



Clinical trial results:

Randomized, double-blind, multicentre study to compare the efficacy and safety of two different dosages of a novel budesonide suppository versus a mesalazine suppository versus a combination therapy of budesonide/mesalazine suppositories in patients with acute ulcerative proctitis

Summary

EudraCT number	2012-003362-41
Trial protocol	DE
Global end of trial date	29 July 2015

Results information

Result version number	v1 (current)
This version publication date	07 January 2017
First version publication date	07 January 2017

Trial information

Trial identification

Sponsor protocol code	BUS-2/UCA
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01966783
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Falk Pharma GmbH
Sponsor organisation address	Leinenweberstrasse 5, Freiburg, Germany, D-79108
Public contact	Department of Clinical Research, Dr. Falk Pharma GmbH, 49 761 1514-0, zentrale@drfalkpharma.de
Scientific contact	Department of Clinical Research, Dr. Falk Pharma GmbH, 49 761 1514-0, zentrale@drfalkpharma.de

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	13 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 July 2015
Global end of trial reached?	Yes
Global end of trial date	29 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this trial are to evaluate the efficacy of two doses of a novel budesonide suppository vs. standard treatment with mesalazine suppository and to evaluate the efficacy of a combined treatment of novel budesonide suppository with standard mesalazine suppository vs. standard mesalazine suppository in patients with acute ulcerative proctitis.

Protection of trial subjects:

Close supervision of subjects by implementing interim visits every 14 days to guarantee their safety and wellbeing.

Prior to recruitment of patients, all relevant documents of the clinical study were submitted and proved 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.

Background therapy:

None.

Evidence for comparator:

Mesalazine 1 g suppository is registered for the treatment of acute mild to moderate ulcerative colitis that is limited to the rectum (ulcerative proctitis).

Actual start date of recruitment	11 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 155
Country: Number of subjects enrolled	Germany: 55
Country: Number of subjects enrolled	Ukraine: 127

Worldwide total number of subjects	337
EEA total number of subjects	55

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)	324
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total 337 patients were included in Germany, Russia and Ukraine from November 2013 to July 2015.

Pre-assignment

Screening details:

Screening Criteria: 1. Signed Informed Consent 2. Aged 18 to 75 years 3. Active ulcerative proctitis

In total, 343 patients were screened. Thereof 337 patients were randomised, received at least one dose of study medication and were included in the safety set and intention-to-treat (ITT) analysis set.

Period 1

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

Blinding implementation details:

Conducted with double-dummy technique to guarantee double-blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

One budesonide 2 mg suppository in the morning.

One mesalazine placebo suppository at bedtime.

Arm type	Experimental
Investigational medicinal product name	Budesonide 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suppository
Routes of administration	Rectal use

Dosage and administration details:

One budesonide 2 mg suppository in the morning.

Investigational medicinal product name	Mesalazine placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suppository
Routes of administration	Rectal use

Dosage and administration details:

One mesalazine placebo suppository at bedtime.

Arm title	Arm B
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Arm description:

One budesonide 4 mg suppository in the morning.

One mesalazine placebo suppository at bedtime.

Arm type	Experimental
Investigational medicinal product name	Budesonide 4mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suppository
Routes of administration	Rectal use

Dosage and administration details:

One budesonide 4 mg suppository in the morning.

Investigational medicinal product name	Mesalazine placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suppository
Routes of administration	Rectal use

Dosage and administration details:

One mesalazine placebo suppository at bedtime.

Arm title	Arm C
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Arm description:

One budesonide placebo suppository in the morning.

One mesalazine 1 g suppository at bedtime.

Arm type	Active comparator
Investigational medicinal product name	Mesalazine 1 g
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suppository
Routes of administration	Rectal use

Dosage and administration details:

One mesalazine 1 g suppository at bedtime.

Investigational medicinal product name	Budesonide placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suppository
Routes of administration	Rectal use

Dosage and administration details:

One budesonide placebo suppository in the morning.

Arm title	Arm D
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Arm description:

One budesonide 2 mg suppository in the morning.

One mesalazine 1 g suppository at bedtime.

Arm type	Experimental
Investigational medicinal product name	Budesonide 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suppository
Routes of administration	Rectal use

Dosage and administration details:

One budesonide 2 mg suppository in the morning.

Investigational medicinal product name	Mesalazine 1 g
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suppository
Routes of administration	Rectal use

Dosage and administration details:

One mesalazine 1 g suppository at bedtime

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	89	79	81
Completed	80	71	77
Not completed	9	8	4
Adverse event, non-fatal	1	-	1
Lack of patient's co-operation	4	1	1
Lack of efficacy	1	3	-
Protocol deviation	3	4	2

Number of subjects in period 1	Arm D
Started	88
Completed	82
Not completed	6
Adverse event, non-fatal	1
Lack of patient's co-operation	1
Lack of efficacy	1
Protocol deviation	3

Baseline characteristics

Reporting groups

Reporting group title	Treatment Phase (overall trial)
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Reporting group description:

343 patients have signed an Informed Consent at Screening. 337 patients were finally randomised in one of the four treatment groups. 6 patients were Screening failures.

Reporting group values	Treatment Phase (overall trial)	Total	
Number of subjects	337	337	
Age categorical			
337 Patients were randomized into the trial aged 20 to 77 years.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	324	324	
From 65-84 years	13	13	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	40.6		
standard deviation	± 12.8	-	
Gender categorical			
Subjects of both sex were recruited in this trial.			
Units: Subjects			
Female	195	195	
Male	142	142	

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: One budesonide 2 mg suppository in the morning. One mesalazine placebo suppository at bedtime.	
Reporting group title	Arm B
Reporting group description: One budesonide 4 mg suppository in the morning. One mesalazine placebo suppository at bedtime.	
Reporting group title	Arm C
Reporting group description: One budesonide placebo suppository in the morning. One mesalazine 1 g suppository at bedtime.	
Reporting group title	Arm D
Reporting group description: One budesonide 2 mg suppository in the morning. One mesalazine 1 g suppository at bedtime.	

Primary: Time to resolution of clinical symptoms

End point title	Time to resolution of clinical symptoms
End point description: Time to resolution of clinical symptoms (defined as the first day of 3 consecutive days with a score of 0 for "rectal bleeding" and "stool frequency"). Analysed by descriptive statistics using the Kaplan-Meier estimator, 50% percentile estimates [days].	
End point type	Primary
End point timeframe: Within 8 weeks starting with Baseline/randomisation to Final Visit (week 8).	

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	89	79	81	88
Units: days				
Time to resolution of clinical symptoms	39	30	26	32

Statistical analyses

Statistical analysis title	Explorative analysis
Statistical analysis description: Pairwise comparison between treatment groups was performed using the log-rank test.	
Comparison groups	Arm C v Arm A

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.041
Method	Logrank

Notes:

[1] - Log-rank test

Statistical analysis title	Explorative analysis
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Statistical analysis description:

Pairwise comparison between treatment groups was performed using the log-rank test.

Comparison groups	Arm C v Arm B
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 0.431
Method	Logrank

Notes:

[2] - Log-rank test

Statistical analysis title	Explorative analysis
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Statistical analysis description:

Pairwise comparison between treatment groups was performed using the log-rank test.

Comparison groups	Arm C v Arm D
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.858
Method	Logrank

Notes:

[3] - Log-rank test

Statistical analysis title	Explorative analysis
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Statistical analysis description:

Pairwise comparison between treatment groups was performed using the log-rank test.

Comparison groups	Arm D v Arm A
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	other ^[4]
P-value	= 0.031
Method	Logrank

Notes:

[4] - Log-rank test

Statistical analysis title	Explorative analysis
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Statistical analysis description:

Pairwise comparison between treatment groups was performed using the log-rank test.

Comparison groups	Arm D v Arm B
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Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	= 0.343
Method	Logrank

Notes:

[5] - Log-rank test

Statistical analysis title	Explorative analysis
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Statistical analysis description:

Pairwise comparison between treatment groups was performed using the log-rank test.

Comparison groups	Arm B v Arm A
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	= 0.191
Method	Logrank

Notes:

[6] - Log-rank test

Secondary: Clinical and endoscopic remission

End point title	Clinical and endoscopic remission
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End point description:

Clinical and endoscopic remission at the final/withdrawal visit was defined as: total modified UC-DAI $\leq$ 1, with a score of 0 for rectal bleeding and stool frequency, no mucosal friability, and at least a 1-point reduction in the subscore for mucosal appearance at the final/withdrawal visit.

End point type	Secondary
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End point timeframe:

Within 8 weeks starting with Baseline/randomisation to Final Visit (week 8).

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	89	79	81	88
Units: Patients	29	35	41	39

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were assessed at all interim visits (Day 14, day 28, day 42 and at the Final Visit (Day56), thus every 2 weeks.

Adverse event reporting additional description:

Treatment-Emergent Adverse Events

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Arm A
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Reporting group description:

1 Budesonide 2 mg suppository in the morning

1 Mesalazine placebo suppository at bedtime

Reporting group title	Arm B
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Reporting group description:

1 Budesonide 4 mg suppository in the morning

1 Mesalazine placebo suppository at bedtime

Reporting group title	Arm C
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Reporting group description:

1 Budesonide placebo suppository in the morning

1 Mesalazine 1 g suppository at bedtime

Reporting group title	Arm D
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Reporting group description:

1 Budesonide 2 mg suppository in the morning

1 Mesalazine 1 g suppository at bedtime

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 89 (0.00%)	0 / 79 (0.00%)	0 / 81 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Arm D		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 88 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 89 (30.34%)	25 / 79 (31.65%)	20 / 81 (24.69%)
Investigations			
Blood cortisol decreased			
subjects affected / exposed	3 / 89 (3.37%)	6 / 79 (7.59%)	1 / 81 (1.23%)
occurrences (all)	3	7	1
Lipase increased			
subjects affected / exposed	3 / 89 (3.37%)	1 / 79 (1.27%)	1 / 81 (1.23%)
occurrences (all)	3	1	2
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 89 (6.74%)	2 / 79 (2.53%)	4 / 81 (4.94%)
occurrences (all)	10	2	5
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 89 (0.00%)	3 / 79 (3.80%)	0 / 81 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 89 (5.62%)	2 / 79 (2.53%)	2 / 81 (2.47%)
occurrences (all)	5	2	2

Non-serious adverse events	Arm D		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 88 (27.27%)		
Investigations			
Blood cortisol decreased			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		
Lipase increased			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	2		
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	4 / 88 (4.55%) 8		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 88 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 88 (3.41%) 4		

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