Clinical trial results:
Randomised, double-blind, double-dummy, multicentre study to compare the efficacy and safety of once daily novel 4 mg budesonide suppository versus once daily 2 mg budesonide foam in patients with acute ulcerative proctitis

Summary

EudraCT number	2016-001921-15
Trial protocol	DE LV HU SK PL
Global end of trial date	30 March 2020

Results information

Result version number	v1 (current)
This version publication date	22 May 2021
First version publication date	22 May 2021

Trial information

Trial identification

Sponsor protocol code	BUS-4/UCA

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dr. Falk Pharma GmbH
Sponsor organisation address	Leinenweberstrasse 5, Freiburg, Germany, 79215
Public contact	Department of Clinical Research, Dr. Falk Pharma GmbH, 49 7611514-0, zentrale@drfalkpharma.de
Scientific contact	Department of Clinical Research, Dr. Falk Pharma GmbH, 49 7611514-0, 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	10 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2020
Global end of trial reached?	Yes
Global end of trial date	30 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To prove the non-inferiority of an 8-week treatment with once-daily 4 mg budesonide suppository vs. active comparator 2 mg budesonide foam in patients with acute ulcerative proctitis.

Protection of trial subjects:

Close supervision of patients by regular intermin visits, safety and wellbeing guarantied. Patient documents e.g. ICF - according to Declaration of Helsinki, ICH-GCP, local laws/regulations - submitted to ECs and approved prior to recruiting any patient. Upfront enrollent of a patient he/she a) was well informed about the trial, b) consented to participate in writing, c) and therefore, participation in trial was voluntary. Withdrawal of study always given without fear about loss of medical care. Patient consented to follow the instructions of the protocol/study team.

Background therapy:

None

Evidence for comparator: -

Actual start date of recruitment	28 June 2017
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	Poland: 84
Country: Number of subjects enrolled	Slovakia: 12
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Latvia: 29
Country: Number of subjects enrolled	Russian Federation: 166
Country: Number of subjects enrolled	Ukraine: 241
Worldwide total number of subjects	577
EEA total number of subjects	170

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)	532
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total 577 patients were included in 7 countries (Germany, Russia, Slovakia, Latvia, Hungary, Poland and Ukraine) from June 2017 to March 2020.

Pre-assignment

Screening details:

Screening criteria: Signed informed consent • Man or woman between 18 and 75 years of age • Active ulcerative proctitis. In total, 695 patients were screened. Thereof 577 patients were randomised, received at least one dose of study medication and were included in the safety analysis set (SAF).

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	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Budesonide 4 mg Suppository

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

Dosage and administration details:

1 Budesonide 4 mg suppository OD, in the morning or evening (stratified)

Investigational medicinal product name	Budesonide Placebo Foam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Rectal foam
Routes of administration	Rectal use

Dosage and administration details:

1 actuation of Budesonide placebo foam OD, in the morning or evening (stratified)

Arm title	Arm B

Arm description:

Budesonide 2 mg Foam

Arm type	Active comparator
Investigational medicinal product name	Budesonide Placebo Suppository
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suppository
Routes of administration	Rectal use

Dosage and administration details:

1 Budesonide placebo suppository OD, in the morning or evening (stratified)

Investigational medicinal product name	Budesonide 2 mg Foam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Rectal foam
Routes of administration	Rectal use

Dosage and administration details:

1 actuation of Budesonide 2 mg foam OD, in the morning or evening (stratified)

Number of subjects in period 1	Arm A	Arm B
Started	286	291
Completed	267	276
Not completed	19	15
Adverse event, non-fatal	4	5
lack of patient´s cooperation	3	3
Delayed exclusion	5	-
Supsected Chickenpox/herpes zoster/measles infect	1	-
Lack of efficacy	5	5
other reason	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Budesonide 4 mg Suppository	

Reporting group title	Arm B
Reporting group description:	
Budesonide 2 mg Foam	

Reporting group values	Arm A	Arm B	Total
Number of subjects	286	291	577
Age categorical			
577 patients were randomized into the trial aged between the age groups ≥ 18 to ≤ 64 years and > 64 to ≤ 75 years			
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)	260	272	532
From 65-84 years	26	19	45
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	44.0	43.4	
standard deviation	± 14.0	± 13.4	-
Gender categorical			
Units: Subjects			
Female	135	156	291
Male	151	135	286

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
Budesonide 4 mg Suppository	

Reporting group title	Arm B
Reporting group description:	
Budesonide 2 mg Foam	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis was performed on 577 patients treated with at least one dose of IMP. None of the patients randomised was to be excluded from the safety analysis set.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS included all randomised patients who received at least one dose of IMP. Moreover, all patients identified as not fulfilling the entry criteria shortly after randomisation (delayed exclusions: 6 in this study) were excluded from the FAS. Accordingly, the ITT analysis was performed on 571 randomised patients included in the FAS.	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP analysis, representing the primary analysis set was performed on 511 patients.	

Primary: Co-primary efficacy endpoint: Clinical Remission

End point title	Co-primary efficacy endpoint: Clinical Remission
End point description:	
0 or 1 for UC-DAI stool frequency subscore and 0 for rectal bleeding subscore	
End point type	Primary
End point timeframe:	
Within 8 weeks starting with Baseline and with EoT Visit.	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	261		
Units: Patients	197	194		

Statistical analyses

Statistical analysis title	Per Protocol Analysis Set
Comparison groups	Arm A v Arm B

Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.00007
Method	Farrington-Manning

Primary: Co-primary efficacy endpoint: Mucosal healing

End point title	Co-primary efficacy endpoint: Mucosal healing
End point description: mucosal appearance of 0 or 1	
End point type	Primary
End point timeframe: Within 8 weeks starting with Baseline and with EoT Visit.	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	261		
Units: Patients	203	212		

Statistical analyses

Statistical analysis title	Per Protocol Analysis Set
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00224
Method	Farrington-Manning

Secondary: Time to resolution of the hallmark symptoms of UC

End point title	Time to resolution of the hallmark symptoms of UC
End point description: Time in days from Baseline visit to the date of the first day with a number of stools not higher than normal (stool frequency in remission) and with no rectal bleeding.	
End point type	Secondary
End point timeframe: Within 8 weeks starting with Baseline and with EoT Visit.	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	290		
Units: Days				
median (confidence interval 95%)	17.0 (15.0 to 22.0)	21.0 (16.0 to 27.0)		

Statistical analyses

Statistical analysis title	Full analysis set (FAS)
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	571
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4552
Method	Logrank

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events were assessed at V1 (Baseline), V2,V3, V4, V5 (EOT) and V6 (FU)	
Adverse event reporting additional description:	
Treatment emergent adverse events.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Budesonide 4mg suppository	
Reporting group title	Arm B
Reporting group description:	
Budesonide 2mg Foam	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 286 (0.70%)	3 / 291 (1.03%)	
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)			
B-cell lymphoma			
subjects affected / exposed	0 / 286 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 286 (0.35%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Endocervical curettage			
subjects affected / exposed	1 / 286 (0.35%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 286 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 286 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	1 / 286 (0.35%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 286 (0.35%)	0 / 291 (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: 1 %

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	141 / 286 (49.30%)	119 / 291 (40.89%)	
Injury, poisoning and procedural complications			
Cortisol decreased			
subjects affected / exposed	69 / 286 (24.13%)	39 / 291 (13.40%)	
occurrences (all)	71	40	
ALT increased			
subjects affected / exposed	5 / 286 (1.75%)	9 / 291 (3.09%)	
occurrences (all)	5	9	
Lipase increased			
subjects affected / exposed	5 / 286 (1.75%)	8 / 291 (2.75%)	
occurrences (all)	5	8	

AST increased			
subjects affected / exposed	3 / 286 (1.05%)	6 / 291 (2.06%)	
occurrences (all)	3	6	
Blood ALP increased			
subjects affected / exposed	2 / 286 (0.70%)	5 / 291 (1.72%)	
occurrences (all)	2	5	
GGT increased			
subjects affected / exposed	3 / 286 (1.05%)	3 / 291 (1.03%)	
occurrences (all)	3	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 286 (1.40%)	3 / 291 (1.03%)	
occurrences (all)	4	3	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 286 (6.64%)	17 / 291 (5.84%)	
occurrences (all)	29	27	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 286 (1.40%)	4 / 291 (1.37%)	
occurrences (all)	4	4	
Leukocytosis			
subjects affected / exposed	4 / 286 (1.40%)	1 / 291 (0.34%)	
occurrences (all)	4	1	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	12 / 286 (4.20%)	9 / 291 (3.09%)	
occurrences (all)	12	9	
Abdominal pain			
subjects affected / exposed	3 / 286 (1.05%)	4 / 291 (1.37%)	
occurrences (all)	5	5	
Dyspepsia			
subjects affected / exposed	5 / 286 (1.75%)	0 / 291 (0.00%)	
occurrences (all)	5	0	
Anorectal discomfort			
subjects affected / exposed	0 / 286 (0.00%)	3 / 291 (1.03%)	
occurrences (all)	0	3	

Nausea subjects affected / exposed occurrences (all)	0 / 286 (0.00%) 0	3 / 291 (1.03%) 3	
Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all)	3 / 286 (1.05%) 3	0 / 291 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 286 (2.10%) 7	10 / 291 (3.44%) 11	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	5 / 286 (1.75%) 5	3 / 291 (1.03%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2017	Amendment 01 has been made to take into account the objections of the Competent Authorities (CAs) and the competent Ethics Committees (ECs).
11 August 2017	Amendment 02 includes revisions to Section 6.1 Reference Safety Information (RSI) in the current version of the IMP's Investigator's Brochure (IB; Version 8.0 F, dated 12/07/2017).
23 January 2018	Amendment 03 became necessary in reason of a procedural change regarding the nomenclature of batch numbers used to identify different packaging campaigns of the investigational medicinal products.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported