MEDICAL & SCIENTIFIC AFFAIRS		
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Title:	Bortezomib and Bendamustine in the Treatment of subjects with Relapsed or Refractory Multiple Myeloma	
Study design:	Prospective, open-label, multicentre dose escalation study, Phase I/II	
Study dates:	Start: 21.01.2006 End: 25.09.2006	
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Janssen-Cilag GmbH

Clinical Study Report

Bortezomib and Bendamustine in the Treatment of subjects with Relapsed or Refractory Multiple Myeloma

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MEDICAL CONCEPT:
Dr. med. R. Angermund; Janssen-Cilag GmbH; Neuss; Germany

DATE STUDY INITIATED:
31. January 2006
21. February 2006 (first patient enrolled)

DATE STUDY EARLY TERMINATED:
09. August 2006 (study stopped early)
25. September 2006 (last patient last visit)

Issue/Report Date: 20. August 2007
Department: Medical & Scientific Affairs
Document No.:

Compliance: The observational study described in this report was performed according to German legislations; the principles of Good Clinical Practices were not applicable as per definition (non-interventional).

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Listings of 8 single patients
Language: German. Issued by ClinAssess, Dated 18.01.2007, 123 pages
A tables of contents is provided therein.

Study plan
Language: German. Dated 6th January 2006, 62 pages

Documentation form/Case report forms (CRF)
Language: German. Dated 21th November 2005, 139 pages plus 14 extra pages without number for SAE

SmPC VELCADE®
Language: German. Dated May 2007, 8 pages

SYNOPSIS

NAME OF SPONSOR/COMPANY:
Janssen-Cilag GmbH Germany

NAME OF FINISHED PRODUCT:
VELCADE®
NAME OF ACTIVE INGREDIENT:
Bortezomib

Protocol No.: 26866138MMY2029

Title of Study: Bortezomib and Bendamustine in the Treatment of subjects with Relapsed or Refractory Multiple Myeloma

Coordinating Investigator:
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Publication (Reference): none

Study Initiation/Completion Dates: January 2006 to September 2006

Phase of development: I/II

Objectives:

In this study, a dose recommendation should be established for the combination of Bortezomib and Bendamustine in subjects with relapsed or refractory Multiple Myeloma

Methodology:

Prospective, open-label, multicentre dose escalation study, Phase I/II in Germany

Number of Subjects (planned and analyzed):

It was planned to enrol a maximum population of 44 patients with relapsed or refractory Multiple Myeloma requiring therapy. According to the protocol the study had to be terminated early after enrolment of 8 patients due to the occurrence of two dose limiting toxicities on the lowest dose level of Bendamustine.

Diagnosis and Selection criteria:

Male and female patients with relapsed or refractory multiple myeloma, aged 18 to 80 years

in 5 German centres

Procedure:

The dose of Bendamustine should have been escalated in increments of 10 mg/m², with a total of 5 dose levels. The starting dose was 60 mg/m². The DLT should have been determined within the scope of the first 2 cycles. At least 3 patients should have been treated at each dose level.

- The dose should have been escalated if there is was DLT (0/3 patients).
- If one DLT occurred in 1/3 patients, 3 additional patients should have been be included at that particular dose level. If no further DLT (1/6 patients) occurred, the dose should have been escalated.
- If there were ≥ 2 DLTs at any dose level (≥ 2/3 patients or ≥ 2/6 patients), the next lower dose level should have been established as the maximum tolerable dose. A total of 6 patients must have been treated at this MTD (no more than 1/6 DLTs).

After completion of the dose finding in the first part of the study, all patients included thereafter in the second part should have been treated with the MTD for Bendamustine which had to be defined in part 1. If a response to therapy was achieved, treatment should have been continued until a maximum remission was reached, or else for a maximum of 8 cycles. Maximum remission was reached when 2 further cycles of therapy failed to achieve an additional reduction in myeloma protein by more than 10% in the serum or urine. In case of NC, a maximum of 8 cycles should have been administered.

Medication, Dose and Mode of Administration:

Bortezomib 1.3 mg/m² i.v. on Days 1, 4, 8, 11 of each cycle

Bendamustine 60, 70, 80, 90, 100 mg/m² i.v. on Days 1, 2 of each cycle

Prednisolone 100 mg orally on Days 1, 2,4, 8, 11 of each cycle

Duration of Treatment: Treatment phase: 24 weeks max. Follow-up phase: 12 months

Criteria for Evaluation:

Effectiveness and tolerability:

Primary endpoints:
- determination of MTD for Bendamustine in combination with a fixed dose of Bortezomib
- safety and tolerability of the combination therapy

Secondary endpoints:
- overall response rate (OR)
- progression-free survival (PFS)
- overall survival (OS)

Safety:

Safety parameters included SAE and AE reporting as well as documentation of dose limiting toxicities

Dose limiting toxicities were defined as:
- Neuropathy NCI-CTCAE grade 2 with pain
- Neuropathy NCI-CTCAE grade 3
- Haematological toxicity NCI-CTCAE grade 4
- Non-haematological toxicity ≥ NCI-CTCAE grade 3 (with the exception of Nausea, Vomiting and Alopecia)

Statistical Methods:

Statistics were planned to be descriptive, declaring frequency, mean, median, range and confidence interval.

Since the study had to be stopped early due to the occurrence of two dose limiting toxicities on the lowest dose level of Bendamustine only 8 patients were enrolled.

Because of the small number of patients recruited, statistical analysis is not usefull and an individual patient summary will be given instead.

SUMMARY – CONCLUSIONS

This study recruited 8 patients from 21-FEB-2006 (first patient in) until 25-JUL-2006 (last patient in). The last patient completed the study on 25-Sep-2006 (last patient last visit).

The study was composed of two phases, a dose finding phase (Phase I) and a efficacy evaluation phase (Phase II). Therefore it was classified as a phase I/II trial.

The dose finding phase of the trial could not be completed because two patients experienced a dose limiting toxicity (DLT) according to the definition in the protocol after being treated with 60 mg/m2 BSA Bendamustine in combination with 1.3 mg/m2 BSA Bortezomib. These concentrations were the lowest dose levels designated, therefore no lower doses could be given to the patient in accordance with the protocol.
The study has been stopped and the patients have been withdrawn from the study.
The evaluation phase was therefore not activated.

Individual patient summary (in the order of recruitment):

Patient No. 1; CRF-No: 32, Screened 21-Feb-2006

This patient was a 75 year old female with a IgG kappa Myeloma stage III, first diagnosed in February 2005. After initial therapy with Melphalan and Prednisone from 3/2005 to 5/2005 with progressive disease he received Dexamethasone pulse therapy (June 2005 - August 2005) with partial response (PR). When he relapsed in 2/2006 he was enrolled into the study.

The patient was irradiated T10 - L3 with a total dose of 36 Gy prior to study entry.

The patient was treated according to protocol starting on 28.02.2005 with a dose of Bendamustine of 60 mg/m² d1 and 2, a dose of Bortezomib of 1.3 mg/m² on days 1,4,8,11 and Prednisone 100 mg orally for 2 cycles. The third cycle which started on the 18.04.2005 was discontinued after d4 due to leukopenia of 1900/µl.

Mild to moderate side effects were GI toxicities with nausea and vomiting as well as neurological toxicities (headache) with possible relationship to Bortezomib according to investigator's assessment. These side effects were completely reversible

Adverse events were thrombocytopenia within cycle 2 (C2d8) of 47.000/µl leading to a dose delay of Bortezomib of 1 day and leukopenia of 1.900/µl in cycle 3 d4 leading to a stop of study medication (21.04.2006). The leukopenia was completely resolved on 09.05.2006.

No serious adverse events were noted for this patient. This patient had no dose limiting toxicities.

Due to investigator's assessment the response was evaluated as Partial Response (PR).

According to protocol, no follow-up was performed.

Patient No. 2: CRF-No. 33, Screened: 21-Feb-2006

This patient was a 57 year old male with pure light chain disease (lambda light chains) Stage III first diagnosed in 08/2002. He received primary treatment with idarubicine and dexamethason followed by high-dose melphalan and autologous stem cell transplantation in 2003 with minor response. Progress was diagnosed in February 2006 and the patient enrolled.

He received Bendamustine 60 mg/m²day 1 and 2 of cycle 1 as well as Bortezomib 1.3 mg/m² day 1,4,8,11 and Prednisone 100 mg orally for one cycle. After this first cycle the patient experienced a pulmonal mycosis on 24.03.2005 (possibly related to study drug) requiring oral antifungal therapy (Voriconazol). The event was regarded as severe leading to study termination. According to the definition of adverse events this event qualified as Non-haematological toxicity NCI-CTCAE grade 2 meaning that it had not to be reported as SAE or DLT. He recovered from this event on 28.06.2005 without sequelea.

Mild / moderate Adverse events were diarrhea, headache, dizziness, dyspnea and visual impairment, which were regarded as doubtfully related to study drug according to investigator's assessment.

Efficacy was assesses as No Change (NC).

Patient No. 3, CRF-No 21, Screened 22-Feb-2006:

This patient was a 47 year old male diagnosed with an IgA lambda Myeloma Stage III in February 2004. He received 6 cycles of Vincristine, Adriamycin and Dexamethasone (VAD) (11/2004 - 4/2005) as primary treatment with a partial remission (PR) diagnosed in April 2005. After relapse in 12/2005 the patient was enrolled into the study.

He received 2 complete cycles of Bendamustine 60 mg/m² days 1 and 2 and Bortezomib 1.3 mg/m² days 1,4,8,11 and Prednisone at a dose of 100 mg intravenously starting with the first cycle on 28.05.2005. In cycle 3 and 4 Bendamustine was given according to protocoll but Bortezomib was omitted on days 8 and 11 in both cycles.

During study treatment the patient experienced mild to moderate anemia and leukopenia (not related to study drug according to investigator's assessment), mild neuopathy (probably related) and mild nausea (possibly related). The patient recovered completely form these events.

The efficacy was evaluated as partial response (PR) at study end (31.05.2006).

Patient No. 4, CRF-No. 34; Screened 21-APR-2006

This patient was a 66 year old female diagnosed with a pure kappa light chain disease Stage II in May 2004 with monosomia 13. She received chemotherapy with Melphalan and Prednisone initially in 7/2004 with unknown outcome followed by high dose melphalan chemotherapy with autologous stem cell transplantation with a partial response diagnosed in March 2005. After relapse in April 2006 the patient was enrolled into the study.

She received only 1 cycle of chemotherapy with Bendamustine 60 mg/m² days 1and 2 and Bortezomib 1.3 mg/m² days 1,4,8,11. (there was a delay within this cycle due to bank holidays).

Due to thrombocytopenia of 52.000//µl the second cycle could not be started and study medication was stopped permanentely.

During this cycle the patient suffered from the following mild to moderate adverse events: bronchitis, dyspnea, pain in right shoulder, cold, muscle cramps in calf and hands (all doubtfully or not related due to investigator's assessment) and mild anemia (possibly related)

The efficacy was evaluated as no change (NC).

Patient No. 5; CRF-No: 41, Screened 05-JUN-2006

This patient is a 48 year old female diagnosed with a pure kappa light chain disease Stage III in February 2005. She received 4 cycles of Vincristine, Adriamycin and Dexamethasone (VAD) followed by high-dose Melphalan and autologous stem cell transplantation as primary therapy and achieved a complete remission (CR) in May 2005. She was irradiated with a total dose of 30 Gy T 8 - 10 prior to enrollment.

Upon relapse in 5/2006 she was enrolled into the study.

She received one cycle of Bendamustine 60 mg/m² days 1and 2 and Bortezomib 1.3 mg/m² days 1,4,8,11 and Prednisone 100 mg according to study protocol. During cycle 2 on day 8 she experienced a life threatening thrombocytopenia of 20.000//µl on 07.07.06 and needed a platelet transfusion to prevent bleeding.

This event was regarded as a dose-limiting toxicity (DLT) and study medication was stopped permanentely on 14.07.2006. The patient recovered completely from this event without sequelae.

Mild and moderate adverse events were: nausea, vomiting, loss of appetite, back pain, mucositis, urinary tract infection with fever, and nephrohydrosis. As severe adverse event, the patient experienced anemia.

The efficacy was assessed as partial response (PR) during to investigator's assessment.

Patient No. 6: CRF-No. 42, Screened 20-JUL-2006

This patient was a 62 year old female with an IgG lambda Myeloma Stage III, diagnosed in October 2002. She received chemotherapy with 4 cycles of Idarubicine and Dexamethasone followed by high-dose Melphalan chemotherapy with autologous stem cell transplantation until February 2003 with a partial remisson (PR). She than was referred to a maintenance therapy with interferon alpha from September 2003 until November 2004.

Date of progressive disease is not recorded.

The patient received one cycle of Bendamustine 60 mg/m² days 1 and 2, Bortezomib 1.3 mg/m2 days 1,4,8,11 and Prednisone 100 mg orally according to study protocol from 28.07.2006 to 07.08.2006.

On day 12 she experienced septical temperatures and a pneumonia without neutropenia was diagnosed and antibiotic therapy initiated. The patient recoverd completely without sequelae from this event. The pneumonia was assessed as possibly related to study drugs.

This event was assessed as a dose limiting toxicity (DLT) and the study drug permanently discontinued on 09.08.2006.

An Efficacy evaluation was not done.

Being the second DLT on the lowest dose level for Bendamustine the whole study had to be stopped on the 9th of August 2006.

The following two patients were already recruited and under treatment at that time:

Patient No. 7: CRF-No: 22, Screened 21-JUL-2006

This patient was a 67 year old male diagnosed with an IgG kappa Myeloma Stage III in October 2003. He received a chemotherapy with 1 cycle of Vincristine, Adriamycin and Dexamethasone (VAD) and 3 cycles of Vincristine, Cyclophosphamid, Adriamycin and Prednisolone (VCAP) followed by high-dose melphalan therapy and autologous stem cell transplantation as primary therapy and achieved a partial remission (PR) in 4/2004. Upon relapse in 12/2004 he received a chemotherapy with Bendamustine and a single dose of Bortezomib until January 2006 with a minor response (MR). Prior to study enrollment, this patient was irradiated with a total dose of 36 Gy T8 - L1,

This patient received 2 cycles od Bendamustine 60 mg/m² days 1 and 2, Bortezomib 1.3 mg/m² days 1,4,8,11 and Prednisone 100 mg orally according to protocol starting on 24.07.2006.

During study treatment this patient experienced the following mild and moderate adverse events: constipation (not related to study drug according to investigator's assessment), heart rhythm disturbances (not related), hypokalemia (not related)

Adverse events were anemia and leukopenia (possibly related). Due to the anemia the patient had to be hospitalized to get a blood transfusion , therefore it was notified as a SAE.

Thrombocytopenia occurred during the second cycle. The platelet count decreased step by step and on C2 d11 (24.08.06) platelet count was 24.000/µl. The thrombocytopenia persisted for one week .Therefore study medication was stopped permanently on 31.08.2206.

The thrombocytopenia of 24.000/µl would formally qualify as DLT being a haematological toxicity NCI-CTCAE grade 4. But since the study had been closed already on 09.08.2006 this event was not assessed as DLT, but was recorded as SAE. During the follow up it was recorded that the thrombocytopenia improved (platelet count 85.000/µl on 17.09.06).

The efficacy was evaluated as no change (NC) upon study end (31.08.2006).

During SAE follow-up we learned that the patient experienced progressive disease and died due to disease progression on 02.10.2006.

Patient No. 8: CRF-No: 12 Screened 25-JUL-2006

This patient was a 57 year olf male diagnosed with an IgA kappa Multiple Myeloma Stage III in March 2005. He received a treatment with 3 cycles of Idarubicine and Dexamethasone followed by 3 cycles of Melphalan and Prednisone as first line treatment achieving a partial remission in 9/2005. Date of relapse is not recorded.

The patient was irradiated with a total dose of 36 Gy T12 until L5 prior to study entry.

Bendamustine was given at a dose level of 60 mg/m² day 1 and 2, Bortezomib was dosed with 1.3. mg/m² d1, beginning as of 31.07.2006. The initial platelet count was 84.000/µl at screening, 53.000/µl at day 1 of cycle 1 and 52.000/µl on day 4 of cycle 1. Due to the persistent thrombocytopenia study drug was permanently withheld and the patient was dropped out of study after cycle 1 d4 on 03.08.06. The patient experienced a gastrointestinal haemorrhage due to the low platelet count. The event was recorded as SAE and was assesed as probably related to Bortezomib.

Other reported adverse events were mild to moderate with depression (not related), diarrhea, nausea and vomiting (not related to study drug) and anemia (possibly related to study drugs)

Efficacy evaluation was not done.

RESULTS

SAFETY:

1. Dose limiting toxicity (DLT)

1. 1. Dose limiting Toxicities causing early termination of the study

CRF No.	DLT	Date of onset	study end	outcome
41	Thrombocytopenia (haematological toxicity grade 4)	07.07.2006	14.07.2006	recovered without sequelea
42	Pneumonia requiring i.v. antibiotic treatment (non-haematological toxicity grade 3)	08.08.2006	09.08.2006	recovered without sequelae

1. 2. Further Case with potential Dose limiting Toxicity

CRF No.	DLT	Date of onset	study end	outcome
22	Thrombocytopenia (haematological toxicity grade 4)	24.08.2006	31.08.2006	improved to haematological toxicity grade 1 (17.09.06)

2. Adverse events (AE)

In total 114 Adverse events were noted;
88 (77%) were classified as mild or moderate, 20 (17,5%) were classified as severe,
4 (3,5%) as life threatening, and 2 (2%) were unclassified.

The 10 most frequent adverse events were:

Preferred Term	Frequency
Thrombocytopenia	21
Anemia	17
Leukopenia	9
Nausea/Vomiting	7/2
Diarrhea	6
Headache	6
Dyspnea	5
Pneumonia	3
Fever	3
Weakness	3

3. Serious adverse events (SAE)

5 SAEs occurred in 4 patients, but all of them were manageable and 4 out of 5 patients recovered without sequelea.
This table includes the cases with dose limiting toxicities, since these DLTs also qualified as SAE.

CRF. Nr	Date of onset	Preferred Term	Severity	Relation to Bortezomib	Relation to Bendamustine	Date of restitutio	Outcome
12	11.08.06	GASTROINTESTINAL HAEMORRHAGE - THROMBOCYTOPENIA	life threatening	probable	doubtful	18.08.06	Restitutio without sequelea
22	01.09.06	ANAEMIA - ARRHYTHMIA - DISEASE PROGRESSION	moderate (hospitalisation)	none	none	N.A.	death 02.10.06 due to PD
22	04.09.06	THROMBOCYTOPENIA	life threatening	doubtful	doubtful	17.09.06	improved to haematological toxicity grade 1
41 (DLT)	07.07.06	THROMBOCYTOPENIA	life threatening	probable	probable	14.07.06	Restitutio without sequelea
42 (DLT)	09.08.06	PNEUMONIA - PYREXIA	severe (hospitalisation)	possible	possible	18.08.06	Restitutio without sequelea

One Patient (CRF No. 22) died 39 days after the last Bortezomib dose on 2.10.06 due to progression of Myeloma.
This event of death was assessed as not related to study medication.

4. Completion of study medication

Only 3 patients had received at least 2 complete cycles of study medication according to protocol.
The first 2 cycles were defined as the scope in which the MTD of Bendamustine should be determined.

CRF No.	cycles given	end of study medication	cause of termination
32	Cycle 1 and 2	after C3 d4	Leukopenia
33	Cycle 1	after C1 d11	Pulmonal mycosis
21	Cycle 1, 2 , 3 and 4	after C4 d11	unknown
34	Cycle 1	after C1 d11	Thrombocytopenia
41	Cycle 1	after C2 d4	Thrombocytopenia
42	Cycle 1	after C1 d11	Sepsis and Pneumonia
22	Cycle 1 and 2	after C2 d11	Thrombocytopenia
12	-	after C1 d4	Thrombocytopenia

EFFICACY:

Due to the small numbers of patients no conclusions regarding efficacy can be drawn from this study

CRF No.	Efficacy
32	NC
33	PR
21	PR
34	NC
41	PR
42	Not done
22	NC
12	Not done

CONCLUSION

This study was early terminated according to protocol after two dose limiting toxicities (DLT) had occurred on the lowest dose level of Bendamustine (CRF 41 and CRF 42).
The first DLT was a thrombocytopenia NCI-CTCAE grade 4 with need for platelet transfusion. The duration of this event was less than one week and no sign or symptom for bleeding occurred. The indication for platelet transfusion was prevention of bleeding. The patient recovered from this event without sequelae.
The second patient experienced fever CTCAE grade 3 with temperatures up to 40.3 °C. X-rays confirmed pneumonia and the patient was treated with antibiotics empirically. At the time of this event, the patient was not neutropenic and the event was never regarded as life-threatening. The body temperatures reached normal levels within a few days and the pneumonia was clinically improving. The patient recovered from this event without sequelea.
One further patient (CRF 22) had experienced a thrombocytopenia NCI-CTCAE grade 4 qualifying as a DLT, however since the study already had been terminated it was not recorded as DLT .

All together 5 SAEs occurred in 4 patients, but all the events were manageable and 3 out of 4 patients recovered without sequelea.
In total 114 Adverse events were noted with the majority of them being mild to moderate (77%).

No patient died during study.
One patient died shortly after the end of study treatment due to progressive disease.

Three patients had completed at least two cycles of study medication. Four patients received one complete cycle and one patient discontinued treatment within the first cycle.

The data of this study are not representative for this chemotherapy combination due to the small number of patients and short duration of therapy.
No conclusion regarding safety and efficacy of a chemotherapy combination with Bortezomib and Bendamustine and Prednisone can be drawn out of this study.

Discussion

The definition of the dose limiting toxicities were made on an empirical base having in mind the common side effects of Bortezomib and Bendamustine to protect the subjects from not unjustifiable toxicity and harm.

Thrombocytopenia of short duration is a common and well known side effect of Bortezomib as well as neuropathy.
The main side effect from Bendamustine is myelosuppression. Infections are a known complication of every cytotoxic drug.
This is why the DLT for this protocol was defined as described above.

According to this definition the events of CRF 41 and 42 qualified as dose limiting toxicities.
But in case of CRF 41 the platelet count as well as the duration of the event can be explained by Bortezomib solely and there was no sign of cumulative toxicity.
In case of CRF 42 the Pneumonia with fever without neutropenia could happen with any cytotoxic drug. Due to the good response to antibiotic therapy, there is no reason to assume a potential risk of infection for this drug combination.
In these particular two cases of DLTs the events both were of short duration and restitutio ad integrum was achieved in both cases.

Having this in mind it might be arguable, that the definition of the DLT was too strict and did not allow a sensible execution of the study.
Therefore the occurrence of these two DLTs should not result in a change of the overall benefit risk assessment of this study . It was due to the protocol design that these events were dose limiting and lead to early termination of the study.

Considering the late stage (mostly Stage III) of disease and the fact that mainly heavily pretreated patients were enrolled, these events would not suffice to judge this treatment option as unsafe.

Given the short duration of the dose-limiting toxicities and the complete recovery in both patients it might be reasonable to evaluate this combination of chemotherapy once more in the future with more clinical orientated rules of dose-limiting toxicities or starting with a different dosing schedule.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AMG	Arzneimittelgesetz (German Drug Law)
CR	complete response
CTCAE	common terminology criteria for adverse events
DLT	Dose limiting toxicity
EBMT Group	European Blood and Marrow Transplantation
GCP	Good Clinical Practice
ICH	International Conference of Harmonization
ISS	International Staging System
BSA	body surface area
PI	Principal Investigator as per AMG
MM	Multiple Myeloma
MR	minimal response
MTD	Maximum tolerated dose
NC	no change
NCI	National Cancer Institute
PD	progressive disease
PR	partial response
SAE	serious adverse event
AE	adverse event
VAD	Vincristine, Adriamycin, Dexamethasone

Definition of terms: not applicable

ETHICS

Independent Ethics Committee/Institutional Review Board

The study protocol was reviewed by an Independent Ethics Committee.

The leading Ethics Committee being in charge for the centre of the Principal Investigator Dr. Pönisch in Leipzig was the Ethic Commission from the University of Leipzig and gave the positive vote for the clinical trial on 10th of November 2005:

EK an der Medizinischen Fakultät der Uni Leipzig Institut für Klinische Pharmakologie

Härtelstr. 16 - 18

4107 Leipzig, Germany

Geschäftsnr. 227-05

Ethical Conduct of the Study

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Known instances of nonconformance were documented and are not considered to have had an impact on the overall conclusions of this study.

Subject Information and Consent

Subjects or their legally acceptable representatives provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment. Known instances of nonconformance were documented and are not considered to have impacted the overall conclusions of this study.

SIGNATURES

Date: 20.08.2007

Author: Dr. med. Claudia-Nanette Gann, MD
Medical Development Manager

Signature: Claudia-N. Gann

I have read this report CTMS-Nr. 26866138MMY2029 written by Dr. med. Claudia-Nanette Gann and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date: ....
Principal Investigator
Dr. med. W. Pönisch

Date: 22.8.07 .....
VP Medical & Scientific Affairs
Prof. Dr. E. Zielke

Date: 23/8/07 .....
Executive director regulatory medicine
Dr. med. F. Seifert

Date: 23/8/07 .....
Associate Director Pharmacovigilance
Dr. med. S. Rielke

Date: ....
Statistician (lead)
Not applicable

SIGNATURES

Date: 20.08.2007

Author: Dr. med. Claudia-Nanette Gann, MD
Medical Development Manager

Signature: Claudia-N. Gann

I have read this report CTMS-Nr. 26866138MMY2029 written by Dr. med. Claudia-Nanette Gann and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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Dr. med. F. Seifert

Date: ....
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Dr. med. S. Rielke

Date: ....
Statistician (lead)
Not applicable

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