Gefördert durch DFG Deutsche Forschungsgemeinschaft

UNIVERSITÄTS KLINIKUM FREIBURG

CLINICAL STUDY REPORT

A randomized, prospective, multicenter, controlled and double-blinded Phase II Clinical Trial to evaluate the influence of inhaled Aviptadil on Cough and Quality of Life in Sarcoidosis patients (Avisarco II)

Name of investigational product(s):	Aviptadil
Indication studied:	Pulmonary sarcoidosis associated with cough
Drug development phase	II
Protocol identification/Study number:	P000554
DRKS no.:	DRKS00013236
Study initiation date (first patient in):	Not applicable
Study completion date (last patient out):	Not applicable
Coordinating investigator: (or Sponsor's responsible medical officer)	Prof. Dr. Joachim Müller-Quernheim Medical Center - University of Freiburg Department of Pneumology Killianstr. 5, 79110 Freiburg, Germany
Sponsor:	Medical Center - University of Freiburg – represented by the Chief Medical Officer (CMO) and the Chief Financial Officer (CFO) Breisacher Str. 153, 79110 Freiburg, Germany
Report ID:	Avisarco II_CSR
Report version:	Final 1.0
Report date:	12 December 2024
Number of pages:	6

Quality Assurance Statement:

This study has been performed in compliance with Good Clinical Practises (GCP), including the archiving of essential documents.

Confidentiality Statement:

APPROVAL

The undersigned agree to the contents of this final report by their signatures. The clinical study reported here was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and applicable laws.

Coordinating Investigator

Prof. em. Dr. Joachim Müller-Quernheim Medical Center - University of Freiburg Department of Pneumology Killianstr. 5, 79110 Freiburg	Date	Signature

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SYNOPSIS

Name of Sponsor: Medical Center - University of Freiburg	Individual Trial Table Referring to Part <<insert part #>> of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Aviptadil	Volume:	
Name of Active Ingredient: Vasoactive Intestinal Polypeptide (VIP)	Page:	

Title of Study: A randomized, prospective, multicenter, controlled and double-blinded Phase II Clinical Trial to evaluate the influence of inhaled Aviptadil on Cough and Quality of Life in Sarcoidosis patients

Protocol no. P000554, DRKS no. DRKS00013236

Investigators: Coordinating Investigator: Prof. Dr. Joachim Müller-Quernheim, Medical Center - University of Freiburg, Department of Pneumology

Study centre(s):

About 10 sites were planned in Germany, which met the structural and personnel requirements for performing the planned regular trial-related investigations. In fact, the study was not carried out in any site in Germany.

Publication (reference):

Not applicable

Study period (years):	**Phase of development**:
First patient in: Not applicable Last patient out: Not applicable	Phase II

Objectives:

Treatment of sarcoidosis-associated cough, dyspnea on exertion, and fatigue by inhalation of Aviptadil (vasoactive intestinal peptide).

Subtrial: collection of samples to be used for transcriptomic and metabolomic studies to be funded by intramural sources in cooperation with the freeze biobank at the Medical Center - University of Freiburg.

Methodology:

This study was planned as a prospective, two-arm, randomised, double-blind, placebo-controlled, multicentre trial.

Number of patients (planned and analysed):

Planned: 236 to be assessed for eligibility, 200 to be randomized and analysed

Randomized: 0

Analysed: 0

Diagnosis and main criteria for inclusion:

Diagnosis:

Pulmonary sarcoidosis associated with cough

Main inclusion criteria:

1. Adult male and female patients ≥ 18 years of age
2. Patient with sarcoidosis and associated chronic cough (Leicester Cough Questionnaire (LCQ) score < 16), any Scadding type, any other organ manifestation as long as it does not require prednisolone therapy > 15 mg, see exclusion criterion 3)
3. Body mass index (BMI) < 30 kg/m^2
4. Patients supposed to be kept on stable medication for the whole study period
5. Written informed consent obtained according to international guidelines and local laws
6. Negative results for HIV, Hepatitis A, B and C within three months prior to study inclusion

7. Ability to understand the nature of the trial and the trial related procedures in German and to comply with them
8. Ability to use the nebulizer in a proper manner
9. Ability to store the IMP according to requirements.

Key exclusion criteria:

1. Patients suffering from other organic causes of cough (e.g. respiratory tract infections, gastroesophageal reflux disease, heart failure, bronchitis associated with any other disorder but sarcoidosis, thoracic tumors, exposure to inhalable irritants, laryngitis)
2. Patients treated with ACE-inhibitors or a history of ACE-inhibitor treatment within the last six weeks (ACE-inhibitors were also not allowed to start during the study)
3. Corticosteroids doses > 15 mg prednisolone equivalent per day
4. Immunosuppressive treatment (except for corticosteroids ≤ 15 mg prednisolone equivalent per day) within 3 months prior randomisation or indications to start or intensify immunosuppressive therapy during the study
5. Patients suffering from other chronic or acute severe diseases besides sarcoidosis manifestations that might impair safe participation in the trial according to the treating physician, e.g.:

- Chronic kidney disease (CKD) stage 4 and 5
- Liver cirrhosis Child-Pugh score B and C
- Intended surgery of heart, lung, liver or abdominal disease during the trial period
- Active malignancies requiring chemo- and / or radiotherapy
- Chronic bowel diseases not sufficiently controlled

6. Conditions or medications supposed to influence the primary or secondary outcomes according to the local investigator's appraisal (e.g. newly diagnosed obstructive sleep apnoea syndrome, newly or recently exacerbated psychiatric disease, modification of psychotic disease)
7. Known HIV infection, infectious hepatitis (type A, B or C) or another currently uncontrolled infection
8. Known hypersensitivity to the active substance or any of the excipients
9. Participation in any other interventional clinical trial during this study or during the last 30 days prior to informed consent; simultaneous participation in registry and diagnostic trials was allowed
10. Previous participation in this trial
11. Known persistent abuse of medication, drugs or alcohol
12. Relationship of dependence/employment with the sponsor or the investigator
13. Current or planned pregnancy, nursing period or patients of reproductive potential who were not using effective birth control methods
14. Male subjects with reproductive potential who refused to use adequate means of contraception during and up to 90 days after stopping treatment with Aviptadil.

Study intervention (planned):

Experimental treatment: Inhalation of Aviptadil (200 µg/day, i.e. 66.6 µg 3 times a day)

Control treatment: Inhalation of placebo 3 times a day

Duration of treatment per patient: 24 weeks

Follow-up per patient: 12 weeks after end of treatment

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Duration of treatment (planned):

Recruitment period: 15 months

First patient in to last patient out: 24 months

Duration of the entire trial: 36 months

Treatment duration per patient: 6 months

Follow-up duration per patient: 3 months

Criteria for evaluation:

Primary endpoint:

- Change in cough-specific Quality of Life (QoL) gauged by LCQ score from baseline to 24 weeks after randomisation.

Key secondary endpoints:

- Change in cough-specific QoL gauged by LCQ score from baseline to 12 weeks after randomisation
- Change in King's Sarcoidosis Questionnaire (KSQ) from baseline to week 12 and week 24
- Fatigue at 12 and 24 weeks after randomisation
- Dyspnea on exertion at 12 and 24 weeks after randomisation
- Cough intensity at 12 and 24 weeks after randomisation
- Lung function parameters at 12 and 24 weeks
- Cumulative steroid dose up to 24 weeks
- Standardized 6-minute walking test (6MWT) and Distance Saturation Product (DSP) at week 12 and week 24
- Transcription patterns at 24 weeks after randomisation (Subtrial)
- Safety: Assessment of adverse events (AEs) and serious adverse events (SAEs).

Statistical methods:

Sample size:

The study was planned for a difference in the LCQ total score of 1.7 points, which was regarded as a clinically meaningful difference. Assuming variance homogeneity with a common standard deviation of 4 and a corresponding effect size of 0.425, the study was planned to achieve statistical significance with a probability (power) of 80% on the basis of a two-sample t-test at two-sided significance level of 0.05. Based on these assumptions, a total of 176 patients with non-missing LCQ score were required. The rate of patients lost to follow-up (LCQ score missing) until week 24 was assumed to be at most 12%. Therefore, 200 patients should have been randomised.

Analysis of primary and secondary endpoints:

For the analysis of the primary estimand (treatment policy), differences between Aviptadil and placebo with respect to the primary endpoint, LCQ change from baseline to week 24, were planned to be estimated and tested (two-sided at 5% level) within a mixed linear model for repeated measures (MMRM), taking into account the 12 week LCQ measurement. The model included randomised treatment, center and gender as independent variables, as well as the baseline LCQ scores, corticosteroid intake at baseline and inhalative treatment at baseline. The two-sided 95% confidence interval for the effect of treatment was planned to be calculated.

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Analyses of the secondary endpoints were planned to be performed in similar regression models as for the primary endpoint and according to both estimand strategies, as appropriate for the respective type of data.

SUMMARY – RESULTS:

Not applicable. The funding of the clinical trial was preliminarily terminated by the funder. No site was initiated and consequently no patients were enrolled in any study center.

Thus, the Avisarco II study was formally deregistered on 09 September 2024.

Funding of the study:

The study was financially supported by the Deutsche Forschungsgemeinschaft (DFG).

DFG support code: 692/12-1

Date of the Report:

12 December 2024