Clinical trial results:
Double-blind, randomised, placebo-controlled, multi-centre phase III clinical study on the efficacy and tolerability of budesonide capsules versus placebo for maintenance of remission in patients with collagenous colitis

Summary

EudraCT number	2007-001315-31
Trial protocol	SE DE HU DK CZ BE
Global end of trial date	16 September 2013

Results information

Result version number	v1 (current)
This version publication date	12 August 2016
First version publication date	12 August 2016
Summary attachment (see zip file)	Gut - Open access paper (Münch-2016-Gut.pdf)

Trial information

Trial identification

Sponsor protocol code	BUC-63/COC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01278082
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr Falk Pharma GmbH
Sponsor organisation address	Leinenweberstrasse 5, Freiburg, Germany, 79108
Public contact	Department of Medical Science, Dr Falk Pharma GmbH, +49 761-1514-0,
Scientific contact	Department of Medical Science, Dr Falk Pharma GmbH, +49 761-1514-0,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 March 2013
Global end of trial reached?	Yes
Global end of trial date	16 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To prove the superiority of budesonide compared to placebo as maintenance therapy in keeping patients with collagenous colitis in remission over a one-year period.

Protection of trial subjects:

Prior to recruitment of patients, all relevant documents of the clinical study were submitted and approved by the Independent Ethics Committees (IECs) responsible for the participating investigators. Written consent documents embodied the elements of informed consent as described in the Declaration of Helsinki, the ICH Guidelines for Good Clinical Practice (GCP) and were in accordance with all applicable laws and regulations. The informed consent form and patient information sheet described the planned and permitted uses, transfers and disclosures of the patient's personal data and personal health information for purposes of conducting the study. The informed consent form and the patient information sheet further explained the nature of the study, its objectives and potential risks and benefits as well as the date informed consent was given. Before being enrolled in the clinical trial, every patient was informed that participation in this trial was voluntary and that he/she could withdraw from the study at any time without giving a reason and without having to fear any loss in his/her medical care. The patient's consent was obtained in writing before the start of the study. By signing the informed consent, the patient declared that he/she was participating voluntarily and intended to follow the study protocol instructions and the instructions of the investigator and to answer the questions asked during the course of the trial.
For colonoscopy and biopsy sampling to be performed for confirmation of diagnosis of collagenous colitis by the central pathologist, the patients received the standard preparation for bowel cleansing and sedation during the colonoscopy as routinely performed at the study sites.

Background therapy:

No concomitant background therapy was allowed during the trial.

Evidence for comparator:

Using a placebo arm in this clinical trial as reference was ethically justified and in accordance with Article 29 of the Declaration of Helsinki (2008), as there were compelling and scientifically sound methodological reasons for the use of a placebo control in this trial, since there were no comparator products with a marketing authorization for the maintenance treatment of collagenous colitis available.

Actual start date of recruitment	18 April 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 73
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Denmark: 4

Country: Number of subjects enrolled	Germany: 10
Worldwide total number of subjects	92
EEA total number of subjects	92

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	64
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This clinical trial was conducted in 22 sites in 5 countries: 1 centre in Belgium, 3 centres in the Czech Republic, 2 centres in Denmark, 4 centres in Germany, and 12 centres in Sweden. First patient was screened (entered) at the 18 Apr 2008. Last patient completed his last visit at 16 Sept 2013.

Pre-assignment

Screening details:

110 patients with active collagenous colitis were enrolled for open-labeled (OL) induction of clinical remission treatment with budesonide. 92 Patients in clinical remission at the end of OL treatment were randomized to a 1-year double-blind maintenance of remission treatment with budesonide or placebo.

Pre-assignment period milestones

Number of subjects started	110[1]
Number of subjects completed	92

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 9
Reason: Number of subjects	Not matching InC/ExC: 9

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 110 patients were enrolled into the open-label induction period; of these 92 fulfill the inclusion criteria for period 1 (double-blind maintenance phase).

Period 1

Period 1 title	Double-blind maintenance of remission (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The appearance and size of the placebo capsules was indistinguishable from the budesonide capsules.

Arms

Are arms mutually exclusive?	Yes
Arm title	Budesonide DB Maintenance

Arm description:

Patients randomized to this treatment arm received alternating administration of 2 and 1 capsule(s), each containing gastro-resistant pellets with 3 mg budesonide as active ingredient, every other morning for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Budenofalk 3mg capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients randomized to this treatment arm received alternating administration of 2 and 1 capsule(s), each containing gastro-resistant pellets with 3 mg budesonide as active ingredient, every other morning for 52 weeks.

Arm title	Placebo DB Maintenance

Arm description:

Patients randomized to this treatment arm received alternating administration of 2 and 1 capsule(s), each containing gastro-resistant pellets with placebo, every other morning for 52 weeks.

Arm type	Placebo
Investigational medicinal product name	Budenofalk placebo capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients randomized to this treatment arm received alternating administration of 2 and 1 capsule(s), each containing gastro-resistant pellets with placebo, every other morning for 52 weeks.

Number of subjects in period 1	Budesonide DB Maintenance	Placebo DB Maintenance
Started	44	48
Completed	32	11
Not completed	12	37
Adverse event, non-fatal	3	2
Lack of efficacy	8	33
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Budesonide DB Maintenance
Reporting group description:	
Patients randomized to this treatment arm received alternating administration of 2 and 1 capsule(s), each containing gastro-resistant pellets with 3 mg budesonide as active ingredient, every other morning for 52 weeks.	
Reporting group title	Placebo DB Maintenance
Reporting group description:	
Patients randomized to this treatment arm received alternating administration of 2 and 1 capsule(s), each containing gastro-resistant pellets with placebo, every other morning for 52 weeks.	

Reporting group values	Budesonide DB Maintenance	Placebo DB Maintenance	Total
Number of subjects	44	48	92
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	34	30	64
From 65-84 years	10	18	28
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	56.7	60.8	
standard deviation	± 9.9	± 11.7	-
Gender categorical Units: Subjects			
Female	40	38	78
Male	4	10	14
Ethnic Group Units: Subjects			
White	44	48	92
Body Mass Index (BMI) Units: kg/m2			
arithmetic mean	26	24.6	
standard deviation	± 4.5	± 3.8	-
Mean number of stools/day Units: number of stools/day			
arithmetic mean	1.7	1.8	
standard deviation	± 0.6	± 0.9	-
Mean number of watery stools/day Units: Number of watery stools/day			
arithmetic mean	0.1	0.2	

standard deviation	± 0.2	± 1	-
Quality of life - Symptom burden			
Assessed by using the visual analogue scale (0-100) for Symptom burden of the SHS (Short Health Scale), with higher scores presenting lower quality of life			
Units: Score			
median	6	6	
inter-quartile range (Q1-Q3)	2 to 14	2 to 21	-
Qualit yof life - Social function			
Assessed by using the visual analogue scale for Social function (0-100) of the SHS (Short Health Scale), with higher scores presenting lower quality of life			
Units: Score			
median	3	3	
inter-quartile range (Q1-Q3)	2 to 11.5	1 to 8	-

End points

End points reporting groups

Reporting group title	Budesonide DB Maintenance
Reporting group description:	
Patients randomized to this treatment arm received alternating administration of 2 and 1 capsule(s), each containing gastro-resistant pellets with 3 mg budesonide as active ingredient, every other morning for 52 weeks.	
Reporting group title	Placebo DB Maintenance
Reporting group description:	
Patients randomized to this treatment arm received alternating administration of 2 and 1 capsule(s), each containing gastro-resistant pellets with placebo, every other morning for 52 weeks.	

Primary: Number (%) of patients with clinical remission over 52 weeks

End point title	Number (%) of patients with clinical remission over 52 weeks
End point description:	
Proportion of patients being in clinical remission over 52 weeks, with clinical remission defined as a mean of < 3 stools/day, thereof a mean of < 1 watery stool/day during the week prior to the final visit (and with no relapses during the 1-year course). Stool consistency was described by patients according to the Bristol Stool Chart.	
End point type	Primary
End point timeframe:	
52 weeks	

End point values	Budesonide DB Maintenance	Placebo DB Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	48		
Units: Number of patients	27	8		

Attachments (see zip file)	Primary efficacy endpoint/BUC63 DB CR over 52wks.JPG

Statistical analyses

Statistical analysis title	Final Analysis (FAS)
Comparison groups	Budesonide DB Maintenance v Placebo DB Maintenance
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	44.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	26.9
upper limit	62.7

Notes:

[1] - The null hypothesis given below will be tested against the alternative hypothesis (α = 0.025, one-sided):
Null hypothesis: H0: πA − πB ≤ 0
Alternative hypothesis: H1: πA − πB > 0

Group A (Verum) vs. Group B (Placebo):
πA and πB denote the proportion of patients with clinical remission

For confirmatory hypothesis testing the inverse normal method of combining the p-values of the normal approximation-test for comparing two rates will be used.
[2] - The hypothesis test for treatment difference yielded to a one-sided overall p-value of <0.0001 with a corresponding inverse test statistic of 4.415. This was above the pre-defined critical value of 1.967.

Secondary: Time to treatment failure

End point title	Time to treatment failure

End point description:

The time to treatment failure has been defined as the number of days between randomisation for the DB phase and seven days before the date of the visit where the remission criteria were not fulfilled anymore. Respective Kaplan-Meier analyses have been performed including Kaplan-Meier curves and the calculation of the mean and median time to treatment failure. Patients withdrawing from the study due to any other reasons than treatment failure and patients with maintaining clinical remission have been considered as censored up from their final visit.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Budesonide DB Maintenance	Placebo DB Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	48		
Units: Days				
arithmetic mean (standard error)	268.1 (± 19.5)	111.4 (± 17.3)		

Attachments (see zip file)	Timt to treatment failure/BUC63 DB Kaplan Meyer.JPG

Statistical analyses

Statistical analysis title	Kaplan-Meier Analysis - Time to treatment failure
Comparison groups	Budesonide DB Maintenance v Placebo DB Maintenance

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank

Secondary: Quality of life - Symptom burden

End point title	Quality of life - Symptom burden

End point description:

Assessed by using the visual analogue scale (0-100) for Symptom burden of the SHS (Short Health Scale), with higher scores presenting lower quality of life.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Budesonide DB Maintenance	Placebo DB Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	48		
Units: Score				
median (inter-quartile range (Q1-Q3))	5.5 (2 to 30.5)	75 (19 to 91)		

Attachments (see zip file)	Quality of life/BUC63 DB QoL.JPG

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life - Social function

End point title	Quality of life - Social function

End point description:

Assessed by using the visual analogue scale (0-100) for Social Function of the SHS (Short Health Scale), with higher scores presenting lower quality of life.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Budesonide DB Maintenance	Placebo DB Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	48		
Units: Score				
median (inter-quartile range (Q1-Q3))	5.5 (2 to 28.5)	63 (11 to 85)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

52 weeks

Adverse event reporting additional description:

It is noteworthy to mention that DB treatment with budesonide was more than twice as long as treatment with placebo (291.2 [125.1] days versus 138.1 [141.51] days; mean [SD]).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Budesonide DB Maintenance

Reporting group description:

Patients randomized to this treatment arm received alternating administration of 2 and 1 capsule(s), each containing gastro-resistant pellets with 3 mg budesonide as active ingredient, every other morning for 52 weeks.

Reporting group title	Placebo DB Maintenance

Reporting group description:

Patients randomized to this treatment arm received alternating administration of 2 and 1 capsule(s), each containing gastro-resistant pellets with placebo, every other morning for 52 weeks.

Serious adverse events	Budesonide DB Maintenance	Placebo DB Maintenance	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 44 (11.36%)	2 / 48 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 44 (2.27%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	1 / 44 (2.27%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	0 / 44 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Spinal nerve stimulator implantation	Additional description: Implantation of neurostimulator on dorsal column of spinal record		
subjects affected / exposed	1 / 44 (2.27%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transurethral prostatectomy	Additional description: Transurethral resection of the prostate gland (elective)		
subjects affected / exposed	0 / 44 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 44 (2.27%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Gallbladder polyp			
subjects affected / exposed	1 / 44 (2.27%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Foot deformity	Additional description: Hospitalisation because of planned Hallux valgus surgery		
subjects affected / exposed	1 / 44 (2.27%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Budesonide DB Maintenance	Placebo DB Maintenance	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 44 (22.73%)	5 / 48 (10.42%)	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 44 (4.55%)	3 / 48 (6.25%)	
occurrences (all)	2	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 44 (9.09%)	2 / 48 (4.17%)	
occurrences (all)	4	2	
Urinary tract infection			
subjects affected / exposed	4 / 44 (9.09%)	0 / 48 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25425655