Ergebnisbericht über die klinische Prüfung nach §42b AMG

"A prospective single center trial of treatment with Lenalidomide-Melphalan-Dexamethasone in patients with AL amyloidosis". LEOMEX-Studie
EudraCT number 2008-001405-41

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1) Name of Sponsor/Company

GMIHO Gesellschaft für Medizinische Innovation - Hämatologie und Onkologie mbH

Alexanderplatz 1

Berolina-Haus

10178 Berlin

2) Name of Finished Product

Revlimid®

Alkeran®

Fortecortin®

3) Name of Active Substance

Lenalidomide

Melphalan

Dexamethasone

4) Individual Study Table: Referring to Part of the Dossier (Volume, Page)

N/A

5) Title of Study

A prospective single center trial of treatment with Lenalidomide-Melphalan-Dexamethasone in patients with AL amyloidosis

6) Investigators

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7) Study centre

Amyloidosis Center, University Hospital Heidelberg

8) Publication (reference)

Blood, 2013; 122: abstr.1993

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

FPI: 20.4.09

LPO: 7.2.13

Study discontinuation did not occur.

Table: Summary of withdrawals and reasons for withdrawal

Subject No	Date of last contact	Reason for withdrawal
8	31.03.2010	Progression of amyloidosis
9	03.05.2010	Progression of amyloidosis
10	11.06.2011	Progression of amyloidosis
14	01.12.2013	Progression of amyloidosis
20	01.11.2010	Serious adverse event
22	06.04.2011	Progression of amyloidosis
37	01.08.2011	Serious adverse event
41	30.07.2012	Progression of amyloidosis
47	17.07.2013	Adverse event

10) Phase of development

Phase 2

11) Objectives

AL amyloidosis is a life threatening disease. Treatment results are still unsatisfactory. Rates of haematological remission (HR) do not exceed 70% for conventional chemotherapies currently used in the upfront setting. Achievement of complete remission (CR) is a very important prognostic factor for long-term survival. In a historical control group treated with Melphalan-Dexamethasone with the same inclusion criteria as in this study the CR rate was only 16%. By addition of lenalidomide to the standard chemotherapy with Mel-Dex we wanted to improve CR rates to >33%.

Primary endpoint:

- To evaluate the rate of CR after 6 cycles L-Mel-Dex

Secondary endpoints:

- Toxicity (hematological and non-hematological)
- Rate of HR (Hematological response (CR and PR))
- Rate of organ response
- To correlate cytogenetic aberrations and GEP (Gene Expression Profiling) results with hematological response to treatment
- Retrospective comparison with a historical control group treated with Mel-Dex in our institution

12) Methodology

Not-randomized, single arm, single center

Amendments to the study protocol: N/A

13) Number of patients (planned and analysed)

50 patients planned

50 patients analysed

14) Diagnosis and main criteria for inclusion

Systemic light chain (AL) amyloidosis

Main inclusion criteria:

a. Biopsy proven systemic untreated AL amyloidosis requiring systemic chemotherapy
b. Age between 18 and 74 years at the time of signing the informed consent form
c. Not eligible for or refused high-dose melphalan (HDM)
d. Measurable plasma cell disease
e. Life expectancy > 3 months
f. WHO performance status ≤ 3
g. NYHA < stage IV
h. Understand and voluntarily sign an informed consent form.
i. Laboratory test results within these ranges:
j. Absolute neutrophil count $\geq$ 1.5 x 10^9/L
k. Platelet count $\geq$ 100 x 10^9/L
l. Creatinine Clearance / MDRD $\geq$ 40 ml/min
m. Total bilirubin $\leq$ 2,5 mg/dL
n. 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.
o. Disease free of prior malignancies for $\geq$ 5 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "insitu" of the cervix or breast.

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

a) Lenalidomide, 10 mg day 1-21, oral

b) Melphalan 0,15 mg/kg day 1-4 oral

c) Dexamethasone 20 mg day 1-4

repetition every 28 days

16) Duration of treatment

6 months

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

N/A

18) Criteria for evaluation: Efficacy, Safety

Efficacy: Hematological remission and organ response, OS, EFS

Safety: Hematological and Non-Hematological toxicity

19) Statistical methods

a) Efficacy

(i) Primary Endpoint: A one-sided exact binomial test was applied. The rate of CR was estimated together with the 95% Clopper-Pearson confidence interval.

(ii) Secondary Endpoints: Hematological and organ response rates were summarized and estimated using 95% Clopper-Pearson confidence intervals. A comparison of response rates with those from a historical control group (n=49 pts.) from the same institution was done using Fisher's exact test as well as univariable and multivariable logistic regression. Additionally overall and event-free survival was compared between the two study cohorts using the logrank test as well as univariable and multivariable Cox regression models.

b) Safety

Adverse and serious adverse events (AEs and SAEs) were summarized by counts and rates with respect to patient and treatment cycles, including a description of the event, its duration, severity, and relationship to treatment.

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

a) **Efficacy results**

Forty-five patients (90%) completed 3 cycles and 35 patients (70%) completed 6 treatment cycles; overall 253 cycles could be applied.

The rate of complete remission (CR) is 9 out of 45 evaluable patients (20 %). The one-sided exact binomial test does not reject the null hypothesis H0 : CR rate of 16%, **p-value = 0.287**. The corresponding 95% confidence interval ranges from 11% to 100%.

The rate of complete remission (CR) after six cycles of treatment is 9 out of 35 evaluable patients (25.7 %). The one-sided exact binomial test does not show a significant increase in CR rate in comparison with the null hypothesis CR rate of 16%, **p-value = 0.0954**. The corresponding two-sided 95% confidence bounds are 14% and 100%.

b) **Safety Results**

Causes of discontinuation of treatment were toxicity in 6 patients (including one treatment-related death in the first cycle) or AL progression (9 patients). Ninety adverse events (AE) > CTC grade 3 were recorded including 16 severe AEs. Seventeen hematologic AEs were observed (CTC grade 4 in 2 patients). Most common non-hematological AE was worsening of cardiac function or symptoms of autonomic neuropathy (14 pts.). Furthermore 8 patients got an infection, one patient acute renal failure and one patient thrombosis. One patient died during the first treatment course from sepsis. No other treatment-related deaths were observed.

c) **Conclusion**: This is the largest phase II trial using lenalidomide, melphalan and dexamethason in newly diagnosed AL amyloidosis patients. Treatment was effective and feasible in this cohort of mostly elderly patients. 78% of evaluable patients achieved a hematologic remission. The early death rate was low with 6% despite of inclusion of a high number of patients with advanced cardiac amyloidosis. Overall, toxicity was manageable in

most patients. Further improvement of these results might be achieved by prolongation of therapy in patients who have responded to and tolerate this combination therapy well.

21) Date of report.

15.12.13