



Clinical trial results:

Double-blind, randomized phase III trial in adult and adolescent patients with eosinophilic esophagitis to prove superiority compared to placebo of an episodic and/or a continuous 48-week treatment with budesonide orodispersible tablets for maintaining clinico-histological remission

Summary

EudraCT number	2017-003516-39
Trial protocol	DE ES IT
Global end of trial date	29 November 2024

Results information

Result version number	v1 (current)
This version publication date	15 August 2026
First version publication date	15 August 2026

Trial information

Trial identification

Sponsor protocol code	BUL-3/EER
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	EOS-3: Acronym

Notes:

Sponsors

Sponsor organisation name	Dr Falk Pharma GmbH
Sponsor organisation address	Leinenweberstrasse 5, Freiburg im Breisgau, 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	29 November 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 November 2024
Global end of trial reached?	Yes
Global end of trial date	29 November 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To prove superiority compared to placebo of episodic treatment with 4 cycles of budesonide 0.5 mg orodispersible tablets twice daily (BID) for 4 weeks followed by 8 weeks placebo BID over a total of 48 weeks and/or of continuous 48-week treatment with budesonide 0.5 mg orodispersible tablets BID in adult and adolescent eosinophilic esophagitis (EoE) patients in maintaining clinico-histological remission.

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	22 July 2021
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	Spain: 57
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Switzerland: 4
Worldwide total number of subjects	112
EEA total number of subjects	108

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)	2
Adults (18-64 years)	108
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total 112 patients were recruited from August 2021 to October 2023. 21 centers randomized patients: 2 centers in Switzerland (CH), 9 centers in Germany (DE), 6 centers in Spain (ES), and 4 centers in Italy (IT).

Pre-assignment

Screening details:

158 patients were screened to fulfill the In-/Exclusion criteria for this study. Of them, 112 patients were randomized and treated with budesonide or placebo.

Period 1

Period 1 title	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

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	episodic BUL 0.5mg BID

Arm description:

4 cycles of 3 months each with one budesonide 0.5 mg orodispersible tablet each in the morning and in the evening for 4 weeks followed by 8 weeks of Placebo

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

Dosage and administration details:

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

Arm title	continuous BUL 0.5mg BID
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Arm description:

one budesonide 0.5 mg orodispersible tablet each in the morning and in the evening continuously

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

Dosage and administration details:

Take one orodispersible tablet each in the morning and in the evening after the meal. The orodispersible tablet has to be placed on the tongue which allows disintegration within several minutes. The dissolved parts of the orodispersible 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 tablet for orodispersible use	
Arm type	Placebo
Investigational medicinal product name	Placebo budesonide tablet for orodispersible use
Investigational medicinal product code	BUL Placebo
Other name	
Pharmaceutical forms	Orodispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Take one orodispersible tablet each in the morning and in the evening after the meal. The orodispersible tablet has to be placed on the tongue which allows disintegration within several minutes. The dissolved parts of the orodispersible 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	episodic BUL 0.5mg BID	continuous BUL 0.5mg BID	Placebo BID
Started	45	45	22
Completed	28	41	11
Not completed	17	4	11
Consent withdrawn by subject	1	1	-
Adverse event, non-fatal	1	1	-
Protocol-specified withdrawal criteria met	-	1	-
Intended pregnancy of patient's wife	-	-	1
Lack of efficacy	15	1	10

Baseline characteristics

Reporting groups

Reporting group title	episodic BUL 0.5mg BID
Reporting group description: 4 cycles of 3 months each with one budesonide 0.5 mg orodispersible tablet each in the morning and in the evening for 4 weeks followed by 8 weeks of Placebo	
Reporting group title	continuous BUL 0.5mg BID
Reporting group description: one budesonide 0.5 mg orodispersible tablet each in the morning and in the evening continuously	
Reporting group title	Placebo BID
Reporting group description: Twice daily Placebo tablet for orodispersible use	

Reporting group values	episodic BUL 0.5mg BID	continuous BUL 0.5mg BID	Placebo BID
Number of subjects	45	45	22
Age categorical Units: Subjects			
Adolescent (16 - <18)	0	1	1
Adults (18-75)	45	44	21
Age continuous Units: years			
arithmetic mean	38.6	41.1	36.6
standard deviation	± 2.0	± 1.9	± 2.4
Gender categorical Units: Subjects			
Female	10	16	5
Male	35	29	17
Smoking status at screening Units: Subjects			
Current smoker	1	3	1
Former smoker	6	6	5
Never smoker	38	35	16
Missing status	0	1	0
Ethnic Group Units: Subjects			
White	45	45	21
Black or African American	0	0	1
Patient global impression of severity (PGI-S) Units: Subjects			
None	35	36	18
Mild	8	8	4
Moderate	2	0	0
Severe	0	1	0
History of allergic disease Units: Subjects			
yes	34	23	21
no	11	22	1

Concomitant use of PPIs Units: Subjects			
yes	3	8	2
no	42	37	20
Body weight Units: kg			
arithmetic mean	73.09	75.24	73.62
standard deviation	± 2.12	± 2.05	± 3.12
BMI Units: kg/m2			
arithmetic mean	23.44	25.21	24.01
standard deviation	± 0.59	± 0.65	± 0.68
EEsAI PRO at baseline Units: points			
arithmetic mean	7.5	7.4	6.0
standard deviation	± 1.47	± 1.83	± 2.5
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	0.6	0.6	0.6
standard deviation	± 0.2	± 0.1	± 0.2
'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	0.4	0.3	0.2
standard deviation	± 0.1	± 0.1	± 0.1
'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	0.2	0.3	0.4
standard deviation	± 0.1	± 0.1	± 0.1
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	0
standard deviation	± 0.0	± 0.0	± 0.0
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	7.5	7.4	6.0
standard deviation	± 1.47	± 1.83	± 2.5
Adult Eosinophilic Esophagitis Quality of			

Life (range of weighted average scores: 0-4)			
Higher scores denote better quality of life.			
Units: points			
arithmetic mean	2.96	3.32	3.33
standard deviation	± 0.16	± 0.10	± 0.21
Dysphagia Numerical Rating Scale [NRS] (0-10)			
0 = no troubles to swallow 10 = most severe troubles to swallow			
Units: points			
arithmetic mean	0.5	0.4	0.1
standard deviation	± 0.1	± 0.1	± 0.1
Odynophagia Numerical Rating Scale [NRS] (0-10)			
0 = no troubles to swallow 10 = most severe troubles to swallow			
Units: points			
arithmetic mean	0.1	0.2	0
standard deviation	± 0.1	± 0.1	± 0.1

Reporting group values	Total		
Number of subjects	112		
Age categorical			
Units: Subjects			
Adolescent (16 - <18)	2		
Adults (18-75)	110		
Age continuous			
Units: years			
arithmetic mean	-		
standard deviation			
Gender categorical			
Units: Subjects			
Female	31		
Male	81		
Smoking status at screening			
Units: Subjects			
Current smoker	5		
Former smoker	17		
Never smoker	89		
Missing status	1		
Ethnic Group			
Units: Subjects			
White	111		
Black or African American	1		
Patient global impression of severity (PGI-S)			
Units: Subjects			
None	89		
Mild	20		
Moderate	2		
Severe	1		
History of allergic disease			
Units: Subjects			
yes	78		

no	34		
Concomitant use of PPIs Units: Subjects			
yes	13		
no	99		
Body weight Units: kg arithmetic mean standard deviation	-		
BMI Units: kg/m2 arithmetic mean standard deviation	-		
EEsAI PRO at baseline Units: points 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	-		
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 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	-		

Adult Eosinophilic Esophagitis Quality of Life (range of weighted average scores: 0-4)			
Higher scores denote better quality of life.			
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	-		
Odynophagia Numerical Rating Scale [NRS] (0-10)			
0 = no troubles to swallow 10 = most severe troubles to swallow			
Units: points arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	episodic BUL 0.5mg BID
Reporting group description: 4 cycles of 3 months each with one budesonide 0.5 mg orodispersible tablet each in the morning and in the evening for 4 weeks followed by 8 weeks of Placebo	
Reporting group title	continuous BUL 0.5mg BID
Reporting group description: one budesonide 0.5 mg orodispersible tablet each in the morning and in the evening continuously	
Reporting group title	Placebo BID
Reporting group description: Twice daily Placebo tablet for orodispersible use	

Primary: Proportion of patients free of treatment failure after a 48-week DB treatment phase

End point title	Proportion of patients free of treatment failure after a 48-week DB treatment phase
End point description: Treatment failure 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 odynophagia in the past 7 days of a severity of ≥ 4 points on a 0–10 NRS for dysphagia or odynophagia, 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 odynophagia, Clinical relapse [EEsAI PRO] defined as a > 20 -point increase compared to DB baseline in EEsAI PRO score, confirmed one week later, whereby DB baseline was defined as screening visit or OLI EOT visit, unless an assessment from visit DB V1 was available, Histological relapse, i.e., a peak of ≥ 48 eos/mm ² hpf at DB week 48/EOT, Experiencing a food impaction which needed endoscopic intervention, Presence of fixed ring/stricture, which prevented the passage of an adult standard endoscope (9-10 mm), Need for an endoscopic dilation, Premature withdrawal for any reason	
End point type	Primary
End point timeframe: after a 48-week DB treatment phase, identified at the latest at visit DB V5/EOT (either after 48 weeks of treatment or earlier)	

End point values	episodic BUL 0.5mg BID	continuous BUL 0.5mg BID	Placebo BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	45	22	
Units: Patients	5	28	2	

Statistical analyses

Statistical analysis title	episodic BUL 0.5 mg BID vs placebo
Comparison groups	Placebo BID v episodic BUL 0.5mg BID

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.3245 ^[2]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[1] - The difference between proportions of patients free of treatment failure in the BUL 0.5 mg BID episodic group and the Placebo group was -0.0202 (97.5% CI [-0.1931, 0.1527]). The one-sided p-value resulting from the Fisher's exact test was 0.3245. Therefore, the null hypothesis for this comparison could not be rejected and BUL 0.5 mg BID episodic was not superior to Placebo.

[2] - Testing of H0 ($n_{Pl} \geq n_{Eff}$) by means of the Fisher's exact test test, Bonferroni adjusted alpha = 0.0125

Statistical analysis title	continuous BUL 0.5mg BID vs placebo
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Statistical analysis description:

The difference between proportions of patients free of treatment failure in the BUL 0.5 mg BID continuous group and the Placebo was -0.5313 in the FAS-DB (97.5% CI [-0.7437, -0.3189]). The one-sided p-value resulting from the Fisher's exact test was <0.0001. All pre-specified subgroup analyses of the primary endpoint were in line with the primary outcome and showed the robustness of the observed superiority of BUL 0.5mg BID continuous over Placebo.

Comparison groups	Placebo BID v continuous BUL 0.5mg BID
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[3]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[3] - Testing of H0 ($n_{Pl} \geq n_{Eff}$) by means of the Fisher's exact test test, Bonferroni adjusted alpha = 0.0125

Secondary: Proportion of patients with histological relapse at DB Week 48/EOT

End point title	Proportion of patients with histological relapse at DB Week 48/EOT
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End point description:

End point type	Secondary
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End point timeframe:

after a 48-week DB treatment phase, identified at the latest at visit DB V5/EOT (either after 48 weeks of treatment or earlier)

End point values	episodic BUL 0.5mg BID	continuous BUL 0.5mg BID	Placebo BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	45	22	
Units: Patients	30	1	18	

Statistical analyses

Statistical analysis title	episodic BUL 0.5mg BID vs placebo
Comparison groups	episodic BUL 0.5mg BID v Placebo BID
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1045 ^[4]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[4] - Testing of H0 (BUL vs. Placebo)

Statistical analysis title	continuous BUL 0.5mg BID vs placebo
Comparison groups	continuous BUL 0.5mg BID v Placebo BID
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[5]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[5] - Testing of H0 (BUL vs. Placebo)

Secondary: Change in the peak eos/mm2 hpf from screening or OLI V2/EOT to DB Week 48/EOT

End point title	Change in the peak eos/mm2 hpf from screening or OLI V2/EOT to DB Week 48/EOT
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End point description:

End point type	Secondary
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End point timeframe:

after a 48-week DB treatment phase, identified at the latest at visit DB V5/EOT (either after 48 weeks of treatment or earlier)

End point values	episodic BUL 0.5mg BID	continuous BUL 0.5mg BID	Placebo BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	42	21	
Units: eos/mm2 hpf				
arithmetic mean (standard deviation)	233 (± 30.3)	9 (± 8.5)	305 (± 53.5)	

Statistical analyses

Statistical analysis title	episodic BUL 0.5mg BID vs placebo
Comparison groups	Placebo BID v episodic BUL 0.5mg BID
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2115 ^[6]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[6] - Testing of H0 (BUL vs. Placebo)

Statistical analysis title	continuous BUL 0.5mg BID vs placebo
Comparison groups	continuous BUL 0.5mg BID v Placebo BID
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[7]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[7] - Testing of H0 (BUL vs. Placebo)

Secondary: Proportion of patients with a clinical relapse during the 48-week DB treatment phase

End point title	Proportion of patients with a clinical relapse during the 48-week DB treatment phase
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End point description:

End point type	Secondary
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End point timeframe:

during a 48-week DB treatment phase, identified at the latest at visit DB V5/EOT (either after 48 weeks of treatment or earlier)

End point values	episodic BUL 0.5mg BID	continuous BUL 0.5mg BID	Placebo BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	45	22	
Units: Patients	35	18	17	

Statistical analyses

Statistical analysis title	episodic BUL 0.5mg BID vs placebo
Comparison groups	Placebo BID v episodic BUL 0.5mg BID

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.243 ^[8]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[8] - Testing of H0 (BUL vs. Placebo)

Statistical analysis title	continuous BUL 0.5mg BID vs placebo
Comparison groups	Placebo BID v continuous BUL 0.5mg BID
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.0034
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[9] - Testing of H0 (BUL vs. Placebo)

Secondary: Proportion of patients with clinical relapse EEsAI PRO increase of >20 points at DB Week 48/EOT

End point title	Proportion of patients with clinical relapse EEsAI PRO increase of >20 points at DB Week 48/EOT
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End point description:

End point type	Secondary
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End point timeframe:

after a 48-week DB treatment phase, identified at the latest at visit DB V5/EOT (either after 48 weeks of treatment or earlier)

End point values	episodic BUL 0.5mg BID	continuous BUL 0.5mg BID	Placebo BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	45	22	
Units: Patients	16	2	12	

Statistical analyses

Statistical analysis title	episodic BUL 0.5mg BID vs placebo
Comparison groups	episodic BUL 0.5mg BID v Placebo BID

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0713 ^[10]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[10] - Testing of H0 (BUL vs. Placebo)

Statistical analysis title	continuous BUL 0.5mg BID vs placebo
Comparison groups	continuous BUL 0.5mg BID v Placebo BID
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[11]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[11] - Testing of H0 (BUL vs. Placebo)

Secondary: Proportion of patients in clinico-histological remission, at DB Week 48/EOT

End point title	Proportion of patients in clinico-histological remission, at DB Week 48/EOT
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End point description:

Clinico-histological remission = defined as clinical remission (with clinical remission based on EEsAI PRO score ≤ 20 and NRS(D-O)7d ≤ 2 points) and histological remission (based on the peak number of eos per hpf, i.e. <16 eos/hpf).

End point type	Secondary
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End point timeframe:

after a 48-week DB treatment phase, identified at the latest at visit DB V5/EOT (either after 48 weeks of treatment or earlier)

End point values	episodic BUL 0.5mg BID	continuous BUL 0.5mg BID	Placebo BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	45	22	
Units: Patients	8	33	2	

Statistical analyses

Statistical analysis title	episodic BUL 0.5mg BID vs placebo
Comparison groups	episodic BUL 0.5mg BID v Placebo BID

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2008 ^[12]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[12] - Testing of H0 (BUL vs. Placebo)

Statistical analysis title	continuous BUL 0.5mg BID vs placebo
Comparison groups	continuous BUL 0.5mg BID v Placebo BID
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[13]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[13] - Testing of H0 (BUL vs. Placebo)

Secondary: Proportion of patients in deep disease remission I at DB Week 48/EOT

End point title	Proportion of patients in deep disease remission I at DB Week 48/EOT
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End point description:

Deep disease remission I = being in deep clinical [i.e., EEsAI PRO score of 0], AND deep endoscopic [modified EREFS subscores: fixed rings = 'Grade 0: none' or 'Grade 1: mild', exudates = 'Grade 0: none', furrows = 'Grade 0: absent', and edema = 'Grade 0: absent'], AND deep histological remission [0 eos/hpf]).

End point type	Secondary
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End point timeframe:

after a 48-week DB treatment phase, identified at the latest at visit DB V5/EOT (either after 48 weeks of treatment or earlier)

End point values	episodic BUL 0.5mg BID	continuous BUL 0.5mg BID	Placebo BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	45	22	
Units: Patients	4	22	1	

Statistical analyses

Statistical analysis title	episodic BUL 0.5mg BID vs placebo
Comparison groups	episodic BUL 0.5mg BID v Placebo BID

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3444 ^[14]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[14] - Testing of H0 (BUL vs. Placebo)

Statistical analysis title	continuous BUL 0.5mg BID vs placebo
Comparison groups	continuous BUL 0.5mg BID v Placebo BID
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 ^[15]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[15] - Testing of H0 (BUL vs. Placebo)

Secondary: Proportion of patients in deep disease remission II at DB Week 48/EOT

End point title	Proportion of patients in deep disease remission II at DB Week 48/EOT
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End point description:

Deep disease remission II = being in deep clinical [i.e., EEsAI PRO score of 0], AND deep endoscopic [total modified EREFS score of 0], AND deep histological remission [0 eos/hpf]).

End point type	Secondary
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End point timeframe:

after a 48-week DB treatment phase, identified at the latest at visit DB V5/EOT (either after 48 weeks of treatment or earlier)

End point values	episodic BUL 0.5mg BID	continuous BUL 0.5mg BID	Placebo BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	45	22	
Units: Patients	4	20	1	

Statistical analyses

Statistical analysis title	episodic BUL 0.5mg BID vs placebo
Comparison groups	episodic BUL 0.5mg BID v Placebo BID

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3444 ^[16]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[16] - Testing of H0 (BUL vs. Placebo)

Statistical analysis title	continuous BUL 0.5mg BID vs placebo
Comparison groups	continuous BUL 0.5mg BID v Placebo BID
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 ^[17]
Method	Fisher exact
Confidence interval	
sides	1-sided

Notes:

[17] - Testing of H0 (BUL vs. Placebo)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

48-week double-blinded phase

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	episodic BUL 0.5mg BID
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Reporting group description: -

Reporting group title	continuous BUL 0.5mg BID
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Reporting group description: -

Reporting group title	placebo
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Reporting group description: -

Serious adverse events	episodic BUL 0.5mg BID	continuous BUL 0.5mg BID	placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	0 / 22 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Pneumonia	Additional description: Aspergillus fumigatus and Pseudomonas aeruginosa lung infection		
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	0 / 22 (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: 2 %

Non-serious adverse events	episodic BUL 0.5mg BID	continuous BUL 0.5mg BID	placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 45 (77.78%)	32 / 45 (71.11%)	18 / 22 (81.82%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 45 (4.44%)	1 / 45 (2.22%)	0 / 22 (0.00%)
occurrences (all)	2	1	0
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 24	5 / 45 (11.11%) 30	0 / 22 (0.00%) 0
General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	2 / 45 (4.44%) 2	0 / 22 (0.00%) 0
Condition aggravated subjects affected / exposed occurrences (all)	15 / 45 (33.33%) 16	3 / 45 (6.67%) 3	8 / 22 (36.36%) 8
Influenza-like illness subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	0 / 45 (0.00%) 0	0 / 22 (0.00%) 0
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 6	0 / 45 (0.00%) 0	1 / 22 (4.55%) 1
Dyspepsia subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 2	1 / 45 (2.22%) 3	2 / 22 (9.09%) 2
Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	2 / 45 (4.44%) 3	0 / 22 (0.00%) 0
Oesophageal food impaction subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	0 / 45 (0.00%) 0	1 / 22 (4.55%) 3
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	2 / 45 (4.44%) 5	0 / 22 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	2 / 45 (4.44%) 3	0 / 22 (0.00%) 0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 45 (4.44%)	1 / 45 (2.22%)	0 / 22 (0.00%)
occurrences (all)	2	2	0
Back pain			
subjects affected / exposed	2 / 45 (4.44%)	1 / 45 (2.22%)	1 / 22 (4.55%)
occurrences (all)	2	1	1
Neck pain			
subjects affected / exposed	2 / 45 (4.44%)	1 / 45 (2.22%)	1 / 22 (4.55%)
occurrences (all)	15	1	1
Pain in extremity			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	0 / 22 (0.00%)
occurrences (all)	3	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	6 / 45 (13.33%)	8 / 45 (17.78%)	1 / 22 (4.55%)
occurrences (all)	6	8	1
Gastroenteritis			
subjects affected / exposed	1 / 45 (2.22%)	2 / 45 (4.44%)	0 / 22 (0.00%)
occurrences (all)	1	3	0
Nasopharyngitis			
subjects affected / exposed	8 / 45 (17.78%)	11 / 45 (24.44%)	6 / 22 (27.27%)
occurrences (all)	13	19	13
Influenza			
subjects affected / exposed	2 / 45 (4.44%)	3 / 45 (6.67%)	0 / 22 (0.00%)
occurrences (all)	2	4	0
Oral candidiasis			
subjects affected / exposed	1 / 45 (2.22%)	4 / 45 (8.89%)	0 / 22 (0.00%)
occurrences (all)	1	5	0
Oropharyngeal candidiasis			
subjects affected / exposed	2 / 45 (4.44%)	4 / 45 (8.89%)	1 / 22 (4.55%)
occurrences (all)	2	7	1
Pharyngitis			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Tonsillitis			

subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	2 / 45 (4.44%) 2	0 / 22 (0.00%) 0
Metabolism and nutrition disorders Vitamin D deficiency subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 5	1 / 45 (2.22%) 1	1 / 22 (4.55%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2021	CSP Amendment 01, version 2.0 18 Mar 2021 (all countries), including eligibility for DB-phase, OLI phase, specifications of exclusion criteria for DB and OLI phase.
28 June 2021	CSP Local Amendment 1 (ES), version 2.1 of 28 Jun 2021 (ES only), including pregnancy of patient as a separate withdrawal reason, risk minimization process clarification, and informed consent during Coronavirus disease 2019 (COVID19).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported