Clinical trial results:
Double-blind, randomised, placebo-controlled multicentre phase III clinical study followed by open-label phase on the efficacy and tolerability of budesonide 3 mg effervescent tablet in patients with resistant oral chronic GvHD

Summary

EudraCT number	2008-004562-10
Trial protocol	DE AT FR SE IT CZ
Global end of trial date	20 July 2015

Results information

Result version number	v1 (current)
This version publication date	26 August 2018
First version publication date	26 August 2018

Trial information

Trial identification

Sponsor protocol code	BUM-5/GVH

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00887263
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Falk Pharma GmbH
Sponsor organisation address	Leinenweberstr. 5, Freiburg, Germany, 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	11 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 July 2015
Global end of trial reached?	Yes
Global end of trial date	20 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To compare the efficacy and tolerability of budesonide 3 mg effervescent tablet (9 mg/day) vs. placebo for the treatment of patients with resistant oral chronic graft versus host disease (cGvHD)
• To study safety and tolerability in the form of adverse events and laboratory parameters

Protection of trial subjects:

Close supervision of subjects by implementing interim visits every 14 days (during 12 weeks double-blind phase) and then every 2 to 12 weeks (during 40 weeks open-label phase) 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: -

Evidence for comparator: -

Actual start date of recruitment	30 March 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Ethical reason, Regulatory reason
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 8
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Switzerland: 13
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Austria: 10

Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 88
Country: Number of subjects enrolled	Italy: 32
Worldwide total number of subjects	183
EEA total number of subjects	140

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)	172
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total 189 patients were enrolled. Thereof 186 patients were randomised to treatment with budesonide or placebo. A total of 184 patients received at least one dose of study medication. 183 patients are included in full analysis set (one patient without erythema and ulcers had to be excluded).

Pre-assignment

Screening details:

Screening criteria:
1. Signed informed consent
2. Aged 18 to 75 years
3. Oral cGvHD of erosive and/or ulcerative type

Period 1

Period 1 title	Double-blind 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

Blinding implementation details:

Budesonide and placebo effervescent tablets had same appearance/taste to guarantee double-blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Budesonide 3 mg effervescent tablet 3 times daily

Arm type	Experimental
Investigational medicinal product name	Budesonide 3 mg effervescent tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Effervescent tablet
Routes of administration	Oromucosal use

Dosage and administration details:

1 budesonide 3 mg effervescent tablet 3 times daily; rinse for at least a duration of 10 minutes

Arm title	Arm B

Arm description:

Placebo effervescent tablet 3 times daily

Arm type	Placebo
Investigational medicinal product name	Placebo 3 mg effervescent tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Effervescent tablet
Routes of administration	Oromucosal use

Dosage and administration details:

1 placebo effervescent tablet 3 times daily; rinse for at least a duration of 10 minutes

Number of subjects in period 1	Arm A	Arm B
Started	89	94
Completed	54	50
Not completed	35	44
Consent withdrawn by subject	5	6
Adverse event, non-fatal	9	7
other	2	2
Lack of efficacy	19	29

Baseline characteristics

Reporting groups	
Reporting group title	Double-blind phase

Reporting group description: -

Reporting group values	Double-blind phase	Total	
Number of subjects	183	183	
Age categorical			
183 patients were randomised and treated aged 18 to 72 years.			
Units: Subjects			
Adults (18-64 years)	172	172	
From 65-84 years	11	11	
Age continuous			
Units: years			
arithmetic mean	46.3		
standard deviation	± 13.5	-	
Gender categorical			
Units: Subjects			
Female	75	75	
Male	108	108	

End points

End points reporting groups	
Reporting group title	Arm A
Reporting group description:	
Budesonide 3 mg effervescent tablet 3 times daily	
Reporting group title	Arm B
Reporting group description:	
Placebo effervescent tablet 3 times daily	

Primary: Objective Response	
End point title	Objective Response
End point description:	
The primary efficacy variable was the proportion of patients showing objective response at the final/withdrawal visit.	
End point type	Primary
End point timeframe:	
12 weeks double-blind Treatment	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	94		
Units: Patients	38	30		

Statistical analyses

Statistical analysis title	Confirmative analysis
Statistical analysis description:	
Confirmative comparison between Arm A (budesonide) and Arm B (placebo)	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0.108
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.247

Secondary: Median time to 1st occurrence of objective response

End point title	Median time to 1st occurrence of objective response

End point description:

Reporung Group 2 (Arm B): upper Limit of CI has to be empty, but system does not allow empty field nor NA. Thus, we entered fictive value of 100.00.

End point type	Secondary

End point timeframe:

NA

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	94		
Units: day				
median (confidence interval 95%)				
days	58 (43.0 to 83.0)	86 (67.0 to 100.00)		

Statistical analyses

Statistical analysis title	Kaplan-Meier analysis
Comparison groups	Arm B v Arm A
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.539
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.007
upper limit	2.353

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were assessed from baseline to final visit.	
Adverse event reporting additional description:	
Treatment-emergent adverse events.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Budesonide 3 mg effervescent tablet 3 times daily	
Reporting group title	Arm B
Reporting group description:	
Placebo effervescent tablet 3 times daily	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 90 (16.67%)	12 / 94 (12.77%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia recurrent			
subjects affected / exposed	1 / 90 (1.11%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Rehabilitation therapy			

subjects affected / exposed	1 / 90 (1.11%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circumcision			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental operation			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PUVA			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	2 / 90 (2.22%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopericarditis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 90 (1.11%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Keratitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryostenosis acquired			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
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			
Obliterative bronchiolitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (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			
Sepsis			
subjects affected / exposed	2 / 90 (2.22%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenoviral haemorrhagic cystitis			

subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotavirus infection			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryocystitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 90 (91.11%)	84 / 94 (89.36%)	
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	7 / 90 (7.78%)	15 / 94 (15.96%)	
occurrences (all)	7	15	
Chronic graft versus host disease			
subjects affected / exposed	11 / 90 (12.22%)	3 / 94 (3.19%)	
occurrences (all)	11	3	
Acute graft versus host disease in skin			
subjects affected / exposed	3 / 90 (3.33%)	5 / 94 (5.32%)	
occurrences (all)	3	5	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 90 (7.78%)	4 / 94 (4.26%)	
occurrences (all)	7	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 90 (7.78%)	11 / 94 (11.70%)	
occurrences (all)	7	11	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	7 / 90 (7.78%)	1 / 94 (1.06%)	
occurrences (all)	7	1	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	11 / 90 (12.22%)	6 / 94 (6.38%)	
occurrences (all)	11	6	
Nasopharyngitis			
subjects affected / exposed	6 / 90 (6.67%)	7 / 94 (7.45%)	
occurrences (all)	6	7	
Oral herpes			

subjects affected / exposed	4 / 90 (4.44%)	9 / 94 (9.57%)	
occurrences (all)	4	9	
Bronchitis			
subjects affected / exposed	6 / 90 (6.67%)	4 / 94 (4.26%)	
occurrences (all)	6	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2009	Exclusion criterion "hepatic function" adapted. Follow-up visit added.
21 May 2010	Exclusion criterion concurrent treatment for muscosal lesions adapted (allowance of prophylactic treatment to prevent infection). Extracorporeal photochemotherapy allowed if unsuccessful 6 months before inclusion. Treatment with posaconazole allowed.
12 April 2012	Inclusion of patients with oral cGvHD only and no need for systemic immunosuppression allowed. Additional country: USA
15 April 2014	List of expected adverse drug reactions updated. Contact details of medical expert updated.

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.

Double-blind phase (period 1) reported only. System does not allow to report open-label phase (period 2) since number of patients of period 2 is higher than number of completers of period 1.
All data will be published.

Notes: