Clinical trial results:
Long-Term, Open-Label Study with a Double-Blind, Placebo-Controlled, Randomized Drug Withdrawal Period of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients with Alagille Syndrome

Summary

EudraCT number	2013-005373-43
Trial protocol	ES PL BE GB FR
Global end of trial date	28 May 2020

Results information

Result version number	v1 (current)
This version publication date	20 December 2020
First version publication date	20 December 2020
Summary attachment (see zip file)	Final Clinical Study Report Overall Conclusions (Overall conclusions only.pdf) Interim Clinical Study Report Synopsis (synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	LUM001-304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02160782
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mirum Pharmaceuticals, Inc
Sponsor organisation address	950 Tower Lane, Suite 1050, Foster City, United States, CA 94404
Public contact	Medical Information Mirum, Mirum Pharmaceuticals, Inc., +1 6506674085, medinfo@mirumpharma.com
Scientific contact	Medical Information Mirum, Mirum Pharmaceuticals, Inc., +1 6506674085, medinfo@mirumpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001475-PIP03-17
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	21 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 May 2015
Global end of trial reached?	Yes
Global end of trial date	28 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study (up to and including Week 48) were:
- To evaluate the long-term safety and tolerability of maralixibat (MRX)
- To evaluate the effect of MRX on serum bile acid (sBA) levels
- To evaluate the effect of MRX on biochemical markers of cholestasis and liver disease
- To evaluate the effect of MRX on pruritus
- To evaluate the long-term effect of MRX during 48 weeks of treatment
in children with Alagille Syndrome (ALGS)

The objectives of the optional long-term extension period (after Week 48) were:
- To offer eligible participants continued study treatment after Week 48
- To explore a twice daily (BID) dosing regimen and higher daily dosing of MRX
- To obtain safety and efficacy data in participants treated long-term with MRX, including genotyping characteristics
- To assess the level of alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma
- To assess palatability of the maralixibat formulation

Protection of trial subjects:

All study participants (caregivers as applicable) were required to read and sign an Informed Consent Form (ICF). Participants were re-consented to the most current version of the ICF(s) during their participation in the study

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 October 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Australia: 9

Worldwide total number of subjects	31
EEA total number of subjects	22

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)	6
Children (2-11 years)	20
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 31 participants were enrolled at 9 sites in 6 countries (Australia, UK, France, Poland, Spain and Belgium). Participants included 12 females (38.7%) and 19 males (61.3%), with a mean (SD) age of 5.4 (4.25) years (range: 1 to 15 years).

Pre-assignment

Screening details:

A total of 36 patients were screened for the study. Five of these patients were screen failures.

Period 1

Period 1 title	Open-label period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Open-label period: MRX

Arm description:

All participants received MRX at doses of up to 400 µg/kg once daily (QD) during a 6-week open-label dose-escalation period, followed by a 12-week open-label stable-dosing period. All participants reached 400 µg/kg QD for this period.

Arm type	Experimental
Investigational medicinal product name	Maralixibat chloride
Investigational medicinal product code	
Other name	LUM001
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Oral use

Dosage and administration details:

During a 6-week dose escalation period, all participants received MRX at doses of up to 400 µg/kg QD. This was followed by a 12-week stable-dosing period, using the dose administered at Week 6, which may have been 400 µg/kg QD or the highest tolerated dose below 400 µg/kg QD.

Number of subjects in period 1	Open-label period: MRX
Started	31
Completed	29
Not completed	2
Adverse event, non-fatal	2

Period 2

Period 2 title	Randomized withdrawal period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Participants were randomized 1:1 to continue to receive MRX or placebo for 4 weeks between the start of Week 19 and the end of Week 22 (the double-blind, placebo-controlled study drug withdrawal period). All participants, monitors, and study center personnel related to the study, except for the central pharmacist who prepared the study drug, were blinded to study treatment and to the participants' study drug withdrawal period treatment assignment during the randomized withdrawal (RWD) period.

Arms

Are arms mutually exclusive?	Yes
Arm title	RWD period: MRX

Arm description:

Participants continued to receive MRX at 400 µg/kg QD during the RWD period

Arm type	Experimental
Investigational medicinal product name	Maralixibat chloride
Investigational medicinal product code	
Other name	LUM001
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants continued to receive MRX at the dose administered at Week 18.

Arm title	RWD period: placebo

Arm description:

Participants received a corresponding placebo during the RWD period

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants received a corresponding placebo.

Number of subjects in period 2	RWD period: MRX	RWD period: placebo
Started	13	16
Completed	13	16

Period 3

Period 3 title	After randomized withdrawal period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	After RWD period: MRX

Arm description:

Participants who received placebo during the RWD period returned to the MRX dose received during the initial escalation in a 26-week long-term exposure period to complete 48 weeks of treatment.
Participants who received MRX during the RWD period continued in a 26-week long-term exposure period to complete 48 weeks of treatment. Participants remained blinded to their assigned arm during the RWD period.

Arm type	Experimental
Investigational medicinal product name	Maralixibat chloride
Investigational medicinal product code	
Other name	LUM001
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants who received placebo in the RWD period received MRX dosed according to the dose escalation schedule that mirrored the initial escalation, i.e., the MRX dose was increased weekly over a 6-week period to the maximum tolerated dose (MTD) up to 400 µg/kg QD, or the highest tolerated dose below the 400 µg/kg QD dose.
Participants who received MRX during the RWD period continued to receive the same dose of MRX and, following Week 22, a simulated dose escalation occurred to maintain the blind in the RWD period.
Dosing with MRX continued in a 26-week long-term exposure period to complete 48 weeks of treatment.

Number of subjects in period 3	After RWD period: MRX
Started	29
Completed	23
Not completed	6
Adverse event, non-fatal	1
Did not consent to protocol amendment for period 4	5

Period 4

Period 4 title	Long-term extension period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Long-term extension period: MRX

Arm description:

The long-term extension (LTE) period consisted of 2 phases: (1) a 52-week optional follow-up treatment period (Weeks 49-100), during which participants received up to 400 µg/kg QD MRX. This was followed by: (2) a long-term optional follow-up treatment period (>Week 100) during which participants received up to 400 µg/kg BID doses of MRX.

Arm type	Experimental
Investigational medicinal product name	Maralixibat chloride
Investigational medicinal product code	
Other name	LUM001
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants continuing into the LTE period were maintained at the same dose level of MRX that they had been taking at Week 48 during the 52-week optional follow-up treatment period (Weeks 49-100). After Week 100, during the long-term optional follow-up treatment period, participants received the same dose level of MRX, or, if they were eligible, started BID dosing up to their MTD or a maximum daily dose of 400 µg/kg BID.

Number of subjects in period 4	Long-term extension period: MRX
Started	23
Completed	14
Not completed	9
Physician decision	1
Withdrawal by caregiver	1
Adverse event, non-fatal	3
Did not consent to protocol amendment	4

Baseline characteristics

Reporting groups	
Reporting group title	Open-label period: MRX
Reporting group description:	
All participants received MRX at doses of up to 400 µg/kg once daily (QD) during a 6-week open-label dose-escalation period, followed by a 12-week open-label stable-dosing period. All participants reached 400 µg/kg QD for this period.	

Reporting group values	Open-label period: MRX	Total	
Number of subjects	31	31	
Age categorical			
The mean (SD) age in the overall study population was 5.4 (4.25) years (range: 1 to 15 years) at baseline. Mean age was similar between the MRX and placebo groups in the different periods of the study.			
Units: Subjects			
<2 years	6	6	
2 to 4 years	9	9	
5 to 8 years	9	9	
9 to 12 years	4	4	
13 to 18 years	3	3	
Gender categorical			
In the overall study population (N = 31), there were more males (61.3%) than females (38.7%) at baseline.			
Units: Subjects			
Female	12	12	
Male	19	19	
Country			
The majority of the participants were from Australia and France (each 29.0% of the overall study population).			
Units: Subjects			
Australia	9	9	
Belgium	5	5	
France	9	9	
Poland	3	3	
Spain	2	2	
United Kingdom	3	3	
Height z-score			
Units: z-score			
arithmetic mean	-1.668		
standard deviation	± 1.3413	-	
Weight z-score			
Units: Z-score			
arithmetic mean	-1.700		
standard deviation	± 1.1840	-	

End points

End points reporting groups

Reporting group title	Open-label period: MRX

Reporting group description:

All participants received MRX at doses of up to 400 µg/kg once daily (QD) during a 6-week open-label dose-escalation period, followed by a 12-week open-label stable-dosing period. All participants reached 400 µg/kg QD for this period.

Reporting group title	RWD period: MRX

Reporting group description:

Participants continued to receive MRX at 400 µg/kg QD during the RWD period

Reporting group title	RWD period: placebo

Reporting group description:

Participants received a corresponding placebo during the RWD period

Reporting group title	After RWD period: MRX

Reporting group description:

Participants who received placebo during the RWD period returned to the MRX dose received during the initial escalation in a 26-week long-term exposure period to complete 48 weeks of treatment. Participants who received MRX during the RWD period continued in a 26-week long-term exposure period to complete 48 weeks of treatment. Participants remained blinded to their assigned arm during the RWD period.

Reporting group title	Long-term extension period: MRX

Reporting group description:

The long-term extension (LTE) period consisted of 2 phases: (1) a 52-week optional follow-up treatment period (Weeks 49-100), during which participants received up to 400 µg/kg QD MRX. This was followed by: (2) a long-term optional follow-up treatment period (>Week 100) during which participants received up to 400 µg/kg BID doses of MRX.

Subject analysis set title	Open-label period: MRX baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

These are the baseline values for participants in the open-label period

Subject analysis set title	Open-label period: MRX Week 18
Subject analysis set type	Sub-group analysis

Subject analysis set description:

These are the Week 18 values for participants in the open-label period. These participants are also represented in the Open-label Period: MRX baseline group; the analyses look at the change from baseline to Week 18 in the same participants.

Primary: Change from Week 18 to Week 22 in fasting sBA levels in participants who had a reduction in sBA ≥50% from baseline to Week 12 or Week 18

End point title	Change from Week 18 to Week 22 in fasting sBA levels in participants who had a reduction in sBA ≥50% from baseline to Week 12 or Week 18

End point description:

The primary efficacy endpoint of this study was the mean change from Week 18 to Week 22 (the RWD period) of fasting sBA levels in participants who previously responded to MRX treatment, as defined by a reduction in sBA ≥50% from baseline to Week 12 or Week 18 (Modified Intent-to-Treat [MITT] Population).
Five participants in the MRX group and 10 participants in the placebo group met the prespecified sBA reduction criteria. The difference of 5 versus 10 participants in the MRX and placebo groups, respectively, was a result of the randomization schedule which used a central by-block randomization process (within IRT), with entire blocks assigned by study site. The randomization allocation method resulted in more participants in the placebo group from those participants with a ≥50% reduction in sBA at Week 12.

End point type	Primary

End point timeframe:

Week 18 to Week 22

End point values	RWD period: MRX	RWD period: placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	10		
Units: µmol/L				
least squares mean (standard error)	-21.73 (± 43.125)	95.55 (± 30.488)		

Statistical analyses

Statistical analysis title	Change from Week 18 to Week 22 in sBA levels

Statistical analysis description:

The difference between treatment groups in change from Week 18 to Week 22 in fasting sBA levels was evaluated using an analysis of covariance (ANCOVA) model with treatment group as a factor, and Week 18 sBA as a covariate. The analysis used a tabulation of fitted summary statistics from ANCOVA in the MITT population, which included all participants who were enrolled, received study drug through Week 18, and had a reduction from baseline in sBA of ≥50% at the Week 12 or Week 18 measurement.

Comparison groups	RWD period: placebo v RWD period: MRX
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.0464 [2]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-117.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-232.38
upper limit	-2.18
Variability estimate	Standard error of the mean
Dispersion value	52.828

Notes:

[1] - The P-value for testing if the treatment group least squares (LS) means were equal was calculated to determine if the change in sBA levels between the treatment groups was statistically significant.
[2] - P-value for change from Week 18 to Week 22 in the MRX group = 0.6234; P-value for change from Week 18 to Week 22 in the placebo group = 0.0086.

Secondary: Change from Week 18 to Week 22 in alkaline phosphatase

End point title	Change from Week 18 to Week 22 in alkaline phosphatase

End point description:

This secondary efficacy endpoint is the mean change from Week 18 to Week 22 in ALP

End point type	Secondary

End point timeframe:

Week 18 to Week 22

End point values	RWD period: MRX	RWD period: placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	16		
Units: U/L				
least squares mean (standard error)	2.8 (± 22.55)	-7.2 (± 20.31)		

Statistical analyses

Statistical analysis title	Change from Week 18 to Week 22 in ALP

Statistical analysis description:

The difference between treatment groups in change from Week 18 to Week 22 in ALP levels was evaluated using an ANCOVA model with treatment group as a factor, and Week 18 ALP as a covariate. The analysis used a tabulation of fitted summary statistics from ANCOVA in the intent-to-treat population, which included all participants who were enrolled, and received at least one dose of study drug.

Comparison groups	RWD period: MRX v RWD period: placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.7455 [4]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.6
upper limit	72.6
Variability estimate	Standard error of the mean
Dispersion value	30.44

Notes:

[3] - The P-value for testing if the treatment group LS means were equal was calculated to determine if the change in ALP levels between the treatment groups was statistically significant.
[4] - P-value for change from Week 18 to Week 22 in the MRX group = 0.9026; P-value for change from Week 18 to Week 22 in the placebo group = 0.7258.

Secondary: Change from Week 18 to Week 22 in alanine aminotransferase

End point title	Change from Week 18 to Week 22 in alanine aminotransferase

End point description:

This secondary efficacy endpoint is the mean change from Week 18 to Week 22 in alanine aminotransferase (ALT)

End point type	Secondary

End point timeframe:

Week 18 to Week 22

End point values	RWD period: MRX	RWD period: placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	16		
Units: U/L				
least squares mean (standard error)	34.5 (± 14.04)	19.4 (± 12.56)		

Statistical analyses

Statistical analysis title	Change from Week 18 to Week 22 in ALT

Statistical analysis description:

The difference between treatment groups in change from Week 18 to Week 22 in ALT levels was evaluated using an ANCOVA model with treatment group as a factor, and Week 18 ALT as a covariate. The analysis used a tabulation of fitted summary statistics from ANCOVA in the intent-to-treat population, which included all participants who were enrolled, and received at least one dose of study drug.

Comparison groups	RWD period: MRX v RWD period: placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	= 0.4472 [6]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	15.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.1
upper limit	55.2
Variability estimate	Standard error of the mean
Dispersion value	19.53

Notes:

[5] - The P-value for testing if the treatment group LS means were equal was calculated to determine if the change in ALT levels between the treatment groups was statistically significant.
[6] - P-value for change from Week 18 to Week 22 in the MRX group = 0.0211; P-value for change from Week 18 to Week 22 in the placebo group = 0.1343.

Secondary: Change from Week 18 to Week 22 in total bilirubin

End point title	Change from Week 18 to Week 22 in total bilirubin

End point description:

This secondary efficacy endpoint is the mean change from Week 18 to Week 22 in total bilirubin

End point type	Secondary

End point timeframe:

Week 18 to Week 22

End point values	RWD period: MRX	RWD period: placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	16		
Units: mg/dL				
least squares mean (standard error)	0.32 (± 0.265)	0.46 (± 0.238)		

Statistical analyses

Statistical analysis title	Change from Week 18 to Week 22 in total bilirubin

Statistical analysis description:

The difference between treatment groups in change from Week 18 to Week 22 in total bilirubin was evaluated using an ANCOVA model with treatment group as a factor, and Week 18 total bilirubin as a covariate. The analysis used a tabulation of fitted summary statistics from ANCOVA in the intent-to-treat population, which included all participants who were enrolled, and received at least one dose of study drug.

Comparison groups	RWD period: MRX v RWD period: placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	equivalence[7]
P-value	= 0.7 [8]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.361

Notes:

[7] - The P-value for testing if the treatment group LS means were equal was calculated to determine if the change in total bilirubin between the treatment groups was statistically significant.
[8] - P-value for change from Week 18 to Week 22 in the MRX group = 0.2447; P-value for change from Week 18 to Week 22 in the placebo group = 0.0665.

Secondary: Change from Week 18 to Week 22 in direct bilirubin

End point title	Change from Week 18 to Week 22 in direct bilirubin

End point description:

This secondary efficacy endpoint is the mean change from Week 18 to Week 22 in direct bilirubin

End point type	Secondary

End point timeframe:

Week 18 to Week 22

End point values	RWD period: MRX	RWD period: placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	15		
Units: mg/dL				
least squares mean (standard error)	0.13 (± 0.195)	0.14 (± 0.174)		

Statistical analyses

Statistical analysis title	Change from Week 18 to Week 22 in direct bilirubin

Statistical analysis description:

The difference between treatment groups in change from Week 18 to Week 22 in ALP levels was evaluated using an ANCOVA model with treatment group as a factor, and Week 18 direct bilirubin as a covariate. The analysis used a tabulation of fitted summary statistics from ANCOVA in the intent-to-treat population, which included all participants who were enrolled, and received at least one dose of study drug.

Comparison groups	RWD period: MRX v RWD period: placebo
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	equivalence[9]
P-value	= 0.9517 [10]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.53
Variability estimate	Standard error of the mean
Dispersion value	0.265

Notes:

[9] - The P-value for testing if the treatment group LS means were equal was calculated to determine if the change in direct bilirubin between the treatment groups was statistically significant.
[10] - P-value for change from Week 18 to Week 22 in the MRX group = 0.5183; P-value for change from Week 18 to Week 22 in the placebo group = 0.4159.

Secondary: Change from Week 18 to Week 22 in pruritus as measured by ItchRO

End point title	Change from Week 18 to Week 22 in pruritus as measured by ItchRO

End point description:

This secondary efficacy endpoint is the change from Week 18 to Week 22 in pruritus as measured by ItchRO(Obs) weekly average morning score and ItchRO(Pt) weekly average morning score. ItchRO scores range from 0 to 4; the higher score indicates increasing itch severity (0 = none; 4 = very severe).

End point type	Secondary

End point timeframe:

Week 18 to Week 22

End point values	RWD period: MRX	RWD period: placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[11]	16[12]		
Units: Points (0-4)				
least squares mean (standard error)				
ItchRO(Obs) weekly average morning score	0.217 (± 0.2345)	1.700 (± 0.2031)		
ItchRO(Pt) weekly average morning score	-0.149 (± 0.3719)	1.839 (± 0.2771)		

Notes:

[11] - n=12 for ItchRO(Obs) weekly average morning score; n=5 for ItchRO(Pt) weekly average morning score.
[12] - n=16 for ItchRO(Obs) weekly average morning score; n=9 for ItchRO(Pt) weekly average morning score.

Statistical analyses

Statistical analysis title	Change from Week 18 to Week 22 in ItchRO(Obs)

Statistical analysis description:

The difference between treatment groups in change from Week 18 to Week 22 in ItchRO(Obs) was evaluated using an ANCOVA model with treatment group as a factor, and Week 18 ItchRO(Obs) as a covariate. The analysis used a tabulation of fitted summary statistics from ANCOVA in the intent-to-treat population, which included all participants who were enrolled, and received at least one dose of study drug.

Comparison groups	RWD period: MRX v RWD period: placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence[13]
P-value	< 0.0001 [14]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.483
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.122
upper limit	-0.844
Variability estimate	Standard error of the mean
Dispersion value	0.3103

Notes:

[13] - The P-value for testing if the treatment group LS means were equal was calculated to determine if the change in ItchRO(Obs) between the treatment groups was statistically significant.

[14] - P-value for change from Week 18 to Week 22 in the MRX group = 0.3639; P-value for change from Week 18 to Week 22 in the placebo group <0.0001.

Statistical analysis title	Change from Week 18 to Week 22 in ItchRO(Pt)

Statistical analysis description:

The difference between treatment groups in change from Week 18 to Week 22 in ItchRO (Pt) was evaluated using an ANCOVA model with treatment group as a factor, and Week 18 ItchRO(Pt) as a covariate.
The analysis used a tabulation of fitted summary statistics from ANCOVA in the intent-to-treat population, which included all participants who were enrolled, and received at least one dose of study drug.

Comparison groups	RWD period: MRX v RWD period: placebo

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence[15]
P-value	= 0.0013 [16]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.988
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.009
upper limit	-0.967
Variability estimate	Standard error of the mean
Dispersion value	0.4641

Notes:

[15] - The P-value for testing if the treatment group LS means were equal was calculated to determine if the change in ItchRO(Pt) between the treatment groups was statistically significant.
While the number of participants included in analysis for the end point indicates 28, there were only 14; n = 5 for ItchRO(Pt): MRX and n = 9 for ItchRO(Pt): placebo.

[16] - P-value for change in ItchRO(Pt) from Week 18 to Week 22 in the MRX group = 0.6956; P-value for change in ItchRO(Pt) from Week 18 to Week 22 in the placebo group <0.0001.

Secondary: Change from baseline to Week 18 in fasting sBA levels

End point title	Change from baseline to Week 18 in fasting sBA levels

End point description:

This secondary efficacy endpoint is the mean change from baseline to Week 18 in fasting sBA levels

End point type	Secondary

End point timeframe:

Baseline to Week 18

End point values	Open-label period: MRX baseline	Open-label period: MRX Week 18		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31[17]	29[18]		
Units: µmol/L				
arithmetic mean (standard deviation)	283.43 (± 210.569)	192.50 (± 161.278)		

Notes:

[17] - Values were collected from 31 participants at baseline.

[18] - Values were collected at Week 18 from 29 of the 31 participants who contributed values at baseline.

Statistical analyses

Statistical analysis title	Change from baseline to Week 18 in sBA levels

Statistical analysis description:

This analysis investigated whether a statistically significant change in sBA levels was observed when comparing baseline to Week 18 (the open-label period, during which all participants received MRX). The analysis was based on the ITT population.

Comparison groups	Open-label period: MRX Week 18 v Open-label period: MRX baseline

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence[19]
P-value	= 0.0005 [20]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-87.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-133.37
upper limit	-42.09
Variability estimate	Standard deviation
Dispersion value	119.979

Notes:

[19] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in sBA levels between baseline and Week 18 (the open-label period) was statistically significant.

[20] - Data for this analysis were obtained from 31 participants at baseline; 29 of those participants contributed Week 18 data.

Secondary: Change from baseline to Week 18 in alkaline phosphatase

End point title	Change from baseline to Week 18 in alkaline phosphatase

End point description:

This secondary efficacy endpoint is the mean change from baseline to Week 18 in ALP

End point type	Secondary

End point timeframe:

Baseline to Week 18

End point values	Open-label period: MRX baseline	Open-label period: MRX Week 18		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31[21]	29[22]		
Units: U/L				
arithmetic mean (standard deviation)	601.3 (± 274.77)	580.8 (± 215.50)		

Notes:

[21] - Values were collected from 31 participants at baseline.

[22] - Values were collected at Week 18 from 29 of the 31 participants who contributed values at baseline.

Statistical analyses

Statistical analysis title	Change from baseline to Week 18 in ALP

Statistical analysis description:

This analysis investigated whether a statistically significant change in ALP levels was observed when comparing baseline to Week 18 (the open-label period, during which all participants received MRX). The analysis was based on the ITT population.

Comparison groups	Open-label period: MRX baseline v Open-label period: MRX Week 18

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence[23]
P-value	= 0.2163 [24]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-27.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-72.8
upper limit	17.2
Variability estimate	Standard deviation
Dispersion value	118.33

Notes:

[23] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in ALP levels between baseline and Week 18 (the open-label period) was statistically significant.

[24] - Data for this analysis were obtained from 31 participants at baseline; 29 of those participants contributed Week 18 data.

Secondary: Change from baseline to Week 18 in alanine aminotransferase

End point title	Change from baseline to Week 18 in alanine aminotransferase

End point description:

This secondary efficacy endpoint is the mean change from baseline to Week 18 in ALT

End point type	Secondary

End point timeframe:

Baseline to Week 18

End point values	Open-label period: MRX baseline	Open-label period: MRX Week 18		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31[25]	29[26]		
Units: U/L				
arithmetic mean (standard deviation)	181.0 (± 108.56)	177.4 (± 92.08)		

Notes:

[25] - Values were collected from 31 participants at baseline.

[26] - Values were collected at Week 18 from 29 of the 31 participants who contributed values at baseline.

Statistical analyses

Statistical analysis title	Change from baseline to Week 18 in ALT

Statistical analysis description:

This analysis investigated whether a statistically significant change in ALT levels was observed when comparing baseline to Week 18 (the open-label period, during which all participants received MRX). The analysis was based on the ITT population.

Comparison groups	Open-label period: MRX baseline v Open-label period: MRX Week 18

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence[27]
P-value	= 0.9358 [28]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.4
upper limit	30.9
Variability estimate	Standard deviation
Dispersion value	84.54

Notes:

[27] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in ALT levels between baseline and Week 18 (the open-label period) was statistically significant.

[28] - Data for this analysis were obtained from 31 participants at baseline; 29 of those participants contributed Week 18 data.

Secondary: Change from baseline to Week 18 in total bilirubin

End point title	Change from baseline to Week 18 in total bilirubin

End point description:

This secondary efficacy endpoint is the mean change from baseline to Week 18 in total bilirubin

End point type	Secondary

End point timeframe:

Baseline to Week 18

End point values	Open-label period: MRX baseline	Open-label period: MRX Week 18		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31[29]	29[30]		
Units: mg/dL				
arithmetic mean (standard deviation)	6.09 (± 5.781)	5.12 (± 5.337)		

Notes:

[29] - Values were collected from 31 participants at baseline.

[30] - Values were collected at Week 18 from 29 of the 31 participants who contributed values at baseline.

Statistical analyses

Statistical analysis title	Change from baseline to Week 18 in total bilirubin

Statistical analysis description:

This analysis investigated whether a statistically significant change in total bilirubin levels was observed when comparing baseline to Week 18 (the open-label period, during which all participants received MRX). The analysis was based on the ITT population.

Comparison groups	Open-label period: MRX baseline v Open-label period: MRX Week 18

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence[31]
P-value	= 0.0893 [32]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.08
Variability estimate	Standard deviation
Dispersion value	1.424

Notes:

[31] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in total bilirubin levels between baseline and Week 18 (the open-label period) was statistically significant.

[32] - Data for this analysis were obtained from 31 participants at baseline; 29 of those participants contributed Week 18 data.

Secondary: Change from baseline to Week 18 in direct bilirubin

End point title	Change from baseline to Week 18 in direct bilirubin

End point description:

This secondary efficacy endpoint is the mean change from baseline to Week 18 in total bilirubin

End point type	Secondary

End point timeframe:

Baseline to Week 18

End point values	Open-label period: MRX baseline	Open-label period: MRX Week 18		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31[33]	28[34]		
Units: mg/dL				
arithmetic mean (standard deviation)	4.57 (± 3.666)	3.98 (± 3.369)		

Notes:

[33] - Values were collected from 31 participants at baseline.

[34] - Values were collected at Week 18 from 28 of the 31 participants who contributed values at baseline.

Statistical analyses

Statistical analysis title	Change from baseline to Week18 in direct bilirubin

Statistical analysis description:

This analysis investigated whether a statistically significant change in direct bilirubin levels was observed when comparing baseline to Week 18 (the open-label period, during which all participants received MRX). The analysis was based on the ITT population.

Comparison groups	Open-label period: MRX baseline v Open-label period: MRX Week 18

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	equivalence[35]
P-value	= 0.0139 [36]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.11
Variability estimate	Standard deviation
Dispersion value	1.012

Notes:

[35] - The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in direct bilirubin levels between baseline and Week 18 (the open-label period) was statistically significant.

[36] - Data for this analysis were obtained from 31 participants at baseline; 28 of those participants contributed Week 18 data.

Secondary: Change from baseline to Week 18 in pruritus as measured by ItchRO

End point title	Change from baseline to Week 18 in pruritus as measured by ItchRO

End point description:

This secondary efficacy endpoint is the change from baseline to Week 18 in pruritus as measured by ItchRO(Obs) weekly average morning score and ItchRO(Pt) weekly average morning score

End point type	Secondary

End point timeframe:

Baseline to Week 18

End point values	Open-label period: MRX baseline	Open-label period: MRX Week 18		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31[37]	29[38]		
Units: Points (0-4)				
arithmetic mean (standard deviation)				
ItchRO(Obs) weekly average morning score	2.909 (± 0.5480)	1.203 (± 0.8446)		
ItchRO(Pt) weekly average morning score	2.903 (± 0.6616)	0.831 (± 0.8122)		

Notes:

[37] - Values collected at baseline from 31 and 14 participants, respectively, for ItchRO(Obs) and (Pt).

[38] - Values were collected at Week 18 from 29 and 14 participants, respectively, for ItchRO(Obs) and (Pt)

Statistical analyses

Statistical analysis title	Change from baseline to Week 18 in ItchRO(Obs)

Statistical analysis description:

This analysis investigated whether a statistically significant change in ItchRO(Obs) score was observed when comparing baseline to Week 18 (the open-label period, during which all participants received

MRX). The analysis was based on the ITT population. ItchRO scores range from 0 to 4; the higher score indicates increasing itch severity.

Comparison groups	Open-label period: MRX baseline v Open-label period: MRX Week 18
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence[39]
P-value	< 0.0001 [40]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-1.704
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.051
upper limit	-1.357
Variability estimate	Standard deviation
Dispersion value	0.9114

Notes:

[39] - The null hypothesis that the mean change was equal to zero was tested using the Student’s t-test to determine if the mean change in ItchRO(Obs) scores between baseline and Week 18 (the open-label period) was statistically significant.
[40] - Data for this analysis were obtained from 31 participants at baseline; 29 of those participants contributed Week 18 data.

Statistical analysis title	Change from baseline to Week 18 in ItchRO(Pt)

Statistical analysis description:

This analysis investigated whether a statistically significant change in ItchRO(Pt) score was observed when comparing baseline to Week 18 (the open-label period, during which all participants received MRX). The analysis was based on the ITT population. ItchRO scores range from 0 to 4; the higher score indicates increasing itch severity.

Comparison groups	Open-label period: MRX baseline v Open-label period: MRX Week 18
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence[41]
P-value	< 0.0001 [42]
Method	Student's t-test
Parameter estimate	Mean difference (net)
Point estimate	-2.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.645
upper limit	-1.498
Variability estimate	Standard deviation
Dispersion value	0.9931

Notes:

[41] - The null hypothesis that the mean change was equal to zero was tested using the Student’s t-test to determine if the mean change in ItchRO(Pt) scores between baseline and Week 18 (the open-label period) was statistically significant.
[42] - Data for this analysis were obtained from 14 participants at baseline; 14 of those participants contributed Week 18 data.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to EOT

Adverse event reporting additional description:

All treatment-emergent AEs, whether observed by the Investigator, reported by the participant, the participant's caregiver, from laboratory findings, or other means, were recorded on the AE eCRF and medical record. 'Occurrences' relates to the number of events; 'subjects affected' relates to the number of participants who experienced the AE.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Open-label period

Reporting group description:

Open-label period: 18-week OL run-in period (Day 1 to Week 18). All participants received MRX.

Reporting group title	Randomized withdrawal period: MRX

Reporting group description:

Randomized withdrawal [RWD] period: MRX
4-week randomized, double-blind, placebo-controlled drug-withdrawal period (Weeks 19 to 22) with participants randomized to receive MRX

Reporting group title	Randomized withdrawal period: Placebo

Reporting group description:

Randomized withdrawal [RWD] period: Placebo
4-week randomized, double-blind, placebo-controlled drug-withdrawal period (Weeks 19 to 22) with participants randomized to receive placebo

Reporting group title	After randomized withdrawal period

Reporting group description:

After randomized withdrawal (ARW) period
26-week stable-dosing period (Weeks >22 - 48): all participants received MRX

Reporting group title	Long-term extension period

Reporting group description:

Long-term Extension (LTE) period
Optional long-term treatment period (> Weeks 48) during which all participants received MRX.

Reporting group title	Safety population

Reporting group description:

The safety population was defined as all participants who were assigned and received at least one dose of the study drug.

Serious adverse events	Open-label period	Randomized withdrawal period: MRX	Randomized withdrawal period: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 31 (12.90%)	1 / 13 (7.69%)	1 / 16 (6.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			

Blood bilirubin increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Marrow hyperplasia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Extradural haematoma			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (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
Forearm fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic rupture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (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
Toxicity to various agents			

subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac dysfunction			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (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
Blood and lymphatic system disorders			
Aplasia pure red cell			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			

subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epstein-Barr virus infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotavirus infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (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
Tonsillitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 13 (7.69%)	0 / 16 (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
Viral pharyngitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (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

Serious adverse events	After randomized withdrawal period	Long-term extension period	Safety population
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 29 (17.24%)	6 / 23 (26.09%)	13 / 31 (41.94%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Marrow hyperplasia			

subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Extradural haematoma			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic rupture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	1 / 29 (3.45%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Shock haemorrhagic			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac dysfunction			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Aplasia pure red cell			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epstein-Barr virus infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotavirus infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			

subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral pharyngitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
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	Open-label period	Randomized withdrawal period: MRX	Randomized withdrawal period: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 31 (96.77%)	7 / 13 (53.85%)	12 / 16 (75.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm skin			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Subclavian artery stenosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Condition aggravated			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Face oedema			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	6 / 31 (19.35%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences (all)	12	0	1
Immune system disorders			
Allergy to animal			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Seasonal allergy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	3 / 31 (9.68%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Dysphonia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			

subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	2 / 31 (6.45%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Sneezing			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Breath holding			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Enuresis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hallucination, visual			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Intentional self-injury			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Psychological trauma			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Product issues			
Skin papilloma			

subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vitamin A increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vitamin D decreased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Bite			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Face injury			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	4 / 31 (12.90%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	7	0	0
Head injury			

subjects affected / exposed	2 / 31 (6.45%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Ligament sprain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Limb injury			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Lip injury			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Muscle strain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Nasal injury			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Overdose			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	2 / 31 (6.45%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Skin laceration			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Thermal burn			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Tooth avulsion			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Traumatic haematoma			

subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Vaccination complication			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Arachnoid cyst			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	5 / 31 (16.13%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	5	0	0
Hyperaesthesia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	2 / 31 (6.45%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Poor quality sleep			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Coagulopathy			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0

Thrombocytopenia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Conductive deafness			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Deafness neurosensory			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Excessive cerumen production			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Middle ear effusion			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Hypermetropia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Visual acuity reduced			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	12 / 31 (38.71%)	1 / 13 (7.69%)	1 / 16 (6.25%)
occurrences (all)	22	1	1
Abdominal pain upper			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Constipation			

subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Dental caries			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	13 / 31 (41.94%)	1 / 13 (7.69%)	1 / 16 (6.25%)
occurrences (all)	18	1	1
Faeces pale			
subjects affected / exposed	2 / 31 (6.45%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Gastritis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Haematochezia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Lip discolouration			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Lip swelling			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 31 (3.23%)	1 / 13 (7.69%)	0 / 16 (0.00%)
occurrences (all)	4	1	0
Proctalgia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Tongue discolouration			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Toothache			

subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	11 / 31 (35.48%)	1 / 13 (7.69%)	1 / 16 (6.25%)
occurrences (all)	15	1	2
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Jaundice			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 31 (0.00%)	1 / 13 (7.69%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	3 / 31 (9.68%)	1 / 13 (7.69%)	5 / 16 (31.25%)
occurrences (all)	4	1	5
Rash			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Dysuria			

subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Glomerulonephropathy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Renal tubular acidosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Back pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Bone cyst			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Growth retardation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Ligamentitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Abscess			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Croup infectious			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Dermatitis infected			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	3 / 31 (9.68%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Epstein-Barr virus infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Fungal skin infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gastritis viral			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Infected bite			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	2 / 31 (6.45%)	1 / 13 (7.69%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Laryngitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0

Localised infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Molluscum contagiosum			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	4 / 31 (12.90%)	1 / 13 (7.69%)	1 / 16 (6.25%)
occurrences (all)	4	1	1
Oral herpes			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	2 / 31 (6.45%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Otitis media acute			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Pharyngotonsillitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Rhinitis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 13 (7.69%)	0 / 16 (0.00%)
occurrences (all)	1	1	0

Rotavirus infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Staphylococcal infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	6 / 31 (19.35%)	2 / 13 (15.38%)	0 / 16 (0.00%)
occurrences (all)	16	3	0
Urinary tract infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Varicella			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	1 / 31 (3.23%)	1 / 13 (7.69%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 31 (6.45%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Dehydration			
subjects affected / exposed	1 / 31 (3.23%)	1 / 13 (7.69%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Malnutrition			

subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Vitamin A deficiency			
subjects affected / exposed	1 / 31 (3.23%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vitamin C deficiency			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Weight gain poor			
subjects affected / exposed	0 / 31 (0.00%)	0 / 13 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	After randomized withdrawal period	Long-term extension period	Safety population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 29 (86.21%)	23 / 23 (100.00%)	31 / 31 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm skin			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Subclavian artery stenosis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Condition aggravated			

subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Face oedema			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	1 / 29 (3.45%)	1 / 23 (4.35%)	3 / 31 (9.68%)
occurrences (all)	1	2	4
Influenza like illness			
subjects affected / exposed	2 / 29 (6.90%)	2 / 23 (8.70%)	3 / 31 (9.68%)
occurrences (all)	2	2	4
Pyrexia			
subjects affected / exposed	7 / 29 (24.14%)	10 / 23 (43.48%)	17 / 31 (54.84%)
occurrences (all)	12	27	52
Immune system disorders			
Allergy to animal			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Seasonal allergy			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	3 / 29 (10.34%)	8 / 23 (34.78%)	13 / 31 (41.94%)
occurrences (all)	3	12	18
Dysphonia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Dyspnoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Epistaxis			

subjects affected / exposed	0 / 29 (0.00%)	2 / 23 (8.70%)	2 / 31 (6.45%)
occurrences (all)	0	2	5
Oropharyngeal pain			
subjects affected / exposed	3 / 29 (10.34%)	3 / 23 (13.04%)	7 / 31 (22.58%)
occurrences (all)	3	5	9
Rhinorrhoea			
subjects affected / exposed	1 / 29 (3.45%)	1 / 23 (4.35%)	4 / 31 (12.90%)
occurrences (all)	1	1	4
Sneezing			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Psychiatric disorders			
Breath holding			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Enuresis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Hallucination, visual			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 23 (8.70%)	2 / 31 (6.45%)
occurrences (all)	0	2	3
Intentional self-injury			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Psychological trauma			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Product issues			
Skin papilloma			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 29 (0.00%)	4 / 23 (17.39%)	4 / 31 (12.90%)
occurrences (all)	0	5	5
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 29 (0.00%)	2 / 23 (8.70%)	2 / 31 (6.45%)
occurrences (all)	0	2	2
International normalised ratio increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	2
Vitamin A increased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Vitamin D decreased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Bite			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Contusion			
subjects affected / exposed	0 / 29 (0.00%)	3 / 23 (13.04%)	4 / 31 (12.90%)
occurrences (all)	0	3	4
Face injury			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	3 / 29 (10.34%)	0 / 23 (0.00%)	6 / 31 (19.35%)
occurrences (all)	5	0	12
Head injury			
subjects affected / exposed	1 / 29 (3.45%)	1 / 23 (4.35%)	3 / 31 (9.68%)
occurrences (all)	1	1	5
Ligament sprain			

subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Limb injury			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Lip injury			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Muscle strain			
subjects affected / exposed	1 / 29 (3.45%)	2 / 23 (8.70%)	3 / 31 (9.68%)
occurrences (all)	1	2	4
Nasal injury			
subjects affected / exposed	2 / 29 (6.90%)	1 / 23 (4.35%)	3 / 31 (9.68%)
occurrences (all)	2	1	3
Overdose			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Procedural pain			
subjects affected / exposed	0 / 29 (0.00%)	2 / 23 (8.70%)	2 / 31 (6.45%)
occurrences (all)	0	2	2
Skin abrasion			
subjects affected / exposed	1 / 29 (3.45%)	1 / 23 (4.35%)	3 / 31 (9.68%)
occurrences (all)	5	1	8
Skin laceration			
subjects affected / exposed	2 / 29 (6.90%)	1 / 23 (4.35%)	3 / 31 (9.68%)
occurrences (all)	3	1	5
Thermal burn			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Tooth avulsion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Traumatic haematoma			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Vaccination complication			

subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 29 (0.00%)	2 / 23 (8.70%)	2 / 31 (6.45%)
occurrences (all)	0	2	2
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Nervous system disorders			
Arachnoid cyst			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Headache			
subjects affected / exposed	2 / 29 (6.90%)	4 / 23 (17.39%)	9 / 31 (29.03%)
occurrences (all)	4	10	19
Hyperaesthesia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Lethargy			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Poor quality sleep			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Coagulopathy			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	2 / 31 (6.45%)
occurrences (all)	1	0	2
Thrombocytopenia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	2	2

Ear and labyrinth disorders			
Conductive deafness			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Deafness neurosensory			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Ear pain			
subjects affected / exposed	3 / 29 (10.34%)	1 / 23 (4.35%)	3 / 31 (9.68%)
occurrences (all)	3	2	6
Excessive cerumen production			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	2
Middle ear effusion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Eye disorders			
Hypermetropia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Visual acuity reduced			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Abdominal pain			
subjects affected / exposed	6 / 29 (20.69%)	12 / 23 (52.17%)	18 / 31 (58.06%)
occurrences (all)	12	31	67
Abdominal pain upper			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Constipation			
subjects affected / exposed	1 / 29 (3.45%)	1 / 23 (4.35%)	3 / 31 (9.68%)
occurrences (all)	1	1	3
Dental caries			

subjects affected / exposed	0 / 29 (0.00%)	2 / 23 (8.70%)	2 / 31 (6.45%)
occurrences (all)	0	3	3
Diarrhoea			
subjects affected / exposed	5 / 29 (17.24%)	7 / 23 (30.43%)	18 / 31 (58.06%)
occurrences (all)	10	18	48
Faeces pale			
subjects affected / exposed	1 / 29 (3.45%)	2 / 23 (8.70%)	3 / 31 (9.68%)
occurrences (all)	1	2	5
Gastritis			
subjects affected / exposed	0 / 29 (0.00%)	2 / 23 (8.70%)	3 / 31 (9.68%)
occurrences (all)	0	2	3
Haematochezia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Lip discolouration			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Lip swelling			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Mouth ulceration			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	1 / 29 (3.45%)	2 / 23 (8.70%)	2 / 31 (6.45%)
occurrences (all)	1	2	8
Proctalgia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Tongue discolouration			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Toothache			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Vomiting			

subjects affected / exposed	2 / 29 (6.90%)	8 / 23 (34.78%)	16 / 31 (51.61%)
occurrences (all)	3	13	34
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Jaundice			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Erythema			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Pruritus			
subjects affected / exposed	2 / 29 (6.90%)	0 / 23 (0.00%)	9 / 31 (29.03%)
occurrences (all)	3	0	13
Rash			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Urticaria			
subjects affected / exposed	1 / 29 (3.45%)	1 / 23 (4.35%)	2 / 31 (6.45%)
occurrences (all)	1	1	2
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	2
Dysuria			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Glomerulonephropathy			

subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Renal tubular acidosis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	2	1	5
Back pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Bone cyst			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Flank pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Growth retardation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Joint swelling			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Ligamentitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Pain in extremity			
subjects affected / exposed	0 / 29 (0.00%)	4 / 23 (17.39%)	4 / 31 (12.90%)
occurrences (all)	0	5	5
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Bronchitis			

subjects affected / exposed	1 / 29 (3.45%)	2 / 23 (8.70%)	3 / 31 (9.68%)
occurrences (all)	1	6	7
Croup infectious			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Dermatitis infected			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Ear infection			
subjects affected / exposed	4 / 29 (13.79%)	5 / 23 (21.74%)	8 / 31 (25.81%)
occurrences (all)	4	6	14
Epstein-Barr virus infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	2
Fungal skin infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Gastritis viral			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Gastroenteritis			
subjects affected / exposed	1 / 29 (3.45%)	5 / 23 (21.74%)	7 / 31 (22.58%)
occurrences (all)	1	7	9
Infected bite			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Influenza			
subjects affected / exposed	1 / 29 (3.45%)	2 / 23 (8.70%)	5 / 31 (16.13%)
occurrences (all)	1	2	6
Laryngitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Localised infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Lower respiratory tract infection			

subjects affected / exposed	0 / 29 (0.00%)	2 / 23 (8.70%)	2 / 31 (6.45%)
occurrences (all)	0	3	3
Molluscum contagiosum			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	8 / 29 (27.59%)	9 / 23 (39.13%)	13 / 31 (41.94%)
occurrences (all)	21	46	73
Oral herpes			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	2
Otitis media			
subjects affected / exposed	0 / 29 (0.00%)	2 / 23 (8.70%)	4 / 31 (12.90%)
occurrences (all)	0	2	4
Otitis media acute			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Pharyngitis			
subjects affected / exposed	0 / 29 (0.00%)	3 / 23 (13.04%)	4 / 31 (12.90%)
occurrences (all)	0	3	4
Pharyngotonsillitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Pneumonia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	3
Rhinitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	3 / 31 (9.68%)
occurrences (all)	0	1	3
Rotavirus infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Sinusitis			

subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Skin infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	2
Staphylococcal infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	1 / 29 (3.45%)	1 / 23 (4.35%)	2 / 31 (6.45%)
occurrences (all)	1	1	2
Upper respiratory tract infection			
subjects affected / exposed	3 / 29 (10.34%)	4 / 23 (17.39%)	9 / 31 (29.03%)
occurrences (all)	3	6	28
Urinary tract infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Varicella			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	1 / 29 (3.45%)	5 / 23 (21.74%)	8 / 31 (25.81%)
occurrences (all)	1	5	8
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	3
Dehydration			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	2
Malnutrition			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Vitamin A deficiency			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1

Vitamin C deficiency			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Weight gain poor			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	1 / 31 (3.23%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2015	Substantial changes made to the protocol were to add additional exclusion criteria of history or presence of gallstones or kidney stones, and known hypersensitivity to MRX or any of its components.
08 May 2015	Substantial changes made to the protocol were to add exclusion of participants weighing over 50 kg at screening, sBA definition for randomization corrected to Week 12, and language added to address the randomization and statistical management of data generated from siblings enrolled in the study and to describe a planned extension study.
13 November 2015	Substantial changes made to the protocol were to add an optional follow-up treatment period (after Week 48) that allowed eligible participants treated in Study LUM001-304 to continue on treatment after Week 48 until the first of the following occurred: (1) up to 52 weeks of additional treatment (Week 100), or (2) in the event that a new study opened to enrollment; add an objective to obtain safety and efficacy data in participants treated long term on maralixibat, including genotyping characteristics; add NOTCH2 to list of laboratory analytes.
28 March 2017	Substantial changes made to the protocol were to allow continued participation in the optional follow-up treatment period, beyond what had been described in Protocol Amendment 3; and describe objectives and assessments of the optional follow-up treatment period; and update the contraceptive requirements to align with the Heads of Medicine Clinical Trials Facilitation Group Recommendations Related to Contraception and Pregnancy Testing. During the optional follow-up treatment period, participants must have met ongoing efficacy (sBA level and ItchRO score) and safety criteria to be eligible to undergo BID dosing with MRX. Only participants with sBA levels above normal and/or ItchRO score ≥1.5 were eligible to start BID dosing. The maximum daily dose was 400 µg/kg BID, that is, 800 µg/kg daily. If a participant experienced intolerance (e.g., GI symptoms such as diarrhea, abdominal pain, cramping) at any time during the study, the investigator, in consultation with the medical monitor, was allowed to lower the dose for the remainder of the study.
06 November 2017	Substantial changes made to the protocol were to change the study design going forward to an OL study beyond what had been described in Protocol Amendment 4; to add details regarding interim analyses up to Week 48 and unblinding of the study; and to add clinician xanthoma scale to the Schedule of Procedures.
08 February 2019	Substantial changes made to the protocol were to reflect the change of sponsorship from Lumena Pharmaceuticals LLC to Mirum Pharmaceuticals, Inc., and to document the change in medical monitor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported