Clinical trial results:
Double-blind, randomized, placebo-controlled, phase III study on the efficacy and tolerability of a 48-week treatment with two different doses of budesonide effervescent tablets vs. placebo for maintenance of clinico-pathological remission in adult patients with eosinophilic esophagitis

Summary

EudraCT number	2014-001485-99
Trial protocol	DE BE GB ES NL DK IT
Global end of trial date	11 December 2020

Results information

Result version number	v1 (current)
This version publication date	04 February 2022
First version publication date	04 February 2022
Summary attachment (see zip file)	BUL-2/EER Full paper (BUL2_2020_Straumann-Lucendo_Gastroenterology_full paper.pdf)

Trial information

Trial identification

Sponsor protocol code	BUL-2/EER

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02493335
WHO universal trial number (UTN)	-
Other trial identifiers	EOS-2: Acronym

Notes:

Sponsors

Sponsor organisation name	Dr Falk Pharma GmbH
Sponsor organisation address	Leinenweberstrasse 5, Freiburg, Germany, 79108
Public contact	Dept. of Clinic. Res. & Development, Dr Falk Pharma GmbH, +49 76115140, zentrale@drfalkpharma.de
Scientific contact	Dept. of Clinic. Res. & 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	05 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 November 2018
Global end of trial reached?	Yes
Global end of trial date	11 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Double-blind phase:
- To assess the efficacy of a 48-week treatment with 2 x 0.5 mg/d or 2 x 1 mg/d budesonide effervescent tablets vs. placebo for the maintenance of clinico-pathological remission in adult patients with eosinophilic esophagitis (EoE).

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 endoscopy and biopsy sampling to be performed for confirmation of diagnosis of eosinophilic esophagitis by the central pathologist, the patients received the standard preparation for sedation during the endoscopy as routinely performed at the study sites.

Background therapy:

No concomitant background therapy, except stable diets and/or stable treatment with protonpumpinhibitors was allowed during the trial.

Evidence for comparator:

Using a placebo arm in this clinical trial was ethically justified 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 treatment of EoE available. Moreover, the use of a placebo group was also justified, as it allowed to control for all other potential influences on the actual or apparent course of the disease other than those arising from the pharmacological action of budesonide (including but not limited to influences such as, spontaneous change in the disease, subject and investigator expectations, the effect of participating in this trial, or subjective elements of diagnosis or assessments), as stated in the “ICH Topic E10: Note for guidance on choice of control group in clinical trials” (CPMP/ICH/364/96).

Actual start date of recruitment	29 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Spain: 74
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Germany: 85
Country: Number of subjects enrolled	Switzerland: 33
Worldwide total number of subjects	204
EEA total number of subjects	171

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)	203
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 29 centers randomized patients: 1 center in Belgium (BE), 13 centers in Germany (DE), 8 centers in Spain (ES), 4 centers in Switzerland (CH), 2 centers in The Netherlands (NL), and 1 center in the United Kingdom (UK).

Pre-assignment

Screening details:

297 patients were screened to fullfill the In-/Exclusion criteria. Of them, 204 patients were randomized and treated with budesonide or placebo.

Period 1

Period 1 title	Double-blind 48-week treatment phase (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:

The appearance and taste of the placebo effervescent tablet for orodispersible use was indistinguishable from the verum effervescent tablet for orodispersible use.

Arms

Are arms mutually exclusive?	Yes
Arm title	BUL 0.5mg BID

Arm description:

Twice daily 0.5mg budesonide effervescent tablet for orodispersible use

Arm type	Experimental
Investigational medicinal product name	0.5mg budesonide effervescent tablet for orodispersible use
Investigational medicinal product code	BUL 0.5mg
Other name	
Pharmaceutical forms	Effervescent tablet
Routes of administration	Oral use

Dosage and administration details:

Take one effervescent tablet each in the morning and in the evening after the meal. The effervescent tablet has to be placed on the tongue which allows disintegration within several minutes. The dissolved parts of the effervescent tablet will be swallowed with saliva little by little. Do not drink or eat during 30 minutes after study drug administration.

Arm title	BUL 1mg BID

Arm description:

Twice daily 1mg budesonide effervescent tablet for orodispersible use

Arm type	Experimental
Investigational medicinal product name	1mg budesonide effervescent tablet for orodispersible use
Investigational medicinal product code	BUL 1mg
Other name	
Pharmaceutical forms	Effervescent tablet
Routes of administration	Oral use

Dosage and administration details:

Take one effervescent tablet each in the morning and in the evening after the meal. The effervescent tablet has to be placed on the tongue which allows disintegration within several minutes. The dissolved parts of the effervescent tablet will be swallowed with saliva little by little. Do not drink or eat during 30 minutes after study drug administration.

Arm title	Placebo BID

Arm description:

Twice daily Placebo effervescent tablet for orodispersible use

Arm type	Placebo
Investigational medicinal product name	Placebo budesonide effervescent tablet for orodispersible use
Investigational medicinal product code	BUL Placebo
Other name	
Pharmaceutical forms	Effervescent tablet
Routes of administration	Oral use

Dosage and administration details:

Take one effervescent tablet each in the morning and in the evening after the meal. The effervescent tablet has to be placed on the tongue which allows disintegration within several minutes. The dissolved parts of the effervescent tablet will be swallowed with saliva little by little. Do not drink or eat during 30 minutes after study drug administration.

Number of subjects in period 1	BUL 0.5mg BID	BUL 1mg BID	Placebo BID
Started	68	68	68
Completed	59	59	23
Not completed	9	9	45
Consent withdrawn by subject	2	2	3
Adverse event, non-fatal	-	2	-
Lack of efficacy	7	5	42

Baseline characteristics

Reporting groups	
Reporting group title	BUL 0.5mg BID
Reporting group description:	
Twice daily 0.5mg budesonide effervescent tablet for orodispersible use	
Reporting group title	BUL 1mg BID
Reporting group description:	
Twice daily 1mg budesonide effervescent tablet for orodispersible use	
Reporting group title	Placebo BID
Reporting group description:	
Twice daily Placebo effervescent tablet for orodispersible use	

Reporting group values	BUL 0.5mg BID	BUL 1mg BID	Placebo BID
Number of subjects	68	68	68
Age categorical Units: Subjects			
Adults (18-64 years)	67	68	68
From 65-84 years	1	0	0
Age continuous Units: years			
arithmetic mean	36	37	36
standard deviation	± 10.9	± 11.1	± 9.9
Gender categorical Units: Subjects			
Female	11	11	13
Male	57	57	55
Ethnic Group Units: Subjects			
White	68	68	68
Previous PPI trial conducted Units: Subjects			
Yes	68	68	68
History of allergic disease Units: Subjects			
yes	54	55	50
no	14	13	18
Duration since first symptoms Units: years			
arithmetic mean	12.6	11.8	9.6
standard deviation	± 8.5	± 9.4	± 8.2
Duration since diagnosis Units: years			
arithmetic mean	4.3	4.2	3.3
standard deviation	± 3.5	± 4.0	± 2.1
Overall peak eos/mm2 hpf			
Overall peak eosinophil count (eos)/mm2 high power field (hpf) derived from 6 biopsies (2 each from the proximal, mid, and distal esophageal segment).			
Units: eos/mm2 hpf			

arithmetic mean	0	0	1
standard deviation	± 1.4	± 1.7	± 3.6
Total Modified Endoscopic Reference Score (EREFS; range: 0-9)			
Worst case assessment from all parts of the esophagus. Lower values reflect lower total endoscopic disease activity.			
Units: points			
arithmetic mean	1	1	1
standard deviation	± 1.1	± 1.1	± 1.0
'Inflammatory signs' subscore - Modified Endoscopic Reference Score (EREFS; range: 0-4)			
Worst case assessment from all parts of the esophagus. Lower values reflect lower endoscopic inflammatory disease activity.			
Units: points			
arithmetic mean	0	0	0
standard deviation	± 0.6	± 0.6	± 0.6
'Fibrotic signs' subscore - Modified Endoscopic Reference Score (EREFS, range: 0-4)			
Worst case assessment from all parts of the esophagus. Lower values reflect lower endoscopic fibrotic disease activity.			
Units: points			
arithmetic mean	1	0	0
standard deviation	± 0.7	± 0.6	± 0.6
Dysphagia Numerical Rating Scale [NRS] (0-10)			
0 = no troubles to swallow 10 = most severe troubles to swallow			
Units: points			
arithmetic mean	1	1	1
standard deviation	± 0.9	± 0.9	± 0.8
Pain during swallowing NRS (0-10)			
0 = no pain during swallowing 10 = most severe pain during swallowing			
Units: points			
arithmetic mean	1	1	0
standard deviation	± 0.9	± 1.0	± 0.8
Patient’s Global Assessment of EoE activity (NRS 0-10)			
0 = no symptoms 10 = most severe symptoms			
Units: points			
arithmetic mean	1	1	1
standard deviation	± 0.8	± 0.8	± 0.9
Physician’s Global Assessment of EoE activity (NRS 0-10)			
considered all findings concerning the severity of the patient’s EoE (clinical, endoscopic, histologic) 0 = inactive EoE 10 = most active EoE			
Units: points			
arithmetic mean	1	1	1
standard deviation	± 0.8	± 1.0	± 0.9
Total weekly EEsAI-PRO (0-100)			
Eosinophilic Esophagitis Activity Index Patient Reported Outcome (EEsAI-PRO) score: The relevant items for the EEsAI-PRO Score were: - Frequency of trouble swallowing (with 4 increments ranging from never to daily) - Duration of dysphagia episodes (≤ 5 / > 5 minutes)			

- Presence / absence of pain during swallowing - Visual Dysphagia Questions (VDQ) on 8 foods of 8 different consistencies (hypothetical test meal; grades 0 to 3) resulting in a VDQ score - Behavioural change strategies on specific foods with 8 different consistencies: Range: 0 (no EoE activity) to 100 (most severe EoE)			
Units: points			
arithmetic mean	16	16	18
standard deviation	± 14.1	± 15.8	± 16.6

Reporting group values	Total		
Number of subjects	204		
Age categorical Units: Subjects			
Adults (18-64 years)	203		
From 65-84 years	1		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	35		
Male	169		
Ethnic Group Units: Subjects			
White	204		
Previous PPI trial conducted Units: Subjects			
Yes	204		
History of allergic disease Units: Subjects			
yes	159		
no	45		
Duration since first symptoms Units: years arithmetic mean standard deviation	- -		
Duration since diagnosis Units: years arithmetic mean standard deviation	- -		
Overall peak eos/mm2 hpf			
Overall peak eosinophil count (eos)/mm2 high power field (hpf) derived from 6 biopsies (2 each from the proximal, mid, and distal esophageal segment).			
Units: eos/mm2 hpf arithmetic mean standard deviation	- -		
Total Modified Endoscopic Reference Score (EREFS; range: 0-9)			
Worst case assessment from all parts of the esophagus. Lower values reflect lower total endoscopic disease activity.			
Units: points arithmetic mean			

standard deviation	-		
'Inflammatory signs' subscore - Modified Endoscopic Reference Score (EREFS; range: 0-4)			
Worst case assessment from all parts of the esophagus. Lower values reflect lower endoscopic inflammatory disease activity.			
Units: points arithmetic mean standard deviation	- -		
'Fibrotic signs' subscore - Modified Endoscopic Reference Score (EREFS, range: 0-4)			
Worst case assessment from all parts of the esophagus. Lower values reflect lower endoscopic fibrotic disease activity.			
Units: points arithmetic mean standard deviation	- -		
Dysphagia Numerical Rating Scale [NRS] (0-10)			
0 = no troubles to swallow 10 = most severe troubles to swallow			
Units: points arithmetic mean standard deviation	- -		
Pain during swallowing NRS (0-10)			
0 = no pain during swallowing 10 = most severe pain during swallowing			
Units: points arithmetic mean standard deviation	- -		
Patient’s Global Assessment of EoE activity (NRS 0-10)			
0 = no symptoms 10 = most severe symptoms			
Units: points arithmetic mean standard deviation	- -		
Physician’s Global Assessment of EoE activity (NRS 0-10)			
considered all findings concerning the severity of the patient’s EoE (clinical, endoscopic, histologic) 0 = inactive EoE 10 = most active EoE			
Units: points arithmetic mean standard deviation	- -		
Total weekly EEsAI-PRO (0-100)			
Eosinophilic Esophagitis Activity Index Patient Reported Outcome (EEsAI-PRO) score: The relevant items for the EEsAI-PRO Score were: - Frequency of trouble swallowing (with 4 increments ranging from never to daily) - Duration of dysphagia episodes (≤ 5 / > 5 minutes) - Presence / absence of pain during swallowing - Visual Dysphagia Questions (VDQ) on 8 foods of 8 different consistencies (hypothetical test meal; grades 0 to 3) resulting in a VDQ score - Behavioural change strategies on specific foods with 8 different consistencies: Range: 0 (no EoE activity) to 100 (most severe EoE)			
Units: points arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	BUL 0.5mg BID
Reporting group description:	
Twice daily 0.5mg budesonide effervescent tablet for orodispersible use	
Reporting group title	BUL 1mg BID
Reporting group description:	
Twice daily 1mg budesonide effervescent tablet for orodispersible use	
Reporting group title	Placebo BID
Reporting group description:	
Twice daily Placebo effervescent tablet for orodispersible use	

Primary: Primary endpoint: Proportion of patients free of treatment failure (i.e. being in remission) after 48 weeks of double-blind treatment

End point title	Primary endpoint: Proportion of patients free of treatment failure (i.e. being in remission) after 48 weeks of double-blind treatment
End point description:	
Proportion of patients free of treatment failure (i.e., being still in remission) after 48 weeks of treatment. Treatment failure after 48 weeks of treatment was "yes", if at least one of the following criteria was met at any time during the DB treatment phase: - Clinical relapse, i.e., experiencing dysphagia or pain during swallowing in the past seven days (7 day recall period) of a severity of ≥4 points on a 0–10 NRS for dysphagia or pain during swallowing, respectively, confirmed by a severity of ≥4 points on at least 1 day during the subsequent week on the respective 0 10 NRS for dysphagia or pain during swallowing (24-hour recall period). - Histological relapse, i.e., a peak of ≥48 eos/mm2 hpf at end-of-treatment, - Experiencing a food impaction which needed endoscopic intervention, - Need for an endoscopic dilation, - Premature withdrawal for any reason.	
End point type	Primary
End point timeframe:	
48 weeks	

End point values	BUL 0.5mg BID	BUL 1mg BID	Placebo BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	68	68	
Units: Patients	50	51	3	

Attachments (see zip file)	Primary endpoint/BUL2_DB_1st EP_FAS_free of Tx

Statistical analyses

Statistical analysis title	Primary endpoint: BUL 0.5mg BID vs placebo

Statistical analysis description:

For the comparison between the BUL 0.5mg BID group and the Placebo group the difference between rates of patients free of treatment failure was 69.1% with the corresponding 97.5% CI [55.89%; 82.34%]. The one-sided p-value resulting from the normal approximation test was <0.0001. Therefore, the null hypothesis for this comparison could be rejected and statistically significant superiority of BUL 0.5mg BID versus Placebo was successfully shown in a confirmatory manner in the FAS population.

Comparison groups	BUL 0.5mg BID v Placebo BID
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	69.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	55.89
upper limit	82.34

Notes:

[1] - The 2 hypotheses of superiority of BUL 0.5mg BID vs placebo and BUL 1mg BID vs placebo were tested each at a one-sided Bonferroni adjusted type I error level of 0.0125 using normal approximation tests for the comparison of rates. For estimating the treatment effect compared to Placebo, two-sided 97.5% (Bonferroni correction) confidence intervals (CI) for the difference of rates were provided.

Statistical analysis title	Primary endpoint: BUL 1mg BID vs placebo

Statistical analysis description:

For the comparison between the BUL 1mg BID group and the Placebo group the difference between rates of patients free of treatment failure was 70.6% in the full analysis set (FAS) with corresponding 97.5% CI [57.56%; 83.61%]. The one-sided p-value resulting from the normal approximation test was <0.0001. Therefore, the null hypothesis for this comparison could be rejected and statistically significant superiority of BUL 1mg BID versus Placebo was successfully shown in a confirmatory manner.

Comparison groups	Placebo BID v BUL 1mg BID
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	70.6
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	57.56
upper limit	83.61

Notes:

[2] - The 2 hypotheses of superiority of BUL 0.5mg BID vs placebo and BUL 1mg BID vs placebo were tested each at a one-sided Bonferroni adjusted type I error level of 0.0125 using normal approximation tests for the comparison of rates. For estimating the treatment effect compared to Placebo, two-sided 97.5% (Bonferroni correction) confidence intervals (CI) for the difference of rates were provided.

Secondary: Major secondary endpoint: Proportion of patients with a histological relapse, defined as a peak of ≥48 eos/mm² hpf at end of treatment

End point title	Major secondary endpoint: Proportion of patients with a histological relapse, defined as a peak of ≥48 eos/mm² hpf at

	end of treatment

End point description:

End point type	Secondary

End point timeframe:
48 weeks

End point values	BUL 0.5mg BID	BUL 1mg BID	Placebo BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	68	68	
Units: Patients	9	7	61	

Attachments (see zip file)	Major secondary endpoint: Histological relapse/BUL2_DB_2nd-

Statistical analyses

Statistical analysis title	BUL 0.5mg BID vs placebo
Comparison groups	BUL 0.5mg BID v Placebo BID
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	-76.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-88.8
upper limit	-64.1

Statistical analysis title	BUL 1mg BID vs placebo
Comparison groups	Placebo BID v BUL 1mg BID
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	-79.4

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-91.1
upper limit	-67.7

Secondary: Major secondary endpoint: Proportion of patients with a clinical relapse, or food impaction which needed endoscopic intervention, or endoscopic dilation during the 48 weeks

End point title	Major secondary endpoint: Proportion of patients with a clinical relapse, or food impaction which needed endoscopic intervention, or endoscopic dilation during the 48 weeks
End point description:	
End point type	Secondary
End point timeframe:	
48 weeks	

End point values	BUL 0.5mg BID	BUL 1mg BID	Placebo BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	68	68	
Units: patients	7	5	41	

Attachments (see zip file)	Major secondary endpoint: Clinical relapse/BUL2_DB_2nd-3-

Statistical analyses

Statistical analysis title	BUL 0.5mg BID vs placebo
Comparison groups	BUL 0.5mg BID v Placebo BID
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	-50
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-65.7
upper limit	-34.3

Statistical analysis title	BUL 1mg BID vs placebo
Comparison groups	BUL 1mg BID v Placebo BID
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	-52.9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-68
upper limit	-37.9

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 48 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	BUL 0.5mg BID
Reporting group description: Twice daily 0.5mg budesonide effervescent tablet for orodispersible use	
Reporting group title	BUL 1mg BID
Reporting group description: Twice daily 1mg budesonide effervescent tablet for orodispersible use	
Reporting group title	Placebo BID
Reporting group description: Twice daily Placebo effervescent tablet for orodispersible use	

Serious adverse events	BUL 0.5mg BID	BUL 1mg BID	Placebo BID
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 68 (4.41%)	1 / 68 (1.47%)	0 / 68 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Cartilage injury	Additional description: cartilage damage in ankle joint worsened		
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture	Additional description: elbow fracture (due to fall)		
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture	Additional description: This event was due to a car accident.		
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Inguinal hernia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sinusitis	Additional description: elective OP of a chronic pansinusitis		
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	BUL 0.5mg BID	BUL 1mg BID	Placebo BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 68 (83.82%)	59 / 68 (86.76%)	61 / 68 (89.71%)
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 68 (20.59%)	10 / 68 (14.71%)	5 / 68 (7.35%)
occurrences (all)	14	10	5
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	4 / 68 (5.88%)	2 / 68 (2.94%)	1 / 68 (1.47%)
occurrences (all)	4	2	1
Condition aggravated	Additional description: Deterioration of underlying disease (i.e, eosinophilic esophagitis)		
subjects affected / exposed	11 / 68 (16.18%)	8 / 68 (11.76%)	44 / 68 (64.71%)
occurrences (all)	11	8	44
Eye disorders			
Blepharitis			
subjects affected / exposed	3 / 68 (4.41%)	2 / 68 (2.94%)	1 / 68 (1.47%)
occurrences (all)	3	2	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 68 (7.35%)	2 / 68 (2.94%)	0 / 68 (0.00%)
occurrences (all)	5	2	0
Dyspepsia			

subjects affected / exposed	3 / 68 (4.41%)	7 / 68 (10.29%)	3 / 68 (4.41%)
occurrences (all)	3	7	3
Oesophageal food impaction	Additional description: Self clearing - without the need for endoscopic intervention		
subjects affected / exposed	0 / 68 (0.00%)	3 / 68 (4.41%)	2 / 68 (2.94%)
occurrences (all)	0	3	2
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 68 (5.88%)	4 / 68 (5.88%)	0 / 68 (0.00%)
occurrences (all)	4	4	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 68 (4.41%)	1 / 68 (1.47%)	0 / 68 (0.00%)
occurrences (all)	3	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 68 (4.41%)	1 / 68 (1.47%)	1 / 68 (1.47%)
occurrences (all)	3	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 68 (1.47%)	4 / 68 (5.88%)	0 / 68 (0.00%)
occurrences (all)	1	4	0
Gastroenteritis			
subjects affected / exposed	3 / 68 (4.41%)	5 / 68 (7.35%)	1 / 68 (1.47%)
occurrences (all)	3	5	1
Influenza			
subjects affected / exposed	3 / 68 (4.41%)	3 / 68 (4.41%)	2 / 68 (2.94%)
occurrences (all)	3	3	2
Nasopharyngitis			
subjects affected / exposed	25 / 68 (36.76%)	20 / 68 (29.41%)	19 / 68 (27.94%)
occurrences (all)	25	20	19
Local fungal infection	Additional description: In 21/136 patients (15%) under budesonide, a local fungal infection (oral , oropharyngeal, and/or esophageal candidiasis) was suspected. Thereof, only 19 patients (14%) showed clinically mild symptoms with no impact on their daily life.		
subjects affected / exposed	12 / 68 (17.65%)	9 / 68 (13.24%)	0 / 68 (0.00%)
occurrences (all)	12	9	0
Pharyngitis			

subjects affected / exposed	3 / 68 (4.41%)	2 / 68 (2.94%)	1 / 68 (1.47%)
occurrences (all)	3	2	1
Urinary tract infection			
subjects affected / exposed	3 / 68 (4.41%)	4 / 68 (5.88%)	0 / 68 (0.00%)
occurrences (all)	3	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/32721437