Len MT was applied for one year in 72 % and 61 % pts in arm A and B (2 years: 44 % vs. 34 %; 3 years: 27 % vs. 15 %). In arm A 51 %, 22 %, 10 % and 3 % pts continued 25 mg Len without dose reductions / discontinuations after CT, 1, 2 and 3 years MT. Dose reductions were mainly due to hematologic AEs (68 %), especially grade 3 neutropenia (56 %). Overall toxicity was higher in the 25 mg arm and infections (≥ grade 2) were the major AE during MT (1st year: 62 % vs. 42 %, 2nd year: 44 % vs. 36 %, 3rd year: 44 % vs. 28 %).
The incidence of second primary malignancies was similar in both arms.

Conclusion:
Low-dose Len is associated with significantly shorter EFS compared to the concept of upholding high-dose Len. Still, the rate of toxicity observed and the need for dose reductions in most patients requires reconsideration of the high-dose schedule and awaiting of long-term OS.

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**Date of Report:** [redacted]

Author: [redacted]
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**Date of Approval:** 16 Jun 2018

Approved: Prof. Dr.med. Guido Kobbe
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