Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Budesonide MMX® 9 mg Extended-release Tablets as Add-on Therapy in Patients with Active, Mild or Moderate Ulcerative Colitis not Adequately Controlled on a Background Oral 5-ASA Regimen

Summary

EudraCT number	2011-005115-82
Trial protocol	HU CZ PL BG EE LV LT
Global end of trial date	02 October 2013

Results information

Result version number	v1 (current)
This version publication date	01 January 2020
First version publication date	01 January 2020

Trial information

Trial identification

Sponsor protocol code	C2011-0401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01532648
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Salix Pharmaceuticals, Inc
Sponsor organisation address	400 Somerset Corporate Blvd, Bridgewater, United States, 08807
Public contact	Director of Clinical Operations, Salix Pharmaceuticals, Inc, 011 908-927-0873, Lindsey.Mathew@bauschhealth.com
Scientific contact	Director of Clinical Operations, Salix Pharmaceuticals, Inc, 011 908-927-0873, Lindsey.Mathew@bauschhealth.com

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	02 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2013
Global end of trial reached?	Yes
Global end of trial date	02 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the efficacy of budesonide multi-matrix system (MMX) 9 milligrams (mg) and placebo as add-on therapy to an existing oral 5-aminosalicylic acid (5-ASA) regimen for the induction of clinical remission in participants with active, mild to moderate ulcerative colitis (UC) when administered for 8 weeks.

Protection of trial subjects:

This study was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, and with Good Clinical Practice (GCP), as required by the US Code of Federal Regulations applicable to clinical studies (21 CFR Parts 11, 50, 54, 56 and 312, 42 USC 282(j), International Council for Harmonisation, Harmonised Tripartite Guideline E6(R1): GCP and E2A: Safety Data Management, and applicable local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 January 2012
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	United States: 115
Country: Number of subjects enrolled	Canada: 35
Country: Number of subjects enrolled	Czech Republic: 38
Country: Number of subjects enrolled	Bulgaria: 48
Country: Number of subjects enrolled	Hungary: 33
Country: Number of subjects enrolled	Poland: 49
Country: Number of subjects enrolled	Ukraine: 54
Country: Number of subjects enrolled	Estonia: 17
Country: Number of subjects enrolled	Latvia: 27
Country: Number of subjects enrolled	Lithuania: 19
Country: Number of subjects enrolled	Russian Federation: 75
Worldwide total number of subjects	510
EEA total number of subjects	231

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)	477
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At Screening and Visit 5 (Day 56), participants were required to undergo a flexible sigmoidoscopy (or colonoscopy, if clinically indicated) with 1 photograph and 3 mucosal biopsies taken from the most severely affected region(s) of the colon visualized during the endoscopy procedure.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Budesonide MMX

Arm description:

Participants received 1 oral tablet of budesonide MMX 9 mg for 56 days. Additionally, participants continued to receive the same dose of their existing oral 5-ASA medication from their treating physician.

Arm type	Experimental
Investigational medicinal product name	Budesonide MMX®
Investigational medicinal product code	
Other name	Budesonide Multi-Matrix System
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Budesonide MMX was administered as per the dose and schedule specified in the respective arms.

Arm title	Placebo

Arm description:

Participants received 1 oral tablet of matching budesonide MMX placebo for 56 days. Additionally, participants continued to receive the same dose of their existing oral 5-ASA medication from their treating physician.

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

Dosage and administration details:

Budesonide MMX matching placebo was administered as per the dose and schedule specified in the respective arms.

Number of subjects in period 1	Budesonide MMX	Placebo
Started	255	255
Safety Population	255	255
Intent-To-Treat (ITT) Population	230	228 [1]
Completed	219	238
Not completed	36	17
Consent withdrawn by subject	16	2
Adverse event, non-fatal	12	9
Lost to follow-up	3	4
Lack of efficacy	4	1
Protocol deviation	1	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of subjects who started is the same as the number of subjects in the arm (N=255).

Baseline characteristics

Reporting groups	
Reporting group title	Budesonide MMX
Reporting group description:	
Participants received 1 oral tablet of budesonide MMX 9 mg for 56 days. Additionally, participants continued to receive the same dose of their existing oral 5-ASA medication from their treating physician.	
Reporting group title	Placebo
Reporting group description:	
Participants received 1 oral tablet of matching budesonide MMX placebo for 56 days. Additionally, participants continued to receive the same dose of their existing oral 5-ASA medication from their treating physician.	

Reporting group values	Budesonide MMX	Placebo	Total
Number of subjects	255	255	510
Age categorical Units: Subjects			
Adults (18-64 years)	239	238	477
From 65-84 years	16	17	33
Age Continuous Units: years			
arithmetic mean	44.5	44.9	
standard deviation	± 13.86	± 13.44	-
Sex: Female, Male Units: Subjects			
Female	122	108	230
Male	133	147	280

Subject analysis sets	
Subject analysis set title	Budesonide MMX (ITT Population)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received 1 oral tablet of budesonide MMX 9 mg for 56 days. Additionally, participants continued to receive the same dose of their existing oral 5-ASA medication from their treating physician.	
Subject analysis set title	Placebo (ITT Population)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received 1 oral tablet of matching budesonide MMX placebo for 56 days. Additionally, participants continued to receive the same dose of their existing oral 5-ASA medication from their treating physician.	

Reporting group values	Budesonide MMX (ITT Population)	Placebo (ITT Population)	
Number of subjects	230	228	
Age categorical Units: Subjects			
Adults (18-64 years)	215	213	
From 65-84 years	15	15	

End points

End points reporting groups

Reporting group title	Budesonide MMX
Reporting group description:	
Participants received 1 oral tablet of budesonide MMX 9 mg for 56 days. Additionally, participants continued to receive the same dose of their existing oral 5-ASA medication from their treating physician.	
Reporting group title	Placebo
Reporting group description:	
Participants received 1 oral tablet of matching budesonide MMX placebo for 56 days. Additionally, participants continued to receive the same dose of their existing oral 5-ASA medication from their treating physician.	
Subject analysis set title	Budesonide MMX (ITT Population)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received 1 oral tablet of budesonide MMX 9 mg for 56 days. Additionally, participants continued to receive the same dose of their existing oral 5-ASA medication from their treating physician.	
Subject analysis set title	Placebo (ITT Population)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received 1 oral tablet of matching budesonide MMX placebo for 56 days. Additionally, participants continued to receive the same dose of their existing oral 5-ASA medication from their treating physician.	

Primary: Number of Participants Who Achieved Clinical Remission at Day 56

End point title	Number of Participants Who Achieved Clinical Remission at Day 56
End point description:	
Clinical remission defined as a score of 0 for rectal bleeding and 0 for stool frequency components from the Ulcerative Colitis Disease Activity Index (UCDAI). UCDAI is the sum (0 to 12) of 4 severity scores (0 to 3). Stool frequency and rectal bleeding were based on information recorded in daily participant diaries. Diary entries were averaged for rectal bleeding and stool frequency for 3 days prior to (and closest to) Day 56 with non-missing diary data, within 5 days prior to (and closest to) Day 56. The averages were rounded to integer values. If either subscore could not be calculated because of missing data, the score for that UCDAI component was set to missing. Participants who had clinical remission at Baseline were classified as non-responders. Population included participants who received at least 1 dose of study drug and had active UC at study entry as a cause of their symptoms (Intent-to-Treat [ITT] Population) with evaluable clinical remission data.	
End point type	Primary
End point timeframe:	
Baseline up to Day 56	

End point values	Budesonide MMX (ITT Population)	Placebo (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	196	204		
Units: participants	56	52		

Statistical analyses

Statistical analysis title	Chi square test
Comparison groups	Budesonide MMX (ITT Population) v Placebo (ITT Population)
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4877
Method	Chi-squared

Secondary: Number of Participants of Who Achieved Clinical Response at Day 56

End point title	Number of Participants of Who Achieved Clinical Response at Day 56

End point description:

Clinical response defined as an improvement in UCDAI from Baseline of ≥3 points with a rectal bleeding score ≤1. UCDAI is the sum (0 to 12) of 4 severity scores (0 to 3). Rectal bleeding was based on information recorded in daily participant diaries. The diary entries were averaged for rectal bleeding for 3 days prior to (and closest to) Day 56 with non-missing diary data, within 5 days prior to (and closest to) Day 56. The 5 days did not include any days of the flexible sigmoidoscopy (or colonoscopy) or the preparation for the flexible sigmoidoscopy (or colonoscopy). The averages were rounded to integer values. If either subscore could not be calculated because of missing data, the score for that UCDAI component was set to missing. Population included participants who received at least 1 dose of study drug and had active UC at study entry as a cause of their symptoms (ITT Population) with evaluable clinical response data.

End point type	Secondary

End point timeframe:

Baseline up to Day 56

End point values	Budesonide MMX (ITT Population)	Placebo (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	193	201		
Units: participants	101	86		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Achieved UCDAI Remission at Day 56

End point title	Number of Participants Who Achieved UCDAI Remission at Day 56

End point description:

UCDAI remission was defined as a total UCDAI score ≤1 with subscores of 0 for rectal bleeding, stool frequency, and mucosal appearance of the colon. UCDAI is the sum (0 to 12) of 4 severity scores (0 to 3). Stool frequency and rectal bleeding were based on information recorded in daily participant diaries, and mucosal appearance was based on endoscopy results. The diary entries were averaged for rectal bleeding and stool frequency for 3 days prior to (and closest to) Day 56 with non-missing diary data, within 5 days prior to (and closest to) Day 56. The averages were rounded to integer values. If the subscore could not be calculated because of missing data, the score for that UCDAI component was set to missing. Population included participants who received at least 1 dose of study drug and had active

UC at study entry as a cause of their symptoms (ITT Population) with evaluable UCDAI remission data.

End point type	Secondary

End point timeframe:

Baseline up to Day 56

End point values	Budesonide MMX (ITT Population)	Placebo (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	193	201		
Units: participants	30	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Achieved Endoscopic Remission at Day 56

End point title	Number of Participants Who Achieved Endoscopic Remission at Day 56

End point description:

Endoscopic remission was defined as a score of 0 in the mucosal appearance component subscore of the UCDAI at Day 56. UCDAI is the sum (0 to 12) of 4 severity scores (0 to 3). Mucosal appearance was based on endoscopy results. If the mucosal appearance subscore could not be calculated because of missing data, endoscopic remission was set to missing. Participants with insufficient data at Day 56 were excluded from the analysis. Population included participants who received at least 1 dose of study drug and had active UC at study entry as a cause of their symptoms (ITT Population) with evaluable endoscopic response data.

End point type	Secondary

End point timeframe:

Screening and Day 56

End point values	Budesonide MMX (ITT Population)	Placebo (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	202	211		
Units: participants	46	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Achieved Histologic Healing at Day 56

End point title	Number of Participants Who Achieved Histologic Healing at Day

	56

End point description:

Participants achieved histologic healing if histologic assessments of all biopsy specimens were graded as 0 (normal mucosa). If the score for ≥1 sample was missing, the overall score at that visit was set to missing. Participants with insufficient data at Day 56 were excluded from analysis. Population included participants who received at least 1 dose of study drug and had active UC at study entry as a cause of their symptoms (ITT Population) with evaluable histologic healing data.

End point type	Secondary

End point timeframe:

Baseline and Day 56

End point values	Budesonide MMX (ITT Population)	Placebo (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	191	205		
Units: participants	62	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Failure at Day 56

End point title	Number of Participants with Treatment Failure at Day 56

End point description:

Treatment failure was defined as an unchanged, worsened, or missing UCDAI score at Day 56. UCDAI is the sum (0 to 12) of 4 severity scores (0 to 3). Stool frequency and rectal bleeding was based on information recorded in daily participant diaries and mucosal appearance was based on endoscopy results. The diary entries were averaged for rectal bleeding and stool frequency for 3 days prior to (and closest to) Day 56 with non-missing diary data, within 5 days prior to (and closest to) Day 56. These averages were rounded to integer values. If the subscore could not be calculated because of missing data, the score for that UCDAI component was set to missing. Participants with insufficient data at Day 56 were excluded from the analysis. Participants who received at least 1 dose of study drug and had active UC at study entry as a cause of their symptoms (ITT Population) with evaluable UCDAI data.

End point type	Secondary

End point timeframe:

Baseline up to Day 56

End point values	Budesonide MMX (ITT Population)	Placebo (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	192	201		
Units: participants	45	61		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Inflammatory Bowel Disease-Quality of Life (IBD-QoL) Questionnaire Scores

End point title	Change From Baseline in Inflammatory Bowel Disease-Quality of Life (IBD-QoL) Questionnaire Scores

End point description:

The IBD-QoL questionnaire was self-completed by the participant. The IBD-QoL is a disease-specific instrument to evaluate the quality of life of participants with UC. This 32-item questionnaire has 4 dimensions: bowel function, emotional function, systemic symptoms, and social function. The total score is presented, which ranges from 32 to 224, with higher scores indicating a better quality of life. The scores of participants in remission usually range from 170 to 190. If >50% of the questionnaire answers for a particular dimension were missing, this dimension score was set to missing. The total score for the IBD-QoL was the sum of the domain scores, however, if any dimension score was missing, the total IBD-QoL score was set to missing. Participants who received at least 1 dose of study drug and had active UC at study entry as a cause of their symptoms (ITT Population) with evaluable IBD-QoL data.

End point type	Secondary

End point timeframe:

Baseline, Days 14, 28, and 56

End point values	Budesonide MMX (ITT Population)	Placebo (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	230	226		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline (N=230, 226)	132.8 (± 31.36)	134.1 (± 32.48)		
Change at Day 14 (N=228, 224)	24.4 (± 27.45)	21.3 (± 29.20)		
Change at Day 28 (N=230, 225)	31.8 (± 33.38)	25.7 (± 33.16)		
Change at Day 56 (N=230, 225)	31.1 (± 38.73)	31.7 (± 37.02)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Day 85	
Adverse event reporting additional description:	
All randomized participants who received at least 1 dose of study drug (Safety Population).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups	
Reporting group title	Budesonide MMX
Reporting group description:	
Participants received 1 oral tablet of budesonide MMX 9 mg for 56 days. Additionally, participants continued to receive the same dose of their existing oral 5-ASA medication from their treating physician.	
Reporting group title	Placebo
Reporting group description:	
Participants received 1 oral tablet of matching budesonide MMX placebo for 56 days. Additionally, participants continued to receive the same dose of their existing oral 5-ASA medication from their treating physician.	

Serious adverse events	Budesonide MMX	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 255 (3.92%)	2 / 255 (0.78%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 255 (0.39%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	6 / 255 (2.35%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis active			
subjects affected / exposed	1 / 255 (0.39%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 255 (0.39%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalemia			
subjects affected / exposed	1 / 255 (0.39%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 255 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Budesonide MMX	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 255 (5.49%)	14 / 255 (5.49%)	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	11 / 255 (4.31%)	9 / 255 (3.53%)	
occurrences (all)	11	9	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 255 (1.18%)	5 / 255 (1.96%)	
occurrences (all)	4	5	

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