



Clinical trial results:

Double-blind, randomized, placebo-controlled, phase III trial on the efficacy and tolerability of a 6-week treatment with budesonide effervescent tablets vs. placebo for induction of clinico-pathological remission in adult patients with active eosinophilic esophagitis

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2014-001484-12 |
| Trial protocol | DE BE ES NL |
| Global end of trial date | 04 October 2016 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 |
| This version publication date | 26 August 2017 |
| First version publication date | 26 August 2017 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | BUL-1/EEA |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02434029 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | EOS-1: Acronym |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Dr Falk Pharma GmbH |
| Sponsor organisation address | Leinenweberstrasse 5, Freiburg, Germany, 79108 |
| Public contact | Department of Medical Science, Dr Falk Pharma GmbH, +49 761-1514-0, |
| Scientific contact | Department of Medical Science, Dr Falk Pharma GmbH, +49 761-1514-0, |

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 | 22 February 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 October 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of budesonide effervescent tablets for orodispersible use vs. placebo for the induction of clinico-pathological remission in adult patients with active 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 protonpump-inhibitors 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 | 11 November 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Netherlands: 3 |
| Country: Number of subjects enrolled | Spain: 34 |

| | |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Germany: 43 |
| Country: Number of subjects enrolled | Switzerland: 8 |
| Worldwide total number of subjects | 88 |
| EEA total number of subjects | 80 |

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) | 86 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

In total, 19 centers randomized patients: 10 centers in Germany (DE), 6 centers in Spain (ES), 2 centers in Switzerland (CH), and 1 center in The Netherlands (NL). First patient was screened (entered) at the 11Nov2015. Last patient completed his last visit at 04Oct2016

Pre-assignment

Screening details:

126 patients were screened to fulfill the In-/Exclusion criteria. Of them, 88 patients were randomized and treated with budesonide or placebo.

Pre-assignment period milestones

| | |
|------------------------------|--------------------|
| Number of subjects started | 126 ^[1] |
| Number of subjects completed | 88 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|------------------------|
| Reason: Number of subjects | Protocol deviation: 38 |
|----------------------------|------------------------|

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Of the 126 patient screened within the pre-assignment period, 38 patients did not fulfill the in-/exclusion criteria and therefore, were not randomized and did not enter the double-blind treatment period

Period 1

| | |
|------------------------------|---|
| Period 1 title | Double-blind 6-week 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:

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 | Budesonide 1mg BID |

Arm description:

Twice daily 1mg budesonide

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | 1mg budesonide effervescent tablet for orodispersible use |
| Investigational medicinal product code | BUET 1mg |
| Other name | Budesonide 1mg orodispersible tablet |
| 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 rapid disintegration. The effervescent tablet dissolves rapidly and 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

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo effervescent tablet for orodispersible use |
| Investigational medicinal product code | Placebo |
| Other name | Placebo orodispersible tablet |
| 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 rapid disintegration. The effervescent tablet dissolves rapidly and 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 | Budesonide 1mg BID | Placebo BID |
|---------------------------------------|-----------------------|-------------|
| Started | 59 | 29 |
| Completed | 56 | 25 |
| Not completed | 3 | 4 |
| Lack of efficacy | 3 | 4 |

Baseline characteristics

Reporting groups

| | |
|--|--------------------|
| Reporting group title | Budesonide 1mg BID |
| Reporting group description: Twice daily 1mg budesonide | |
| Reporting group title | Placebo BID |
| Reporting group description: Twice daily Placebo | |

| Reporting group values | Budesonide 1mg BID | Placebo BID | Total |
|---|--------------------|-------------|-------|
| Number of subjects | 59 | 29 | 88 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 57 | 29 | 86 |
| From 65-84 years | 2 | 0 | 2 |
| Age continuous Units: years | | | |
| arithmetic mean | 37 | 36.9 | |
| standard deviation | ± 11.5 | ± 9.2 | - |
| Gender categorical Units: Subjects | | | |
| Female | 11 | 4 | 15 |
| Male | 48 | 25 | 73 |
| Ethnic Group Units: Subjects | | | |
| White | 59 | 29 | 88 |
| Previous esophageal dilation Units: Subjects | | | |
| yes | 9 | 5 | 14 |
| no | 50 | 24 | 74 |
| Previous PPI trial conducted Units: Subjects | | | |
| yes | 59 | 29 | 88 |
| History of allergic disease Units: Subjects | | | |
| yes | 47 | 23 | 70 |
| no | 12 | 6 | 18 |
| Endoscopic disease activity Units: Subjects | | | |
| none | 1 | 0 | 1 |
| mild | 9 | 3 | 12 |
| moderate | 30 | 17 | 47 |
| severe | 19 | 9 | 28 |
| Duration since first symptoms Units: months | | | |
| arithmetic mean | 134 | 139 | |
| standard deviation | ± 104.6 | ± 98.8 | - |

| | | | |
|---|----------------|----------------|---|
| Duration since diagnosis Units: months arithmetic mean standard deviation | 48.8 ± 44.3 | 57.6 ± 49.3 | - |
| Overall peak eos/mm2 hpf Units: eos/mm2 hpf arithmetic mean standard deviation | 242 ± 140.7 | 239 ± 125 | - |
| Total Modified EEsAI Endoscopic Score (range: 0-9) | | | |
| Worst case assessment from all parts of the esophagus | | | |
| Units: points arithmetic mean standard deviation | 3.8 ± 1.46 | 4.6 ± 1.32 | - |
| 'Inflammatory signs' subscore - Modified EEsAI Endoscopic Score (range: 0-4) | | | |
| Worst case assessment from all parts of the esophagus | | | |
| Units: points arithmetic mean standard deviation | 2.7 ± 0.96 | 3 ± 0.98 | - |
| 'Fibrotic signs' subscore - Modified EEsAI Endoscopic Score (range: 0-4) | | | |
| Worst case assessment from all parts of the esophagus | | | |
| Units: points arithmetic mean standard deviation | 1 ± 1 | 1.4 ± 0.91 | - |
| Dysphagia Numerical Rating Scale [NRS] (0-10) | | | |
| 0 = no troubles to swallow 10 = most severe troubles to swallow | | | |
| Units: points arithmetic mean standard deviation | 5.8 ± 2.02 | 5.9 ± 1.69 | - |
| Pain during swallowing NRS (0-10) | | | |
| 0 = no pain during swallowing 10 = most severe pain during swallowing | | | |
| Units: points arithmetic mean standard deviation | 3.5 ± 2.78 | 3.4 ± 3.17 | - |
| Patient's Global Assessment of EoE activity (NRS 0-10) | | | |
| 0 = no symptoms 10 = most severe symptoms | | | |
| Units: points arithmetic mean standard deviation | 5.9 ± 1.5 | 6 ± 1.5 | - |
| 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 | 6.1 ± 1.3 | 6.2 ± 1.3 | - |
| 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 | 54.1 | 55.3 | |
| standard deviation | ± 15.5 | ± 15.8 | - |

End points

End points reporting groups

| | |
|------------------------------|--------------------|
| Reporting group title | Budesonide 1mg BID |
| Reporting group description: | |
| Twice daily 1mg budesonide | |
| Reporting group title | Placebo BID |
| Reporting group description: | |
| Twice daily Placebo | |

Primary: Number (%) of patients with clinico-pathological remission at week 6 (LOCF) of double-blind phase

| | |
|--|---|
| End point title | Number (%) of patients with clinico-pathological remission at week 6 (LOCF) of double-blind phase |
| End point description: | |
| Rate of patients with clinico-pathological remission at week 6 (LOCF) DB defined as fulfilling both criteria: | |
| - Histological remission, i.e., peak of <16 eos/mm ² hpf at week 6 (LOCF), AND | |
| - Resolution of symptoms (i.e., no or only minimal problems) defined as a severity of ≤2 points on 0 to 10-point (0-10) NRS for dysphagia AND a severity of ≤2 points on 0-10 NRS for pain during swallowing on each day in the week prior to week 6 (LOCF). | |
| Patients experiencing a food impaction at any time during the DB-treatment phase which needed endoscopic intervention or who needed an endoscopic dilation during the DB-treatment phase were assessed as treatment failures, and thus did not fulfill by definition the clinico-pathological remission criterion. | |
| In case the primary endpoint proved to show superiority of budesonide over placebo, further key secondary endpoints could confirmatorily be tested in an a priori ordered manner until the first of them did not prove a superiority of budesonide | |
| End point type | Primary |
| End point timeframe: | |
| at week 6 (LOCF) double-blind phase | |

| End point values | Budesonide 1mg BID | Placebo BID | | |
|-----------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 29 | | |
| Units: patients | | | | |
| yes | 34 | 0 | | |
| no | 25 | 29 | | |

| | |
|----------------------------|--|
| Attachments (see zip file) | Primary endpoint (FAS-DB)/BUL1_Clin-histol_rem_source 2- |
|----------------------------|--|

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Final Analysis (FAS): Budesonide 1mg vs placebo |
| Comparison groups | Budesonide 1mg BID v Placebo BID |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1E-8 ^[1] |
| Method | Fisher exact |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 57.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 38.22 |
| upper limit | 71.97 |

Notes:

[1] - The RD was 57.63% with two-sided 95% RCI [38.22%; 71.97%]. The one-sided p-value resulting from the Fisher's exact test was 0.00000001. The inverse normal was 5.5935 and exceeded the critical value of 2.452, thus superiority was confirmatorily shown

Secondary: Number (%) of patients with histological remission at week 6 (LOCF) double-blind phase

| | |
|-----------------|--|
| End point title | Number (%) of patients with histological remission at week 6 (LOCF) double-blind phase |
|-----------------|--|

End point description:

First of the a priori ordered key secondary endpoints to be confirmatorily tested for superiority when the primary endpoint showed superiority of budesonide 1mg vs placebo.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

at week 6 (LOCF) double-blind phase.

| End point values | Budesonide 1mg BID | Placebo BID | | |
|-----------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 29 | | |
| Units: patients | | | | |
| yes | 55 | 0 | | |
| no | 4 | 29 | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | First a priori ordered key secondary endpoint |
| Statistical analysis description: | |
| | Efficacy significance testing continued in hierarchical fashion in support of labeling claims for the key secondary endpoints until the first of these comparisons of BUET 1mg BID versus Placebo showed a one-sided p-value >0.025 (FAS-DB). |
| Comparison groups | Budesonide 1mg BID v Placebo BID |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[2] |
| Method | Fisher exact |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 93.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 86.8 |
| upper limit | 99.6 |

Notes:

[2] - one-sided p-value

Secondary: Change in the peak eos/mm2 hpf from baseline to week 6 (LOCF) double-blind phase

| | |
|-----------------|--|
| End point title | Change in the peak eos/mm2 hpf from baseline to week 6 (LOCF) double-blind phase |
|-----------------|--|

End point description:

Second of the a priori ordered key secondary endpoints to be confirmatorily tested for superiority when the primary endpoint showed superiority of budesonide 1mg vs placebo.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

at week 6 (LOCF) double-blind phase

| End point values | Budesonide 1mg BID | Placebo BID | | |
|--------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 29 | | |
| Units: eos/mm2 hpf | | | | |
| arithmetic mean (standard deviation) | -225.5 (± 150.37) | -4.3 (± 135.64) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Second a priori ordered key secondary endpoint |
|----------------------------|--|

Statistical analysis description:

Efficacy significance testing continued in hierarchical fashion in support of labeling claims for the key secondary endpoints until the first of these comparisons of BUET 1mg BID versus Placebo showed a one-sided p-value >0.025 (FAS-DB).

| | |
|-------------------|----------------------------------|
| Comparison groups | Budesonide 1mg BID v Placebo BID |
|-------------------|----------------------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[3] |
| Method | linear least squares model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -221.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -285 |
| upper limit | -157.5 |

Notes:

[3] - One-sided p-value for effect between treatment groups from linear least squares model with treatment group and baseline value as covariate.

Secondary: Number (%) of patients with resolution of symptoms on each day in the week prior to week 6 (LOCF) double-blind phase

| | |
|------------------------|--|
| End point title | Number (%) of patients with resolution of symptoms on each day in the week prior to week 6 (LOCF) double-blind phase |
| End point description: | Third of the a priori ordered key secondary endpoints to be confirmatorily tested for superiority when the primary endpoint showed superiority of budesonide 1mg vs placebo. |
| End point type | Secondary |
| End point timeframe: | at week 6 (LOCF) double-blind phase |

| End point values | Budesonide 1mg BID | Placebo BID | | |
|-----------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 29 | | |
| Units: patients | | | | |
| yes | 35 | 4 | | |
| no | 24 | 25 | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Third a priori ordered key secondary endpoint |
| Statistical analysis description: | Efficacy significance testing continued in hierarchical fashion in support of labeling claims for the key secondary endpoints until the first of these comparisons of BUET 1mg BID versus Placebo showed a one-sided p-value >0.025 (FAS-DB). |
| Comparison groups | Budesonide 1mg BID v Placebo BID |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[4] |
| Method | Fisher exact |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 45.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 27.79 |
| upper limit | 63.27 |

Notes:

[4] - one-sided p-value

Secondary: Number (%) of patients with a total weekly EEsAI-PRO score of ≤ 20 at week 6 (LOCF) double-blind phase

| | |
|---|--|
| End point title | Number (%) of patients with a total weekly EEsAI-PRO score of ≤ 20 at week 6 (LOCF) double-blind phase |
| End point description: Fourth of the a priori ordered key secondary endpoints to be confirmatorily tested for superiority when the primary endpoint showed superiority of budesonide 1mg vs placebo. | |
| End point type | Secondary |
| End point timeframe: at week 6 (LOCF) double-blind phase | |

| End point values | Budesonide 1mg BID | Placebo BID | | |
|-----------------------------|-----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 29 | | |
| Units: patients | | | | |
| yes | 30 | 2 | | |
| no | 29 | 27 | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Fourth a priori ordered secondary endpoint |
| Statistical analysis description: Efficacy significance testing continued in hierarchical fashion in support of labeling claims for the key secondary endpoints until the first of these comparisons of BUET 1mg BID versus Placebo showed a one-sided p-value >0.025 (FAS-DB). | |
| Comparison groups | Placebo BID v Budesonide 1mg BID |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[5] |
| Method | Fisher exact |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 43.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 28.21 |
| upper limit | 59.69 |

Notes:

[5] - one-sided p-value

Secondary: Number (%) of patients with an improvement from baseline to week 6 (LOCF) double-blind phase in the weekly Visual Dysphagia Questionnaire (VDQ) score

| | |
|-----------------|---|
| End point title | Number (%) of patients with an improvement from baseline to week 6 (LOCF) double-blind phase in the weekly Visual Dysphagia Questionnaire (VDQ) score |
|-----------------|---|

End point description:

Fifth of the a priori ordered key secondary endpoints to be confirmatorily tested for superiority when the primary endpoint showed superiority of budesonide 1mg vs placebo.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

at week 6 (LOCF) double-blind phase

| End point values | Budesonide 1mg BID | Placebo BID | | |
|-----------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 29 | | |
| Units: patients | | | | |
| yes | 30 | 11 | | |
| no | 29 | 18 | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Fifth a priori ordered key secondary endpoint |
|-----------------------------------|---|

Statistical analysis description:

Efficacy significance testing continued in hierarchical fashion in support of labeling claims for the key secondary endpoints until the first of these comparisons of BUET 1mg BID versus Placebo showed a one-sided p-value >0.025 (FAS-DB).

| | |
|-------------------|----------------------------------|
| Comparison groups | Placebo BID v Budesonide 1mg BID |
|-------------------|----------------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1804 ^[6] |
| Method | Fisher exact |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 12.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.87 |
| upper limit | 34.7 |

Notes:

[6] - one-sided p-value.

As the one-sided p-value was above 0.025, statistical superiority in this endpoint, despite numerical higher values under budesonide, could not be proven and thus confirmatory testing had to be stopped at this point.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 week double-blind phase

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Budesonide 1mg BID |
|-----------------------|--------------------|

Reporting group description:

Twice daily 1mg budesonide

| | |
|-----------------------|-------------|
| Reporting group title | Placebo BID |
|-----------------------|-------------|

Reporting group description:

Twice daily Placebo

| Serious adverse events | Budesonide 1mg BID | Placebo BID | |
|---|-----------------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 29 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

Frequency threshold for reporting non-serious adverse events: 0.03 %

| Non-serious adverse events | Budesonide 1mg BID | Placebo BID | |
|---|-----------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 37 / 59 (62.71%) | 12 / 29 (41.38%) | |
| Investigations | | | |
| Blood cortisol decreased | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 0 / 29 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Vascular disorders | | | |

| | | | |
|--|---|---|--|
| Hypertension subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 2 | 0 / 29 (0.00%) 0 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 4 / 59 (6.78%) 4 | 1 / 29 (3.45%) 1 | |
| Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 29 (3.45%) 1 | |
| General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 29 (3.45%) 1 | |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 29 (3.45%) 1 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Oesophageal food impaction subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 1 / 59 (1.69%) 1 3 / 59 (5.08%) 3 2 / 59 (3.39%) 2 0 / 59 (0.00%) 0 | 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1 0 / 29 (0.00%) 0 0 / 29 (0.00%) 0 1 / 29 (3.45%) 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---------------------|--|
| Asthma subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 2 / 29 (6.90%) 2 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 29 (3.45%) 1 | |
| Infections and infestations Laryngitis subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 1 / 29 (3.45%) 1 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 2 | 1 / 29 (3.45%) 1 | |
| Local fungal infection | Additional description: In 14 patients under budesonide a local fungal infection (oral , oropharyngeal, and/or esophageal candidiasis) was suspected. Thereof, only 3 patients (5.1%) showed clinically mild symptoms with no impact on their daily life. | | |
| subjects affected / exposed occurrences (all) | 14 / 59 (23.73%) 14 | 0 / 29 (0.00%) 0 | |
| Pharyngitis subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 2 / 29 (6.90%) 2 | |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 29 (3.45%) 1 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 29 (3.45%) 1 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 29 (3.45%) 1 | |

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