Clinical trial results:
Randomised, double-blind, placebo-controlled, multi-centre trial on the efficacy and safety of budesonide for induction of remission in incomplete microscopic colitis

Summary

EudraCT number	2013-001912-31
Trial protocol	DE HU ES SE NL DK LT PT AT IT
Global end of trial date	13 January 2020

Results information

Result version number	v1 (current)
This version publication date	14 May 2021
First version publication date	14 May 2021

Trial information

Trial identification

Sponsor protocol code	BUG-3/MIC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02142634
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Falk Pharma GmbH
Sponsor organisation address	Leinenweberstr. 5, Freiburg, Germany, 79108 Freiburg
Public contact	Clinical Research and Development, Dr. Falk Pharma GmbH, 49 76115140, zentrale@drfalkpharma.de
Scientific contact	Clinical Research and Development, Dr. Falk Pharma GmbH, 49 76115140, 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	18 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 January 2020
Global end of trial reached?	Yes
Global end of trial date	13 January 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to demonstrate efficacy of budesonide for induction of remission in patients with active incomplete microscopic colitis

Protection of trial subjects:

Close supervision of patients by regular intermin visits, safety and wellbeing guaranteed.
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 enrollment 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:

Placebo granules

Actual start date of recruitment	11 August 2014
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	Netherlands: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 25
Country: Number of subjects enrolled	Lithuania: 2
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	31
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total 63 patients were screened of which 44 patients were randomized in Germany, Denmark, Hungary, Lithuania, The Netherlands, Spain, Sweden. Recruitment period: January 2014 - June 2019.

Pre-assignment

Screening details:

Screening Criteria: 1) Informed Consent signed, 2) Age between 18 - 80, 3) incomplete microscopic colitis.

In total, 63 patients were screened, thereof, 44 patients were randomized, received at least one dose of study medication and were inculded into the analyses as described below.

Period 1

Period 1 title	Treatment Phase (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 9 mg

Arm type	Experimental
Investigational medicinal product name	Budesonide Granules (Budenofalk 9 mg gastro-resistant granules)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

1 Budesonide sachet once daily in the morning.

Arm title	Arm B

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo Granules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

1 Placebo sachet once daily in the morning.

Number of subjects in period 1	Arm A	Arm B
Started	21	23
Completed	15	17
Not completed	6	6
Consent withdrawn by subject	2	2
Inclusion/exclusion criteria not met	1	-
Adverse event, non-fatal	1	1
Lack of efficacy	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Budesonide 9 mg	

Reporting group title	Arm B
Reporting group description:	
Placebo	

Reporting group values	Arm A	Arm B	Total
Number of subjects	21	23	44
Age categorical			
44 patients were randomized into the trial aged between the age groups ≥ 18 to ≤ 64 years and > 64 to ≤ 80 years			
Units: Subjects			
Adults (18-64 years)	11	20	31
From 65-84 years	10	3	13
Age continuous			
Units: years			
arithmetic mean	52.2	46.5	
standard deviation	± 18.97	± 15.51	-
Gender categorical			
Units: Subjects			
Female	16	14	30
Male	5	9	14

Subject analysis sets	
Subject analysis set title	Safety Analyse Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set (SAF) includes all randomised patients (as treated) who were treated at least one time with the IMP.	
Subject analysis set title	Intention-to-treat (ITT) Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The full analysis set (FAS) includes all randomised patients (as randomised) who received at least one dose of the IMP.	
Subject analysis set title	Per-protocol (PP) Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description:	
The per-protocol (PP) set includes all patients of the FAS, if e.g. all of the major inclusion criteria, none of the major exclusion criteria fulfilled.	

Reporting group values	Safety Analyse Set	Intention-to-treat (ITT) Analysis Set	Per-protocol (PP) Analysis Set
Number of subjects	44	44	28
Age categorical			
44 patients were randomized into the trial aged between the age groups ≥ 18 to ≤ 64 years and > 64 to ≤ 80 years			
Units: Subjects			
Adults (18-64 years)	31	31	
From 65-84 years	13	13	
Age continuous			
Units: years			
arithmetic mean	49.2	49.2	
standard deviation	± 17.28	± 17.28	±
Gender categorical			
Units: Subjects			
Female	30	30	
Male	14	14	

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: Budesonide 9 mg	

Reporting group title	Arm B
Reporting group description: Placebo	
Subject analysis set title	Safety Analyse Set
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set (SAF) includes all randomised patients (as treated) who were treated at least one time with the IMP.	
Subject analysis set title	Intention-to-treat (ITT) Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: The full analysis set (FAS) includes all randomised patients (as randomised) who received at least one dose of the IMP.	
Subject analysis set title	Per-protocol (PP) Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description: The per-protocol (PP) set includes all patients of the FAS, if e.g. all of the major inclusion criteria, none of the major exclusion criteria fulfilled.	

Primary: Clinical Remission

End point title	Clinical Remission
End point description: mean of < 3 stools/day and a mean of < 1 watery stool/day	
End point type	Primary
End point timeframe: After 8 weeks of treatment with study medication starting with Baseline.	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	23		
Units: numbers of patients				
number (confidence interval 95%)	71.4 (47.8 to 88.7)	43.5 (23.2 to 65.5)		

Statistical analyses

Statistical analysis title	Full analysis set (FAS)
Comparison groups	Arm A v Arm B

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0582
Method	Fisher exact

Secondary: Median time to Clinical Remission

End point title	Median time to Clinical Remission

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	23		
Units: days				
median (confidence interval 95%)	7 (7 to 21)	33 (7 to 1000)		

Statistical analyses

Statistical analysis title	Full analysis set (FAS)
Comparison groups	Arm B v Arm A
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0915
Method	Logrank

Secondary: Mean number of watery stools

End point title	Mean number of watery stools

End point description:

Mean change from Baseline/randomisation to Final Visit/LOCF

End point type	Secondary

End point timeframe:

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

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	23		
Units: Number of watery stools				
arithmetic mean (confidence interval 95%)	-12.5 (-17.83 to -7.22)	-5.4 (-10.69 to -0.03)		

Statistical analyses

Statistical analysis title	Full analysis set (FAS)
Statistical analysis description: Mean difference (Budesonide - Placebo)	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0542
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events were assessed at all interim visits and at the Final Visit, thus every 2 weeks.	
Adverse event reporting additional description:	
Treatment emergent adverse events	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
1 sachet Budesonide granules	
Reporting group title	Arm B
Reporting group description:	
1 Sachet Placebo granules	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 21 (42.86%)	8 / 23 (34.78%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Transaminases increased			

subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 21 (14.29%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Migraine			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 21 (4.76%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Abdominal distension			
subjects affected / exposed	2 / 21 (9.52%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	1 / 21 (4.76%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Vomiting			

subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 21 (4.76%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Infections and infestations			
Gingivitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Pulpitis dental			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Skin infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 May 2016	a) clarification of exclusion criterion regarding bowel resections, b) clarification of exclusion criterion regarding celiac disease, c) consideration of bismuth and probiotics for exclusion criteria and forbidden concomitant medication, d)inclusion of an optional pregnancy test at baseline and e) administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Small numbers of subjects analysed. Low recruitment rate.

Notes: