1 TITLE PAGE (VERSION: 12.08.2013)

Title:
Effect of postsurgical systemic doxycycline after regenerative periodontal therapy. A randomized placebo-controlled clinical trial

Name of test drug:
Doxycyclin-Filmtabletten; INN: Doxycyclin (Alpha-6-Desoxy-5-hydroxytetracyclin); 200 mg p.d. (230.8 mg Doxycyclinhyclat)

Indication: Untreated and recurrent moderate to severe periodontal disease

Name of sponsor:
Prof. Dr. med. dent. Peter Eickholz
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EudraCT-Nr.:	2006-001367-36
Prüfplan-Code:	DoxP-01/2006
Ethical Committee Johann Wolfgang Goethe-University Frankfurt:	159/06
Ethical Committee Heidelberg University:	ABmu-179/2006
ClinicalTrial-Nr.:	NCT01030666

Development phase of study: December 2, 2005

Study initiation date: April 11, 2007

Study completion date: January 10, 2011

Principal investigator:
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This clinical study was performed according to the guidelines of the Declaration of Helsinki in its revised version from October 7, 2000, according to §§ 10, 29, 40-42, 47, 63 a, 64, 66, 67, 96 and 97 of the German Drug Law (Arzneimittelgesetzes: AMG) in its version from August 9, 2004, the German "Datenschutzgesetz (Law on the protection of data)" and according to the principles for the proper realisation of clinical studies as well as the EG-GCP Guidelines (Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen [GCP-Verordnung – GCP-V] from August 9, 2004).
Date: August 12, 2013

2 SYNOPSIS

<table>
<tr><td>1) Name of Sponsor/Company:
Prof. Dr. Peter Eickholz</td><td rowspan="3">Individual Study Table
Referring to Part
of the Dossier
Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>2) Name of Finished Product:
Doxycyclin-Filmtabletten</td></tr>
<tr><td>3) Name of Active Ingredient:
Doxycyclin (Alpha-6-Desoxy-5-hydroxytetracyclin); 200 mg p.d. (230,8 mg Doxycyclinhyclat)</td></tr>
<tr><td colspan="3">4) Individual Study Table: does not apply; only required for approval dossiers</td></tr>
<tr><td colspan="3">5) Title of Study: Effect of postsurgical systemic doxycycline after regenerative periodontal therapy. A randomized placebo-controlled clinical trial</td></tr>
<tr><td colspan="3">6) Investigators: P. Eickholz[A], B. Schacher[A], M. Wohlfeil[A], L. Röllke[A], K. Nickles[A], B. Dannewitz[A,B], T.-S. Kim[B], J. Kaltschmitt[B], D. Krigar[B], J. Krieger[B]</td></tr>
<tr><td colspan="3">7) Study Centre(s): A) Department of Periodontology, University Dental Clinic of Frankfurt, Germany (F), B) Section of Periodontology, Department of Conservative Dentistry, University Dental Clinic of Heidelberg, Germany (HD)</td></tr>
<tr><td colspan="3">8) Publication (reference):
Röllke, L., Schacher, B., Wohlfeil, M., Kim, T.-S., Kaltschmitt, J., Krieger, J., Krigar, D. M., Reitmeir, P., Eickholz, P.: Regenerative therapy of infrabony defects with or without systemic doxycycline. A randomised placebo-controlled trial. J Clin Periodontol 39, 448-456 (2012)
Eickholz, P., Röllke, L., Schacher, B., Wohlfeil, M., Dannewitz, B., Kaltschmitt, J., Krieger J. K., Krigar, D. M., Reitmeir, P., Kim, T.-S.: Enamel matrix derivative in propylene glycol alginate for treatment of infrabony defects with or without systemic doxycycline: 12 and 24 months results. J Periodontol (accepted for publication)</td></tr>
<tr><td colspan="2">9) Study Period (Years):
date of first enrolment: 11.04.2007
date of last completed: 10.01.2011
The trial was terminated prematurely because the shelf life of the investigational drug ran out before 90 patients could be included</td><td>10) Phase of Development:
Phase IV</td></tr>
<tr><td colspan="3">11) Objectives:
This study was designed to compare the outcome of regenerative periodontal therapy with or without postsurgical administration of 200 mg doxycycline once a day for 7 days</td></tr>
<tr><td colspan="3">12) Methodology:
double blind randomized placebo controlled two-centre clinical trial</td></tr>
<tr><td colspan="3">13) Number of Patients (planned and analysed):
planned sample size: 90; intent to treat population (ITT): 61; safety population: 61</td></tr>
<tr><td colspan="3">14) Diagnosis and Main Criteria for Inclusion:
Sites with infrabony defects and persisting pockets after antiinfective therapy of moderate to severe periodontal disease</td></tr>
<tr><td colspan="3">15) Test Product, Dose and Mode of Administration, Batch Number:
DOXY: 7 tablets with 200 mg doxycycline (230.8 mg doxycyclinehyclat), tablet for oral intake, Batch-No. 061190</td></tr>
<tr><td colspan="3">16) Duration of Treatment: 7 days</td></tr>
<tr><td colspan="3">17) Reference Therapy, Dose and Mode of Administration, Batch Number:
PLAC: 7 tablets (Placebo), tablet for oral intake, Batch-No. 061190</td></tr>
</table>

Clinical Study Report: "DoxP-01/2006"

(Clinical study according §§ 40-42 AMG)

1) Name of Sponsor/Company: Prof. Dr. Peter Eickholz	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
2) Name of Finished Product: Doxycyclin-Filmtabletten	Volume:	
3) Name of Active Ingredient: Doxycyclin (Alpha-6-Desoxy-5-hydroxytetracyclin); 200 mg p.d. (230,8 mg Doxycyclinhyclat)	Page:	

18) Criteria for Evaluation:

Efficacy: The main outcome variables for the comparison of the therapeutical effects of DOXY and PLAC was chosen to be early wound healing, change of PAL-V after 6 months, and bony fill after 12 months. PAL-V gain (12, 24 months), PPD reduction, bony fill (6, 24 months), and microbiology were looked upon as secondary outcome variables. All other parameters (PlI, GI, postsurgical pain) were control variables.

Safety: Safety was assessed as posttherapeutical control and self reported subjective complaints of the individual patients.

19) Statistical methods:

Primary and secondary outcome variables for the 2 test groups (DOXY/PLAC) were compared using an independent t/Kruskal Wallis test. A multiple regression model was calculated for the dependent variable PAL-V gain with the independent variables baseline clinical parameters (PAL-V, PPD, GI, PlI), postsurgical medication (DOXY/PLAC), defect parameters (INFRA, % 1, 2, 3wall component, CEJ-BD), baseline microbiological parameters, smoking. Smoking habits were defined by indicator variables

20) Summary – Conclusions

Efficacy Results: 58 patients (DOXY: 27; PLAC: 31) were re-examined 6 months after surgery using enamel matrix derivative (EMD) (mean age 51.6±10.4 years; 33 female, 15 smoker). The study failed to find differences between both groups regarding early wound healing. In both groups statistically significant ($p < 0.001$) PPD reduction (DOXY: 3.87±1.20 mm; PLAC: 3.69±1.13 mm) and PAL-V gain (DOXY: 3.11±1.23 mm; PLAC: 3.40±1.34 mm) were observed 6 months after surgery. However, the differences between both groups failed to be statistically significant (PPD: 0.18 mm; $p = 0.621$; PAL-V: 0.29 mm; $p = 0.507$). Only for PLAC statistically significant ($p = 0.002$) bony fill (DOXY: 1.09±2.70 mm; PLAC: 1.51±2.89 mm) was observed 12 months after surgery. The differences between both groups failed to be statistically significant (0.42 mm; $p = 0.205$). Seven days after therapy, less pain (prevalence, intensity, duration, number of pain killers taken) was reported for DOXY ($p < 0.05$). After correction for sex the effect was not significant any more. All microbiological parameters exhibited reductions from baseline to 14 days of which more were statistically significant for DOXY than for PLAC.

Safety Results: The healing phase passed uneventfully for all patients and all teeth. Complete necrosis of interdental tissues was never seen. Partial necrosis occurred in 3 defects (DOXY: 1; PLAC: 2). Serious or unexpected adverse events were not reported. Most common adverse events were head ache (DOXY: 1; PLAC: 4), nausea (DOXY: 3; PLAC: 1), transitory shortsightedness (DOXY: 2; PLAC: 0).

Conclusion: 200 mg systemic doxycycline for 7 days after regenerative therapy of intrabony defects using EMD failed to result in better early wound healing, better PAL-V gain 6 month, or better bony fill 12 months after surgery compared to placebo.

21) Date of report: August 12, 2013