Clinical trial results:
A Phase 1, Multicenter, Open-label Study to Determine the Safety and Pharmacokinetics of MMX Mesalamine Following Administration in Children and Adolescents With Ulcerative Colitis

Summary

EudraCT number	2011-000164-10
Trial protocol	GB SK
Global end of trial date	27 June 2013

Results information

Result version number	v1 (current)
This version publication date	04 September 2018
First version publication date	15 February 2015

Trial information

Trial identification

Sponsor protocol code	SPD476-112

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01130844
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Development LLC
Sponsor organisation address	725 Chesterbrook Boulevard, Wayne, United States, 19087
Public contact	Medical Communications, Shire Pharmaceutical Development, +44 0800556614,
Scientific contact	Medical Communications, Shire Pharmaceutical Development, +44 0800556614,

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	27 June 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 June 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the pharmacokinetics (PK) of 5-aminosalicylic acid (5-ASA) and its major metabolite acetyl 5-aminosalicylic acid (Ac-5-ASA) after administration of Multi-Matrix System (MMX) mesalamine at 3 different doses (30mg/kg/day, 60mg/kg/day, or 100mg/kg/day) for 7 days in children and adolescents with a history of ulcerative colitis.

Protection of trial subjects:

The study protocol, protocol amendments, the informed consent document, relevant supporting information, and all types of subject recruitment information were submitted and approved by the IEC/IRB and regulatory agency (if appropriate) prior to study initiation. This study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements. The subject's parent(s) or LAR-signed informed consent and documentation of assent by the subject (indicating the subject was aware of the investigational nature of the study, was able and willing to participate in the study, and was aware of the required restrictions and procedures) were mandatory conditions for taking part in the study. They were obtained in
writing prior to the performance of any study-specific procedures. The subject's informed consent was documented (on an appropriate form approved by the IEC/IRB) by the signature of the subject's LAR/parents (and the subject) and investigator or investigator's delegate and dated.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 October 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	7 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	52
EEA total number of subjects	44

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)	11
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:

This was a multicenter study conducted in 12 sites across 3 countries (United States, Poland, and Slovakia)

Pre-assignment

Screening details:

For subjects who were on a mesalamine product at the Screening Visit (Days -28 to -2), both they (and their LARs) and the investigator needed to feel confident that switching them from their current therapy was appropriate. Subjects who were on another product or not currently on any product for their UC had to have been on a regimen for 4 weeks.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)

Arm description:

MMX Mesalamine: 30 mg/kg/day of MMX Mesalamine tablets, dosed once daily (QD) for 7 days.

Arm type	Experimental
Investigational medicinal product name	MMX Mesalamine
Investigational medicinal product code	
Other name	Lialda, SPD476
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MMX Mesalamine tablets, 30 mg/kg/day, QD for 7 days, as achievable by the nearest and most appropriate combination of the available dosage strengths (300, 600, and/or 1200mg)

Arm title	MMX Mesalamine (60 mg/kg)

Arm description:

MMX Mesalamine: 60 mg/kg/day of MMX Mesalamine tablets, QD for 7 days.

Arm type	Experimental
Investigational medicinal product name	MMX Mesalamine
Investigational medicinal product code	
Other name	Lialda, SPD476
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MMX Mesalamine tablets, 60 mg/kg/day, QD for 7 days, as achievable by the nearest and most appropriate combination of the available dosage strengths (300, 600, and/or 1200mg)

Arm title	MMX Mesalamine (100 mg/kg)

Arm description:

MMX Mesalamine: 100 mg/kg/day of MMX Mesalamine tablets, QD for 7 days.

Arm type	Experimental

Investigational medicinal product name	MMX Mesalamine
Investigational medicinal product code	
Other name	Lialda, SPD476
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MMX Mesalamine tablets, 100 mg/kg/day, QD for 7 days, as achievable by the nearest and most appropriate combination of the available dosage strengths (300, 600, and/or 1200mg)

Number of subjects in period 1	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)
Started	21	22	9
Completed	21	22	9

Baseline characteristics

Reporting groups	
Reporting group title	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)
Reporting group description:	
MMX Mesalamine: 30 mg/kg/day of MMX Mesalamine tablets, dosed once daily (QD) for 7 days.	
Reporting group title	MMX Mesalamine (60 mg/kg)
Reporting group description:	
MMX Mesalamine: 60 mg/kg/day of MMX Mesalamine tablets, QD for 7 days.	
Reporting group title	MMX Mesalamine (100 mg/kg)
Reporting group description:	
MMX Mesalamine: 100 mg/kg/day of MMX Mesalamine tablets, QD for 7 days.	

Reporting group values	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)
Number of subjects	21	22	9
Age categorical Units: Subjects			
5-17 years, inclusive	21	22	9
Age continuous Units: years			
arithmetic mean	14	13.9	10.6
standard deviation	± 2.88	± 2.59	± 3.28
Gender categorical Units: Subjects			
Female	14	11	5
Male	7	11	4
Region of enrollment Units: Subjects			
United States	3	4	1
Slovakia	2	1	0
Poland	16	17	8

Reporting group values	Total		
Number of subjects	52		
Age categorical Units: Subjects			
5-17 years, inclusive	52		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	30		
Male	22		

Region of enrollment Units: Subjects			
United States	8		
Slovakia	3		
Poland	41		

End points

End points reporting groups

Reporting group title	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)
Reporting group description:	
MMX Mesalamine: 30 mg/kg/day of MMX Mesalamine tablets, dosed once daily (QD) for 7 days.	
Reporting group title	MMX Mesalamine (60 mg/kg)
Reporting group description:	
MMX Mesalamine: 60 mg/kg/day of MMX Mesalamine tablets, QD for 7 days.	
Reporting group title	MMX Mesalamine (100 mg/kg)
Reporting group description:	
MMX Mesalamine: 100 mg/kg/day of MMX Mesalamine tablets, QD for 7 days.	

Primary: Area Under the Plasma Concentration Versus Time Curve (AUC) of Multi-Matrix System (MMX) Mesalamine (5-ASA) at Steady State

End point title	Area Under the Plasma Concentration Versus Time Curve (AUC) of Multi-Matrix System (MMX) Mesalamine (5-ASA) at Steady State[1]

End point description:

AUC can be used as a measure of drug exposure. It is derived from drug concentration and time so it gives a measure how much and how long a drug stays in a body.
This end point used the Pharmacokinetic Set (PKS), which consisted of all subjects in the Safety Analysis Set who generated sufficient plasma samples to allow reliable determination of Cmax and AUC. The Safety Analysis Set consisted of subjects who took at least 1 dose of investigational product and had at least 1 post-dose safety assessment.

End point type	Primary

End point timeframe:

Over a 24-hour period starting on day 7

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no inferential statistical analysis of the pharmacokinetic data. Summary statistics (number of subjects, mean, SD, CV, medium, maximum, minimum, and geometric mean) were presented by treatment group and by treatment group within age group (5-12 years; 13-17 years) for all pharmacokinetic parameters. Plasma concentrations at each nominal sampling time were also summarized using descriptive statistics.

End point values	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	22	9	
Units: ug*h/L				
arithmetic mean (standard deviation)	21411 (± 11081)	46173 (± 22864)	49213 (± 17664)	

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Plasma Concentration (Cmax) of MMX Mesalamine (5-ASA) at Steady State

End point title	Maximum Plasma Concentration (Cmax) of MMX Mesalamine (5-ASA) at Steady State[2]

End point description:

Cmax is a term that refers to the maximum (or peak) concentration that a drug achieves in the body after the drug has been administrated.
This end point used the Pharmacokinetic Set (PKS), which consisted of all subjects in the Safety Analysis Set who generated sufficient plasma samples to allow reliable determination of Cmax and AUC. The Safety Analysis Set consisted of subjects who took at least 1 dose of investigational product and had at least 1 post-dose safety assessment.

End point type	Primary

End point timeframe:

Over a 24-hour period starting on day 7

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no inferential statistical analysis of the pharmacokinetic data. Summary statistics (number of subjects, mean, SD, CV, medium, maximum, minimum, and geometric mean) were presented by treatment group and by treatment group within age group (5-12 years; 13-17 years) for all pharmacokinetic parameters. Plasma concentrations at each nominal sampling time were also summarized using descriptive statistics.

End point values	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	22	9	
Units: ug/L				
arithmetic mean (standard deviation)	1884 (± 1018)	3825 (± 1979)	4314 (± 2602)	

Statistical analyses

No statistical analyses for this end point

Primary: Time to Maximum Plasma Concentration (Tmax) of MMX Mesalamine (5-ASA) at Steady State

End point title	Time to Maximum Plasma Concentration (Tmax) of MMX Mesalamine (5-ASA) at Steady State[3]

End point description:

Tmax is the time after administration of a drug when the maximum plasma concentration in the body is reached.
This end point used the Pharmacokinetic Set (PKS), which consisted of all subjects in the Safety Analysis Set who generated sufficient plasma samples to allow reliable determination of Cmax and AUC. The Safety Analysis Set consisted of subjects who took at least 1 dose of investigational product and had at least 1 post-dose safety assessment.

End point type	Primary

End point timeframe:

Over a 24-hour period starting on day 7

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no inferential statistical analysis of the pharmacokinetic data. Summary statistics (number of subjects, mean, SD, CV, medium, maximum, minimum, and geometric mean) were presented by treatment group and by treatment group within age group (5-12 years; 13-17 years) for

all pharmacokinetic parameters. Plasma concentrations at each nominal sampling time were also summarized using descriptive statistics.

End point values	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	22	9	
Units: hours				
median (full range (min-max))	6 (0 to 24)	8.98 (0 to 24)	1.98 (0 to 24)	

Statistical analyses

No statistical analyses for this end point

Primary: Total Body Clearance (CL) of MMX Mesalamine (5-ASA) at Steady State

End point title	Total Body Clearance (CL) of MMX Mesalamine (5-ASA) at Steady State[4]

End point description:

Clearance of a substance from the blood by the kidneys.
This end point used the Pharmacokinetic Set (PKS), which consisted of all subjects in the Safety Analysis Set who generated sufficient plasma samples to allow reliable determination of Cmax and AUC. The Safety Analysis Set consisted of subjects who took at least 1 dose of investigational product and had at least 1 post-dose safety assessment.

End point type	Primary

End point timeframe:

Over a 24-hour period starting on day 7

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no inferential statistical analysis of the pharmacokinetic data. Summary statistics (number of subjects, mean, SD, CV, medium, maximum, minimum, and geometric mean) were presented by treatment group and by treatment group within age group (5-12 years; 13-17 years) for all pharmacokinetic parameters. Plasma concentrations at each nominal sampling time were also summarized using descriptive statistics.

End point values	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	22	9	
Units: L/h				
arithmetic mean (standard deviation)	6.48 (± 2.99)	5.94 (± 2.95)	4.95 (± 2.07)	

Statistical analyses

No statistical analyses for this end point

Primary: AUC of MMX Mesalamine Major Metabolite (Ac-5-ASA) at Steady State

End point title	AUC of MMX Mesalamine Major Metabolite (Ac-5-ASA) at Steady State[5]

End point description:

This end point used the Pharmacokinetic Set (PKS), which consisted of all subjects in the Safety Analysis Set who generated sufficient plasma samples to allow reliable determination of Cmax and AUC. The Safety Analysis Set consisted of subjects who took at least 1 dose of investigational product and had at least 1 post-dose safety assessment.

End point type	Primary

End point timeframe:

Over a 24-hour period starting on day 7

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no inferential statistical analysis of the pharmacokinetic data. Summary statistics (number of subjects, mean, SD, CV, medium, maximum, minimum, and geometric mean) were presented by treatment group and by treatment group within age group (5-12 years; 13-17 years) for all pharmacokinetic parameters. Plasma concentrations at each nominal sampling time were also summarized using descriptive statistics.

End point values	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	22	9	
Units: ug*h/L				
arithmetic mean (standard deviation)	30942 (± 13743)	58119 (± 22729)	63067 (± 21752)	

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of MMX Mesalamine Major Metabolite (Ac-5-ASA) at Steady State

End point title	Cmax of MMX Mesalamine Major Metabolite (Ac-5-ASA) at Steady State[6]

End point description:

This end point used the Pharmacokinetic Set (PKS), which consisted of all subjects in the Safety Analysis Set who generated sufficient plasma samples to allow reliable determination of Cmax and AUC. The Safety Analysis Set consisted of subjects who took at least 1 dose of investigational product and had at least 1 post-dose safety assessment.

End point type	Primary

End point timeframe:

Over a 24-hour period starting on day 7

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no inferential statistical analysis of the pharmacokinetic data. Summary statistics (number of subjects, mean, SD, CV, medium, maximum, minimum, and geometric mean) were presented by treatment group and by treatment group within age group (5-12 years; 13-17 years) for all pharmacokinetic parameters. Plasma concentrations at each nominal sampling time were also summarized using descriptive statistics.

End point values	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	22	9	
Units: ug/L				
arithmetic mean (standard deviation)	2396 (± 1217)	4113 (± 1641)	4968 (± 2911)	

Statistical analyses

No statistical analyses for this end point

Primary: Tmax of MMX Mesalamine Major Metabolite (Ac-5-ASA) at Steady State

End point title	Tmax of MMX Mesalamine Major Metabolite (Ac-5-ASA) at Steady State[7]

End point description:

This end point used the Pharmacokinetic Set (PKS), which consisted of all subjects in the Safety Analysis Set who generated sufficient plasma samples to allow reliable determination of Cmax and AUC. The Safety Analysis Set consisted of subjects who took at least 1 dose of investigational product and had at least 1 post-dose safety assessment.

End point type	Primary

End point timeframe:

Over a 24-hour period starting on day 7

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no inferential statistical analysis of the pharmacokinetic data. Summary statistics (number of subjects, mean, SD, CV, medium, maximum, minimum, and geometric mean) were presented by treatment group and by treatment group within age group (5-12 years; 13-17 years) for all pharmacokinetic parameters. Plasma concentrations at each nominal sampling time were also summarized using descriptive statistics.

End point values	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	22	9	
Units: hours				
median (full range (min-max))	9 (0 to 24)	7.48 (0 to 24)	1.98 (0 to 24)	

Statistical analyses

No statistical analyses for this end point

Primary: CL of MMX Mesalamine Major Metabolite (Ac-5-ASA) at Steady State

End point title	CL of MMX Mesalamine Major Metabolite (Ac-5-ASA) at Steady State[8]

End point description:

This end point used the Pharmacokinetic Set (PKS), which consisted of all subjects in the Safety Analysis Set who generated sufficient plasma samples to allow reliable determination of Cmax and AUC. The

Safety Analysis Set consisted of subjects who took at least 1 dose of investigational product and had at least 1 post-dose safety assessment.

End point type	Primary

End point timeframe:

Over a 24-hour period starting on day 7

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no inferential statistical analysis of the pharmacokinetic data. Summary statistics (number of subjects, mean, SD, CV, medium, maximum, minimum, and geometric mean) were presented by treatment group and by treatment group within age group (5-12 years; 13-17 years) for all pharmacokinetic parameters. Plasma concentrations at each nominal sampling time were also summarized using descriptive statistics.

End point values	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	22	9	
Units: L/h				
arithmetic mean (standard deviation)	16.2 (± 6.72)	12.2 (± 4.43)	10 (± 4.36)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Absorption of MMX Mesalamine (5-ASA) in Urine at Steady State

End point title	Percent Absorption of MMX Mesalamine (5-ASA) in Urine at Steady State

End point description:

This end point used the Pharmacokinetic Set (PKS), which consisted of all subjects in the Safety Analysis Set who generated sufficient plasma samples to allow reliable determination of Cmax and AUC. The Safety Analysis Set consisted of subjects who took at least 1 dose of investigational product and had at least 1 post-dose safety assessment.

End point type	Secondary

End point timeframe:

Over a 24-hour period starting on day 7

End point values	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	22	9	
Units: percentage of dose absorbed				
arithmetic mean (standard deviation)	29.4 (± 14.5)	27 (± 13.5)	22.1 (± 13.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Amount of MMX Mesalamine (5-ASA) Recovered in Urine at Steady State

End point title	Cumulative Amount of MMX Mesalamine (5-ASA) Recovered in Urine at Steady State

End point description:

This end point used the Pharmacokinetic Set (PKS), which consisted of all subjects in the Safety Analysis Set who generated sufficient plasma samples to allow reliable determination of Cmax and AUC. The Safety Analysis Set consisted of subjects who took at least 1 dose of investigational product and had at least 1 post-dose safety assessment.

End point type	Secondary

End point timeframe:

Over a 24-hour period starting on day 7

End point values	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	22	9	
Units: mg				
arithmetic mean (standard deviation)	162 (± 132)	298 (± 221)	235 (± 121)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Amount of MMX Mesalamine Major Metabolite (Ac-5-ASA) Recovered in Urine at Steady State

End point title	Cumulative Amount of MMX Mesalamine Major Metabolite (Ac-5-ASA) Recovered in Urine at Steady State

End point description:

This end point used the Pharmacokinetic Set (PKS), which consisted of all subjects in the Safety Analysis Set who generated sufficient plasma samples to allow reliable determination of Cmax and AUC. The Safety Analysis Set consisted of subjects who took at least 1 dose of investigational product and had at least 1 post-dose safety assessment.

End point type	Secondary

End point timeframe:

Over a 24-hour period starting on day 7

End point values	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	22	9	
Units: mg				
arithmetic mean (standard deviation)	532 (± 411)	708 (± 341)	593 (± 251)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

12 to 14 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)

Reporting group description:

MMX Mesalamine: 30 mg/kg/day of MMX Mesalamine tablets, QD for 7 days.

Reporting group title	MMX Mesalamine (60 mg/kg)

Reporting group description:

MMX Mesalamine: 60 mg/kg/day of MMX Mesalamine tablets, QD for 7 days.

Reporting group title	MMX Mesalamine (100 mg/kg)

Reporting group description:

MMX Mesalamine: 100 mg/kg/day of MMX Mesalamine tablets, QD for 7 days.

Serious adverse events	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Multi-Matrix System (MMX) Mesalamine (30 mg/kg)	MMX Mesalamine (60 mg/kg)	MMX Mesalamine (100 mg/kg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 9 (0.00%)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: None occurred at a frequency that was equal to or greater than the threshold for reporting non-serious adverse events.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2010	*The maximum daily dose of investigational product (4800 mg) was specified. *The adverse drug reaction "nausea" was added to the safety background section. *The word "visit" was added to the footnote of the schedule of assessments: "A follow-up telephone call or visit is to be made/conducted 5 to 7 days after the last dose of investigational product." *The word "screening" was added to clarify that the subject screening number was combined with the site number to form the unique subject identifier. *Language was added to clarify the investigational product had to be swallowed whole and can not be chewed, broken, or crushed. *Text that required subjects to fast overnight (for at least 8 hours) prior to blood collection for biochemistry analysis was removed. For children and adolescents, aged 5-17 years, fasting was not required in this situation.
04 August 2010	*Efficacy data were updated to include protocol SPD476-304 and SPD476-404 study results and SPD476-409 study start date. *Safety data were updated to include the most frequently reported adverse drug reactions.
09 February 2011	*Text was added to reflect the addition of Eastern European countries. *Text was added to concomitant medication section to allow for the administration of the influenza vaccine. *Text was added to refer the reader to the current investigator's brochure. *Prescribing information was removed.
18 August 2011	*The selection of a primary investigator was added. *An ECG assessment was added at screening and on Day 7 to meet European Regulatory Agency request. *Text was revised to reflect a change in the participating Eastern European countries, and increase in the enrollment (and thus total study) period. *The biochemistry and hematology blood sample collection was revised: the Day 7 pre-dose samples were removed and it was specified that if the baseline (Day -1) assessment was within 21 days of screening, samples were not required. This lowered the total blood volume collected to approximately 43mL-51mL depending on subject visit scheduling. At no point during any 4-week period more than 43mL of blood was collected from a subject. The change was made to meet the European Union guidance that not more than 3% of total blood volume can be collected in a 4-week period. *The need to record abnormal physical examination findings in the eCRF, unless they are clinically significant, was removed. *Vital signs were revised such that they were only collected after being in a supine position for 5 minutes, instead of sitting, to match ECG collection. *Text was revised to clarify that only clinically significant changes in physical examination and ECGs were captured (as AEs) and analyzed. *The physical examination section was removed, as physical examination findings were not being captured in the eCRF unless they were reported as an AE or SAE.

04 September 2012	*The rationale text was updated to include reference to the Phase 3 efficacy and safety study. *An error in exclusion criterion 4 was corrected (from L.73 to 1.73). *Text in the dose group reference was corrected (from children older than 6 years to older than 5 years). *Labeling and packaging information was updated to include information for sites in Australia and the Russian Federation. *Text was revised to better define the expectation for collection of AEs that may be related to the subject's chronic disease. *Text was revised to include an interim analysis. *Name and contact details of the principal investigator were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 June 2013	Results of the interim population pharmacokinetic analysis demonstrated that 5-ASA and Ac-5-ASA exposures in children (5-12 years) and adolescents (13-17 years) given SPD476 at 30, 60, and 100 mg/kg/day dose are likely to be within the range of exposures at which the efficacy and safety have been confirmed in adults: 1) The interim 5-ASA/Ac-5-ASA pharmacokinetic data in children and adolescents with UC were well described by a structural model with first-order absorption from 2 depot compartments, absorption lag times, separate central compartments for 5-ASA and Ac-5-ASA with respective urine compartments for renal clearance. 2) Allometric scaling based on body weight was successfully incorporated as predictors of clearance and volume parameters. 3) Dosing on a mg/kg basis (30, 60 and 100 mg/kg/day) in children (5-12 years) and adolescents (13-17 years) provides similar steady-state exposure to that observed in adults for approved fixed doses (2400 mg and 4800 mg). The above conclusions were endorsed by the FDA and it was decided to stop the enrollment of new subjects into this Phase 1 study and to allow initiation of a larger efficacy study in children and adolescents with UC post-approval of the final protocol.	-

Notes:

Limitations and caveats

None reported