A Clinical Phase II Study in Patients with Prostate Cancer and Bone Metastases with KML001 (KOMINOX®). A placebo-controlled, randomized, multicentric trial.

Study Report

(Final Version 1.0)

Author: Marianne Lützke, Dipl.-Bw. Date: 19-Feb-2010

Project number: 411-IP-06-01-0000 (CRO) / IPSS-D039 (Sponsor)	**Clinical study phase:** II
EudraCT number:	2006-005607-33
Sponsor: KOMINOX USA Inc. 14 Truman Court Closter, NJ 07624 USA Phone: +1-201-894-9300 Fax: +1-201-894-9903	**Study Director on behalf of the Sponsor and responsible for Drug Safety:** R. Koytchev, MD, PhD CCDRD AG Cooperative Clinical Drug Research and Development AG Fontanestr. 84-90 15366 Neuenhagen b. Berlin, Germany Phone: +49-3342-2379-0 Fax: +49-3342-2379-16
Study period: from 03-Apr-2008 to 28-Apr-2009	**Early termination:** Yes: ☒ No: ☐
End of clinical trial: 28-Apr-2009	
Coordinating Investigator: PD Dr. med. F. König, Rüdesheimer Str. 43, 14197 Berlin-Wilmersdorf, Germany, Phone: +49-30-821-6021, Fax: +49-30-821-6031	
Indication: hormone-refractory prostate cancer with bone metastases	
Generic name: sodium meta-arsenite	
Earlier reports from the same study: None	**Archiving:** Source data of patients: at the investigator's sites as specified in the ICH-GCP guideline (essential documents, chapter 8)

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This study was conducted in compliance with Good Clinical Practice (GCP).

The report was produced on a word-processing system and bears no signatures.
The signatures of all persons responsible are filed separately in chapter 16.1.5

2. Synopsis

NAME OF COMPANY **KOMINOX USA, Inc.** **NAME OF FINISHED PRODUCT:** **KML001** **NAME OF ACTIVE INGREDIENT(S):** **sodium meta-arsenite**	**INDIVIDUAL STUDY TABLE REFERRING TO CLINICAL DOCUMENTATION OF THE DOSSIER:** **Volume:** **Page:**	*(FOR NATIONAL AUTHORITY USE ONLY)*

Title of the study:

A Clinical Phase II Study in Patients with Prostate Cancer and Bone Metastases with KML001 (KOMINOX®). A placebo-controlled, randomized, multicentric trial.

Investigator(s):

Coordinating investigator: PD Dr. med. F. König

Principal investigators:
Centre 01: PD Dr. med. F. König
Centre 02: Dr. med. Cristina Schurwanz
Centre 03: Dr. h.c. Doris Diekhans

Study centers:

n=3 in Germany

Publication (reference):

the results are not yet published

Studied period:		**Phase of development:**
date of first enrolment:	03-Apr-2008	Phase II
date of last completion:	28-Apr-2009	

Objectives:

The primary objective of the present trial was to establish the effective dose of KML001 based on the percentage of patients with PSA response, defined as a reduction of at least 30% from baseline, in patients with hormone-refractory prostate cancer with bone metastases.

The secondary objective of the present trial was to evaluate the efficacy and safety of different doses of KML001 based on the remaining efficacy and safety parameters.

Study design:

- Double-blind
- Randomized
- Placebo-controlled
- Multiple-dose
- Multicentric
- Phase II trial
- At least 40 patients planned for randomization (10 patients in each treatment group)
- Administration of study medication (KML001 at three different dose levels or placebo): oral, prior to food intake)
- Duration of study drug administration: 6 cycles, each cycle consisting of 14 consecutive days of treatment separated by a wash-out period of 7 days

Subjects (planned and analyzed):	planned for completion:	40
	screened:	26
	randomized:	22 (15 Test, 7 Placebo)
	drop-outs after randomization:	12
	evaluated:	
	– safety population:	22
	– full analysis set:	22 (15 Test, 7 Placebo)
	– per protocol set:	10 (7 Test, 3 Placebo)
Diagnosis and criteria for selection:	**Inclusion criteria:** • patients with hormone-refractory prostate cancer • prostate cancer confirmed histologically or cytologically (Gleason score ≥ 7 or histological grade ≥ 3)	

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	• PSA at least 10 ng/ml • at least one bone metastasis confirmed by bone scintigraphy as well as computer tomography • patients receiving androgen suppression treatment with LH-RH analogues and/or anti-androgens and showing complete androgen blockade defined as baseline total testosterone level of up to 0.5 ng/ml • prostate cancer no longer amenable to established forms of therapy • age over 18 years • overall life expectancy >16 weeks • informed consent given in a written form after being provided with detailed information about the nature, risks, and scope of the clinical trial as well as the expected desirable and adverse effects of the drug.
Diagnosis and criteria for selection:	**Exclusion criteria:** • patients who are at visit 1 not eligible for treatment according to the criteria relevant for chemotherapy (i.e. one of following criteria is present): - Zubrod score higher than 2, - hemoglobin lower than 100 g/l, - neutrophils <1,5 G/l, - platelets <100 G/l, - creatinine >140 mmol/l, - ALT, AST >2 times above upper reference range for patients without liver metastasis, - ALT, AST >5 times above upper reference range for patients with liver metastasis • any concomitant cancer therapy within 30 days before the first administration of study medication or during the study other than stable therapy with LH-RH analogues, anti-androgens, and/or bisphosphonates • change of concomitant treatment with LH-RH analogues, anti-androgens, or bisphosphonates within 6 weeks before the first administration of study medication or during the study • any concomitant other cancer type • QTc prolongation above 500 ms • concomitant severe arrhythmias • known history of increased risk for torsade de pointes (TdP) like hypokalemia, family history of Long-QT-Syndrome • present moderate to severe heart failure (NYHA class III-IV) • brain metastases • history of major gastrointestinal surgery or pathology (such as severe malabsorption) likely to influence absorption of the study medication • severe dehydration • treatment with parenteral antibiotics within 7 days before randomization • patients on hemodialysis • patients with clinically manifested liver failure (ascites or esophageal varices) • uncontrolled hypertension at visit 1 • known hypersensitivity to any of the active or inactive components of the final product • symptoms suggestive of serious acute arsenic toxicity after treatment start (e.g. convulsions, muscle weakness and confusion) • patients with hemodynamically relevant bleeding • severe physical or mental concomitant diseases that might hamper the realization of the trial according to protocol or the evaluation of efficacy or safety • participation in another clinical trial within the last 28 days • legal incapacity and/or other circumstances rendering the patient unable to understand the nature, scope and possible consequences of the study • unreliability or lack of cooperation • lack of a possibility to attend the visits required by protocol.

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Test product, dose and mode of administration, batch number:	name:	KML001
	active ingredient:	sodium meta-arsenite
	dosage form:	tablet
	strength:	2.5 mg sodium meta-arsenite per tablet
	route / regimen:	oral, prior to food intake (1-2 times a day)
	manufacturer:	Pharmatek Laboratories Inc., USA
	lot no. and expiry date:	07-0096 (APR 2009)
Reference product (placebo), dose and mode of administration, batch number:	name:	Placebo
	active ingredient:	none
	dosage form:	tablet
	strength:	NA
	route / regimen:	oral, prior to food intake (1-2 times a day)
	manufacturer:	Pharmatek Laboratories Inc., USA
	lot no. and expiry date:	07-0062 (APR 2009)

Duration of treatment:

Each patient was planned to receive in a random way the study medication for 6 cycles, each cycle consisting of 14 consecutive days of treatment separated by a wash-out period of 7 days either KML001 or Placebo.

No dose changes were allowed within any patient.

If clinical response or at least lack of disease progression (defined as stable disease according to adapted RECIST criteria plus no increase of PSA of more than 20% over baseline) was shown upon completion of the six study cycles in any patient, the respective patient could continue to take the same treatment as long as needed. The treatment was continued under blinded conditions until the blinding of the study was opened. Thereafter, the patient could be treated under open conditions as long as needed based on the clinical judgment of the investigator. Continuing treatment was defined as cycles 7, 8, 9, etc.. The treatment scheme and dosage in these cases remained unchanged as for cycles 1-6.

Criteria for evaluation:

Efficacy:

Primary endpoints:

- percentage of patients with PSA response, defined as a reduction of at least 30% from baseline.

Secondary endpoints:

- percentage of patients with PSA reduction of at least 50% from baseline,
- time to PSA progression (defined as increase of PSA of more than 20% over baseline),
- overall bone metastasis response,
- overall survival,
- intake of narcotic analgesics,
- performance status (Zubrod),
- pharmacokinetics of total arsenic,
- prostate cancer pain by means of a visual analogue scale,
- quality of life by means of FACT-P,
- bone turnover markers.

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Safety:

Safety endpoints:

- evaluation of results of audiometry,
- assessment of overall tolerability of the study drug by patient and investigator,
- evaluation of adverse events.

Statistical methods:

PSA is an accepted biochemical marker for screening agents that produce an anti-cancer effect against prostate cancer. An evaluation of the criteria for surrogacy of PSA decline based on the results of the Southwest Oncology Group trial was performed by Petrylak et al (2006)[1]. This evaluation demonstrated that a 3-month PSA decline of at least 30% in patients with progressive disease was associated with a more than 50% decrease in the risk of death compared to patients with a lack of such a decline. This was the reason for the definition of PSA response in the present trial.

The primary endpoint in the present trial (percentage of patients with PSA response, defined as a reduction of at least 30% from baseline) was compared between all 4 study groups by means of a Chi-Square test. In a previously performed phase I trial with KML001 in a similar patient population dramatic PSA reductions were observed in some of the patients although no clear-cut relationship to dosage could be established. A spontaneous PSA reduction is normally not observed in such patients. Due to this reason a relatively big difference between treatment groups was taken into account for the estimation of sample size. The sample size was calculated by means of NCSS/PASS 2000 based on following assumptions:

Alpha = 0.05,

Beta = 0.2 (power of 0.8),

Degrees of freedom = 3 (number of columns -1) x (number of rows -1),

Effect size (W) = 0.55 (indicative for a considerable effect).

The resulting sample size was at least 40 patients.

The primary type of statistical analysis was based on the full analysis set.

In addition, the primary endpoint was evaluated in the per-protocol population (comprising all patients who complete the trial and do not present major protocol deviations). This type of analysis only have a supporting function.

The secondary endpoints were subjected to descriptive and comparative evaluations of the full analysis set whereby the treatment groups were compared with the placebo group and with each other. Depending on their distribution the endpoints were presented with their means, SD, SEM, median and quartiles or with their incidence. The type of statistical tests used for comparisons were also depend on the type of distribution of the respective parameter. In general a non-parametric test (Mann-Whitney-Wilcoxon) was applied for endpoints with continuous distribution and a Chi-square test was applied for parameters with discrete distribution.

RESULTS

Disposition of patients:

A total number of 26 male patients with prostate cancer and bone metastases were informed about the aim of the study and were screened after giving their consent in written form. After careful consideration of all inclusion and exclusion criteria, 4 patients were not eligible for the trial. Therefore, only 22 patients were eligible to start double-blind treatment and were randomised to one of both study drugs (KML001 or Placebo) (safety population). 15 patients were allocated to different doses of the test medication and 7 patients to placebo. None of these patients were excluded from the full analysis set (n=22). 12 patients were excluded from the per protocol set in all cases due to dropping out before reaching the minimum planned duration of treatment. Therefore, the per protocol set consists of 10 patients.

The present trial was terminated preliminary by the Sponsor due to unexpectedly slow randomization progress (only 22 randomized patients for a period longer than 1 year) and higher than expected drop-out rate (12 of 22 patients dropped out before reaching the minimum planned duration of treatment). Both problems were mainly related to the presence of a placebo treatment group: a factor which prevented a significant number of potentially available patients from giving their consent to participate and which also increased the percentage of patients who decided to withdraw from the trial.

The following table provides an overview of the disposition of patients during the main treatment phase of the trial.

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TT 1 Disposition of patients according to their presence at respective visits (all randomized patients)

Visit	Placebo	2.5 mg KML001	10.0 mg KML001	17.5 mg KML001
Visit 1	7	6	4	5
Visit 2	7	6	4	5
Visit 3	7	6	4	3
Visit 4	7	6	4	3
Visit 5	7	5	4	3
Visit 6	6	4	4	3
Visit 7	7	2	4	3
Visit 8	7	2	3	3
Visit 9	6	2	3	3
Visit 10	5	2	3	3
Visit 11	4	2	3	3
Visit 12	4	2	3	3
Final	3	2	3	2

Efficacy

Due to the early termination of the present trial after reaching only approximately half of the number of patients planned to be randomized the groups of patients treated with any of the study drugs were extremely small: between 4 and 7 patients. The statistical power of the present trial is correspondingly low and the results presented here should be interpreted in this context.

The 4 treatment groups were comparable regarding their demographic and baseline features.

Primary endpoint

Percentage of patients with PSA response, defined as a reduction of at least 30% from baseline:

The percentage of patients with PSA response or progression according to the definitions given in the protocol (response: at least 30% reduction from baseline values, progression: at least 20% increase from baseline values) is presented in the following table. Patients who dropped out were evaluated based on their last available PSA value (last value carried forward principle).

TT 2 PSA response (all randomized patients)

Frequency Row Pct	neither	progression	response	Total
Placebo	0 0.00	7 100.00	0 0.00	7
2.5 mg KML001	0 0.00	5 83.33	1 16.67	6
10.0 mg KML001	0 0.00	3 75.00	1 25.00	4
17.5 mg KML001	2 40.00	2 40.00	1 20.00	5
Total	2	17	3	22

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No case of PSA response was registered in the placebo group. One case of PSA response was registered in each of the verum treatment groups. If the patients who had progression of PSA are also taken into account, a clear trend in favor of the highest dosage can be detected: 7 of 7 placebo patients had PSA progression; 5 of 6 patients treated with the low dose had progression; 3 of 4 patients treated with the medium dose had progression and 2 of 5 patients treated with the highest dose had progression.

Due to the low numbers of patients statistical significance was not present.

Secondary endpoints

Percentage of patients with PSA reduction of at least 50% from baseline

The percentage of patients with PSA reduction of at least 50% from baseline is presented in the following table

TT 3 Patients with PSA reduction of at least 50% from baseline

Frequency Row Pct	no	yes	Total
Placebo	7 100.00	0 0.00	7
2.5 mg KML001	5 83.33	1 16.67	6
10.0 mg KML001	4 100.00	0 0.00	4
17.5 mg KML001	4 80.00	1 20.00	5
Total	20	2	22

Only two patients (one in the lowest verum dosage group and one in the highest verum dosage group) had a decrease of PSA of at least 50% from baseline.

Time to PSA progression (defined as increase of PSA of more than 20% over baseline)

The next table provides an overview on the time until PSA progression.

TT 4 Time point of observing PSA progression

Frequency Row Pct	Visit 3	Visit 5	Visit 7	Visit 11	Total
Placebo	3 42.86	2 28.57	2 28.57	0 0.00	7
2.5 mg KML001	3 60.00	1 20.00	1 20.00	0 0.00	5
10.0 mg KML001	0 0.00	1 33.33	1 33.33	1 33.33	3
17.5 mg KML001	1 50.00	0 0.00	0 0.00	1 50.00	2
Total	7	4	4	2	17

The table demonstrates that in the majority of cases in the placebo group and in the low dose group PSA progression was observed relatively early (up to visit 5). On the contrary: most of the cases of PSA progression in the medium and high dose treatment groups were observed after visit 5.

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Overall bone metastasis response

TT 5 Overall bone metastasis response

Overall response	Placebo		2.5 mg KML001		10.0 mg KML001		17.5 mg KML001	
	n	%	n	%	n	%	n	%
unassessed	2	28.6	2	33.3	1	25.0	2	40.0
assessed	5	71.4	4	66.7	3	75.0	3	60.0
- complete response	0	0	0	0	0	0	0	0
- partial response	0	0	0	0	0	0	0	0
- stable disease	3	60.0	0	0	1	33.3	0	0
- progression of disease	2	40.0	4	100.0	2	66.7	3	100.0

Complete or partial response was not registered in any of the patients. All patients had either stable disease or progression of bone metastases. No specific trend for any difference between treatment groups could be observed regarding this parameter.

Overall survival

Two patients died in the course of the trial. Both patients were in the lowest verum dosage group. Both patients died due to progression of the main disease. No specific trend for any difference between treatment groups could be observed regarding this parameter.

Intake of narcotic analgesics

The information about any new intake of narcotic analgesics in the course of the trial is presented in the following table.

TT 6 Proportion of patients with any new intake of narcotic analgesics

Any NEW usage of Narcotics	Placebo		2.5 mg KML001		10.0 mg KML001		17.5 mg KML001	
	N	%	N	%	N	%	N	%
no	5	71.4	2	33.3	2	50.0	2	40.0
yes	2	28.6	4	66.7	2	50.0	3	60.0

No specific trend for any difference between treatment groups could be observed regarding this parameter.

Performance status (Zubrod)

The Zubrod score remained generally stable throughout the trial. No relevant differences could be observed between treatment groups.

Prostate cancer pain by means of a visual analogue scale

The prostate cancer pain was not very pronounced in all treatment groups at baseline (mean values between 20 and 40 on a 100 mm Analogue scale). No particular changes were observed during treatment in any of the treatment groups and no relevant differences between treatment groups could be registered.

Quality of life by means of FACT-P

The total FACT-P quality of life score was around 100 in all treatment groups at baseline. No relevant changes were registered within any of the treatment groups during treatment. No differences were present also between treatment

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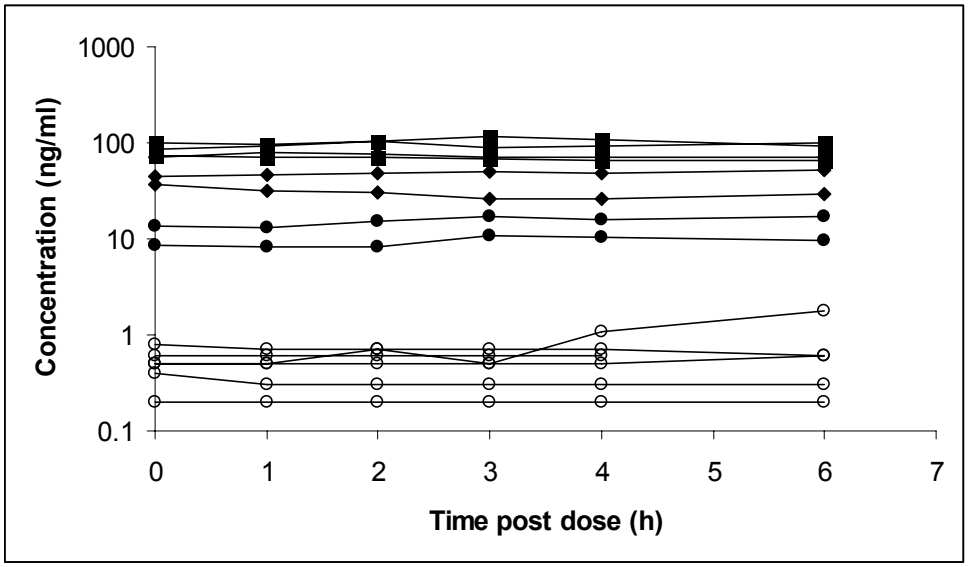
groups.

Bone turnover markers

Both biochemical markers for bone turnover (NTX corrected for urinary cortisol and bone-specific alkaline phosphatase) remained relatively constant for the duration of treatment in all treatment groups and revealed no differences between treatment groups.

Pharmacokinetics of total arsenic

The results of concentration measurements of total arsenic in plasma revealed comparable baseline concentrations of less than 1 ng/ml before the start of treatment in all treatment groups. The concentrations measured confirmed the compliance of the patients and were in agreement with dose administered as can be seen from the figure below.



TF 1 Concentration of total arsenic in plasma at visit 9

Legend: ○ Placebo
● 2.5 mg KML00
◆ 10 mg KML001
■ 17.5 mg KML001

The concentrations of arsenic measured in plasma corresponded also to the total amount of arsenic excreted in urine which is confirmed by the following figure.

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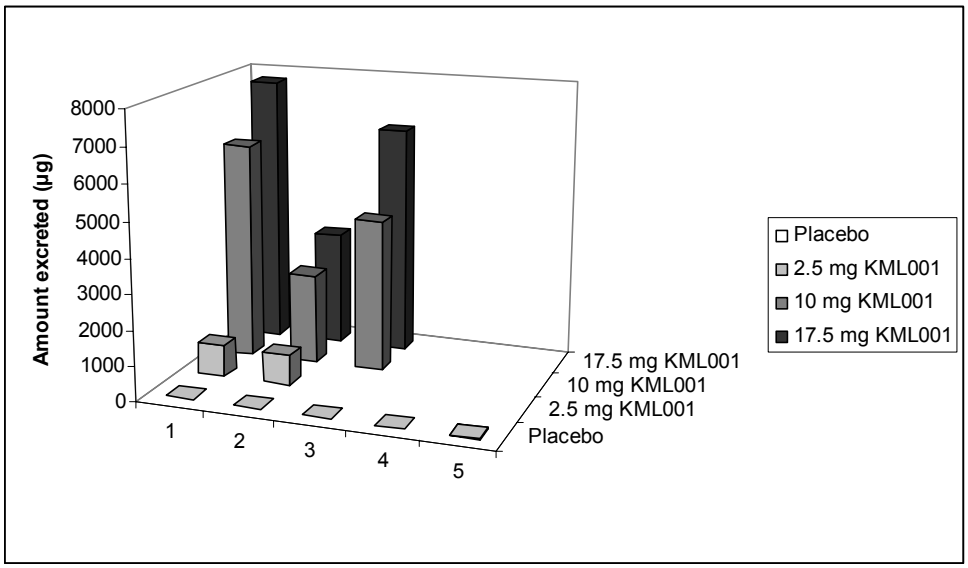

TF 2 Total amount of arsenic excreted for 24 hours post dose in urine at visit 9

Safety:

Deaths

A total number of 2 patients died in the course of double-blind treatment: patient #101 and patient #217. Both patients were treated with the low dose of the test drug. In both cases the cause of death was progression of the main disease (metastatic prostate cancer) and, correspondingly, the investigator regarded the causal relationship to the intake of study medication as unlikely.

Adverse events and serious adverse events

As can be expected in a group of seriously ill patients adverse events were registered in all patients. An overview on the numbers of reported adverse events (AEs), serious adverse events (SAEs) and the numbers of patients affected is presented in the following table.

TT 7 Summary of adverse events, safety population

Number of ...	Placebo (N=7)	2.5 mg KML001 (N=6)	10.0 mg KML001 (N=4)	17.5 mg KML001 (N=5)	total
Adverse Events (AEs)	40	33	56	50	179
AE reports	38	29	49	46	162
Patients with AEs	7	6	4	5	22
Serious Adverse Events (SAEs)	3	4	0	5	12
SAE reports	3	3	0	4	10
Patients with SAEs	2	3	0	3	8
Deaths	0	2	0	0	2
Patients withdrawn due to AE	3	4	0	3	10

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All patients experienced more than one AE. The numbers of AEs were comparable in all 4 treatment groups.

The numbers of patients withdrawn due to AEs was comparable in the groups of patients treated with placebo, low and high doses of the study drug. The only treatment group without withdrawals due to AEs was the one treated with the medium dose of KML001. Having in mind the low numbers of patients in general the latter finding is most probably a matter of chance as no plausible medical explanation could be provided.

The severity of adverse events was mild to moderate in most of the cases. The severe adverse events were as follows:

Placebo:	2 events in 2 patients
2.5 mg KML001:	4 events in 3 patients
10 mg KML001:	no severe AEs
17.5 mg KML001:	6 events in 2 patients

No difference was registered between the numbers of severe adverse events in the groups of patients treated with placebo, low and high doses of the study drug. The only treatment group without severe AEs was the one treated with the medium dose of KML001. Having in mind the low numbers of severe AEs in general the latter finding is most probably a matter of chance.

Most of the AEs were either not related or unlikely related to the study medication. The number of events with some relationship to the study medication (possible, probable or certain) was as follows:

Placebo:	15 events in 4 patients
2.5 mg KML001:	7 events in 3 patients
10 mg KML001:	25 events in 5 patients
17.5 mg KML001:	20 events in 8 patients

A slight trend for a higher number of medication-related AEs was observed in the medium and the high dose treatment groups. The most frequent medication-related AEs in the medium and high dose groups were gastrointestinal disorders (nausea, vomiting, loss of appetite).

No specific trend or a difference between groups could be observed regarding SAEs. The only treatment group without SAEs was the one treated with the medium dose of the test drug. Having in mind the low numbers of patients in general the latter finding is most probably a matter of chance as no plausible medical explanation could be provided.

The study drug was withdrawn due to an SAE in only two cases: patient 216 (test drug, low dose) who experienced atrial fibrillation and in patient 104 (test drug, high dose) who experienced fever, fatigue, dizziness, and vomiting.

The analysis of adverse events and serious adverse events, which included severity, outcome, relationship to study medication as well as the action taken with study medication revealed no particular differences between treatments.

Safety laboratory evaluation

The results of safety laboratory parameters were evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0). Laboratory values belonging to CTCAE grades 3 and 4 were registered as follows:

Placebo:	16 observations in 5 patients
2.5 mg KML001:	14 observations in 4 patients
10 mg KML001:	no observations
17.5 mg KML001:	15 observations in 2 patients

These results demonstrate no specific differences between verum and placebo and also no dose-related trends within the different verum dosage groups.

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Assessment of overall tolerability

The assessment of overall tolerability revealed that moderate intolerability was only registered in the medium and in the high verum dose groups (two cases in each group). The only case of severe intolerability was registered in the high verum dose group. This reveals a trend for deterioration of overall tolerability with increase of dosage.

Assessment of audiometry

The assessment of audiometry also revealed a trend for dose-dependent deterioration: only two cases of deterioration were registered but they were in the medium (minor deterioration) and in the high dose (major deterioration) groups.

CONCLUSIONS

The present trial was prematurely terminated after only approximately half of the number of patients planned for randomization were really randomized. This reduced the statistical power of the trial and no statistically significant results could be observed. Still some clear and relevant general trends became obvious:

1. The group of patients treated with the highest dose of the test drug (17.5 mg/day) showed the lowest proportion of patients with PSA progression
2. The tolerability of the highest dose of the test drug was somewhat worse than that of lower doses and placebo but still no dose-limiting toxicity was observed. This observation was strongly supported by the results of safety laboratory evaluation and evaluation of adverse events and serious adverse events.

Based on these findings the highest dose of the test drug can clearly be favored for future Phase III trials.

Date of Study Report (Final Version 1.0): 19-Feb-2010