Clinical Study Report Synopsis

Version/Date: v 2.0 / 16 Jan 2014

Randomised, double-blind, placebo-controlled, multicentre, comparative phase II pilot study on the efficacy and tolerability of an 8-week rectal treatment with 2 mg budesonide or placebo for the prevention of acute radiation proctitis

Project No.:	BUF-17/RAP
EudraCT No.:	2007-002082-13
Short title:	Budesonide foam versus placebo for prevention of acute radiation proctitis
Investigational drug:	Budesonide 2 mg rectal foam (Budenofalk® Rektalschaum)
Reference drug:	Placebo foam
Indication:	Prevention of acute radiation proctitis
Phase of study:	II (exploratory pilot trial)
First patient enrolled:	09 Dec 2008
Last patient completed:	22 Aug 2011
Date of prefinal report:	16 Jan 2014

Sponsor:
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Germany

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GCP Statement: This study was conducted in compliance with Good Clinical Practices (GCP) and the Declaration of Helsinki, and in accordance with applicable legal and regulatory requirements, including archiving of essential documents.

SYNOPSIS

Name of Sponsor/Company **Dr. Falk Pharma GmbH**	*Individual Study Table Referring to Part of the Dossier*	*(For National Authority Use only)*
Name of Finished Product: **Budenofalk® Rektalschaum**	*Volume:*	
Name of Active Ingredient: **Budesonide**	*Page:*	

Title of Study:
Randomised, double-blind, placebo-controlled, multicentre, comparative phase II pilot study on the efficacy and tolerability of an 8-week rectal treatment with 2 mg budesonide or placebo for the prevention of acute radiation proctitis

Study Centres: Two centres in Germany enrolled patients.
Publications: None

Study Period:
First patient enrolled: 09 Dec 2008
Last patient completed: 22 Aug 2011

Phase of Development:
II (exploratory pilot trial)

Objectives:
Primary Objective:

- To proof the superiority of an 8-week rectal treatment with once-daily 2 mg budesonide versus placebo for the prevention of acute radiation proctitis.

Secondary Objectives:

- To evaluate the occurrence of acute radiation proctitis (RAP) 6 weeks after end of radiation therapy (RT),
- To evaluate the occurrence of chronic RAP 1 year after start of RT,
- To study safety and tolerability in the form of adverse events and laboratory parameters,
- To assess patients' quality of life.

Methodology:

This was a randomised, double-blind, placebo-controlled, multicentre, comparative, 8-week treatment, phase II pilot trial. The study was conducted with two arms in the form of a parallel group comparison and served to compare once-daily rectal treatment with 2 mg budesonide or placebo for the prevention of acute RAP in prostatic cancer patients.

The patients were assigned to one of the two following treatment groups in conformity with a randomisation list:

- Treatment Group A ('**Budesonide**': 2 mg budesonide rectal foam (Budenofalk® Rektalschaum)
- Treatment Group B ('**Placebo**'): Placebo foam

Number of Patients (Planned and Analysed):
The planned sample size was 2 x 16 randomised patients. Due to the unexpectedly low recruitment rate and the expiry date of the study medication, the trial was stopped after 17 patients overall had been randomised. The safety analysis set and the intent-to-treat analysis set included 17 patients.

Analysed in the Final Analysis:

Number of patients	Total	Budesonide	Placebo
Randomised	17	8	9
Safety	17	8	9
ITT	17	8	9

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Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion Criteria:

1. Signed informed consent,
2. Men aged at least 18 years,
3. Patients with ECOG performance status ≤ 2 or Karnofsky Performance Status Scale ≥ 70%,
4. Estimated life expectancy more than 3 years,
5. Diagnosis of prostate carcinoma,
6. Indication for local RT in patients with prostatic cancer.

Main Exclusion Criteria:

1. Crohn's disease, indeterminate colitis, ulcerative colitis, microscopic colitis (i.e. collagenous colitis and lymphocytic colitis),
2. Severe or symptomatic ischaemic colitis at baseline,
3. Grade III internal haemorrhoids at baseline,
4. High risk patients needing extended radiation therapy,
5. Acute EORTC/RTOG lower GI toxicity score of ≥ 1 at baseline,
6. Bacterial, amoebic, fungal, or viral infections of the gut,
7. Tuberculosis, hypertension, infection, diabetes mellitus (included familiarly predisposition), active peptic ulcer, osteoporosis, glaucoma, or cataract, if careful medical monitoring was not ensured,
8. Portal hypertension or liver cirrhosis,
9. Abnormal hepatic function (ALT, AST or AP > 2.5 x ULN).

Duration of Treatment: Eight weeks

Test Drug, Dose and Mode of Administration, Batch Numbers:
Budesonide 2 mg/d (Budenofalk® Rektalschaum) once daily (OD).
Patients of Treatment Group A were to administer rectally:
One actuation (20 ml) of Budenofalk® Rektalschaum containing 2 mg budesonide once daily.
Batch numbers:

07 H 29 001	(fictitious batch no. BF170807)	Expiry date: 08/2009
09 B 13 006	(fictitious batch no. BF170807)	Expiry date: 02/2011

Reference Drug, Dose and Mode of Administration, Batch Number:
Placebo rectal foam once daily (OD), no active ingredient.
Patients of Treatment Group B were to administer rectally:
One actuation (20 ml) of Placebo foam once daily.
Batch numbers:

07 H 27 001	(fictitious batch no. BF170807)	Expiry date: 02/2011

Rescue Medication, Dose and Mode of Administration, Batch Number:
Budesonide 2 mg/d (Budenofalk® Rektalschaum).
Patients assessed as treatment failures were planned to administer rectally:
One actuation (20 ml) of Budenofalk® Rektalschaum containing 2 mg budesonide once daily.
Batch numbers:

07 H 29 001	(fictitious batch no. BF17open0807)	Expiry date: 08/2009
09 B 13 006	(fictitious batch no. BFopen170209)	Expiry date: 02/2011

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Criteria for Evaluation:

Primary Efficacy Endpoint:

Proportion of patients developing an acute EORTC/RTOG lower GI toxicity score ≥ 1 on at least 2 consecutive days during treatment, need of rescue medication, or premature withdrawal due to lack of efficacy or intolerable adverse drug reaction (occurrence of acute RAP).

Secondary Efficacy Endpoints:

- Acute EORTC/RTOG lower GI toxicity score,
- Acute radiation proctitis score,
- Late EORTC/RTOG lower GI toxicity score,
- Number of bowel events per week (stools [total], bloody / formed / soft / watery / painful stools, respectively, mucous discharge, tenesms),
- Number (%) of days with acute EORTC/RTOG lower GI toxicity score ≥ 1 or ≥ 2,
- Number (%) of days with radiation proctitis score of ≥ 1 or ≥ 2,
- Number (%) of days with bowel events:
  (abdominal pain, abdominal cramps, formed / soft / watery / bloody stools, diarrhoea, urgency),
- Vienna Rectoscopy Score (VRS),
- Time to occurrence of acute radiation proctitis and clinical symptoms during the double-blind phase,
- Occurrence of acute radiation proctitis and clinical symptoms during the follow-up phase,
- General well-being in the course of the study,
- Patient's Quality of Life (SHS and EPIC Bowel Domain score).

Safety:

- Adverse Events (AEs),
- Blood and urine laboratory,
- Vital signs (blood pressure, heart rate and body weight),
- Laboratory assessments,
- Assessment of tolerability by investigator and patient.

Statistical Methods:

Primary efficacy evaluation:	
Rates of occurrence of acute RAP	Fisher's Exact Test (α = 0.025, one-sided)
Secondary efficacy evaluation:	
Acute or chronic radiation proctitis at visits (according to varying thresholds of acute/late EORTC/RTOG lower GI toxicity score and radiation proctitis score)	Fisher's Exact Test (α = 0.05, two-sided), risk differences (incl. 95% CI), absolute and relative frequencies
Change in degree of radiation proctitis from baseline to visits 4, 5 and 6 (according to acute EORTC/RTOG lower GI toxicity score and radiation proctitis score)	Exact Wilcoxon 2-Sample Tests (α = 0.05, two-sided), summary statistics (incl. mean, standard deviation, quartiles)
Number of bowel events per week and changes in the number of bowel events from baseline to the final week of the double-blind phase	Summary statistics (incl. mean, standard deviation, quartiles) for the number of the respective bowel events per week and the change

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○ for all weeks during the double-blind phase, final week of the double-blind phase (LOCF), weeks prior to Visit 5 and Visit 6 ○ number of all stools, formed stools, soft stools, watery stools, bloody stools, painful stools, mucous discharges, tenesms	from baseline to the final week.
Number and percentage of days during the double-blind phase fulfilling a certain criterion regarding ○ radiation proctitis criteria (according to acute EORTC/RTOG lower GI score and radiation proctitis score), ○ patient ratings (abdominal pain, abdominal cramps and urgency), ○ bowel movements	Summary statistics (incl. mean, standard deviation, quartiles) for the number and percentage of days fulfilling the respective criterion.
Time to occurrence of radiation proctitis and clinical symptoms during the double-blind phase ○ Radiation proctitis (according to acute EORTC/RTOG lower GI score and radiation proctitis score) ○ Clinical symptoms: >3 soft or watery stools/day, at least 1 bloody stool/day, abdominal or rectal pain of moderate or severe intensity, abdominal cramps of severe intensity, urgency of at least moderate or severe intensity, >3 soft or watery stools/day, thereof at least 1 stool with blood, any clinical symptom	Median times to events (with consideration of right censored times) and summary statistics (incl. mean, standard deviation, quartiles)
Occurrence of radiation proctitis and clinical symptoms during the follow-up phase ○ Radiation proctitis (according to acute/late EORTC/RTOG lower GI score and radiation proctitis score) ○ Clinical symptoms: >3 soft or watery stools/day, at least 1 bloody stool/day, abdominal or rectal pain of moderate or severe intensity, abdominal cramps of severe intensity, urgency of at least moderate or severe intensity, >3 soft or watery stools/day, thereof at least 1 stool with blood, any clinical symptom	Summary statistics (absolute and relative frequencies)
Vienna Rectoscopy Score (VRS) at Visit 1, Visit 4, Visit 5 and Visit 6	Summary statistics (incl. mean, standard deviation, quartiles) for the Vienna Rectoscopy Score at visits.
Change in the general well-being score from baseline to the last value under treatment	Summary statistics (incl. mean, standard deviation, quartiles) for the change in the general well-being.

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Patient's Quality of Life (Short Health Scale [SHS] and Expanded Prostate Cancer Index Composite Bowel Domain Scores [EPIC])	Summary statistics (incl. mean, standard deviation, quartiles) for the Quality of Life Scores at visits.
Safety evaluation:	
Adverse events (AEs), adverse drug reactions (ADRs)	Absolute frequencies of events and absolute and relative frequencies of patients with at least one event
Blood laboratory	Summary statistics (incl. mean, standard deviation, quartiles) for blood laboratory values at visits and their absolute and relative change from baseline to visits during the double-blind phase. Frequencies of shifts from normal to abnormal values and vice versa.
Urine laboratory	Absolute and relative frequencies of urine laboratory values
Assessment of tolerability by investigator and patient	Absolute and relative frequencies of assessments.
Vital signs	Summary statistics (incl. mean, standard deviation, quartiles) for vital signs at visits during the double-blind phase.
Others (e.g. baseline characteristics):	
Categorical variables	Absolute and relative frequencies
Continuous variables	Summary statistics

Summary statistics include mean, standard deviation, minimum, maximum, upper and lower quartile, median.

Results:

Patient disposition

In total, 17 patients were recruited and randomised into the study. All patients completed the entire double-blind phase. Two patients from the placebo group discontinued the follow-up phase prematurely. Reasons for premature discontinuation were lack of patient's cooperation and an intolerable (serious) post-treatment adverse event which was not related to study treatment.

Allocation to analysis sets

	Number of patients		
	Total	**Budesonide**	**Placebo**
Randomised	17	8	9
Safety	17	8	9
ITT	17	8	9

All randomised patients were included into the safety and ITT analysis set as well.

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Key demographic and baseline characteristics (ITT analysis set)

		Budesonide (N=8)	Placebo (N=9)
Sex			
Male	n (%)	8 (100%)	9 (100%)
Race			
White	n (%)	8 (100%)	9 (100%)
Smoking behaviour			
Non-Smoker	n (%)	7 (87.5%)	9 (100%)
Smoker	n (%)	1 (12.5%)	0 (0.0%)
Age at baseline [years]	Mean (SD)	67.4 (9.93)	69.9 (8.64%)
BMI at baseline [kg/m²]	Mean (SD)	28.3 (3.43)	27.1 (2.85)
Duration of disease [years]			
Time since 1st symptoms	Mean (SD)	0.86 (0.630)	0.58 (0.366)
Radiation therapy of the pelvic			
primary	n (%)	7 (87.5%)	6 (66.7%)
recurrent	n (%)	1 (12.5%)	3 (33.3%)
Risk stratum			
1) low risk	n (%)	0 (0.0%)	2 (22.2%)
2) intermediate risk	n (%)	7 (87.5%)	5 (55.6%)
3) high risk	n (%)	0 (0.0%)	0 (0.0%)
4) PSA-relapse	n (%)	1 (12.5%)	2 (22.2%)
Duration of radiotherapy [days]	Mean (SD)	55 (6.3)	56 (5.0)
Total dose of radiotherapy [Gy]	Mean (SD)	67.5 (7.1)	70.3 (5.1)

The demographics and baseline characteristics presented above did not show relevant differences between treatment groups.

Efficacy results:

Primary efficacy results:

Proportion of patients developing acute radiation proctitis defined as an acute EORTC/RTOG lower GI toxicity score ≥ 1 on at least 2 consecutive days) during 8 weeks of treatment or need for rescue medication or premature withdrawal due to lack of efficacy or intolerable ADR

		Budesonide (N=8)	Placebo (N=9)	Difference in proportions* [95% CI]
Acute radiation proctitis	n (%)	6 (75.0%)	6 (66.7%)	8.3% [-34.7; 51.3%]
No acute radiation proctitis	n (%)	2 (25.0%)	3 (33.3%)	- - -

*difference = $\pi_{Budesonide} - \pi_{Placebo}$

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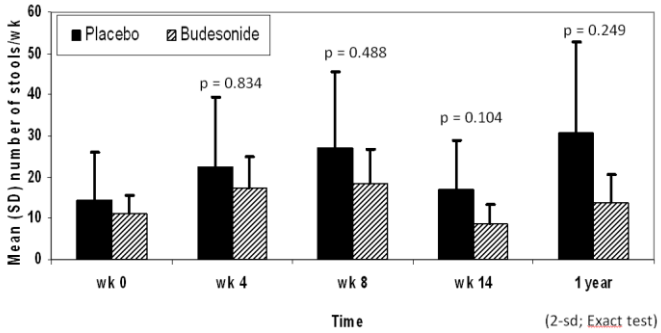
No difference between treatment groups could be seen regarding the rate of acute radiation proctitis. The one-sided p-value of Fisher's Exact Test testing the superiority of budesonide over placebo was not significant (p = 0.8167). The 95% CI for the difference in proportions was wide and included 0. Superiority of budesonide rectal foam over placebo regarding the rates of radiation proctitis during 8 weeks of treatment could not be shown.

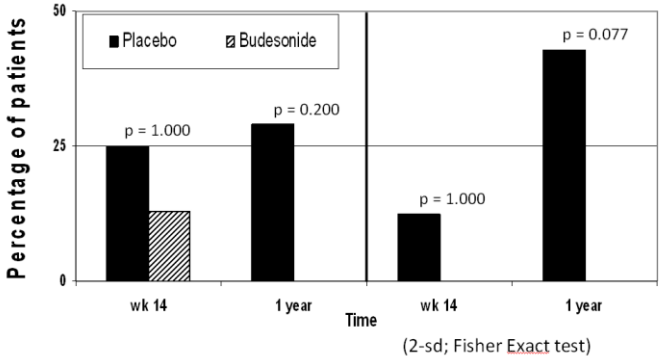
Due to the small sample size (N=17) the statistical power of the primary efficacy evaluation was too low to demonstrate significant differences between both treatment groups.

Secondary efficacy results:

Overall, clinical symptoms of proctitis could be reduced and the appearance of late radiation proctitis was diminished under treatment with budesonide. However, due to the small sample size findings from secondary efficacy endpoints did not show any statistically significant differences between budesonide rectal foam and placebo.

Mean (SD) number of stools/wk:





Mean (SD) Vienna Rectoscopy Score:

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	Wk 0	Wk 8	Wk 14	Wk 52
Placebo	0 (0)	0.1 (0.3)	0.3 (0.5)	1.7 (0.5)
Budesonide	0 (0)	0.4 (0.5)	0 (0)	1.0 (0.8)
p-value*		0.2393	0.1700	0.0664

*Wilcoxon 2-sample test, 2-sided

Patient's quality of life deteriorated in both treatment groups during the radiation phase and returned thereafter back to pre-radiation levels. No clinically meaningful differences between the treatment groups were observed.

Safety results:

A total of 7 treatment-emergent AEs (TEAEs) occurred in 5 of 8 patients (62.5%) in the budesonide group and 8 TEAEs in 6 in 9 patients (66.7%) of the placebo group. A total of 16 post-TEAEs were reported in 7 of 8 patients (87.5%) in the budesonide group and 10 post-TEAEs in 7 of 9 patients (77.8%) in the placebo group. The overall incidences of TEAEs and post–TEAEs were similar between the treatment groups. No AE was assessed as being related to the study medication by the investigators. No death occurred during the study.

One SAE in 1 of 8 patients (12.5%) in the budesonide group and two SAEs in 2 of 9 patients (22.2%) in the placebo group were observed in this study. None of them was related to the study medication.

Overall, laboratory results after 8 weeks of treatment with budesonide rectal foam were comparable to results after 8 weeks of treatment with placebo.

All patients and investigators assessed the tolerability as 'very good' or 'good' for both treatments.

Conclusions:

- Rectal treatment with 2 mg/d budesonide did not significantly prevent acute radiation proctitis in this small pilot study,
- However, clinical symptoms of proctitis could be reduced and the appearance of late radiation proctitis was diminished under treatment with budesonide,
- Quality of life was mainly influenced by the radiation, with no meaningful differences between the treatment groups.
- There was no hint for a new safety signal for budesonide rectal foam 2 mg in that special patient population.

Date of the report:	16 Jan 2014