



Clinical trial results:

Double-blind, randomized, placebo-controlled, Phase II/III trial on the efficacy and tolerability of treatment with budesonide oral suspension vs. placebo in children and adolescents with eosinophilic esophagitis
Summary

EudraCT number	2017-003737-29
Trial protocol	DE ES PT NL GR GB
Global end of trial date	07 August 2023

Results information

Result version number	v1 (current)
This version publication date	05 April 2025
First version publication date	05 April 2025

Trial information

Trial identification

Sponsor protocol code	BUU-5/EEA
-----------------------	-----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	PEDEOS-1: Acronym

Notes:

Sponsors

Sponsor organisation name	Dr. Falk Pharma GmbH
Sponsor organisation address	Leinenweberstr. 5, Freiburg Im Breisgau, Germany, 79100
Public contact	Dept. of Clinic. Res. & Development, Dr Falk Pharma GmbH, +49 76115140, zentrale@drfalkpharma.de, Dr Falk Pharma GmbH, 0049 76115140,
Scientific contact	Dept. of Clinic. Res. & Development, Dr Falk Pharma GmbH, +49 76115140, zentrale@drfalkpharma.de, Dr Falk Pharma GmbH, 0049 76115140,

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 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2022
Global end of trial reached?	Yes
Global end of trial date	07 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Double-blind phase:

To prove superior efficacy of budesonide oral suspension compared to placebo in children and adolescents 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	03 September 2019
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: 8
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Türkiye: 1
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Israel: 2
Worldwide total number of subjects	76
EEA total number of subjects	64

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)	35
Adolescents (12-17 years)	41
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 15 centers randomized patients: 1 center in Australia, 2 centers in Greece, 2 centers in Israel, 3 centers in Portugal, 3 centers in Spain, 2 centers in the Netherlands, 1 center in Turkey and 1 center in the United Kingdom.

Pre-assignment

Screening details:

105 patients were screened to assess the In-/Exclusion criteria. Of them, 76 patients were randomized and treated with budesonide or placebo.

Period 1

Period 1 title	Double-blind 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

Blinding implementation details:

At the start of the DB treatment phase, patients were assigned to one of the treatment groups via a central stratified randomization procedure using a 1:1:1 balance. To guarantee the double-blinding, the study was conducted using placebo oral suspension identical in appearance and taste to active substance oral suspension. The patients' allocation to one of the treatment groups by means of a computer-generated randomization list.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test arm high dose

Arm description:

Budesonide oral suspension 0.5 mg/1 mg BID (2-11 /12-17 years)

Arm type	Experimental
Investigational medicinal product name	Budesonide oral suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Budesonide oral suspension 0.5 mg/1 mg BID (2-11 /12-17 years)

Arm title	Test arm low dose
------------------	-------------------

Arm description:

Budesonide oral suspension 0.5 mg/1 mg OD (2-11 /12-17 years)

Arm type	Experimental
Investigational medicinal product name	Budesonide oral suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Budesonide oral suspension 0.5 mg/1 mg OD (2-11 /12-17 years)

Arm title	Placebo
------------------	---------

Arm description:

Placebo arm

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

Dosage and administration details:

Placebo oral suspension

Number of subjects in period 1	Test arm high dose	Test arm low dose	Placebo
Started	26	26	24
Completed	26	26	23
Not completed	0	0	1
Adverse event, non-fatal	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	Test arm high dose
Reporting group description:	
Budesonide oral suspension 0.5 mg/1 mg BID (2-11 /12-17 years)	
Reporting group title	Test arm low dose
Reporting group description:	
Budesonide oral suspension 0.5 mg/1 mg OD (2-11 /12-17 years)	
Reporting group title	Placebo
Reporting group description:	
Placebo arm	

Reporting group values	Test arm high dose	Test arm low dose	Placebo
Number of subjects	26	26	24
Age categorical			
Stratum I: Age 2 to 11 years			
Stratum II: Age 12 to <18 years			
Units: Subjects			
Children (2-11 years)	12	12	11
Adolescents (12-17 years)	14	14	13
Age continuous			
Stratum I + II: 2 - < 18 years			
Units: years			
arithmetic mean	11.2	12.3	11.7
standard deviation	± 4.5	± 3.8	± 3.8
Gender categorical			
Units: Subjects			
Female	3	8	6
Male	23	18	18
Age categorical			
Units: Subjects			
Stratum I: age 2 to 11 years	12	12	11
Stratum II: age 12 to <18 years	14	14	13
Ethnic Group			
Units: Subjects			
White	23	26	24
Asian	2	0	0
Other	1	0	0
History of allergic disease			
Units: Subjects			
yes	22	22	22
no	4	4	2
Previous PPI EoE treatment			
Units: Subjects			
yes	21	21	22
no	5	5	2

Duration since first symptoms Units: years arithmetic mean standard deviation	4.2 ± 3.67	6.0 ± 3.80	5.0 ± 2.51
Duration since first diagnosis Units: years arithmetic mean standard deviation	2.1 ± 2.45	3.7 ± 2.83	3.1 ± 2.87
Overall peak eos/mm2 hpf			
Overall peak eosinophil count (eos)/mm2 high power field (hpf) derived from biopsies at screening (proximal, mid, and distal esophageal segment).			
Units: eos/mm2 hpf arithmetic mean standard deviation	237.7 ± 123.1	245.9 ± 108.7	238.6 ± 122.1
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	3.2 ± 1.0	3.6 ± 1.4	3.2 ± 1.8
'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	2.8 ± 1.1	2.9 ± 1.0	2.5 ± 1.1
'Fibrotic signs' subscore - Modified Endoscopic Reference Score (EREFS, range: 0-4) at DB week 12			
Worst case assessment from all parts of the esophagus. Lower values reflect lower endoscopic fibrotic disease activity.			
Units: points arithmetic mean standard deviation	0.3 ± 0.6	0.6 ± 0.9	0.5 ± 0.7
Dysphagia Numerical Rating Scale [NRS] (0-10)			
0 = no troubles to swallow 10 = most severe troubles to swallow			
Units: points arithmetic mean standard deviation	4.7 ± 2.5	5.2 ± 2.4	5.0 ± 2.2
Pain during swallowing NRS (0-10)			
0 = no pain during swallowing 10 = most severe pain during swallowing			
Units: points arithmetic mean standard deviation	3.0 ± 2.8	3.1 ± 2.8	2.0 ± 2.6
Patient's Global Assessment of EoE activity (NRS 0-10)			
0 = no symptoms 10 = most severe symptoms			
Units: points arithmetic mean standard deviation	5.8 ± 1.3	6.3 ± 1.4	6.2 ± 1.4
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	6.8	6.1	6.4
standard deviation	± 1.2	± 1.3	± 1.4

Reporting group values	Total		
Number of subjects	76		
Age categorical			
Stratum I: Age 2 to 11 years			
Stratum II: Age 12 to <18 years			
Units: Subjects			
Children (2-11 years)	35		
Adolescents (12-17 years)	41		
Age continuous			
Stratum I + II: 2 - < 18 years			
Units: years			
arithmetic mean	-		
standard deviation			
Gender categorical			
Units: Subjects			
Female	17		
Male	59		
Age categorical			
Units: Subjects			
Stratum I: age 2 to 11 years	35		
Stratum II: age 12 to <18 years	41		
Ethnic Group			
Units: Subjects			
White	73		
Asian	2		
Other	1		
History of allergic disease			
Units: Subjects			
yes	66		
no	10		
Previous PPI EoE treatment			
Units: Subjects			
yes	64		
no	12		
Duration since first symptoms			
Units: years			
arithmetic mean	-		
standard deviation			
Duration since first diagnosis			
Units: years			
arithmetic mean	-		
standard deviation			
Overall peak eos/mm2 hpf			
Overall peak eosinophil count (eos)/mm2 high power field (hpf) derived from biopsies at screening (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) at DB week 12			
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	-		

End points

End points reporting groups

Reporting group title	Test arm high dose
Reporting group description: Budesonide oral suspension 0.5 mg/1 mg BID (2-11 /12-17 years)	
Reporting group title	Test arm low dose
Reporting group description: Budesonide oral suspension 0.5 mg/1 mg OD (2-11 /12-17 years)	
Reporting group title	Placebo
Reporting group description: Placebo arm	

Primary: Rate of patients with pathological remission and clinical response at DB week 12 (LOCF)

End point title	Rate of patients with pathological remission and clinical response at DB week 12 (LOCF)
End point description: Rate of patients with pathological remission and clinical response at DB week 12 (LOCF) defined as fulfilling both criteria: - Histological remission, i.e., peak of <16 eos/mm2 hpf at DB week 12 (LOCF), AND - Clinical response defined as: Stratum I: Age 2 to 11 years at DB V1: ≥ 30% drop in the total score of PEESS Version 2.0 – parent report for children and teens (ages 2-18) from baseline to DB week 12 (LOCF), Stratum II: Age 12 to <18 years at DB V1: ≥ 30% drop in the total score of PEESS Version 2.0 – children and teens report (ages 8-18) from baseline to DB week 12 (LOCF).	
End point type	Primary
End point timeframe: DB week 12	

End point values	Test arm high dose	Test arm low dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	24	
Units: Patients				
Yes	18	12	0	
No	8	14	23	

Statistical analyses

Statistical analysis title	Primary: BUU-L vs. Placebo
Statistical analysis description: The rate of patients with histological remission (peak eos < 16 eos/mm2 hpf [i.e. <5 eos/hpf]) and clinical response (≥30% decrease in the total score of PEESS v2.0) at DB Week 12 (LOCF)	
Comparison groups	Placebo v Test arm low dose

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 1-sided
Parameter estimate	Risk difference (RD)
Point estimate	46.2
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	21.73
upper limit	70.57

Statistical analysis title	Primary: BUU-H vs. Placebo
Comparison groups	Test arm high dose v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 1-sided
Parameter estimate	Risk difference (RD)
Point estimate	69.2
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	46.62
upper limit	91.84

Secondary: Rate of patients with histological remission, defined as a peak of <16 eos/mm2 hpf at DB week 12 (LOCF),

End point title	Rate of patients with histological remission, defined as a peak of <16 eos/mm2 hpf at DB week 12 (LOCF),
End point description:	
End point type	Secondary
End point timeframe:	
DB week 12 (LOCF)	

End point values	Test arm high dose	Test arm low dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	24	
Units: Patients				
Yes	23	16	0	
No	3	10	24	

Statistical analyses

Statistical analysis title	Primary secondary: BUU-L vs. Placebo
Comparison groups	Test arm low dose v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 1-sided
Parameter estimate	Risk difference (RD)
Point estimate	61.5
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	37.7
upper limit	85.4

Statistical analysis title	Primary secondary: BUU-H vs. Placebo
Comparison groups	Test arm high dose v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 1-sided
Parameter estimate	Risk difference (RD)
Point estimate	72.8
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	72.8
upper limit	100

Secondary: Change in the peak eos/mm2 hpf from screening to DB week 12 (LOCF)

End point title	Change in the peak eos/mm2 hpf from screening to DB week 12 (LOCF)
End point description:	

End point type	Secondary
End point timeframe:	
From Screening to DB week 12 (LOCF)	

End point values	Test arm high dose	Test arm low dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	26	22	
Units: eos/mm2				
least squares mean (standard deviation)	-230.3 (\pm 25.5)	-165.7 (\pm 25)	-11.4 (\pm 27.2)	

Statistical analyses

Statistical analysis title	Secondary Second endpoint: BUU-L vs. Placebo
Comparison groups	Test arm low dose v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	-154.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-228
upper limit	-80.6
Variability estimate	Standard deviation
Dispersion value	36.9

Statistical analysis title	Secondary Second endpoint: BUU-H vs. Placebo
Comparison groups	Test arm high dose v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	-218.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-293.3
upper limit	-144.5

Variability estimate	Standard deviation
Dispersion value	37.3

Secondary: Rate of patients with clinico-pathological remission

End point title	Rate of patients with clinico-pathological remission
End point description:	
Rate of patients with clinico-pathological remission defined as:	
o Histological remission, i.e., peak of <16 eos/mm ² hpf at DB week 12 (LOCF), and	
o Clinical remission (i.e., no or only minimal problems) defined as clinical response ($\geq 30\%$ drop in the total score of PEES Version 2.0 from baseline to DB week 12 [LOCF]) AND	
Stratum I: Age 2 to 11 years at DB V1:	
PEES Version 2.0 – parent report for children and teens (ages 2-18)	
<ul style="list-style-type: none"> • ≤ 4 points in each of the subdomains GERD/nausea-vomiting/pain, and • ≤ 7 points in the subdomain dysphagia, or • ≤ 5 points in the total score and ≥ 2 subdomains with a drop of at least 50% compared to baseline at DB week 12 (LOCF), 	
Stratum II: Age 12 to <18 years at DB V1:	
PEES Version 2.0 – children and teens report (ages 8-18)	
<ul style="list-style-type: none"> • ≤ 4 points in each of the subdomains GERD/nausea-vomiting/pain, and • ≤ 7 points in the subdomain dysphagia, or • ≤ 5 points in the total score and ≥ 2 subdomains with a drop of at least 50% compared to baseline 	
End point type	Secondary
End point timeframe:	
DB week 12 (LOCF).	

End point values	Test arm high dose	Test arm low dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	24	
Units: Patients				
Yes	9	7	0	
No	17	19	24	

Statistical analyses

Statistical analysis title	Third secondary endpoint: Primary: BUU-L vs. Place
Comparison groups	Test arm low dose v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0066
Method	t-test, 1-sided
Parameter estimate	Risk difference (RD)
Point estimate	26.9

Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	5.2
upper limit	48.7

Statistical analysis title	Third secondary endpoint: Primary: BUU-H vs. Place
Comparison groups	Test arm high dose v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012
Method	t-test, 1-sided
Parameter estimate	Risk difference (RD)
Point estimate	34.6
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	11.3
upper limit	57.9

Secondary: Rate of patients with clinical remission (i.e., no or only minimal problems) defined as above (clinical remission component of the endpoint clinico-pathological remission) at DB week 12 (LOCF)

End point title	Rate of patients with clinical remission (i.e., no or only minimal problems) defined as above (clinical remission component of the endpoint clinico-pathological remission) at DB week 12 (LOCF)
End point description:	
End point type	Secondary
End point timeframe:	
DB week 12	

End point values	Test arm high dose	Test arm low dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	24	
Units: Patients				
Yes	10	11	12	
No	16	15	12	

Statistical analyses

Statistical analysis title	Fourth secondary endpoint: BUU-L vs. Placebo
Comparison groups	Test arm low dose v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7964
Method	t-test, 1-sided
Parameter estimate	Risk difference (RD)
Point estimate	-7.7
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-42.8
upper limit	27.5

Statistical analysis title	Fourth secondary endpoint: BUU-H vs. Placebo
Comparison groups	Test arm high dose v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8657
Method	t-test, 1-sided
Parameter estimate	Risk difference (RD)
Point estimate	-11.5
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-46.4
upper limit	23.4

Secondary: Rate of patients with clinical response at DB week 12 (LOCF)

End point title	Rate of patients with clinical response at DB week 12 (LOCF)
End point description:	
Rate of patients with clinical response at DB week 12 (LOCF), defined as	
Stratum I: Age 2 to 11 years at DB V1:	
≥ 30% drop in the total score of PEESS Version 2.0 – parent report for children and teens (ages 2-18) from baseline to DB week 12 (LOCF),	
Stratum II: Age 12 to <18 years at DB V1:	
≥ 30% drop in the total score of PEESS Version 2.0 – children and teens report (ages 8-18) from baseline to DB week 12 (LOCF)	
• In the subgroup of patients with ≥ 4 points in NRS for dysphagia on the day of the baseline visit (only patients of Stratum II: Age 12 to <18 years at DB V1), the rate of patients with resolution of dysphagia symptom (i.e., no or only minimal problems). Resolution of dysphagia symptom is defined as a severity of ≤2 points on 0 to 10-point (0-10) NRS on each day in the week prior to DB week 12 (LOCF).	
End point type	Secondary
End point timeframe:	
DB week 12	

End point values	Test arm high dose	Test arm low dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	24	
Units: Patients				
Yes	20	18	17	
No	6	8	7	

Statistical analyses

Statistical analysis title	Fifth secondary endpoint: BUU-L vs. Placebo
Comparison groups	Test arm low dose v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6663
Method	t-test, 1-sided
Parameter estimate	Risk difference (RD)
Point estimate	-1.6
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-34
upper limit	30.8

Statistical analysis title	Fifth secondary endpoint: BUU-H vs. Placebo
Comparison groups	Test arm high dose v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4328
Method	t-test, 1-sided
Parameter estimate	Risk difference (RD)
Point estimate	6.1
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-24.9
upper limit	37.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 weeks

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	26.0
--------------------	------

Reporting groups

Reporting group title	Test arm high dose
-----------------------	--------------------

Reporting group description:

Budesonide oral suspension 0.5 mg/1 mg BID (2-11 /12-17 years)

Reporting group title	Test arm low dose
-----------------------	-------------------

Reporting group description:

Budesonide oral suspension 0.5 mg/1 mg OD (2-11 /12-17 years)

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Placebo arm

Serious adverse events	Test arm high dose	Test arm low dose	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 26 (7.69%)	1 / 26 (3.85%)	1 / 24 (4.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Arthroscopy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 24 (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
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 24 (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
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 24 (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
Musculoskeletal and connective tissue disorders			
Neck mass			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Test arm high dose	Test arm low dose	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 26 (84.62%)	19 / 26 (73.08%)	20 / 24 (83.33%)
Vascular disorders			
Vascular disorders			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	5 / 26 (19.23%)	4 / 26 (15.38%)	4 / 24 (16.67%)
occurrences (all)	6	7	6
Immune system disorders			
Immune system disorder			
subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	1 / 24 (4.17%)
occurrences (all)	1	1	1
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)	0 / 24 (0.00%)
occurrences (all)	1	4	0
Respiratory, thoracic and mediastinal disorders			

Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	7 / 26 (26.92%) 9	4 / 26 (15.38%) 5	4 / 24 (16.67%) 8
Psychiatric disorders Psychiatric disorder subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 26 (0.00%) 0	0 / 24 (0.00%) 0
Investigations Investigations subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 3	1 / 26 (3.85%) 1	1 / 24 (4.17%) 2
Injury, poisoning and procedural complications Injury, poisoning and procedural complications subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 7	2 / 26 (7.69%) 3	1 / 24 (4.17%) 2
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 18	6 / 26 (23.08%) 22	4 / 24 (16.67%) 7
Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0	1 / 24 (4.17%) 1
Eye disorders Eye disorders subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	0 / 24 (0.00%) 0
Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all)	11 / 26 (42.31%) 22	10 / 26 (38.46%) 21	10 / 24 (41.67%) 15
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	3 / 26 (11.54%) 3	1 / 24 (4.17%) 1
Renal and urinary disorders			

Renal and urinary disorders subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0	0 / 24 (0.00%) 0
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 26 (3.85%) 1	3 / 24 (12.50%) 3
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	12 / 26 (46.15%) 20	9 / 26 (34.62%) 14	10 / 24 (41.67%) 19
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	3 / 26 (11.54%) 3	0 / 24 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2019	<p>1) It was specified that patients with a <i>Helicobacter pylori</i> associated gastritis shall not be randomized into the study.</p> <p>2) An ACTH test has been integrated as mandatory test to be performed at screening, and of double-blind phase and end of treatment (end of tapering phase).</p> <p>3) To assess patient's acceptance of the study drug, an objective has been added, relating to analysis of newly added questionnaire asking for patient's acceptance of study medication related to taste and handling.</p> <p>4) To incorporate assessment and analyses of height, head circumference and pubertal stage the assessments, an additional safety endpoint was added. Additionally growth retardation has been specified as adverse event of special interest.</p> <p>5) To specify the study population regarding steroid treatment versus potential PPI or dietary treatment, inclusion and exclusion criteria have been modified and added.</p> <p>6) To specify the study population regarding severity of disease and immediate treatment need, inclusion and exclusion criteria have been modified and added.</p>
22 July 2019	<p>1) To specify the study population regarding steroid treatment versus potential PPI or dietary treatment, inclusion and exclusion criteria have been modified and added.</p> <p>2) Inclusion criteria no. 10 has been amended concerning pregnancy and birth control measures.</p> <p>3) It was specified that patients with a <i>Helicobacter pylori</i> associated gastritis shall not be randomized into the study.</p> <p>4) To specify the study population regarding severity of disease and immediate treatment need, exclusion criteria have been modified and added.</p> <p>5) An ACTH test has been integrated as mandatory test to be performed at screening, end of double-blind phase and end of treatment (end of tapering phase).</p> <p>6) To assess patient's acceptance of the study drug, an objective has been added, relating to analysis of newly added questionnaire asking for patient's acceptance of study medication related to taste and handling.</p> <p>7) To incorporate assessment and analyses of height, head circumference and pubertal stage the assessments, an additional safety endpoint was added. Additionally growth retardation has been specified as adverse event of special interest.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported