Name of sponsor/company: Freistaat Bayern represented by Universität Regensburg (represented by Kaufmännischer Direktor des Universitätsklinikums Regensburg Dipl.-Kfm. Klaus Fischer) 93042 Regensburg, Germany	Individual study table referring to part of the dossier not applicable	
Name of finished product: Signifor® LAR		
Name of active ingredient: SOM230 LAR (Pasireotide, SOM230C)		

Title of study:
Efficacy of medical treatment with SOM230 LAR in patients with primary inoperable thymoma and/or with local recurrent thymoma to reduce tumor size.

Investigators:
Prof. Dr. med. Berthold Schalke (Project leader and principal investigator)

Study centre(s): 1

Centre 1: Klinik und Poliklinik für Neurologie der Universität Regensburg
am Bezirksklinikum Regensburg
Universitätsstraße 84
93053 Regensburg
Germany

Publications (reference):

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Studied period (years):		Phase of development:
Date of first enrolment	07-Mar-2012	Phase II
Date of last completed	02-Oct-2015	

Objectives:

Primary objectives:

- Tumor shrinkage
  Response is defined as the decrease in tumor volume of 20 % at EOS as compared to baseline.

Secondary objectives:

- Operability
  Evaluation of the number and the percentage of patients reaching operability at EOS.
- Resection status
  Evaluation of the frequency distribution of the resection status based on the categories R0, R1 and R2.
- Evaluation of histological and flow cytometric changes under treatment with SOM230 LAR.
  1. percentage of necrotic area (*analysis not performed*)
  2. degree of depletion (none, slight; moderate; marked) of immature T-cells (immunohistochemistry for CD1a, CD99, CD3 expression) (*analysis not performed*)
  3. change of T-cell subset composition as revealed by FACS analysis (Ströbel et al. Blood, 2002) (*analysis not performed*)
- Safety
  The assessment of safety will be based mainly on the frequency of Adverse Events and on the number of laboratory values that fall outside of pre-determined ranges.

Methodology:

Monocentric, single-arm, open label clinical trial

Number of patients (planned and analysed):

Planned: 16 Analysed: 16

Diagnosis and main criteria for inclusion:

Trial indication:
Inoperable thymoma

Inclusion criteria:

1. Male or female patients aged ≥18 years
2. Diagnosis of thymoma as assessed by biopsy and/or szintigraphy
3. Inoperability of thymoma or loco-regional metastases. Inoperability is defined as at least adherence of the tumor to the neighbored organs, suspicious to infiltrate neighbored organs or local metastasis so that R0 resection cannot be expected and /or local recurrence of thymic tumor
4. Tumor stage: Thymomas of all WHO based histological subtypes (WHO A, AB, B1, B2, B3) (Rosai, 1999; Travis 2004) at Masaoka stage II to IVa based on histological examination of resection specimens or core biopsies.
5. Patients with and without thymoma associated paraneoplastic syndrome.
6. Performance status 0,1, or 2 (ECOG)
7. Patients for whom written informed consent to participate in the study has been obtained

Exclusion criteria:

1. Patients having received radiolabeled somatostatin analogue therapy within the 6 months or any cytotoxic chemotherapy or interferon therapy within the 2 months prior to recording baseline symptoms
2. Patients who have undergone major surgery/surgical therapy for any cause within 1 month or surgical therapy of loco-regional metastases within the last 3 months before recording baseline symptoms
3. Patients who have received radiotherapy for any reason within the last 4 weeks and must have recovered from any side effects of radiotherapy before recording baseline symptoms
4. Patients who are not biochemically euthyroid
5. Diabetic patients on antidiabetic medications whose fasting blood glucose is poorly controlled as indicated by HbA1C > 8%
6. Patients with symptomatic cholelithiasis
7. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, clinically significant bradycardia, advanced heart block or a history of acute myocardial infarction within the six months preceding enrollment
8. Patients with QT related risk factors:
    - QTcF at screening > 450 msec
    - History of syncope or family history of idiopathic sudden death
    - Sudden or clinically significant cardiac arrhythmias
    - Risk factors for Torsades de Pointes such as hypokalemia, hypomagnesemia, cardiac failure, clinically significant / symptomatic bradycardia, or high-grade AV block
    - Concomitant disease(s) that could prolong QT such as autonomic neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism or cardiac failure
    - Concomitant medication(s) known to increase the QT interval
9. Patients with potassium <3.0 mmol/L at study entry, magnesium <0.4 mmol/L at study entry, calcium <1.75 mmol/L at study entry, family history of long QT syndrome, and concomitant medications known to prolong the QT interval. If the electrolyte abnormalities are corrected prior to study commencement, the patient may become eligible for the trial.
10. Patients with liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis with serum bilirubin > 1.5 X ULN, serum albumin < 0.67 X LLN, and/or ALT or AST more than 2 X ULN for patients without liver metastases or ALT or AST more than 5X ULN for patients with documented liver metastases
11. Patients with additional active malignant disease within the last five years (with the exception of basal cell carcinoma or carcinoma in situ of the cervix)
12. Patients with the presence of active or suspected acute or chronic uncontrolled infection or with a history of immunocompromise, including a positive HIV test result (ELISA and Western blot). A HIV test will not be required; however, previous medical history will be reviewed
13. Patients with abnormal coagulation (PT or APTT elevated by 30% above normal limits)
14. Patients with WBC <2.5 X 109/L; Hgb <10 g/dL; PLT <100 X 109/L (patients with paraneoplastic pan-, leuco-, erythro- or thrombopenia can be included if this seems to be the only reason for pan-, leuco-, erythro- or thrombopenia)

15. Known hypersensitivity to somatostatin analogues or any component of the pasireotide or octreotide LAR or s.c. formulations
16. Patients who have any current or prior medical condition that may interfere with the conduct of the study or the evaluation of its results in the opinion of the investigator
17. Female patients who are pregnant or lactating, or are of childbearing potential and not practicing a medically acceptable method of birth control. Female patients must use a secure method of contraception if sexually active and the partner should use a condom. If oral contraception is used, the patient must have been practicing this method for at least two months prior to enrollment and must agree to continue the oral contraceptive throughout the course of the study, and for three months after the study has ended. Male patients who are sexually active are required to use condoms during the study and for three months afterwards as a precautionary measure (available data do not suggest any increased reproductive risk with the study drugs). Female partners of these male patients should use a secondary barrier contraception.
18. Patients who are currently part of or have participated in any clinical investigation with an investigational drug within 1 month prior to dosing
19. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study
20. Patient has received any other investigational agents within 28 days of first day of study drug dosing
21. Abnormal clinical laboratory values considered by the investigator to be clinically significant and which could affect the interpretation of the study results

Test product, dose and mode of administration, batch number:

Test product and mode of administration: Pasireotide (SOM230 LAR, microparticle powder for reconstitution with vehicle solution), suspension for i.m. injection (once a month)

Dose: 60 mg; 30 mg/ml

Batch numbers:

- SOM230 LAR (microparticle powder):
- 40 mg: Y064 0408, Y074 0912, Y031 0313
- 20 mg: Y139 0709, Y029 0213, Y099 0813

- Vehicle (2ml reconstitution solution):
- Y048DE, Y032 0312

Duration of treatment:

6 months (with optional extension of treatment in case of tumor inoperability)

Reference therapy, dose and mode of administration, batch number:

Not applicable, single arm study.

Criteria for evaluation

Efficacy:

- Tumor shrinkage:

  Tumor volume, as determined by CT or MRI scan at Baseline and EOS.

  Each lesion found in the mediastinum had to be measured separately. The efficacy evaluation is based on the total volume of all those tumor manifestations. Lesions that were not measurable should still have been recorded by numbers. The lesions must have been localized by SMS szintigraphy beforehand. The tumor volume percent change from baseline (day 1) to time X will be calculated as:

  [(Total volume at time X – total volume at baseline) / total volume at baseline] × 100

  A decrease in tumor volume of 20% at EOS as compared to Baseline is considered as response.
- Operability & Resection status:

  Operability of tumor as stated by the surgeon and resection status, as evaluated based on the categories R0, R1 and ≥ R2 using CT or MRI imaging at Baseline and EOS.
- Histological changes:

  Necrosis (percentage of necrotic tissue) of tumor samples gained after surgery evaluated by a central pathologist. (*analysis not performed*)
- Depletion of T-cells & changes in T-cell subset composition:

  Determination of depletion of T-cells by immunohistochemical staining of cells using appropriate markers and determination of the impact of therapy on intratumorous mature and immature T-cell subsets (thymocytes), by FACS (fluorescence activated cell sorting) analysis, respectively. (*analysis not performed*)

Safety

- Frequency of Adverse Events & Serious Adverse Events
- Number of laboratory values that fall outside of pre-determined ranges.

Statistical methods:

Analysis Sets:
ITT (Intend to treat) population, Safety population, Enrolled population.

Primary efficacy analysis:
Tumor shrinkage:
Tumor volume values are summarized at each visit by means of descriptive statistics. At each post-baseline visit, mean and SD of the change and the percent change from baseline is also calculated with the relative 95% CI. The number and the percentage of responders and non-responders patients is provided.

According to Fleming's "one-sample multiple testing procedure for phase II clinical trials" (Biometrics. 1982 Mar;38(1):143-51), a response rate of lower than 0.050 is considered not to warrant further investigation of

the drug, whereas a response rate of at least 0.300 is considered to warrant further investigation, i.e. the following hypothesis is tested:

H_0: P ≤ 0.050 versus H_1: P ≥ 0.300

16 patients are required to decide whether the response proportion, P, is less than or equal to 0.050 or greater than or equal to 0.300. If the number of responses is 3 or more, the hypothesis H_0 is rejected with a target error rate, α, of 0.050. If the number of responses is 2 or less, the hypothesis H_1 is rejected with a target error rate, β, of 0.100.

Based on the number of responders one of the following decisions will be made:

≤2 responders ➔ reject H1: P≥0.300
≥3 responders ➔ reject H0: P≤0.05

Secondary efficacy analysis:
Operability
The number and the percentage of patients reaching operability at the EOS will be presented.

Resection status
The number and the percentage of patients in each resection status category (R0, R1, and ≥R2) will be presented.

Further secondary efficacy variables will also be provided as descriptive statistics.

Analysis of Safety:
Adverse events
The number of AEs, SAEs and AEs leading to discontinuation, and the number and the percentage of patients experiencing AEs, SAEs and AEs leading to discontinuation are summarised.
AEs will be coded using the MedDRA dictionary. The SOCs and PTs are used for tabulation. The number of AEs and the number and the percentage of patients with at least one AE will be presented by SOC and PT for AEs, SAEs and AEs leading to discontinuation.

Laboratory parameters & other safety assessments
Shift tables presenting the number and the percentage of patients in each bivariate category (Screening versus Day 1 and each post baseline visit) with regards to investigator's interpretation (normal, abnormal without clinical significance, abnormal with clinical significance) are presented. Results of other tests such as electrocardiogram, vital signs and gallbladder ultrasound are listed.

Summary - Conclusions

In this monocentric, single-arm, open label study a total of 16 patients were enrolled.

The study population comprised 7 female and 9 male patients and was thus not significantly shifted towards a specific gender. Mean height was 172.1 ± 9.9 cm and mean weight was 80.84 ± 14.07 kg. Mean systolic blood pressure was 124.7 ± 22.1 mmHg, mean diastolic blood pressure was 78.4 ± 12.3 mmHg and mean heart rate 73.7 ± 12.1 bpm. Thymoma were classified according to WHO classification. 6.3% of the tumors were classified as AB, 6.3% as B1, 37.5% as B2 and 50.0% as B3. The majority of thymoma (15 out of 16; 93.8%) were staged IVa, one thymoma (6.2%) was staged III. Tumor samples were approximately equally frequent taken by fine needle biopsy (31.3%), open biopsy (31.3%) and previous surgery (37.5%).

Of note, for one of the enrolled patients, initial diagnosis of thymoma could not be confirmed by the central pathologist. The tumor of this patient was subsequently classified as squamous cell carcinoma. Nevertheless, the patient was included in the ITT and considered for the primary analysis.

Efficacy results:

The mean change in tumor volume for the ITT population at EOS was -37.38±44.10%. The median change was -55.31 [-92.2; 81.8]. 75% of the patients showed a decrease in tumor volume of >20% at EOS and were classified as responders. According to Fleming's "one-sample multiple testing procedure" H0 is rejected and thus the drug can be considered to warrant further investigation.

62.5% of the tumors were operable at EOS. The resection status of 60% of the operated tumors was R0 and for 40% of the tumors the resection status was R1.

Analysis of the SF-36 questionnaires showed higher numerical domain scores at EOS compared to screening values, indicating slightly increased disease burden in the distinct domains at the end of the study. The question regarding the health in general showed numerical higher scores at EOS compared to screening, indicating a slight general improvement in health. However, results showed no statistical significance.

Safety results:

Until completion of the study, 113 Adverse Events (AEs) for 16 patients (100%) were reported. 15 of the AEs were classified as Serious Adverse Events (7 patients; 43.75%). One of the SAEs led to study drug discontinuation. For 31 AEs a causal relationship to the study drug was anticipated.

In the current SmPc of Signifor® (Pasireotide, SOM230 LAR; Version Mar-2015) most frequent AEs reported for treatment with SOM230 LAR were diarrhea, hyperglycemia and cholelithiasis. In line with this, the most frequent reported AEs in this study were also diarrhea and hyperglycemia. Patients with previous cholelithiasis were excluded from study participation. No abnormal gall bladder ultrasound findings with clinical significance nor cholelithiasis was reported during this study.
Analysis of laboratory parameters showed 65 abnormal laboratory values with clinical significance for 11 patients (68.75%). The most frequent abnormal laboratory values with clinical significance were abnormal glucose values assessed by clinical chemistry or urinary analysis. This is in line with the most frequent adverse events reported in the SmPc of Signifor®.

Sinus bradycardia and prolonged QT intervals were reported in the SmPc of Signifor®. However, patients with QT related risk factors were excluded from study participation; 9 out of 16 patients showed abnormal ECG findings without clinical significance; however, none of the patients showed abnormal ECG findings with clinical significance during the study.
Evaluation of weight fluctuations during the study until EOS revealed no shift towards increasing nor decreasing weight. Pre- and post-dose values for temperature, blood pressure and heart rate revealed no significant differences. No tendency of increasing or decreasing values for heart rate or blood pressure over time were noticed.

For none of the patients liver induced injury by SOM230 (in terms of Hy's law) could be observed in this study.

Conclusion

This was a monocentric, single-arm, open label phase II trial evaluating the effect of Pasireotide (SOM230 LAR) in adult patients with inoperable primary thymoma and thymoma metastasis (Masaoka II-IVa). SOM230 LAR in a dosage of 60 mg was administered i.m. once every 4 weeks. The purpose of this trial was a proof of concept.

The primary efficacy variable was tumor shrinkage from baseline to EOS. Response was defined as the decrease in tumor volume of 20% at EOS as compared to baseline. MRI/CT data were analyzed descriptively and response data evaluated according to Fleming's "one-sample multiple testing procedure". 75% of the patients showed a decrease of tumor volume of at least 20% and were classified as responders. Consequently, the null hypothesis H0 was rejected and thus the drug can be considered to warrant further investigation. The tumors of 10 out of 16 patients (62.5%) were operable at EOS. 60% of the operated tumors could be completely removed (resection status: R0). In the remaining 40% of the procedures margins of the resected tumor parts show tumor cells when viewed microscopically (resection status: R1).

For addressing safety, tolerability and clinical symptoms, adverse events and vital signs were recorded and a wide panel of laboratory parameters were defined. The evaluation of the safety parameters showed a safety profile which was comparable to the data provided in the current version of the SmPC of SOM230 LAR (Signifor®).

Date of report

24-Oct-2016

Substantial protocol amendments

The protocol was amended once during the study. The main purpose of the amendment was to update the safety information for patients after new data about SOM230 were available (safety update only).
The study protocol was amended to implement urgent safety communication from the pharmaceutical manufacturer of the study drug (Novartis Pharma). It was observed in other SOM230-studies that healthy subjects treated with SOM230 fulfilled criteria for Hy's Law (i.e., that patients treated with a specific drug

suffer from certain abnormities of liver enzymes, resulting in a higher risk of hepatotoxicity). Thus, Hy's Law should be considered as prognostic indicator for a pure drug-induced liver injury.
In addition, the sponsor's procedures and responsibilities of safety monitoring were described in more detail.